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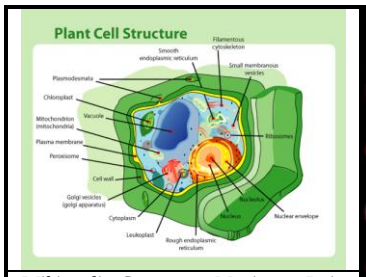
Molecular Theory of

THE LIVING CELL

Concepts, Molecular Mechanisms, and Biomedical Applications



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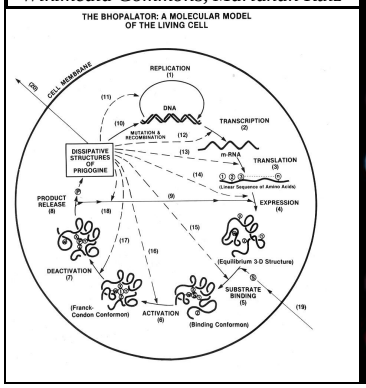

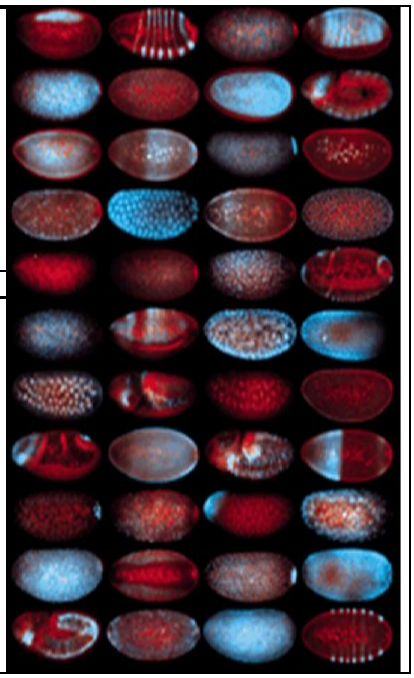

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Preface

There are three main objectives underlying this book – i) to summarize the key experimental observastions on the living cell, ii) to develop a *molecular theory* of the living cell consisting of a set of concepts, molecular mechanisms, laws and principles, and iii) to apply the new theory of the living cell to solving concrete problems in biology and medicine, including morphogenesis and evolution itself.

The cell is arguably one of the most complex material systems in nature, in no small part because it is the building block of all living systems, including us. *We are cells, and cells are us.* To know how cells work, therefore, will contribute to understanding not only how our bodies work, which will advance medicine, but also how our mind works, which may help answer some of age-old philosophical and religion-related questions from a new perspective. It is hoped that the molecular theory of the living cell presented in this book will contribute to the emergence of "the new science of human nature" that can lead "to a realistic, biologically informed humanism" (Pinker 2003). As a result of the research efforts of biologists around the world over the past several centuries, especially since the middle of the last century when the *DNA double helix* was discovered, we now have, as pointed out by de Duve (1991), a complete list of the components that constitute a living cell (e.g., see Table 17-2), and yet we still do not understand how even a single enzyme molecule works. There are tens of thousands of different kinds of enzymes in the human cell. We do not yet know how the cell expresses the right sets of genes at right times and right places for right durations in order to perform its functions under a given environmental condition.

Although many excellent books have been written on specialized aspects of the cell, such as the *Molecular Biology of the Cell* (Alberts et al. 2008), *Computational Cell Biology* (Fall et al. 2002), *Thermodynamics of the Machinery of Life* (Kurzynski 2006), and *Mechanics of the Cell* (Boal 2002), to cite just a few, there is a paucity of books that deal with the general principles, concepts, and molecular mechanisms that apply to the living cell as a whole, with some exceptions such as Schrődinger's *What Is Life* written in the middle of the last century, Crick's *From Molecules to Men* (1966), Rizzotti's *Defining Life* (1996), and de Duve's *Blueprint of Life* (1991). The present book is probably the most recent addition to the list of the books on what may be called *theoretical cell biology* (in analogy to *theoretical physics*) that attempts to answer the same kind of questions raised by Schrődinger more than a half century ago (see Sections 16 and 21) and subsequently by many others.

During the course of writing the present book, I have often been reminded of a statement made by G. Simpson (1964) to the effect that

> Physicists study principles that apply to all phenomena; biologists study phenomena to which all principles apply.

For convenience, we may refer to this statement as the *Simpson thesis.*

More recently, I came across another truism which may be referred to as the *de Duve thesis*:

> The problems of life are so fundamental, fascinating and complex that they attract the interest of all and can be encompassed by none (de Duve 1991, Preface).

True to *the Simpson thesis*, the present work deals with unusually wide-ranging topics, from inorganic electron transfer reactions (Section 2.2), to single-molecule enzymology (Section 11.3), gene expression (Section 12.9), morphogenesis (Chapter 15), category theory (Section 12.13), the origin of life (Chapter 13), biological evolution itself (Chapter 14), personalized medicine (Chapter 18) and drug discovery (Chapter 19). True to *the de Duve thesis*, the readers will find numerous gaps in both the kinds of topics discussed (e.g., photosynthesis and immunology) and the factual details presented in some of the topics covered, reflecting the limitations of my personal background (as a physical-organic chemist-turned-theoretical-cell-biologist) in experimental cell biology and mathematical and computational skills.

Two revolutionary experimental techniques appeared more or less simultaneously and independently in the last decade of the 20th century – the *DNA microarrays* (Section 12.1) (Watson and Akil 1999) and the *single-molecule manipulation* and *monitoring techniques* (Section 11.3) (Ishii and Yanagida 2000, 2007, van Oijen and Loparo 2010). With the former, cell biologists can measure tens of thousands of mRNA levels in cells simultaneously, unlike in the past when only a few or at most dozens of them could be studied at the same time. The DNA microarray technique has opened the window into a whole new world of complex molecular *interactions* underlying the phenomenon of life at the cellular level (see *interactomes*, Section 9.3), the investigation of which promises to contribute to deepening our understanding of the phenomenon of life as well as mind on the most basic level (Pattee 1982, Thompson 2009).

In contrast to the DNA microarray technique which provides a global view of cell metabolism, the single-molecule measuring techniques (Ishii and Yanagida 2000, 2007, van Oijen and Loparo 2010) make it possible to probe cell metabolism at the level of single enzyme or DNA molecules. The single-molecule mechanical measurements are truly amazing, since, for the first time in the history of science, it is now possible to observe and measure in real time how a single molecule of *myosin*, for example, moves along an actin filament utilizing the free energy supplied by the hydrolysis of a single molecule of ATP (see Panel D in Figure 11-34).

The theoretical investigations into the molecular mechanisms of *oxidative phosphorylation* in *mitochondria* that I began in 1970 as a postdoctoral fellow under David E. Green (1910-1983) at the Institute for Enzyme Research, University of Wisconsin, Madison, had led me to formulate the concept of the *conformon* in 1972-1985 (see Chapter 8) and the *Principle of Slow and Fast Processes* (also known as the *generalized Franck-Condon principle*) in 1974 (Section 2.2.3) and construct what appears to be the first *theoretical model* of the living cell called the *Bhopalator* in 1985 (Section 10.1). These theoretical models and related theoretical ideas and principles are summarized in this book, and an attempt has been made to apply them to analyze some of

the rapidly expanding experimental data generated by the two revolutionary techniques mentioned above. In addition, these theoretical results have been utilized to formulate possible solutions to many of the basic problems facing the contemporary molecular, cell and evolutionary biology.

When I invoked the concept of the *conformon* in 1972 (see Section 8) in collaboration with D. E. Green, I did not realize that I would be spending a good part of the next four decades of my life doing theoretical research on this concept and related physical, chemical and philosophical principles, including the g*eneralized Franck-Condon principle* (GFCP), or the *Principle of Slow and Fast Processes* (PSFP) (Section 2.2). If *conformons* do indeed exist in biopolymers as appears likely on the basis of the currently available experimental data and theoretical considerations (see Chapter 8 and Section 11.4), the following generalizations may hold true:

(1) The cell is an organized system of *molecular machines*, namely, biopolymers (DNA, RNA, proteins) that carry out microscopic work processes including enzymic catalysis, active transport, molecular motor movement, gene expression, DNA repair, and self-replication.
(2) Conformons are packets of mechanical energy stored in sequence-specific sites within biopolymers derived from *chemical reactions based on generalized* Franck-Condon mechanisms (Section 8.4).
(3) Therefore, the living cell is a supramolecular machine driven by chemical reactions mediated by conformons.

These statements can be schematically represented as follows:

CHEMICAL REACTIONS → *Conformons* → LIFE (0-1)

The most recent and most direct experimental verification to date of the conformon concept was reported by Uchihashi et al. (2011, Junge and Müller 2011; see Section 7.1.4) who, using the high-speed atomic force microscopy, succeeded in visualizing the propagation of the conformational waves (or *conformons*) of the β subunits of the isolated F_1 ATPase stator ring. It now can be said that the conformon concept has been verified over four decades after it was proposed by Green and Ji (1972a,b, Ji 1974, 1991, 2000; Section 8 in tis book). In (Ji 1991), conformons were postulated to mediate what I elected to call *the cell force*. The cell force was invoked to account for the *functional stability* of the living cell in analogy to the strong force which was invoked by physicists to account for the *structural stability* of the atomic nuclei (Han 1999, Huanf 2007). One of the most significant findings resulting from writing this book, I believe, has been the recognition that the whole-cell RNA metabolic data measured with microarrays may provide the first experimental evidence for the cell force. This is discussed in Chapter 12.13.

My desire to test the validity of Scheme (0-1) as objectively and as rigorously as possible has led me to explore a wide range of disciplines during the past four decades, including not only biology, physics, chemistry, engineering, and computer science but also mathematics, linguistics, semiotics and philosophy. The numerous principles, laws, and concepts that I have found necessary to account for the phenomenon of life on the

molecular and cellular levels have been collected and explained in Part I of this book. Part II applies these principles, laws and concepts to formulate a comprehensive *molecular theory of life* which I have at various times referred to as *biognergetics* (Ji 1985), *biocybernetics* (Ji 1991), *microsemiotics* (Ji 2002a), *molecular information theory* (Ji 2004a), and *renormalizable network theory of life* (Section 2.4), depending on the points of emphasis or of prescinding (to use a Peircean idiom (Section 6.2.12)). The molecular theory of life developed in Part II is then utilized in Part III to formulate possible solutions to some of the basic problems facing the contemporary molecular and cell biology, including the definitions of the gene and life, mechanisms of morphogenesis and evolution, and the problems of interpreting DNA microarray data (Ji et al. 2009a) and the single-molecule enzymological data of Lu, Xun and Xie (1998), Xie and Lu (1999) and Ishijima et al. (1998). Possible applications of the molecular theory of the living cell developed in this book to drug discovery research and personalized medicine are also included in Chapters 18 and 19.

To see a world in a grain of sand . . . . .
-- William Blake (1757-1827)

The Universe in a single atom
-- Dalai Lama (1935 -)

To see the Universe in a living cell . . . . .
-- 2011

CHAPTER 1

Introduction

The cell doctrine stating that all living systems are built out of one or more cells was formulated by M. J. Schleiden and T. Schwann in 1838-39 (Swanson 1964, Bechtel 2010). Since then an enormous amount of experimental data has been accumulating in the literature and on the World Wide Web, pre- and post-Google, on the structure and function of the cell, based on which many authoritative books have been written, one of the most recent publications being *The Molecular Biology of the Cell*, Fifth Edition, by Alberts and his colleagues (2008). Other publications include "Computational Cell Biology" (Fall et al. 2002) and *Mechanics of the Cell* (Boal 2002), which are highly mathematical and computer model-based and deal with rather specialized subfields within molecular cell biology. To the best of my knowledge (as of June, 2011), there has been no general book published that deals with the *molecular theory* of the living cell as a whole, except, as mentioned in *Preface*, the books by Schrödinger (1998), Crick (1966), and Rizzotti (1996). The present book may be viewed as the 21st century version of *What Is Life?* that has been updated taking into account the biological knowledge that has accumulated since 1944 when *What Is Life?* was published. The molecular theory of life formulated by Schrödinger and that described in this book are compared in Sections 16.2 and 16.6 and Chapter 21.

To emphasize the importance of *theory* in relation to *experiment* in biology, I elected to entitle the present book after the title of the book by Alberts et al. (2008) by i) replacing *Biology* with *Theory* and ii) adding the adjective *Living* in front of the word *Cell*, resulting in *The Molecular Theory of the Living Cell.* The first modification highlights the difference between the *theory* of life emphasized in this book and the *experiment* on life comprehensively summarized in books such as the one written by Alberts et al. (2008). The second modification emphasizes the difference between the *static picture* of the cell normally found in textbooks (analogous to *sheet music*) and the *dynamic* picture of the cell (analogous to *audio music*) emphasized in the present book. Also, unlike the books by Alberts et al. and by others that focus on experimental data obtained from broken (and hence 'dead') cells, the present book attempts to understand the essential characteristics of cells that are 'alive', by developing a molecular *theory* of

life based on both the experimental findings on dead cells and theoretical concepts applicable to *living* cells.

The concept of 'theory' in biology is relatively new and seemingly alien to most practicing biologists. Biologists have learned throughout the recent history of molecular cell biology that many breakthroughs in biology are possible without any deep biological theory (witness the discovery of the DNA double helix, the deciphering of the genetic code, the completion of the human genome sequencing project, and many fundamental findings in stem cell research (Holden and Vogel 2008)). As a consequence, biologists may have unwittingly come to entertain the view that no deep theory, comparable to quantum mechanics in physics and chemistry, is needed in biology. In fact many bioscientists may hold the opinion that living systems are too complex for any deep theoretical approaches to be possible, as one of the most respected living biologists whom I know once challenged me: *Why do theory when you can solve problems by doing experiments?* Such a perspective on theory found among many biologists contrasts with that of contemporary physicists who most often carry out experiments in order to test the predictions made by theory (Moriyasu 1985). It is hoped that the publication of the present book will contribute to establishing a culture in biology wherein theory is viewed as essesntial in solving problems in biology as is currently the case in physics.

To gauge what a future *molecular theory of biology* may look like, it may be useful to survey other fields of human inquiries where *experiment* and *theory* have established firm relations. As summarized in Table 1-1, physics, chemistry, and linguistics appear to have progressed through three distinct stages of development, viewed either globally/macroscopically or locally/microscopically. Some of the boxes in the table are empty by definition. Assuming that biology will also follow the three stages of *description*, *organization*, and *theory building*, I have filled in the boxes belonging to Biology based primarily on my own research experience over the past four decades. It is possible that there are many other possible candidates that can fill these boxes and that any of my own theories may be replaced by some of these in the future. There are a total of 10 theories listed in the last column of the Biology section, all of which are discussed throughout this book in varying details.

Table 1-1 The three stages of the development of human knowledge. ' TOE' stands for the Theory of Everything. Examples of each field are selected from two levels -- global (or macroscopic) and local (or microscopic). Boxes labeled (3, 1), (3, 2), (6, 1), (6, 2), (9, 1), (9, 2), (12, 1), and (12, 2) are empty because the third row of each field applies to the Theory Building column only.

Field		Description	Organization	Theory Building
Physics	**1.** Global	Astronomy	Kepler's laws	Newton's laws of motion Einstein's relativity
	2. Local	Atomic line spectra	Lyman, Balmer, Ritz-Paschen, etc. series	Bohr's atomic model Quantum mechanics

	3. TOE	(3, 1)	(3, 2)	Standard Model Superstring theory
Chemistry	**4.** Global	Chemical reactions	Chemical kinetics	Thermodynamics Transition-state theory
	5. Local	Molecular structures	Periodic table	Statistical mechanics Electron density functional theory
	6. TOE	(6, 1)	(6, 2)	Quantum statistical mechanics (?)
Linguistics	**7.** Global	Descriptive linguistics	Chomsky's Universal Grammar (?)	F. de Saussure's semiology (?)
	8. Local	Descriptive linguistics	Grammars Lexicon	F. de Saussure's linguistics (?)
	9. TOE	(9, 1)	(9, 2)	Peirce's semiotics (Section 6.2)
Biology	**10.** Global	Behavioral biology Human genome project Transcriptomics 'Synthetic" stem cells	Physiology Human anatomy Cell doctrine Cell structure and function Reprogrammable genome	Darwin's theory of evolution Prigogine's dissipative structure theory Cell language theory IDS-cell function identity hypothesis (Sections 3.1, 6.1.2, 10.2)
	11. Local	Single-molecule mechanics	DNA double helix Genetic code Metabolic pathways Single-molecule enzymology	Molecularized second law **of thermodynamics** (Section 2.1.4) Generalized Franck-Condon **Principle** (Section 2.2.3) Conformon theory of molecular machines (Chapter 8)
	12. TOE	(12, 1)	(12, 2)	Biocybernetics (Ji 1991) Renormalizable network **Theory** (Section 2.4) Microsemiotics (Section 6.2.4)

2.2 The Franck-Condon Principle (FCP)

2.2.1 FCP and Born-Oppenheimer Approximation

The Franck-Condon Principle originated in molecular spectroscopy in 1925 when J. Franck proposed (and later Condon provided a theoretical basis for) the idea that, when molecules absorb photons to undergo an electronic transition from the ground state (see E_0 in Figure 2-3) to an excited state (E_1), the electronic transition occurs so rapidly that heavy nuclei do not have time to rearrange to their new equilibrium positions (see q_{01}). In effect, this means that the photon-induced electronic transitions are most likely to occur from the ground vibrational level (i.e., $\nu'' = 0$) of the ground electronic state to an excited vibrational level (i.e., $\nu' = 2$) of the upper electronic state (see the vertical upward arrow in Figure 2-3) which rapidly decays to the ground vibrational level , $\nu' = 0$, from which electron transfer is most likely to occur to the excited vibrational level of the ground electronic state, i.e., $\nu'' = 2$ (see the downward arrow), with the concomitant emission of the photon or fluorescence. A year later, Born and Oppenheimer justified what later became known as the Franck-Condon principle in terms of the large mass difference between the electron and average nuclei in a molecule (Born and Oppenheimer 1927). The proton is 1,836 times as massive as the electron.

The Born-Oppenheimer approximation is also known as the "adiabatic pathway" meaning that there is a complete separation between nuclear and electronic motions within atoms. Although this approximation has been found to be generally valid in atomic and molecular spectroscopy and in chemical reactions, there are also well-established exceptions, which are referred to as "non-adiabatic pathways", "non-Born-Oppenheimer coupling" (Bowman 2008, Garand, Zhou and Manolopoulos 2008).

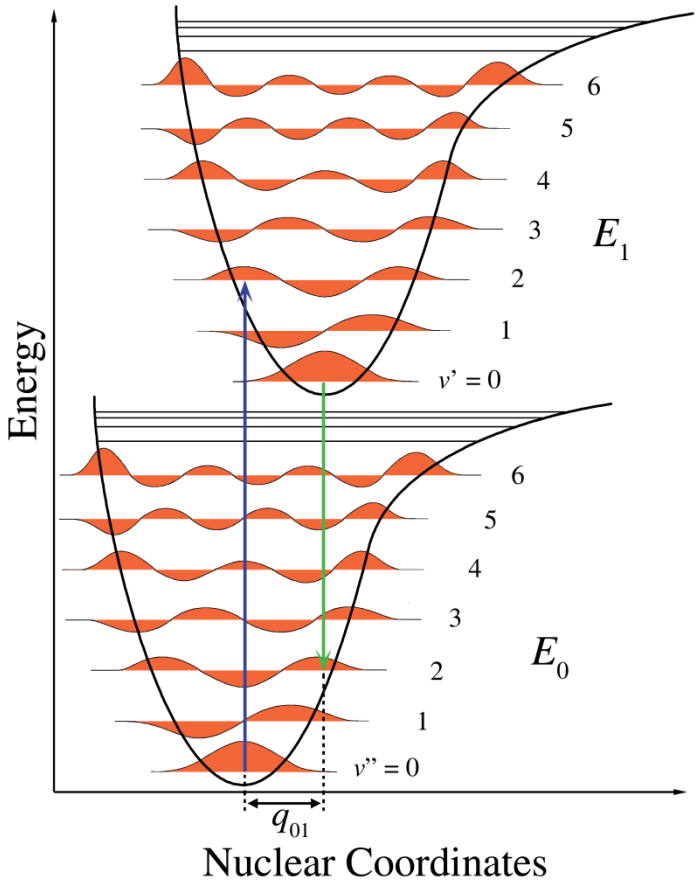


Figure 2-3 A schematic representation of the Franck-Condon principle (reproduced from http://en.wikipedia.org/wiki/Franck-Condon_principle). The upward arrow indicates the most favored vibronic (i.e., both vibrational and electronic) transition predicted by the Franck-Condon principle. The downward arrow indicates electron transfer from the electronic excited state, E_1, to the ground electronic state, E_0. See text for more detail.

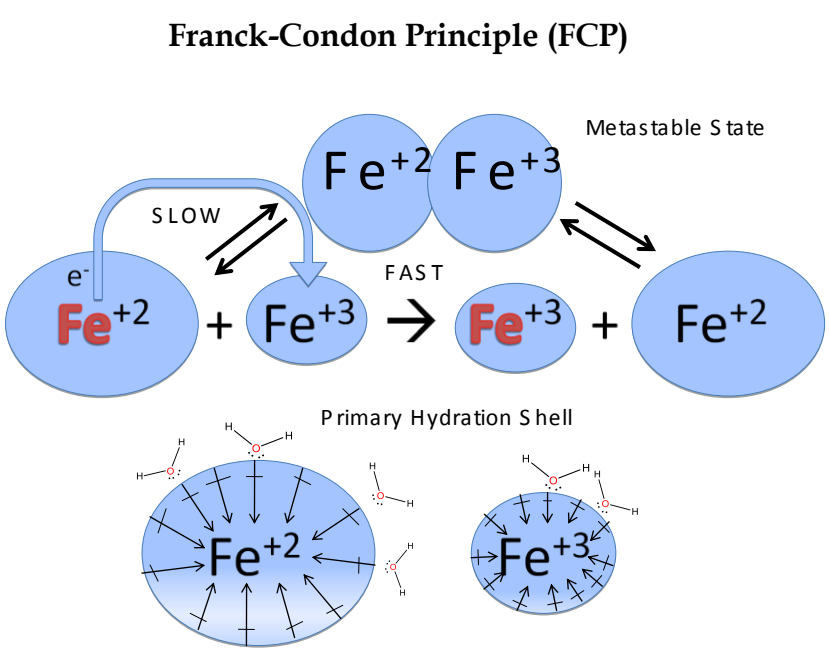
2.2.2 Franck-Condon Principle in Chemistry

It is well established in inorganic electron transfer reactions that electron transfer processes must be preceded by the reorganization of the *solvation* (also called hydration) *shells* surrounding reactants (Reynolds and Lumry 1966). It was Libby (1952) who accounted for this phenomenon based on the Franck-Condon principle, suggesting that, *before the fast electron transfer can occur, the slower nuclear rearrangements of water molecules in the hydration shells must take place* (the proton being 1,836 times as massive as the electron). This is schematically illustrated in Figure 2-4. The overall reaction involves the transfer of one electron from the ferrous ion, Fe^{+2}, to the ferric ion, Fe^{+3}. Due to the charge difference, the hydration shell around the ferric ion is more compact than the hydration shell around the ferrous ion. Despite this, there is a finite probability that the two hydration shells assume similar sizes at some time points (as the result of thermal fluctuations) as depicted by the two identically sized spheres partially

overlapping in the upper portion of Figure 2-4. Such a transient, metastable state is known as the *Franck-Condon state* or the *transitions state*, and it is only in this state that one electron can be transferred from Fe^{+2} to Fe^{+3} resulting in the electron being on either of the iron ions. That is, in the Franck-Condon state, the two iron ions are chemically equivalent, within the limits set by the *Heisenberg Uncertainty Principle* (Reynolds and Lumry 1966). The Franck-Condon complex (i.e., the reaction system at the Franck-Condon state) can now relax back to the reactant state or forward to the product state, depending on the sign of the Gibbs free energy change, ΔG, accompanying the redox reaction. If ΔG given by Eq. (2-24) is negative, the reaction proceeds forward (from left to right), and if it is positive, the reaction proceeds backward (from right to left).

$$\Delta G = G_{final} - G_{initial} = \Delta G^0 - RT \log [{}^*Fe^{+2}]/[Fe^{+3}] \quad \ldots\ldots\ldots\ldots \quad (2\text{-}24)$$

where G_{final} and $G_{initial}$ are the Gibbs free energy levels of the final and initial states of the reaction system, ΔG^0 is the standard Gibbs free energy (i.e., ΔG at unit concentrations of the reactants and products), R is the universal gas constant, T is the absolute temperature of the reaction medium, $[{}^*Fe^{+2}]$ is the concentration of the radioactively labeled ferrous ion (to be distinguished from the unlabeled ferrous ion, Fe^{+2}), and $[Fe^{+3}]$ is the concentration of the ferric ion.



(Drawn by Julie Bianchini, 2008)

Figure 2-4 The Franck-Condon Principle in action in one of the simplest chemical reactions known, i.e., the one-electron redox reaction of the iron ions. (*Lower*) Due to the greater charge density around the ferric ion (Fe^{+3}), as compared with that around the ferrous ion (Fe^{+2}), water dipoles (depicted as crossed arrows) are more strongly attracted to the former than to the latter, forming smaller and tighter primary hydration shell around Fe^{+3} than around Fe^{+2}. (*Upper*) The electron transfer process is much faster than

the nuclear rearrangements accompanying hydration shell changes (due to the proton being ~ 2000 times more massive than the electron). The hydration shells around the Fe^{+3} and Fe^{+2} ions contract and expand (i.e., "breath") periodically as a consequence of thermal fluctuations or Brownian motions (not shown).

2.2.3 The Generalized Franck-Condon Principle (GFCP) or the Principle of Slow and Fast Processes (PSFP)

It was postulated in (Ji 1974a) that the *Franck-Condon principle* need not be restricted to electron transfer processes in molecular spectroscopy or inorganic electron transfer reaction in aqueous media but could be extended to any physicochemical processes that involve coupling between two processes whose rates differ significantly. The generalized version of the Franck-Condon principle was also referred to as the *Principle of Slow and Fast Processes* (PSFP) (Ji 1991, p. 52-56), which states that

> "Whenever an observable process, P, results from the coupling of two partial processes, one slow (S) and the other fast (F), with F proceeding faster than S by a factor of 10^2 or more, then S must precede F." (2-25)

Statement (2-25) as applied to enzymic catalysis can be schematically represented as follows:

$$(A^\circ + B)_r \text{ <--> } [(A^\circ + B)^\ddagger \Leftrightarrow (A + B^\circ)^\ddagger] \text{ <--> } (A + B^\circ)_p \qquad (2\text{-}26)$$

where A and B are the donor (or source) and the acceptor (or sink) of a particle denoted by ° (which can be any material entities, either microscopic or macroscopic), and the parentheses indicate the immediate environment (also called microenvironment) surrounding the reactant system, i.e., $(A^\circ + B)_r$, or the product system, i.e., $(A + B^\circ)_p$, where the subscripts r and p stand for reactant and product, respectively. The superscript ‡ denotes the so-called Franck-Condon state which is intermediate between the reactant and product states so that the particle now loses its preference for either A or B and can be associated with A or B with equal probability within the constraints imposed by the Heisenberg uncertainty principle (Ryenolds and Lumry 1966). The Franck-Condon states, connected by a double-headed arrow, $\Leftrightarrow$, and enclosed within the square brackets, can be either two distinct states separated by a free energy barrier large relative to thermal energies or may be two aspects of a common resonance state (Ji 1974a), in which case the free energy barrier between the two states are less than or comparable to thermal energies (i.e., 0.6 Kcal/mole at physiological temperatures).

So generalized, the Franck-Condon principle can be applied to a wide range of biological processes as pointed out in Table 1.12 in (Ji 1991), which is reproduced below as Table 2-3:

Table 2-3 The application of the generalized Franck-Condon principle to biological processes at different levels of organization. Reproduced from (Ji 1991, p. 54).

Table 1.12. The application of the generalized Franck-Condon Principle to various biological rate processes.

	Partial Processes	
Overall Process (P)	Fast (F)	Slow (S)
1. Enzymic catalysis	Covalent bond rearrangements (i.e., electronic transitions)	Conformational rearrangements of catalytic groups (i.e., nuclear rearrangements)
2. Gene expression	Enzymic reactions	Conformational rearrangements of double-stranded DNA
3. Memory	Input of signals to neurons	Rearrangements of genes in DNA(?)
4. Morphogenesis	Gene expression	Rearrangements of the connections between cells and between cells and extracellular matrix(?)
5. Evolution	Events in individual organisms	Rearrangements of physical and social environments of organisms

The processes accounted for by GFCP include ligand binding to receptors (Section 7.1), enzymic catalysis (Section 7.2), ion pumping (Section 8.5), action of molecular motors (Sections 8.4 and 11.4), gene expression, cell migration, morphogenesis (Section 15.1), and biological evolution itself (Chapter 14).

After over two decades since the list in Table 2-3 was prepared, the list of the fields where GFCP has been found to apply has grown from 5 to 10 (see Table 2-4).

Table 2-4 The universality of the Generalized Franck-Condon Principle (GFCP), or the Principle of Slow and Fast Processes (PSFP). GFCP (or PSFP) has been postulated to act at the levels of molecules, chemical reactions, the origin of life, receptors, enzymes, photosynthesis, cells, brain processes, and the biological evolution.

Level	Fast (F)	Slow (S)	Overall Process (P)
1. Molecules (*Figure 2-3*)	Electronic transitions (intramolecular)	Nuclear movements (intramolecular)	Absorption or emission of photons
2. Chemical Reactions (*Figure 2-4*)	Electron transfer (intermolecular)	Nuclear movements (intermolecular)	Oxidation-Reduction reactions
3. Origin of Life (*Figure 13-3*)	Thermal motions	Heating-cooling cycle attending the rotation of the Earth	Self-replication
4. Ligand Receptors (*Figure 7-1*)	Ligand diffusion into and out of the binding pocket	Conformational change of the receptor	Molecular recognition by receptors and enzymes
5. Enzymes (*Figures 7-5)*	Electronic rearrangements	Conformational changes of enzymes,	Enzymic catalysis
6. Photon Receptors	Light-induced electronic excitation of chromophores	Conformational change of reaction center proteins	Photosynthesis (Conversion of radiation energy to chemical energy)
7. Metabolic Network	Local metabolic fluctuations	Intracellular microenvironmental changes	gene-directed intracellular processes
8. Cells	Intracellular metabolic fluctuations	Extracellular environmental changes	Goal-directed cell functions (i.e., space- and time-dependent gene expression)
9. Brains (*Figure 15-21)*	Neuronal firings	Neural assembling and disassembling	Micro-macro coupling through neural synchrony
10. Evolution	a) DNA/RNA	a) Conformational	a) Gene expression

	polymerization reactions (Devo) b) Life cycles of organisms (Evo)	changes of DNA and chromatins b) Geological and environmental changes	b) Natural selection

The photosynthetic reaction centers (PSRC) may provide a good example of the *slowing down by increasing mass* (SDBIM) principle in action: PSRC may be viewed as molecular machines that have evolved to couple fast-moving photons (i.e., light) and slow-moving proteins in 5 steps:

Photons → **Electrons** → **Protons** → **Cofactors** → (2-27)

Intrinsic Membrane Proteins → Extrinsic Membrane Proteins

Another example may be provided by the muscle (see Figure 15-19):

Actomyosin → **Myofilaments** → **Myofibrils** → (2-28)

Muscle Fiber → **Fascicle** → **Muscle**

Wang et al. (2007) conclude that

> " . . . initial photosynthetic charge separation is limited by protein dynamics rather than by a static electron transfer barrier . . .",

which seems to support the predictions made by the generalized Franck-Condon principle that the fast electron transfer processes would be rate-limited by the slow conformational changes of the proteins constituting the photosynthetic reaction centers. The results of Wang et al. (2007) may turn out to be the strongest experimental support so far for the validity of the GFCP as applied to enzymic processes.

2.3 Complementarity

2.3.1 Complementarity vs. Supplementarity

The term "complementary" first appears in William James' book, *Principles of Psychology* (1890), in the context of the idea that human consciousness consists of two parts:

". . .in certain persons, at least, the total possible consciousness

may be split into parts which coexist but mutually ignore each other, and share the objects of knowledge between them. More remarkable still, they are *complementary*. . . . "

There is a great similarity between the concept of complementarity that James introduced into psychology in 1890 and that Bohr introduced into physics about four decades later. Whether Bohr's *complementarity* was influenced directly or indirectly by James' notion of *complementarity* is a challenging question for philosophers of science to answer.

The concept of complementarity emerged in 1926-7 from the intense discussions that transpired between Bohr and his then-assistant Heisenberg in the wake of the latter's discovery of the *matrix mechanics* and *uncertainty relations* (Lindley 2008). Bohr discussed his philosophy of *complementarity* in public for the first time at a meeting held in Como, Italy, in 1927 and published the first paper on complementarity in 1928 (Bohr 1928, Camillieri 2007). In 1958, Bohr summarized the concepts of *supplementarity* and *complementarity* as follows (Bohr 1958):

> " . . . Within the scope of classical physics, all characteristic properties of a given object can in principle be ascertained by a single experimental arrangement, although in practice various arrangements are often convenient for the study of different aspects of the phenomenon. In fact, data obtained in such a way simply supplement each other and *can be combined* into a consistent picture of the behavior of the object under investigation. In quantum mechanics, however, evidence about atomic objects obtained by different experimental arrangements exhibits a novel kind of *complementary relationship*.
>
> Indeed, it must be recognized that such evidence which appears contradictory when combination into a single picture is attempted, exhausts all conceivable knowledge about the object. Far from restricting our efforts to put questions to nature in the form of experiments, the notion of *complementarity* simply characterizes the answers we can receive by such inquiry, whenever *the interaction between the measuring instruments and the objects forms an integral part of the phenomenon*. . . . (my italics) "

(2-29)

The *supplementary* and *complementary* relations defined above can be conveniently represented as triadic relations among three entities labeled A, B, and C. *Supplementarity* refers to the relation in which the sum of a pair equals the third:

Supplementarity: $C = A + B$ (2-30)

As an example of supplementarity, Einstein's equation in special relativity, $E = mc^2$ (Shadowitz 1968), may be cited. Energy (A) and matter (B) may be viewed as extreme manifestations of their source C that can be quantitatively combined or added to

completely characterize C. As already indicated there is no common word to represent the C term corresponding to the combination of *matter* and *energy*. Therefore, we will adopt in this book the often-used term "mattergy" (meaning *matter* and ener*gy*) to represent C. Through Einstein's equation, matter and energy can be interconverted quantitatively. The enormity of the numerical value of c^2, namely, 10^{21}, justifies the statement that

"Matter is a highly condensed form of energy." (2-31)

In contrast to supplementarity, *complementarity* is nonadditive: i.e., A and B cannot be combined to obtain C. Rather, C can be said to become A or B depending on measuring instruments employed: i.e., C = A or C = B, depending on measurement. We can represent this complementary relation symbolically as shown in Eq. (2-32):

Complementarity: C = A^B (2-32)

where the symbol ^ is introduced here to denote a "complementary relation". Eq. (2-32) can be read in two equivalent ways:

"A and B are *complementary aspects* of C. " (2-33)

"C is the *complementary union* of A and B." (2-34)

Statements (2-33) and (2-34) should be viewed as short-hand notations of the deep philosophical arguments underlying complementarity as, for example, discussed recently by Plotnitsky (2006) and Camillieri (2007). The principles of *complementarity* and *supplementarity* defined above may operate not only in physics but also in biology as first suggested by Bohr (1933, Pais 1991). In other words, it may be said that

"*Physics and biology are symmetric with respect to the operation of supplementarity and complementarity principles."* (2-35)

We will refer to Statement (2-35) as the *Symmetry Principle of Biology and Physics* (SPBP). SPBP is supported by the symmetry evident in Table 2-5.

Table 2-5 *The Symmetry Principle of Biology and Physics* (SPBP): the principles of *supplementarity* and *complementarity* in action in physics and biology. 'Wavecles' are complementary unions of waves and particles, and 'quons' are quantum mechanical objects exhibiting wave or particle properties depending on the measuring apparatus employed (Herbert 1987). 'Gnergy' is defined as a complementary union of information (gn-) and energy (-ergy) (Ji 1991, p. 152). In other words, energy and information (or more accurately *mattergy* and *liformation*) are the complementary aspects of gnergy.

	Physics	**Biology**

Supplementarity (from Special Relativity Theory)	1. Matter-Energy Equivalence $E = mc^2$	6. Life-Information Equivalence[a]
	2. Matter-Energy or 'Mattergy'[b]	7. Life-Information or 'Liformation'[c]
	3. "*Matter is a highly condensed form of energy*."	8. "*Life is a highly condensed form of information*."
Complementarity (from Quantum Mechanics)	4. Wave-Particle[d] Complementarity Kinematics-Dynamics Complementarity[e]	9. 'Liformation-Mattergy' Complementarity
	5. 'Wavicles' or 'Quons'	10. 'Gnergons'[g]

[a]Just as the *matter-energy equivalence* was unthinkable before Einstein's special relativity theory published in 1905 (Shadowitz 1968), so it is postulated here that the *life-information equivalence* was unthinkable prior to the emergence of molecular theories of life that began with Watson and Crick's discovery of the DNA double helix in 1953.

[b]The term often used to denote the equivalence between (or supplementary union of) matter and energy as indicated by $E = mc^2$ (Shadowitz 1968).

[c]A new term coined here to represent the postulated supplementary relation (or the equivalence or continuity) between life and *information*, in analogy to mattergy, embodying the supplementary relation between matter and energy.

[d] The Airy pattern (see Figure 4.2 in Herbert 1987) may be interpreted as the evidence for a *simultaneous* measurement of both waves and particles of light, and if such an interpretation proves to be correct, it would deny the validity of the wave-particle complementarity and support the notion of the wave-particle supplementarity.

[e]The kinematics-dynamics complementarity is a logically different kind of complementarity that was recognized by Bohr in addition to the wave-particle complementarity (Murdoch 1987, pp. 80-88).

[f]Any material entities that exhibit both wave and particle properties, either simultaneously (as claimed by L. de Broglie and D. Bohm) or mutually exclusively (as claimed by N. Bohr) (Herbert 1987).

[g]Gnergons are defined as discrete units of gnergy, the complementary union of information and energy (Ji 1991). Gnergy is a *type* and gnergons are its *tokens* (see Section 6.3.9).

In Table 2-5, two new terms appear, 'mattergy' (see Item 2) and 'liformation' (Item 7) whose meanings are explained in footnotes. One of the most significant conclusions resulting from Table 2-5 is the assertion that *life* and *information* are intimately related in biology just as *matter* and *energy* are so related in physics (see Items 1, 2, 6 and 7), leading to the coining of the new term 'liformation' in analogy to 'mattergy' (see Items 2 and 7). Another important insight afforded by the symmetry inherent in Table 2-5 is the "liformation-mattergy complementarity" (see Item 9), which may be related to the view recently expressed by Lloyd (2006, p. 38), if *computation* can be identified with

liformation or information processing:

". . . *The computational universe is not an alternative to the physical universe. The universe that evolves by processing information and the universe that evolves by the laws of physics are one and the same. The two descriptions, computational and physical, are complementary ways of capturing the same phenomena*." (2-36)

To highlight the symmetry properties embedded in Table 2-5, Table 2-6 is prepared as its geometric version. Please note that the terms enclosed in single quotation marks are predicted by the symmetry inherent in the table. That is, the symmetry properties of the table entail their existence.

Table 2-6 The Symmetry Principle of Biology and Physics represented diagrammatically. Based on the postulated symmetry, the new term in red was coined. The inverted T symbolizes the *supplementarity* relation, and the triangle symbolizes the *complementarity* relation.

Principles	**Physics**	**Biology**
Supplementarity:	Mattergy	'Liformation'
	Matter — Energy	Life — Information
Complementarity:	Quons	'Gnergy'
	Particle — Wave	Mattergy — 'Liformation'

The gnergy triangle in Table 2-6 has three nodes. Since Mattergy and Liformation can be decomposed into matter and energy, and life and information, respectively, resulting in 5 nodes, the gnergy triangle can be alternatively represented as a body-centered tetrahedron which possesses 5 nodes (see Figure 10-7).

If the above symmetries turn out to be true, the following three inferences may be made:

1) Biology and physics may be more deeply related with each other than previously thought.

2) Information cannot exist without life (nor *vice versa*), just as energy cannot exist without matter (as in chemical reactions) due to $E = mc^2$.

3) The Universe may be described in two complementary ways – the energy/matter-based and the information/life-based, in agreement with Statement (2-36) (Lloyd 2006).

If these inferences turn out to be valid, especially inference 3), they may have important implications for philosophical discourses on the phenomenon of life, including the problem of vitalism (Crick 1966).

2.3.2 Information-Energy Complementarity and 'Gnergy'

Gnergy was originally defined as *the complementary union of information and energy* that drives all self-organizing processes in the Universe (Ji 1991, 1995). Although *information-energy complementarity* is now more accurately expressed as *liformaiton-mattergy complementarity* for the reasons provided in Table 2-5 and 2-6, gnergy may continue to be thought of as the complementary union of *information* and *energy* for the sake for brevity.

Unless indicated otherwise, 'information' refers to 'chemical' and 'genetic' informations among many other kinds of informations (e.g., physical information, mathematical information, literary information), and 'energy' will refer to 'free energy' or the 'useful form of energy', e.g., for living systems under physiological conditions, among many other kinds of energies (e.g., thermal energy, nuclear energy, gravitational energy). It is important to realize that information (e.g., software, the mechanical structure of a car) and energy (e.g., electricity, gasoline) can be separated only in macroscopic machines, and not in molecular machines that are *structurally flexible and deformable* (e.g., molecular motors, including ATP-driven proton pumps). Because of the structural deformability, it is claimed here that information and energy cannot be separated on the microscopic level and exist as a *fused* entity which has been referred to as the *gnergon* (a term coined by combining three Greek roots, *gn-* meaning information, *-erg-* meaning work or energy, and *–on* meaning discrete entity or particle). Gnergons are discrete units of gnergy. One concrete example of gnergons in action in molecular and cell biology is the *conformon*, the mechanical energy stored in sequence-specific sites within biopolymers as conformational strains (for the experimental evidence for conformons, see Chapter 8).

The concept of gnergy embodies the *principle of information and energy complementarity* (PIEC), according to which gnergy is responsible for driving all self-organizing processes in the Universe, including the origin of life, physicochemical processes occurring in the living cell such as self-replication and chemotaxis, cognitive

processes in the human brain, biological evolution, and the evolution of the Universe Itself. According to PIEC, the ATP molecule which plays a fundamental role in most, if not all, self-organizing processes inside the cell carries not only *energy* as is usually assumed (about 16 Kcal/mole under physiological conditions) but also *chemical information* encoded in its 3-dimensional molecular shapes. Thus, it can be predicted that, for some biochemical processes driven by ATP, ATP cannot be replaced by deoxy-ATP even though the latter can be hydrolyzed by ATPase to generate the same amount of free energy, because the deoxy-ATP molecule does not have the same information (i.e., molecular shape) as ATP. An analogy may be suggested here: Although a US dollar bill and a Korean 1000-Won bill have approximately the same monetary value (analogous to *energy*), the latter cannot replace the former in a vending machine in the US because it has different *information* (e.g., a different shape, color, and size) from that of a US dollar bill.

PIEC is expected to be manifested in the Universe in many different guises. The wave/particle complementarity is perhaps the best known example PIEC in science, and the principle of matter-symbol complementarity (PMSC), championed by H. Pattee (1982, 1995, 1996), may be viewed as another important manifestation of PIEC. According to PMSC (later re-named as *the von Neumann-Pattee principle of matter-sign complementarity* (Ji 1999b)), all self-reproducing systems have two complementary aspects – i) *physical law-governed material/energetic aspect* and ii) *the evolutionary rule-governed informational (or symbolic) aspect.* According to Pattee, open-ended evolution is possible if and only if evolving systems have both these two complementary aspects (Pattee 1995, Umerez 2001).

2.3.3 Complementarian Logic

In order to capture the essential characteristics of Bohr's *complementarity*, the author formulated what is referred to as 'complementarian logic' in (Ji 1995) that comprises three logical elements:

Exclusivity. A and B are mutually exclusive in the sense that A and B cannot be measured/observed/thought about simultaneously within a given context. For example, light under most experimental conditions exhibit wave or particle properties, depending on the measuring apparatus employed, but it is impossible to measure these properties simultaneously under a given measuring environment. Even the Airy experiment (Herbert 1985, pp. 60-64) may not be an exception although the Airy pattern shows both the particle property (as the dots) and the wave property (as the concentric circles) on the same record, since they were not recorded simultaneously. That is, dots appear first and then the concentric waves appear gradually over time when enough dots accumulate on the screen. Thus, the particle property and wave property of light were not measured/recorded *simultaneously*, thereby satisfying the exclusivity criterion.

It is also interesting to note that, on the *formal* level (Murdoch 1987, pp. 34-36), particle
and wave properties are not exclusive in the sense that they are related to each other through the de Broglie equation,

$$\lambda = h/mv \qquad (2\text{-}37)$$

where λ is the wavelength associated with a particle of mass m moving with velocity v, and h is the Planck constant. Therefore, at least on the formal level (in contrast to the real or physical level), the wave and particle properties of light are derivable from each other just as energy and matter are derivable from each other based on $E = mc^2$. However, whether this mutual derivability on the formal level can be physically realized depends on the availability of the mechanisms (and environment) to implement such an interconversion. In the case of the energy-matter equivalence, there exist physical mechanisms by which energy and matter can be interconverted as in chemical reactions or nuclear reactions. However it is not certain whether particles can be converted into waves and waves into particle. Hence *complementarity* and *supplementarity* may be distinguished on the basis of the Exclusivity criterion. If the condition is found under which particles and waves can be interconverted, then complementarity and supplementarity may lose their distinction under such conditions. For convenience, we may refer to such conditions as *the U point*, where the capital letter U stands for *uncertainty*, and the parameter whose numerical value characterizes the U point may be denoted by U in analogy to the Planck constant *h* that characterizes the point where quantum effects become non-negligible. Thus, in terms of the concept of the U point, the Exclusivity criterion and hence the distinction between Complementarity and Supplementarity are meaningful only above the U point and lose their meanings below it, just as space and time lose their individuality when objects move with speeds close to that of light, c, or just as the de Broglie waves lose their practical consequences when the momentum of moving objects becomes large.

2) ***Essentiality.*** A and B are both essential for completely describing/understanding a third term C. Light cannot be described completely in terms of either particle or wave properties alone but both these properties are *essential* to our understanding of the nature of light or any other 'quantum objects' often called 'quons' or ‘wavicles’ (Herbert 1987, p. 64).

3) ***Transcendentality.*** C transcends the level of description where A and B have meanings and serves as the source of, or as the ground for, the irreconcilably opposite A and B. The quality of light as directly perceived through the human eye transcends the level of instrument-mediated observations/measurements where it is registered as either waves or particles.

These three elements of the complementarian logic can be represented diagrammatically as a triangle (Figure 2-5):

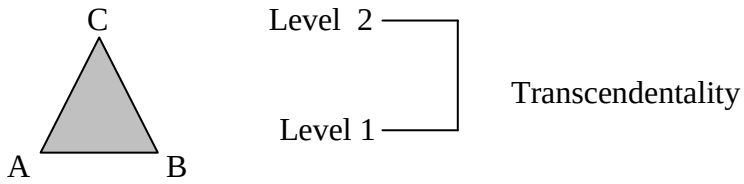


Figure 2-5 An iconic representation of the *complementarian logic*.
Each node is occupied by one of the three entities constituting a complementary relation (e.g., wave, particle, light), and the edges have the following meanings: A-B = Exclusivity; A-C or B-C = Essentiality; Levels 1 and 2 = Transcendentality.

The complementarian logic helps to distinguish *supplementarity* from *complementarity* because the former does not satisfy the conditions of Exclusivity and Transcendentality. Thus most of the over 200 so-called "complementary pairs" that Kelso and Engström (2006) list in their book, Complementary Nature, may be considered as "supplementary pairs" according to the complementarian logic.

Complementarity began its philosophical career as Bohr's interpretation of quantum mechanics (Murdoch 1987, Lindley 2008, Plotnitsky 2006), but the complementarism (see Section 2.3.4) that I formulated in the mid-1990's (Ji 1993, 1995), although inspired by Bohr's complementarity initially, is based on the complementarian logic (see above) whose validity is no longer solely dependent upon the validity of Bohr's complementarity and can stand on its own feet. The wave-particle duality, which served as the model for the complementarian logic, may or may not obey all the three logical criteria (especially the exclusivity criterion), depending on how one interprets experimental data such as the Airy patterns (Herbert 1985, pp. 60-64) and de Broglie equation, Eq. (2-37).

2.3.4 The Principle of Generalized Complementarity and Complementarism

The term "complementarity" was introduced in 1927 by Niels Bohr (Pais 1991) in an attempt to describe the novel situations arising from i) the wave-particle duality of light and ii) the Heisenberg uncertainty principle (Murdoch 1987, Plotnitsky 2006, Lindley 2008, Camillieri 2007). But Bohr did not give any rigorous definition of complementarity in his writings. One exception may be the following quotation from (Bohr 1934), where he states that the *quantum of action*

> " . . . . . forces us to adopt a new mode of description designated as complementary in the sense that any given application of classical concepts preclude the simultaneous use of other classical concepts which in a different connection are equally necessary for the elucidation of the phenomena."

The Bohr's concept of complementarity so defined is not universally accepted by contemporary physicists (Herbert 1987, Bacciagaluppi and Valenti 2009), and there are recent reports in the physics literature claiming to have invalidated the wave-particle complementarity (e.g., google "wave nature of matter"). Although Bohr popularized the term "complementarity" beginning in 1927, the main semantic content of this word was known to philosophers as early as 4-6th century BCE (e.g., Lao-tzu, and Aristotle). Complementarity, in this broad sense of the word, appears to reflect the following three characteristics of human language:

1) Words evolve to represent familiar concepts (e.g., waves, particles).
2) As human experience expands, new concepts are formed in the human mind which cannot be adequately represented by familiar words, often leading to paradoxes (e.g., wave-particle duality).
3) New words are coined to represent new experiences (e.g., wavicles, or quons, gnergy, etc.).

On the basis of this reasoning, it may be suggested that the definition of complementarity entails using three key terms, A and B, which are familiar but have mutually incompatible or contradictory meanings, and C which represents a new concept foreign to A and B and yet capable of reconciling the opposition between them. The A-B-C "triads" collected in Table 2-7 all appear to comply with the three characteristics of human language given above.

Table 2-7 Some examples (numbered (1) through (14)) of complementarities found in physics, biology, and philosophy. The term "quons" refer to quantum objects (e.g., photons, electrons) that exhibit wave-particle duality.

Fields	Familiar Concept (Macroscopic, Commonsensical, Traditional, Superficial) (A & B)	Unfamiliar Concept (Microscopic, Specialized, Nontraditional, Deep) (C)
Physics	(1) waves & particles	quons (or wavicles) (Herbert 1987)
	(2) kinematics & dynamics	quantum mechanics
Biology	(3) information & energy	gnergy (Ji 1985a, 1991)
	(4) living & nonliving	biomolecular processes
Philosophy	(5) matter & form	hylomorph (Aristotle)
	(6) Extension & Thought	Substance (also called Nature, or God) (Spinoza)
	(7) Secondness & Thirdness	Firstness (Peirce) ?
	(8) mind & body	Flesh (Merleau-Ponty) (Dillon 1997)
	(9) mind & matter	Implicate order (Bohm 1980)
	(10) Yin & Yang	Tao (Lao-tzu)
	(11) global & local	complementarism? (Pais 1991, Ji 1995)
	(12) forest & trees	complementarism ? (Pais 1991, Ji 1995)

	(13) whole & parts	complementarism ? (Pais 1991, Ji 1995)
	(14) holism & reductionism	complementarism ? (Pais 1991, Ji 1995)

In agreement with Bohr, I believe that the complementarity concept as used in physics and the Taoist philosophy can be applied to biology. Furthermore, I have long advocated the idea that *information* and *energy* constitute *a new complementary pair* (i.e., A & B in Figure 2-5) with gnergy serving as their source, i.e., the C term. Organisms and abiotic objects may be another example of the complementary pair, with molecular biological processes (e.g., enzyme-catalyzed chemical reactions, molecular motor actions) serving as the C term. If this reasoning is valid, we can conclude that biomolecular processes can be viewed as either living or nonliving, depending on the context, namely, the way one measures (or observes) them, just as light can be viewed as waves or particles depending on the measuring instruments employed. This would resolve the controversy about whether or not biochemical processes are living processes. *They are living when occurring inside the cell and not when occurring in a test tube*. That is, the meaning of biochemical processes is context-dependent. The importance of the context and perspectives in philosophical discourses have recently been emphasized in *transcendental perspectivism* of Krieglstein (2002), which should apply to biological theorizing with an equal force as illustrated in a recent review article in theoretical biology (Lesne 2008).

Bohm's idea of implicate order (Bohm and Hiley 1993) as the source of mind and matter may be accommodated within the complementarity framework described in Table 2-5. This is surprising because, within the field of quantum physics itself, Bohr and Bohm represent the two opposite schools of thought as regards their interpretation of quantum objects (i.e., acausal vs. causal interpretations) (Plotnitsky 2006).

Table 2-5 also includes the dichotomies (or dualities) between the *global* and the *local*, the *forest* and *trees*, *whole* and *parts*, or *holism* and *reductionism*. These dualities may reflect the same human cognitive limitations as exemplified by our inability to see both the forest and trees at the same time. Thus we may refer to these dichotomies as the "forest-tree complementarity (FTC)" for convenience. The simple notion of FTC may help resolve the controversies arising between molecular neurobiologists (reductionism) and behavioral biologists (holism), just as the wave-particle complementarity helped settle the controversy between Einstein and his followers who believed in the primacy of particles over waves and Bohr and his school believing the opposite, namely, the primacy of waves over particle, in the early decades of the 20th century. *The philosophical framework erected on the basis of the assumption that the complementarity principle of Bohr (generalized as the information-energy complementarity or the gnergy principle) applies to all self-organizing processes in the Universe has been named "complementarism" in the early 1990's (Ji 1993, 1995)*, independently of Pais (1991) who coined the same term to represent Bohr's assertion that his complementarity concept can be extended to fields beyond physics.

2.3.5 Two Kinds of Complementarities: Kinematics vs. Dynamics and Wave vs. Particle

Kinematics refers to the study of the *space* and *time* (or spacetime in the relativistic frame of reference, where objects move with speeds close to that of light) coordination of moving objects *without considering the causes underlying the motion* (http://en.wikipedia.org/wiki/Kinematics), while *dynamics* refers to the study of the causal roles of the *energy* and the *momentum (or momenergy* in the relativistic frame of reference) (Wheeler 1990, pp. 110-121) underlying the motions of objects. Bohr referred to the *kinematic* relation as "space-time coordination" and the *dynamic* relation as "causality". The wave-particle complementarity which is more widely known than the kinematics-dynamics complementarity is "logically independent notion" according to Murdoch (1987, p. 67). It is interesting to note that Heisenberg had a different interpretation of Bohr's concept of the kinematics-dynamics complementarity (Camilleri 2007). The *wave-particle* and *kinematics-dynamics* complementarities are compared in

Table 2-8 Two kinds of complementarity in physics. The quoted phrases are from Murdoch (1987, p. 67).

Complementarity	**Classical Mechanics**	**Quantum Mechanics**
Wave vs. Particle (*Logical incompatibility)*	"fall apart"	"come together"
Position vs. Momentum Spacetime vs. Momenergy Kinematics vs. Dynamics (*Empirical or epistemic incompatibility*)	"go together"	"fall apart"

The concepts of wave and particle are distinct, clearly separable, and logically compatible in classical mechanics but become inseparable, fused, or "logically incompatible" in quantum mechanics in the sense that they together, rather than separately, describe quantum objects or quons. In other words, the classical concepts of wave and particle cannot be applied to quons as they can to classical objects. Murdoch (1987, p. 80) also states that

"Kinematic and dynamic attributes in quantum mechanics are mutually exclusive in the sense that they cannot be simultaneously measured; they are, in this sense, espistemically incompatible".

As pointed out by Bohr (1934, p. 60), it is only in classical physics that momentum and energy can be measured precisely on the basis of spatio-temporal measurements (i.e.,

space and time "go together" with momentum and energy). In quantum physics, where effect of the quantum of action is large enough to be negligible, these properties are no longer deterministically related and hence "fall apart" (Murdoch 1987, p. 67).

The Heisenberg uncertainty relations/principle can be expressed in two equivalent forms (Murdoch 1987):

$$(\Delta q)(\Delta p) \geq h/2\pi \qquad (2\text{-}38)$$

$$(\Delta t)(\Delta E) \geq h/2\pi \qquad (2\text{-}39)$$

where Δq, Δp, Δt, and ΔE are the uncertainties about the position, momentum, time, and energy associated with moving objects, respectively, and h is the Planck constant. As evident in these equations, the two horizontal pairs, namely, q and p, and t and E are related by Heisenberg uncertainty principle, while the two vertical pairs, namely, q and t, and p and E are related *kinematically* and *dynamically*, respectively (Table 2-5) (Murdoch 1987, pp. 80-85).

We can represent these relations diagrammatically as shown in Table 2-9, where the Heisenberg uncertainty principle appears in the margins – the *horizontal* margin for the q and p conjugate pair, and the *vertical* margin for the t and E conjugate pair. Thus, we may refer to Eq. (2-38) and (2-39) as the *horizontal uncertainty principle* and the *vertical uncertainty principle*, respectively. In contrast, Bohr's Complementarity Principle appears as *a diagonal* in the interior of the table. There are six complementary pairs listed in the diagonal boxes in Table 2-9 that are related to Bohr's complementarity concept:

1) the *wave-particle* complementary pair (Murdoch 1987, pp. 58-61),
2) the *kinematic-dynamic* complementary pair (Murdoch 1987, pp. 80-88),
3) the *spacetime-momenergy* complementary pair (just as 'spacetime' is the combination of *space* and *time* that remains invariant in general relativity, so 'momenergy' is the combination of *momentum* and *energy* that remains invariant),
4) the *continuity* vs. *discontinuity* complementary pair may be viewed as the philosophical basis for the wave vs. particle duality to the extent that wave is continuous and particle is discontinuous in space,
5) the *group* vs. *individuality* complementary pair can also be viewed as a general principle that accommodates wave vs. particle duality, if we associate wave with superposition which presupposes more than one wave, i.e., a group of waves.

The phrase 'A-B complementary pair' embodies the following notions:

1) A and B have well-defined meanings only in classical physics, i.e., in situations where the *quantum of action* (i.e., the *finite non-zero value of* the product of *energy* and *time*) has no measurable effects and thus can be ignored.
2) In quantum mechanics where the *quantum of action* has significant effects during the interactions between the object under observation and the measuring apparatus, the object can no longer be described in terms of A and B but only in terms of non-standard, nonclassical models denoted by C in Figure 2-5 that can be characterized as "neither A nor B", or as "both A and B".

3) In relativity theory where objects under observation move at speeds close to that of

Table 2-9 A tabular representation of the relation between the *Heisenberg Uncertainty Principle* (HUP) and *Bohr's Complementarity Principle* (BCP). The Planck constant, h, and the speed of light c are displayed in the upper-left

light, well beyond our ordinary experience, a similar complementarity principle may apply as pointed out by Bohr (1934, pp. 55, 98):

"*In both cases we are concerned with the recognition of physical laws which lie outside the domain of our ordinary experience and which presents difficulties to our accustomed forms of perception. We learn that these forms of perception are idealizations, the suitability of which for reducing our ordinary sense impressions to order depends upon the practically infinite velocity of light and upon the smallness of the quantum of action.*" (2-40)

hand corner of the table to emphasize the fact that both HUP and BCP are manifest only under the conditions *where molecular interactions play critical roles or* objects under consideration move with speeds close to that of light.		
h, c	**q**	**p**
t	1. Wave 2. Kinematics 3. Spacetime 4. Continuity 5. Group property (Superposition) (**A**)	-
E	-	1. Particle 2. Dynamics 3. Momenergy 4. Discontinuity 5. Individuality (**B**)

Of the 5 complementary pairs listed in Table 2-9 (Murdoch 1987, pp. 58-66, Bohr 1934, pp. 19, 61, 623), the first two are the consequences of the smallness of the quantum of action, $h = 6.63 \times 10^{-34}$ Joules sec, and the third results from the constancy of the speed of light, $c = 3 \times 10^{10}$ cm/sec, as already indicated. What is common to the first two (if not all) of the 5 complementarities may be the dichotomy of *continuity* vs. *discontinuity* as described by Murdoch (1987, p. 46):

> "Bohr's view now was that when *continuity* obtains, the standard models are applicable, i.e., matter may be conceived of as corpuscular and radiation as undulatory; when, however, *discontinuity* prevails, the standard models break down, since they presuppose continuity, and the non-standard models then suggest themselves. . . . " (2-41)

It is interesting to note that the *quantum of action* is implicated only in the two margins of Table 2-9, in the form of Inequalities (2-38) and (2-39), but not in the diagonal boxes. This suggests that HUP and BCP belong to two different logical classes; i.e., one is about *measurement* (or results of measurements) and the other about *measurability* (or measuring conditions). To understand the difference between these two terms, it is

necessary to return to Heisenberg's original explanation for his uncertainty relation, Inequality (2-38), based on his thought experiments with the 'gamma-ray microscope'. Heisenberg describes his experiment thus (Murdoch 1987, p. 48):

> "At the moment of the position determination, when the light-quantum is diffracted by the electron, the momentum of the electron is changed discontinuously. The shorter the wavelength of the light, i.e., the more accurate the position measurement, the greater the change in the momentum. At the moment the position of the electron is ascertained, its momentum can be known only within a magnitude that corresponds to this discontinuous change . . ." (2-42)

In short, Heisenberg originally thought that the reason for his uncertainty principle resided in the discontinuous change in the trajectory of the electron due to collision with the light-quantum. But Bohr claimed, according to Murdoch (1987, p. 49), that

> " . . . what precludes the measurement of the momentum of the electron in the 'gamma-ray microscope' experiment is not the discontinuity of the momentum change as such but rather the impossibility of *measuring* the change. What prevents measurement of the momentum change is the indispensability of the wave model for the interpretation of this experiment. The Compton-Simon experiment shows that the discontinuous change in momentum can be accurately determined provided the angle of scatter of the incident photon can be precisely determined. In the gamma-ray microscope' experiment, however, the angle of scatter cannot be determined within an uncertainty which is less than the angle 2θ subtended by the diameter of the lens: it is thus impossible to tell at what angle within the angular aperture of the lens the photon is scattered; . . . . . Bohr's point is that it is the wave-particle duality of radiation that makes it impossible to measure the momentum of the electron: while gamma radiation may appropriately be described in terms of the particle model, it is the indispensability of the wave model for the interpretation of the experiment that precludes the precise measurement of the momentum of the electron." (2-43)

Heisenberg later agreed with Bohr (Murdoch 1987, p. 51) that his uncertainty principle is a natural consequence of the wave-particle duality of light and the peculiarity of the measuring apparatus or the consequence of *the kinematic-dynamic complementarity* (Murdoch 1987, pp. 58-61).

Since the applicability of the *wave-particle pair* and the *liformation-mattergy pair* are symmetric with respect to the *complementarity principle* (see Statement (2-35), and Tables 2-5 and 2-6), we may be justified to construct two possible tables, each analogous to Table 2-9, that can be associated with the *liformation-mattergy* complementarity (see Tables 2-10 and 2-11). Of these two choices, Table 2-11 may be preferred because of its greater similarity to Table 2-9 with respect to the position of E.

Table 2-10 The liformation-mattergy complementarity and its predicted uncertainty principles. The symbol γ indicates the biological counterpart of the Plank constant whose characteristics are yet to be characterization.		
γ	**Information** (**I**)	**Energy** (**E**)
Life (L)	1. Liformation 2. Structure 3. Cell biology 4. Holism (A)	-
Matter (**M**)	-	1. Mattergy 2. Function 3. Molecular biology 4. Reductionism (**B**)

Table 2-11 Another version of the liformation-mattergy complementarity and its predicted uncertainty principles. The symbol γ indicates the biological counterpart of the Plank constant whose identity is yet to be characterized.

γ	**Life (L)**	**Matter (m)**
Information (I)	1. *Liformation* 2. Function 3. Cell biology 4. Holism (**A**)	-
Energy (E)	-	1. *Mattergy* 2. Structure 3. Molecular biology 4. Reductionism (**B**)

New

complementary pairs appear in Table 2-11, i.e., *liformation-mattergy*, *structure* vs. *function*, *cell biology vs. molecular biology*, and *holism vs. reductionism*. If the content of Table 2-11 is valid, it may be concluded that the structure-function dichotomy widely discussed in biology belongs to the same logical class as the kinematics-dynamics dichotomy in physics (compare Tables 2-8 and 2-10). If this conjecture is correct, the following generalization may be made:

"Just as the *kinematics* (i.e., the position-time coordination) and *dynamics* (i.e., energy-momentum changes or causality) of moving objects cannot be measured simultaneously in physics with arbitaray accuracy so it is impossible to measure the *structure* and *function* of an organism simultaneously." (2-44)

We may refer to Statement (2-44) as *the principle of the structure-function complementarity* (PSFC) in biology in analogy to the principle of *the kinematics-dynamics complementarity* (PKDC) in physics (Murdoch 1987, pp. 58-61). From Table 2-11, it is clear that PSFC is isomorphic with (or belongs to the same logical class as) the principle of *liformation-mattergy complementarity* which is a newer designation for what is more often referred to as the *information-energy complementarity* for brevity (Section

2.3.2) (Ji 1991, 2000). Table 2-11 suggests that the cell biology-molecular biology and holism-reductionism pairs also belong to the liformation-mattergy complementarity class.

From Table 2-11, we can generate two inequalities in analogy to Inequalities (2-38) and (2-39):

$$(\Delta L)(\Delta m) \geq \gamma \qquad (2\text{-}45)$$

$$(\Delta I)(\Delta E) \geq \gamma \qquad (2\text{-}46)$$

where γ is a constant that is postulated to play a role in biology comparable to that of the Planck constant, namely the *quantum of gnergy*, or the *gnergon*. The best characterized example of the gnergon is the *conformon*, the sequence-specific confomational strains of biopolymers that carry both *genetic information* and *mechanical energy* (Chapter8). If we assume (based on the principle of excluded middle) that the minimum uncertainty in measuring information content of a conformon is 1 bit and that the minimum energy required to measure biological information is 1 kT or the thermal energy per degree, the minimum value of the product, $(\Delta I)(\Delta E)$, is 4.127×10^{-14} erg or 0.594 Kcal/mole at T = 298 °K, which may be considered to be the value of γ at this temperature (Ji 1991, pp. 119-122). If these conjectures are valid, Inequality (2-45) would suggest that

"The more precisely one defines what life is, the less precisely can one define what the material constituents of the organism are." (2-47)

Conversely,

"The more precisely one determines what the material basis of of an organism is, the less precisely can one define what life is." (2-48)

Statements (2-47) and (2-48) that are derived from the principle of Bohr's complementarity are consistent with the more general statement about the uncertainty in human knowledge, called the Knowledge Uncertainty Principle" (KUP), to be discussed in Section 5.2.7. KUP can be viewed as a generalization of what was previously referred to as the *Biological Uncertainty Principle* (BUP) (Ji 1990, pp. 202-203, 1991, pp. 119-122).

If proven to be correct after further investigation, Statements (2-47) and (2-48) may find practical applications in medicine, science of risk assessment, and law, where the question of defining what life and death often arises.

The two forms of the Heisenberg uncertainty principle appearing in the margins of Table 2-8 are quantitative because they can be expressed in terms of quantifiable entities, q, p, t and E. In contrast, many of the complementary pairs appearing in the interior of Tables 2-9 and 2-11 are qualitative. Hence it may be concluded that

"The Heisenberg uncertainty principle is quantitative: Bohr's complementarity principle is qualitative." (2-49)

If we can consider *quantity* and *quality* as complementary to each other in the sense of Bohr and the Taoist philosophy, the Heisenberg uncertainty principle (HUP) and Bohr's complementarity principle (BCP) would become complementary to each other, leading to the following statement:

"The Heisenberg uncertainty principle (HUP) and Bohr's complementarity principle (BCP) reflect the complementary aspects of reality." (2-50)

Statement (2-50) is obviously self-referential, reminiscent of the Mőbius strip, the Klein bottle, or recursion formulas in computer science discussed in Sections 5.2.4. Hence, Statement (2-50) may be referred to as the "Recursivity of Complementarity and Uncertainty" (RCU).

It may be possible to represent the quantitative and qualitative complementarities geometrically. One possibility would be to use a pair of orthogonal axes, one representing the *quantitative complementarity* and the other the *qualitative complementarity*. The resulting plane may be interpreted as representing *reality*, the source of both these complementarities.

Another way to characterize the difference between HUP and BCP may be that HUP involves two variables (e.g., position and momentum of a moving object) that occur within a measurement system whereas BCP implicates two independent measurement systems that cannot be implemented simultaneously (e.g., two-slit experiment vs. photoelectric effect measurement). That is, HUP may be viewed as an *intra-system* principle while BCP as an *inter-system* principle.

The difficulty that Einstein and his followers have been encountering in unifying the gravitational and other forces of nature (i.e., the electroweak and strong forces) (Kaku and Trainer 1987) may be accounted for by BCP, if we assume that the measurement system, A, involving the gravitational force and that, B, involving the other forces are *complementary* in the sense of Bohr. Complementarism would predict that these complementary opposites, A and B, can be unified through the discovery of the C term, which was referred to as the cosmological DNA and suggested to be identical with superstrings (Ji 1991, pp. 154-163). If this conjecture is right, superstrings should contain not only *energy/matter* as now widely believed but also the *information* of the algorithmic type and/or the Shannon type as was suggested in (Ji 1991, p. 155). If further research substantiates this idea, it may represent one of the rare examples of theoretical concepts (e.g., information intrinsic to material objects) flowing from biology to physics (see Figure 2-6).

2.3.6 Three Types of Complementary Pairs (or Complemetarities)

There are numerous complementary pairs suggested in the literature. Kelso and EngstrØm (2006) list over 450 pairs and Barab (2010) over 100, but only a small fraction of these so-called "complementary pairs" appear to satisfy the three logical criteria of complementarity proposed in Section 2.3.3, and most of them satisfy only one or two of them. Therefore it may be useful to classify complementary pairs (or

complementarities) into three types as shown in Table 2-12.

Type I complamentary pairs satisfy the *exclusivity* criterion only (see the second row in Table 2-12), as was the case for the two types of the consciousnesses that James invoked on the basis of his observation on a patient exhibiting the phenomenon of hysterical anesthesia (James 1890). The views of Einstein and Bohr may be said to exemplify a Type I complementarity, since their theories of quantum reality are mutually exclusive (determinism vs. contenxtualism) (Herbert 1987). The body and mind dichotomy as conceived by Descartes qualifies as an example of Type I complementarity, since mind and body are mutually exclusive according to Descartes. Type I complementarity may be referred to as the *Jamesian complementarity* or *psychological complementarity* since James (1890) introduced the adjective 'complementary' into psychology.

Type II complementary pairs satisfy two of the three complementarian criteria – i.e., *Exclusivity* and *Essentiality* (see the third row in Table 2-12). The wave and particle attributes of photons (demonstrated by Einstein 1905) and electrons (predicted by Broglie in 1923 and experimentally confirmed about 5 years later) constitute Type II complementarity, since waves and particles are both mutually *exclusive* (at least under most experimetal conditions, although exceptions may exists as in the Airy pattern formation by electrons; Section 2.3.3) and *necessary* for the complete characterization of quons (Herbert 1987). It appears to me that the Airy pattern can be accounted for equally well by two opposing views on quantum reality – the Bohrian perspective based on non-reality of dynamic attributes of quons and the Bohmian view that quons possess wave and particle properties simultaneously and intrinsically (Herbert 1987). Another way to describe the difference between the Bohrian and Bohmian perspectives is to state that

> "Wave and particle attributes of quantum entities or quons are complementary according to Bohr and supplementary according to Bohm." (2-51)

(See Statement (2-29) for the definitions of complementarity and supplementarity.)

Since the concepts of *complementarity* and *supplementarity* are themselves mutually exclusive, it may be stated that the Bohrian and Bohmian views on quons are of the Type I complementarity as is the Einstein-Bohr debate.

The *kinematic-dynamic complementarity* is considered to be of Type II as well, since kinematics and dynamics are mutually exclusive (i.e., one cannot replace, nor can be derived from, the other) but necessary for a complete description of motions of material objects, as illustrated below using DNA. Type II complementarity will be referred to as the *Bohrian* or *physical complementarity*.

Type III complementary pairs satisfy all of the three logical criteria of complementarity. As evident in the last row of Table 2-12, all of the examples given for Type III complementarity derive from philosophy because of the transcendentality criterion playing an important role. The transcendentality criterion entails invoking the two levels of reality that transcends each other – for example, the *epistemological* level where the complementary pair, A and B, has meanings and the *ontological* level, C, that transcends the epistemological level. In some cases, C may exist in the same level as A

and B, for example, the triad of father (A), mother (B), and a child (C). We may refer to such cases as representing the Type III' complementarity as compared to Type III.

Table 2-12 A classification of complementarities (or complementary pairs) based on the three criteria of the complementarian logic (see Section 2.3.3).

Types of Complementarities	Exclusivity (A)	Essentiality (B)	Transcend-entality (C)	Examples
I (Jamesian or psychological complementarity)	+			W. James (1890) (Hysterical anesthesia) Einstein-Bohr debate (Herbert 1987) Descartes (Mind-body dichotomy)
II (Bohrian or physical complementarity)	+	+		N. Bohr (Wave-particle duality; kinematic-dynamic complementarity*)
III (Lao-tsian or philosophical complementarity)	+	+	+	Complementarism (Information and Energy as the complementary aspects of Gnergy)
				Lao-tse (Yin and Yang as the complementary aspects of the Tao)
				Aristotle (Matter and Form are the two aspects of Hylomorph)
				Spinoza (Humans can know only the Thought and Extension aspects of Substance)
				Merleau-Ponty (Dillon 1997) (Mind and Body as the complementary aspects of Flesh)

*See Section 2.3.5.

The complementarity between the Watson-Crick base pairs (i.e., AT and GC) has been known since the helical structure of DNA duplex was discovered by Watson and Crick in 1953. About a decade later, it was discovered that the linear arrangements of three nucleotides along the long axis of a DNA strand encoded amino acids and the strings of nucleotide triplets in turn encoded genetic information specifying the structure of proteins.

The natural question that now arises is to which type of *complementarity* does the Watson-Crick base pairs belong? To answer this question, we must ask three related questions. i) Do Watson-Crick base pairs satisfy the Exclusivity criterion? In other words, are the Waston-Crick base pairs mutually exclusive? The answer must be Yes, since these molecular pairs are distinct and mutually irreplaceable. ii) Do the Watson-Crick base pairs satisfy the Essentiality criterion? In other words, is there a third term C for which the Wason-Crick pairs are essential? Again the answer seems to be Yes, since without these base pairs, molecular copying (i.e., information transfer from one nucleic acid to another) would be impossible. iii) What is the third term that transcends the level of Watson-Crick base pairs and yet serve as their ground or source? One plausible answer seems to that the C term is the living cell, for the replication of which the Watson-Crick base pairs are essential and without which no Watson-Crick base pairs can exists. Based on these answers, it may be concluded that the *Waston-Crick base pairs exhibit Type III complementarity*.

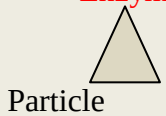
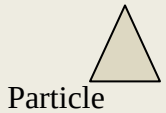
The above considerations are almost exclusively focused on the *information* aspects of life – complementry shapes of base pairs, nucleotide triplets, nucleotide sequences encoding genetic information, etc. Important as these aspects of life are, they alone are incomplete to account for the dynamics of life, since the utilization of genetic information encoded in DNA requires expending requisite free energy derived from chemical reactions catalyzed by enzymes. In other words, the *energy* aspect of DNA must be explicated along with the information aspect. Indeed, it can be stated that DNA carries not only genetic information but also mechanical energy, as evident in the formation of DNA supercoils catalyzed by ATP-driven topoisomerases and DNA gyrases (Section 8.3). Therefore, it can be asserted that the DNA duplex molecule embodies the *information-energy complementarity* that satisfies i) Exclusivity (genetic information and mechanical energy are mutually exclusive), ii) Essentiality (genetic information and mechanical energy are both needed for DNA replication and transcription), and iii) Transcendentality (self-replication is possible because of the existence of organisms which transcend the epistemological level of information and energy).

The two seemingly unrelated descriptions of DNA given above, one in terms of *information*, and the other in terms of *energy*, appear to be related to *kinematics* and *dynamics*, respectively (see Section 2.3.5 for the complementary relation between kinematics and dynamics, as first recognized by Bohr (Murdoch 1987)). If these analyses are valid, we can conclude that the DNA molecule embodies three different complementarities – the Watson-Crick base pair complementarity, ii) the information-energy complementarity, and iii) the kinematic-dynamic complementarity.

2.3.7 The Wave-Particle Complementarity in Physics, Biology and Philosophy

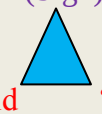
The wave-particle duality refers to the fact that quantum objects (or quons) exhibit both wave and particle properties. The particle property of light was demonstrated by the phenomenon of photoelectric effect which was quantitatively accounted for by Einstein in 1905 by assuming that light was a stream of particles. This idea may be denoted as Einstein's "wave → particle" postulate (see the upper portion of Table 2-13) (Herbert 1987). Inspired by the success of Einstein's "wave→particle" postulate, de Broglie hypothesized in his 1923 Ph.D. thesis the reverse, namely, that quantum particles exhibit wave properties (see "particle → wave" in Table 2-13), which was experimentally proven to be true a few years later by two American physicists, Davisson and Germer (Herbert 1987).

Table 2-13 The universality of the principle of wave/particle duality (or complementarity) in physics, biology and philosophy.

Fields	Observations/Facts	Theory	Reality Question
Physics	1. Photoelectric effect 2. Electron diffraction	Wave → Particle (Einstein 1905) Particle → Wave (de Broglie 1923)	(1) *The Copenhagen interpretation* (Herbert 1987): Quons are neither particles nor waves but exhibit particle or wave properties upon measurement. (2) *The de Broglie/Bohm interpretation* (Herbert 1987): Quons possess wave and particle properties simultaneously and inherently even before measurement.
Biology	3. Single enzyme molecules show wave properties since they obey a Planck radiation law-like equation (Ji 2008b) 4. Microarray data on RNA levels in yeast cells also obey the Planck radiation law-like equation (Ji and So 2009d).	Enzyme  Particle Wave RNA  Particle Wave	(3) Enzymes and biochemicals inside the cell obey the principle of wave/particle duality: i.e., biomolecules are *wave/particle-dual*[1] as are quons in physics.

<table>
<tr>
<td rowspan="3">Philosophy</td>
<td>5. Memory is not localized in any specific regions of the brain (Pribram 2010).</td>
<td>Memories are interference patterns of brain waves (Pribram 2010)</td>
<td rowspan="3">(4) We think in waves.
(5) Thoughts are wave-like processes.
(6) Thoughts are waves.
(7) Thoughts are dissipatons[2]
(8) Dissipatons are wave/particle-dual[1].
(9) Thoughts are wave/particle dual[1].
(10) Thoughts as waves are constrained by the spectral area code, ΔW ΔM > 1 (Herbert 1987), which provides the mathematical basis for the Knowledge Uncertainty Principle (see Section 5.2.8).
(11) Peirce's theory of signs is based on the triad of sign, object, and interpretant (Short 2007). Based on quantum physics and cell biology, we can now identify Peirce's 'interpretant' with cell language or cellese (Ji 1999b) that living cells use to represent the world internally.</td>
</tr>
<tr>
<td>6. We think in signs.</td>
<td>Semiotics or the theory of signs (C. S. Peirce late 19th and early 20th centuries)(Short 2007)</td>
</tr>
<tr>
<td>7. All objects, including signs, obey the principle of wave/particle duality.</td>
<td>Quantum physics (Herbert 1987, Pribram 2010)

Isomorphism between human and cell languages (Ji 1997a, 1999b)

'Humanese'
(Sign)
 
World (Object) 'Cellese' (Interpretant)</td>
</tr>
</table>

	8. Both humans and living cells use languages as means to communicate. Human language (*humanese*) utilizes sound waves and electromagnetic waves; cell language (*cellese*) utilizes chemical concentration waves.	'Cosmese' (Quantum waves)  Humanese (Sound waves) 'Cellese' (Concen-tration waves)	(12) *Humanese* and *cellese* may be the complementary aspects of the cosmological language (or *cosmese*) which can be identified with quantum mechanics in agreement with Pagels (1982).

[1]The term "wave/particle dual" is used to indicate that some physical objects or entities exhibit both wave- and particle-like properties such as light and electrons.
[2]*Dissipatons* are synonymous with "dissipative structures", the structures that require the dissipation of free energy to exist and hence disappear upon the cessation of free energy supply (see Section 3.1). Examples of dissipatons include the flame of a candle, EEG (electroencephalogram), and life itself.

Although the wave/particle duality of quons is an experimental fact beyond any doubt, the question is still unsettled as to whether quons possess wave and particle properties intrinsically regardless of measurement (as asserted by de Broglie, Einstein, and Bohm) or they exhibit wave or particle properties only upon measurements, depending on the measuring apparatus employed (as maintained by Bohr, Heisenberg and other so-called 'Copenhagenists') (Herbert 1987, Mermin 1990, Bacciagaluppi and Valenti 2009). It is truly astounding to me that, even after over a century's experimental work and mathematical theorizing, quantum physicists have yet to reach a consensus on the real nature of quons with respect to wave and particle properties (see the last column of the first row in Table 2-13).

The terms "wave/particle duality" and "wave/particle complementarity" differ in an important way – the former refers to an empirical fact, and the latter represents the interpretation of this fact according to Bohr and his school which contrasts with the interpretation offered by de Broglie and Bohm (Herbert 1987). That is, the wave/particle complementarity signifies that

"Quons are neither waves nor particles but exhibit either of these two properties only upon their interactions with the measuring apparatus." (2-52)

Statement (2-52) is often synonymously expressed as follows:

"*Quons are complementary union of waves and particles*." (2-53)

"Waves and particles are the complementary aspects of quons." (2-54)

Statements (2-53) and (2-54) clearly satisfy the three criteria of the complementarian *logic* presented in Section 2.3.3, if quons are identified with the C term, and waves and particles with A and B terms. According to complementarism (Section 2.3.4), C transcends the level where A and B have meanings. Perhaps this provides one possible reason for the endless debates among quantum physicists over the real nature of C, i.e., light, electrons and other quons.

There are two kinds of waves discussed in physics – i) what may be called 'physical waves' whose amplitude squared is proportional to the energy carried by waves, and ii) 'non-physical' or 'information waves' (also called 'proxy waves', "quantum waves', or 'probability waves' in quantum mechanics) whose amplitude squared is proportional to the probability of observing certain events occurring. According to the Fourier theorem, any wave can be expressed as a sum of *sine waves*, each characterized by three numbers – a) *amplitude*, b) *frequency*, and c) *phase*. A generalization of the Fourier theorem known as the 'synthesizer theorem' (Herbert 1987) states that any wave, say X, can be decomposed into (or analyzed in terms of) a sum of waveforms belonging to any waveform family, say W, the sine waveform family being just one such example. The waveform family W whose members resemble X the closest is referred to as the *kin waveform family*, and the waveform family M whose members resemble X the least is called the 'conjugate' waveform family of W. That is, the waveform family W is the conjugate of the waveform family M. When X is expressed as a sum of W waveforms, the number of W waveforms required to synthesize (or describe) wave X is smaller than the number of M waveforms needed to reconstruct X wave. The numbers of waveforms essential for reconstructing wave X in terms of W and M waveforms are called, respectively, the 'spectral width' (also called 'bandwidth') of W and M waveform families, denoted as ΔW and ΔM, respectively. The *synthesizer theorem* states that the product of these two bandwidths cannot be less than one

$$\Delta W \Delta M > 1 \qquad (2\text{-}55)$$

Inequality (2-55) is called the *spectral area code* (Herbert 1987) and can be used to derive the Heisenberg Uncertainty Relation, since the momentum attribute of quons is associated with the sine waveform family (with spatial frequency, k, which is the inverse of the more familiar temporal frequency, f) and the position attribute is associated with the impulse waveform family, these two waveform families are conjugates of each other.

Most biologists, including myself until recently, assume that the wave/particle duality is confined to physics where microscopic objects (e.g., electrons, protons, neutrons) are studied but has little to do with biology since biological objects are much too large to exhibit any wave/particle-dual properties. I present below three pieces of evidence to refute this assumption.

(1) The DNA level: In Section 2.3.6, I have presented detailed analysis of the structure and function of the DNA molecule, leading to the conclusion that DNA embodies three kinds of complementarities – i) the *Watson-Crick base pair complementarity*, ii) the *information-energy complementarity*, and iii) the *kinematics-dynamics complementarity* which includes the *wave/particle complementarity* (Section 2.3.5) (Murdoch 1987). Of these three kinds of complementarities, the information-energy complementarity and kinematics-dynamics complementarity may be viewed as

belonging to the same family of what I often call the *global/local or (forest/tree) complementarity* which may be considered as the generalization of the wave-particle complementarity, wave being global and particle being local.

(2) The Catalysis Level: Single-molecule enzymic activity data (i.e., waiting time distribution) of cholesterol oxidase measured by Lu, Xun and Xie (1998) fit the equation, $y = a(Ax + B)^{-5}/(\exp(b/(Ax + B)) - 1)$, where a, b, A and B are constants (see Section 11.3.3) (Ji 2008b). This equation reduces to the blackbody radiation equation discovered by M. Planck in 1900 when x = wavelength λ, y = the spectral energy density (i.e., the intensity of radiation emitted or absorbed at wavelength λ by the blackbody wall when heated to T °K), $a = 8\pi hc$, $b = hc/kT$ (where h is the Planck constant, c is the speed of light, and k is the Boltzmann constant), A = 1, and B = 0. This unexpected finding strongly indicates that enzyme molecules exhibit both particle (e.g., their *nucleotide sequences*) and wave properties (e.g., the electromagnetic waves generated by the *vibrational motions* of covalent bonds within proteins) as symbolized by the first triangle appearing in Table 2-13). *It appears possible that the enzymic activity of a protein is the result of the electronic transitions (or quantum jumps) triggered by the coincidence of the phase angles of a set of vibrating bonds within an enzyme-substrate complex.*

(3) The Control Level: The Planck radiation law-like equation described above also fit the microarray data measured in budding yeast undergoing glucose-galactose shift (Ji and So 2009d). Garcia-Martinez, Aranda and Perez-Ortin (2004) measured the genome-wide RNA levels of budding yeast at six time points (0, 5, 120, 360, 450 and 850 minutes after the nutirtional shift) which showed pathway-specific trajectories (see Figure 12-1). It is well known that the RNA levels inside the cell are determined by the balance between two opposing processes, i.e., *transcription* and *transcript degradation* (Ji et al. 2009a) (see Steps 4 and 5 in Figure 12-22, Secion 12.11). When these RNA level data are mapped onto a 6-dimensional mathematical space (called the 'concentration space'), each RNA trajectory (also called an "RNA expression profile") is represented as a single point and the whole budding yeast genome appears as a cluster of approximately 6,000 points. There are about 200 metabolic pathways in budding yeast, and each one of these pathways occupies a more or less distinct region in the 6-D concetration sapce. If a metabolic pathway contains n genes, n being typically 10 – 50, it is possile to calculate the distances between all posible RNA pairs belonging to a given metabolic pathway as n(n-1)/2. When these distances are 'binned' (i.e., grouped into different 'bins' based on the different classes of distance values, e.g., 1-10, 11-20, 21-30, etc), a *histogram* or *distribution curve* is obtained (see Figures 12-24 and 12-25) that fits the Planck radiaiton law-like equation (Ji and So 2009d). Again this unexpected finding indicates that the enzyme systems (i.e., transcriptosomes and transcript degrading enzymes to be called 'degradosomes', a term imported from bacteriology) that regulate the RNA levels inside the budding yeast exhibit wave/particle duality as symbolized by the second triangle in Table 2-13 (see Section 12.12 for more details). One possible mechanism of coupling *transcriptosomes* and *degradosomes* involves the transformation of the complex vibrational motions of the combined *transcriptosomes* and *degradosomes* into the *concentration waves* of RNA molecules in the cytosol through the electronic transsitions (also called chemical reactions or quantum jumps) coincident on the phase synchronization among relevant waves of protein vibrations. This idea may be referred to as the 'bond vibration/quantum jump/chemcial concentration' coupling hypothesis.

The same coupling mechanism is most likely implicated in the single-molecule enzyme catalysis (see the last column in the second row of Table 2-13).

The evidence that the human brain obeys the wave/particle duality is more direct—the existence of electroencephalograms (EEG) resulting from neuronal firings or action potentials, the producers of the electromagnetic waves in the brain. Pribram (2010) proposed a wave-based model of memeory, according to which the brain stores information as *holograms* resulting from phase-sensitive interactions among brain waves. A hologram (from Greek *holo* meaning whole and *gram* meaning drawing), unlike photography which records an image as seen from a single viewpoint, is a record of an object as seen from many viewpoints using cohrerent laser beams. Thus, it is here postulated that the brain obeys the wave/particle duality -- the particle aspect of thoughts being identified with the local biochemical components of the chemical reactions supplying the free energy needed for thinking processes, and the wave aspect with the global biochemical network property of the brain as a whole (see the last row in Table 2-13).

According to C. S. Peirce (1839-1914), *we think in signs. Signs are defined as* any physical or symbolic entities that stand for things other than themselves (see Section 6.2.1). Based on the principles of physics, it can be maintained that all signs possess wave properties (e.g., electromagnetic waves of visible objects, sound waves of music or speeches). Since all thoughts are accompanied by electromagnetic waves, it follows that we think in waves which are in turn signs. Therefore it may be concluded that modern brain science has amply demonstrated the validity of Peirce's thesis that we think in signs. Furthermore, signs being waves, human thoughts must obey the *spectral area code*, i.e., Eq. (2-55), which may underlie the Knowledge Uncertainty Principle to be described in Section 5.2.7.

It was found that the human language ('humanese') and the cell language ('cellese') obey a common set of linguistic (or semiotic) principles (Ji 1997a, 1999b) (see Section 6.1.2). This finding led me to conjecture that there exists a third language for which *humanese* and *cellese* may be complementary aspects. The conjectured third language was named the 'cosmological language ' or 'cosmese' (Ji 2004b), and the *cosmese* may be identified with quantum mecahnics in agreement with Pagels (1982) (see the last row in Table 2-13). It is here suggested that the *cellese* can be identified with the *interpretant* of Peirce who defined it as *the effects that a sign has on the mind of the interpreter* (see the third triangle in Table 2-13). According to this view, humanese can refer to objects in the world if and only if mediated by cellese, *the molecular language of brain cells*.

What is common to all these different classes of languages is the *waving process*, either physical or non-physical (as in the probability wave) and hence these languages may obey the principle of *non-locality* in addition to that of *spectral area code*, Eq. (2-55), the two consequences of the wave/particle duality or complementarity (Herbert 1987). The *principle of non-locality* states that the influence of an event occurring at one region in space can be instantly correlated with another event occurring elsewhere, no matter how distant, without any exchange of signals between the two correlated events, in apparent violation of the predictions made by the special relativity theory. In the 1970's and 80's, it was experimentally demonstrated that the principle of non-locality is obeyed by quantum objects (Herbert 1987, Mermin 1990). I here postulate that all biological

processes such as enzymic catalysis (Section 7.2) and morphogenesis (Section 15.1) embody *non-local phenomena* that may be identified with all the physicochemical processes of living systems which cannot be completely accounted for in terms of the laws of classical physics and chemistry. Biological evolution itself (Section 14) may embody non-locality, both in space and time. Most non-local phenomena discussed in physics (e.g., the Eistein-Podolsky-Rosen (EPR) experiments) deals with non-locality in the spatial dimension, but the non-locality of biological evolution may involve both the spatial and temporal dimensions. Thus we can recognize two kinds of non-localities – the spatial and temporal non-localities. By "temporal non-locality", I have in mind those situations in nature where an event occurring at one time point is correlated with another event occurring at the same or different time points, without any exchange of signals between the two events. Karl Jung's synchronicity (Jung 1972), e.g., precognition, and coincidences of dreams, may be the best documented example of what is here called the *temporal non-locality*. *Synchronicity* is defined as *"the experience of two or more events that are apparently causally unrelated occurring together in a meaningful manner. To count as synchronicity, the events should be unlikely to occur together by chance."* http://en.wikipedia.org/wiki/Synchronicity)

In conclusion, the *wave/particle duality* that was first demonstrated by Einstein (1905) in connection with the photoelectric effect was found to apply to electrons by de Broglie in 1923 (de Broglie 1924, Bacciagaluppi and Valenti 2009), to molecular biology in (Ji 2008b), to cell biology in (Ji and So 2009d), and to the human brain, a system of neurons, in (Pribram 2010) (see Steps 1 in Figure 2-6). If these developments can be substantiated by future investigations, it would be possible to conclude that quantum physics plays a pivotal role in unraveling the mysteries of life (see Step 2 in Figure 2-6). It is hoped that the enlightening influence of physics on biology is not a one-way street but a two-way one in the sense that a deep understanding of living processes (including human thinking) will eventually aid physicists in solving their challenging problems such as the ultimate nature of quons and the origin of the Universe (see Step 3 in Figure 2-6).

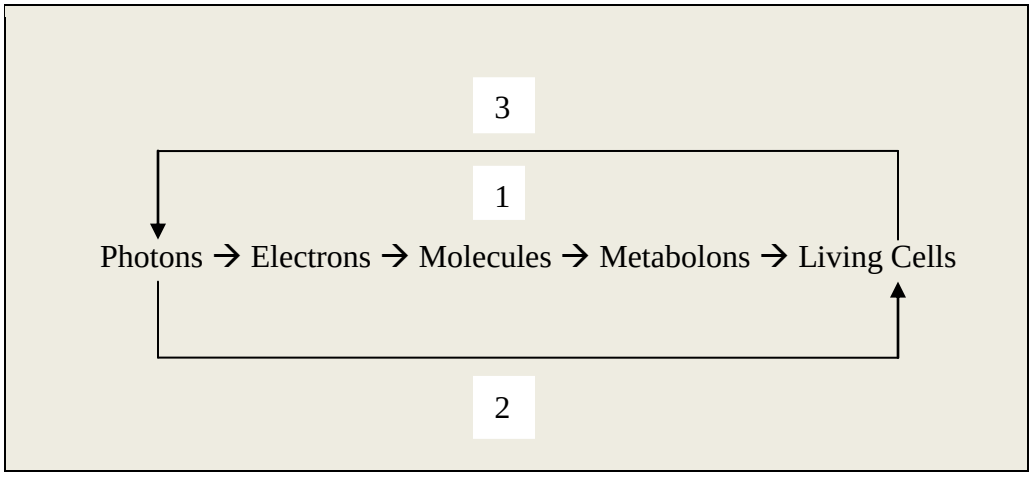


Figure 2-6 A diagrammatic representation of the postulate that the *principle of complementarity* is *universal* and *circularly causal*. 1 = the progressive discovery of the principle of wave-particle complementarity from simple to complex material systems. 2 = the influence of physical principles on our understanding of living systems. 3 = the influence of the principles of biology on our undersanding of non-living systems.

2.3.8 The Conic Theory of Everything (CTE)

Complementarity began its philosophical career as Bohr's interpretation of quantum mechanics (Murdoch 1987, Plotnitsky 2006, Lindley 2008), but the complementarism (see Section 2.3.4) that was formulated in the mid-1990's (Ji 1993, 1995), although inspired by Bohr's complementarity initially, is now based on the complementarian logic (see 2.3.3) whose validity is no longer critically dependent upon the validity of Bohr's complementarity as a philosophy of quantum mechanics (Murdoch 1987, Plotnitsky 2006, Lindley 2008) and can stand on its own feet. The wave-particle duality, which served as the model for the complementarian logic, may or may not obey all the three logical criteria of complementarism (especially the exclusivity criterion), depending on how one interprets experimental data such as the Airy patterns (Herbert 1987) and de Broglie equation, Eq. (2-37).

In July, 2000 (see Appendix I), I proposed to divide all complementary triads into two classes – one residing on the base of a circular cone (called 'in-plane' or 'horizontal triads') and the other standing on the circular base (called 'out-of-plane' or 'vertical triads') (see Figure 2-7). One interesting consequence of dividing all triads into these two classes is that only the vertical triads possess a common apex (i.e., C), the horizontal triads having an infinite number of the apexes (i.e., C', C'', A, B, etc.). This geometric feature of the circular cone may be useful in representing some of the profound philosophical ideas such as the Tao (viewed as C in Figure 2-7) as the source of everything (A, B, C', C'', etc on the base of the circular cone) in the Universe.

The Conic theory of Everything (CTOE) consists of the following elements:

All the regularities of objects in this Universe, both living and non-living, can be represented in terms of triads, each consisting of a pair of opposites (A & B) and a third term, C. All these triads form a circular cone, some constituting the base of the cone and others the body of the cone erected on it.

These triads, A-C-B, can be divided into two groups – the epistemological triads (E-triads) identified with the horizontal triads (e.g., AC'B, AC''B in Figure 2-7) , and the ontological triads (O-triads) identified with the vertical ones (e.g., ACB, C'CC''). One example of the E-triad is the well-known complementary relation between the wave (A) and particle (B) behaviors of light (C). An example of the O-triad is the triadic relation among Spinoza's Extension (A), Thought (B), and Substance (also called God or Nature) (C); or the recently postulated complementary relation among energy/matter (A), information (B) and gnergy (C) (Ji 1991, 1995). The main difference between E- and O-triads is that the validity of the relations embodied in the former can in principle be tested

by scientific/experimental means, while the validity of the relations represented by the latter cannot be so tested and must be judged on the basis of its utility in organizing data into coherent models or pictures.
The Universe consists of two worlds – the Visible consisting of E-triads, and the Invisible, converging on the Apex of the O-triads. The Visible World is characterized by multiplicity and diversity as represented by the large number of points on the periphery of the base of the cone, whereas the Invisible World is characterized by a unity as symbolized by the Apex of the cone.

It is beyond the scope of the present book to discuss the possibility of classifying all the triads (numbering close to a hundred or more) that I have formulated during the past decade or so (e.g., see Table 2-7 and Appendix II) and probably equally numerous triads that C. S Pierce described in the late 19th century, but it appears feasible to utilize the geometric properties of the circular cone depicted in Figure 2-7 to divide them into the E- and O-triads as defined in the conic theory of everything.

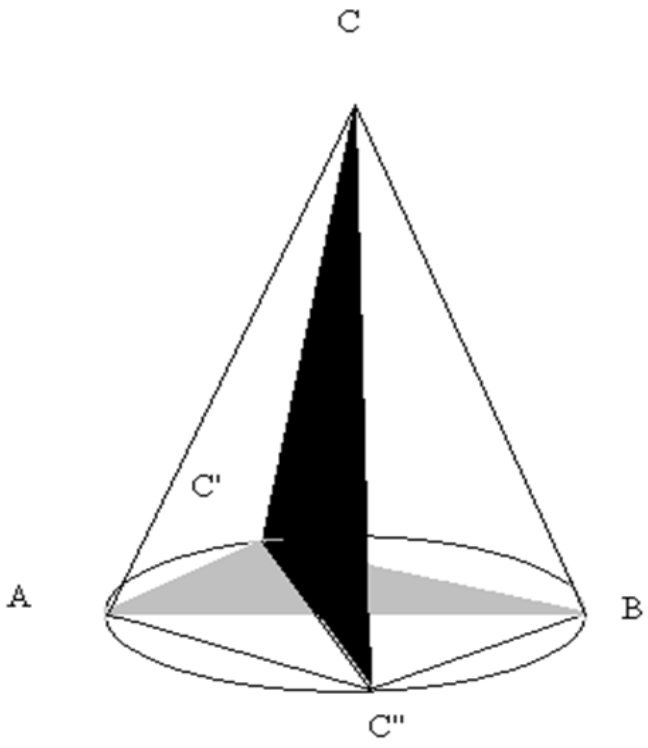


Figure 2-7 A circular cone treated as a combination of the two sets of triangles or triads – the horizontal (or 'in-plane') triads (e.g., AC'B and AC''B) and the vertical (or 'out-of-plane') triads (e.g., ACB and C'CC'').

2.4 Renormalizable Networks and SOWAWN Machines

2.4.1 Definition of Bionetworks

A bionetwork (BN), i.e., the networks representing the structure of biological systems, can be defined as a system of nodes connected by edges that exhibits some biological functions or emergent properties not found in individual nodes. Thus a bionetwork can be represented as a 3-tuple:

$$BN = (n, e, f) \tag{2-56}$$

where n is the *node*, e is the *edge*, and f is the function or the emergent property of BN.

The term 'renormalization' originated in quantum field theory and condensed matter physics. In the latter field, the term is employed to refer to the fact that, under some unusual conditions known as the critical points, a group of microscopic entities (e.g., atoms, molecules) can form (or act as) a unit to exhibit novel properties (e.g., convection, rigidity, superconductivity, and superfluidity) that are beyond (and hence unobservable in) individual component entities (Anderson 1972, Cao and Schweber 1993, Huggett and Weingard 1995, Domb 1996, Laughlin 2005). The essential idea of "renormalization' is captured by Barabasi (2002, p. 75) thus:

> ". . . In the vicinity of the critical point we need to stop viewing atoms separately. Rather, they should be considered communities that act in unison. Atoms must be replaced by boxes of atoms such that within each box all atoms behave as one."

For the purpose of biological applications, we will define "renormalization" as the process of grouping or 'chunking' (Hofstadter 1980, pp. 285-309) two or more entities or processes (to be called *interactons*) into one unit of action (to be called *emergentons*), leading to the emergence of new properties not possessed by individual *interactons*. We may represent this idea schematically as shown in Figure 2-8.

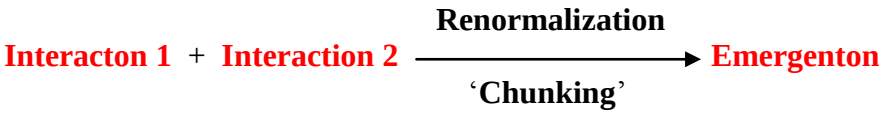


Figure 2-8 A schematic representation of the definition of renormalization. *Interactons* are defined as material entities or processes that interact with one another physically or chemically to produce new entities or processes called *emergentons*. The process of interaction between *interactons* leading to the production of an *emergenton* is here defined as "renormalization", which is deemed equivalent to the concept of 'chunking' used in computer science (Hofstatder 1980).

One of the simplest examples of renormalization as defined in Figure 2-8 is provided by the chemical reaction occurring in a test tube between two reactants, A and B, to form product C:

$$A + B \longrightarrow C \qquad (2\text{-}57)$$

Using the language of 'renormalization', Reaction (2-57) can be described as "A and B combining to form a new unit called C which exhibits some emergent properties". The speed of Reaction (2-57) is determined by the concentrations of A and B, the properties of the agents mediating the reactions (e.g., enzymes), and the physical conditions of the reactor (e.g., pressure, temperature, surface characteristics of reactor walls).

Most chemical reactions essential for maintaining the living state of the cell do not occur without being catalyzed by enzymes. That is, they have too high activation energy barriers to be overcome through thermal collisions alone (Ji 1974b, 1991, 2004a). This can be represented schematically as:

$$A + B \xrightarrow{E} C \qquad (2\text{-}58)$$

where E stands for the enzyme catalyzing the reaction. Since A and B combining to form C can be described as a *renormalization* (or *chunking*) process and since this process does not occur without E, we can refer to E as the *renormalizer* (or a *'chunkase'*). That is, all enzymes are *renormalizers* or *chunkases* consistent with the definition of renormalization or chunking given in Figure 2-8. Also, since renormalization leads to the emergence of novel properties, we can state that

"Enzymes provide the physical mechanisms for the emergence of new properties in the cell." (2-59)

Since one of the unique features of all networks is the emergence of a new property beyond the properties of individual nodes, it may be claimed that

"The *raison d'être* of a network is its *emergent* property." (2-60)

That is, there is an inseparable connection between *networks* and *emergences* in the sense that no emergence is possible without a network. Therefore we may refer to Statement (2-60) as the Emergent Definition of Networks (EDN).

Emergence has become a topic of great theoretical and philosophical interests in recent years (Laughlin 2005, Clayton and Davies 2006, Reid 2007), and the concept of network is even more widely discussed in natural, computer, and human sciences (Barabasi 2002, Sporns 2011). However, to the best of my knowledge, not much attention has been given so far to formulating possible *mechanisms* connecting networks to their emergent properties. One of the major aims of this book is to suggest that 'renormalization' as defined in Figure 2-8 can serve as a universal mechanism of

emergence in all networks in physics, chemistry, biology, and beyond. For a related discussion, readers are referred to (Cao and Schweber 1993).

2.4.2 'Chunk-and-Control' (C&C) Principle

As indicated in Figure 2-8, the concepts of renormalization and chunking can be viewed as essentially equivalent in content, the only difference being that the former emerged in physics and the latter in computer science independently. The main point of this section is to suggest that the principle of renormalization or chunking has also been in operation in the living cell since eukaryotes emerged on this planet over 1.5 billion years ago.

Computer scientists have discovered the utility of the so-called *divide and conquer* (D&C) strategy in software programming in which they break down a large and complex problem into two or more smaller sub-problems repeatedly until the sub-problems become easy enough to be solved directly. Cells apparently utilize a similar strategy on the molecular level. For example when cells divide they must control the behaviors of all the DNA molecules (46 of them in the human genome, each 10^7 base-pair long) in the nucleus so that they are reproduced and divided into two identical sets. To accomplish this gigantuan task, cells appear to chunk the DNA components into increasingly larger units as shown in Figure 2-9, first into nucleosmes which are 'strung' together into 11 nm-diameter "beads-on-a-string' form. This is wound into a 30 nm chromatin fiber (also known as solenoid) with 6 nucleosomes per turn, which is further condensed into 300 nm looped domain, 50 turns per loop. The next stage of condensation or chunking is 'miniband', each containing 18 loops. Finally these minibands are stacked together to form the metaphase chromosomes with the cross-sectional diameter of about 1.4×10^{-6} m. Thus the cross-section diameter of a DNA double helix (or DNA duplex) (2×10^{-9} m) has increased by a factor of about 10^3, resulting in a 10^9-fold compaction of DNA volume. Since this compaction has taken place in 5 steps, the average rate of compaction per step is about 10^2. This would mean that on average, each chunking process reduces the motional degree of freedom of DNA components by a factor of about 10^2. Thus, we can conclude that 'chunking' is synonymous with 'constraining' and hence the acronym, C&C, can be interpreted to mean either "chunking-and-constrain" or "chunking-and-control".

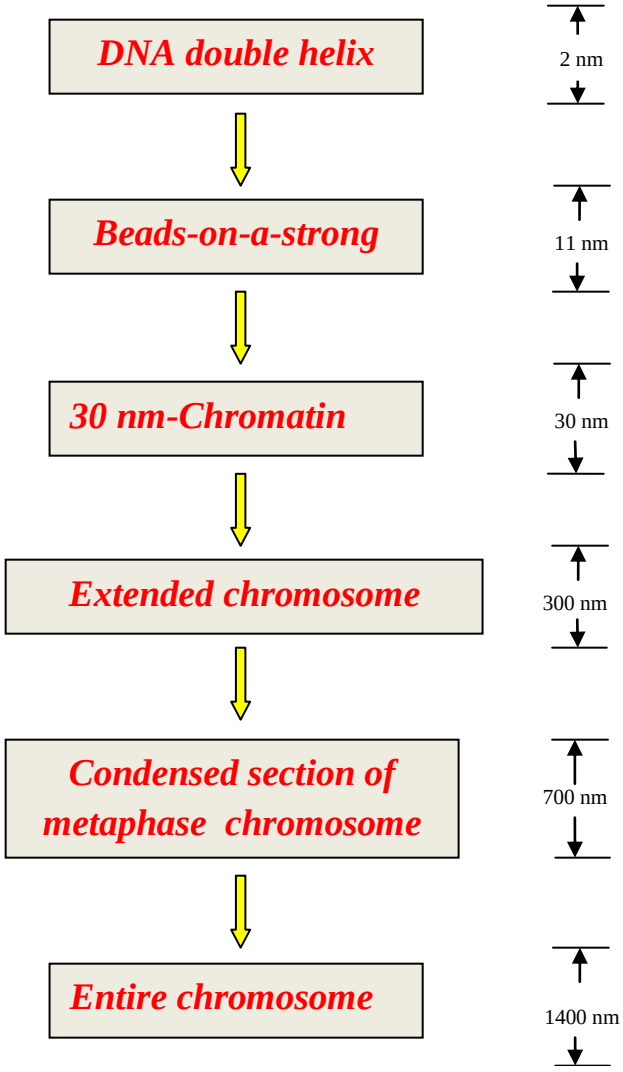


Figure 2-9 The step-wise packaging of a single strand DNA double helices into a chromosome in the metaphase. The "chuncking" of the single strand DNA duplexes into chromosmomes facilitates DNA replication and sorting during cell division. Downloaded from http://library.thinkquest.org/C004535/media/chromosome_packing.gif, May 2009

The 'chuncking' phenomenon depicted in Figure 2-9 is a highly organized process and thus requires dissipating free energy catalyzed by enzymes. Therefore it would be reasonable to predict that there will be discovered 5 different classes of enzyme complexes catalyzing each of the the 5 chuncking (or coding, or renormalizing) operations shown in the figure. I coined the term "chunckase" around 2005 while teaching "Theoretical Aspects of Pharmacology" to Pharm D students at Rutgers. Each chunckase is probably as large as ribosomes or spliceosomes, whose orderly motions would be driven by conformons derived from chemical reactions (Section 8.4).

As already alluded to, one of the main reasons for the 'chuncking operations' found in the eukaryotes is most likely to facilitate self-replication of the cell which entails replicating DNA. In principle, DNA replication can be achieved in two ways --

i) *Replication without chuncking* -- First replicate n DNA molecules into 2n DNA molecules, separating them into two identical groups by transporting only one of the sets across a membrane through an active transport mechanism.

ii) *Replication with chuncking* -- Replicate n DNA molecules into 2n molecules, each chuncked into smaller, more compact particles, which can be more easily *counted* and *sorted* than the original, unchunked DNA double helices.

It is intuitively clear that Mechanism i) would be much more difficult to implement than Mechanism ii) in agreement with von Neumann who also considered similar mechanisms of cell divisions in (von Neumann 1966). In fact it should be possible to compute the two different efficiencies of cell divisions (or mitosis) based on the two mechanisms of DNA replications described above. Such chuncking-based cell division may not be necessary for prokaryotes but becomes important as the number of chromosomes to be replicated increases in eukaryotes.

Chuncking is reversible: What gets chuncked must get 'de-chuncked' at some point during a cell cycle, catalyzed by enzyme complexes distinct from associated chunckases. The enzyme complexes postulated to catalyze de-chuncking operations may be referred to as "i->j de-chunckase", where i and j refer to the adjacent levels of chuncking with i > j.

The purpose of chunking the $(n-1)^{th}$ level components of a network into a node at the n^{th} level may be construed as producing a new function at the n^{th} level that is not available on the $(n-1)^{th}$ level (see Figure 2-10). The function at the n^{th} level may be viewed as a chuncked version of (structure, processes and mechanisms) at the $(n-1)^{th}$ level.

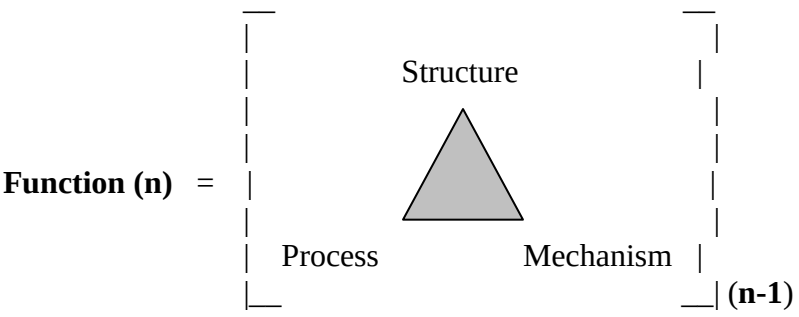


Figure 2-10 The function viewed as a node (or sign) on the n^{th} level of organization 'encoding' (or 'chuncking') a network on the $(n-1)^{th}$ level. Conversely, a function on the n^{th} level of organization can be decoded (de-chuncked) into a network of structures, processes and mechanisms on the $(n-1)^{th}$ level. (See Section 6.2.11 for a triadic model of function) .

Since the Peircen sign (Section 6.2.1) can also be defined in a traidic manner as shown in Figure 6-2, we can conclude that chuncking and de-chuncking operations can be viewed as sign processes (or coding and decoding processes, i.e., semiosis). In other words,

"Chunking and de-chunking operations are the molecular equivalents of coding and decoding processes in semiotics." (2-61)

The chuncking and de-chuncking operations shown in Figure 2-9 occur within one language, namely DNA language. It is interesting to note that chuncking and de-chuncking processes can occur involving two or more different languages, for example, from *DNese* to *RNese* (during transcription), from *RNese* to *proteinese* (during translation), and *proteinese* to *biochemicalese* (during catalysis) (see Table 11-3 and Footnote 4 for the background behind the various '-eses').

The suggestion seems reasonable that the chuncking and de-chuncking operations occurring within DNese may be mainly to facilitate cell *replication* (or *mitosis*). An equally reasonable suggestion may be made concerning the role of the chuncking and de-chuncking operations occurring between different languages: The chuncking and dechuncking operations involving two or more different languages may be mainly for facilitating cell *differentiation* in space and time.

Since *cell divisions* and *cell differentiations* are essential for both development and evolution, it may be concluded that chuncking and dechuncking operations involving DNese, RNese, proteinese and biochemicalese taking place in cells are necessary and sufficient for ontogeny (under the synchronic environment; see Section 15.4) and phylogeny (under the diachronic environment). Individual cells can only experience synchronic environment, not the diachronic one, while populations of cells as a group can experience both the diachronic and synchronic environments.

If the above analysis is correct, chuncking and de-chunking (or 'renormalization') operations may turn out to be fundamental to life, and the reason for this may well lie in the fact that when complex processes or structures are chuncked into simpler processes or structures, it becomes easier to control or regulate them. For this reason, we may refer to this idea as the "chunck-and-regulate' (C&C) principle, which may be isomorphic with the "divide-and-conquer' (D&C) principle in computer science.

2.4.3 Living Systems as Renormalizable Networks of SOWAWN Machines

It has been known for over one and a half centuries that all living systems are composed of networks (i.e., systems) of cells. Since the development of biochemistry in the early decades of the 20th century, cells have in turn been known to be composed of networks of biopolymers (e.g., DNA, RNA, proteins, carbohydrates) and small molecular and submolecular entities (e.g., ATP, glucose, metal ions) that are transformed and organized in space and time. Based on these observations alone, it appears logical to conclude that living systems are examples of *networks of networks* – i.e., networks in which individual nodes can in turn act as networks at a lower level of organization (or a higher level of resolution). The phenomenon of a network acting as a unit to constitute a node in a higher-order (or higher-level) network represents "renormalization" as defined in Figure 2-8. In addition, networks are renormalizable in that a network can act as a node of a larger network or accept as its nodes smaller networks. Therefore, a renormalizable network can act as any one of the following – i) a network, ii), a node, and iii) a network of networks -- depending on the level of resolution at which it is viewed. The concept of a *renormalizable network* can be applied to at least three distinct levels in biology, as shown in Table 2-13. It is here postulated that, at each level of the networks, a new property emerges that is unique to that level (see the last column in Table 2-13). The emergent property of a renormalizable network is in turn thought to result from a unique set of mechanisms of interactions operating among its component nodes (or *interactons*) and it is such mechanisms that implement renormalization.

As evident in Table 2-13, the *renormalizable network theory* (RNT) described here is a general molecular theory that can be applied to all living systems, ranging from unicellular to multicellular organisms and their populations. The RNT described in this book combines the molecular theories of enzymic catalysis formulated in 1974 (Ji 1974a, 1979), the concept of renormalization imported from condensed matter physics (Cao and Schweber 1993, Stauffer and Aharony 1994, Huggett and Weingard 1995, Domb 1996, Fisher 1998, Stanley 1999), and the language of networks that has emerged in recent years as a powerful new tool in science (Barabasi 2002).

Table 2-13 Three major classes of renormalizable networks in biology				
Renormalizable Network	Node	Network	Network of Networks	Emergent Properties
1. Cells	Atoms	Molecules	System of Molecules	Self-reproduction (Cell cycle)
2. Organisms*	Molecules	Cells	System of Cells	Development (Ontogeny)
3. Populations	Cells	Organisms	System of Organisms	Evolution (Phylogeny)

*Organisms can be either multicellular or unicellular. In other words, the term 'organism' can signify either an independent organism or a part of an organism, depending on the context of the discourse.

Renormalizable networks as defined above are synonymous with SOWAWN (**S**elf-**O**rganizing-**W**henever-**A**nd-**W**herever-**N**eeded) machines (Ji 2006b, 2007b). The concept of machines (or systems) is indispensable in understanding living structures and processes at all levels of organization -- from molecules, to cells, to the blood coagulation cascade, to the human body, and to societies. One of the reasons for the universal usefulness of the machine concept in living systems appears to be the possibility of applying to biosystems the Law of Requisite Variety (LRV; see Section 5.3.2) , which provides the principles underlying the complexity of the internal structures of machines or systems.

In the course of teaching Theoretical Aspects of Pharmacology to Pharm D students at Rutgers University in 2005, it occurred to me that there may be a new kind of machines operating in cells and the human body, which the author elected to call "self-organizing-whenever-and-wherever-needed" (SOWAWN) machine, for the lack of a better term. The idea of SOWAWN (pronounced "sow-on") machine came as I was discussing the blood coagulation system with students, one of the most complicated biochemical, biophysical and cellular processes that go on in our body. At least a dozen proteins (called blood coagulation factors) and two cell types (platelets and red blood cells) and several biochemical entities (e.g., thromboxane) participate in a dynamic process triggered by signals released from ruptured blood vessels whose purpose is to stop bleeding by forming insoluble clots around the damaged vessel (and not anywhere else). The blood coagulation cascade is a good example of SOWAWN machines, because:

1) It is activated (or assembled) only when and where needed in order to prevent interfering with normal blood flow in body compartments without any damaged vessels.
2) It does not exist pre-assembled, because any pre-assembled components of the blood cascade system may plug up capillaries due to their bulky molecular dimensions.
3) The necessary components of the blood coagulation cascade are randomly distributed in the blood compartment and are constantly available anywhere in our vascular system so that they can be signaled to carry out pre-programmed actions at

moment's notice.

4) The free energy needed to drive the self-assembling processes may be derived from the hydrolysis of proteins which provides about ¼ of the Gibbs free energy of ATP hydrolyis. (In other words, peptide bonds may serve as the extracellular analogs of ATP.)

Another example of SOWAWN machines is the so-called signal transduction cascades or pathways inside the cell. A signal transduction pathway (comprising, again, about a dozen proteins) in cells are activated by signals (e.g., hormones) binding to cell membrane receptors (Table 12-14 and Figure 12-33). A signal-bound cell membrane receptor undergoes a shape (or conformational) change which triggers a self-assembling process of about a dozen proteins (called signal transducing proteins known as as MAPKKK, MAPKK, MAPK, STAT, JAK, etc.) (Figure 12-35), driven by free-energy releasing phosphorylation-dephosphorylation reactions catalyzed by ubiquitous (about 100 different kinds!) proteins called kinases and phosphoprotein phosphatases present inside the cell. The biological function of a signal transduction cascade, viewed as a SOWAWN machine, is to turn on or off a target gene (related to V_O in Eq. (5-63)) under complex intracellular environmental conditions (related to V_E) by increasing the complexity of the internal state of the cascade (indicated by V_M).

As was suggested for the blood coagulation system, the components of a signal transduction cascade do not exist inside the cell pre-assembled (most likely to prevent cellular jam up) but are distributed randomly throughout the cell volume and are programmed to assemble wherever and whenever needs arise inside the cell.

It is clear that SOWAWN machines are examples of what Prigogine called "dissipative structures" (Prigogine 1977, 1980) and share common characteristics with what Norris et al. refer to as 'hyperstructures' (Norris et al 1999), what Hartwell et al. (1999) called 'modules', and what I referred to as "IDSs" (intracellular dissipative structures) (Ji 1991, pp. 69-73) (see Chapter 9).

Machines and tools have been used by *Homo sapiens* probably for 2-3 millions years. The concept of machines was generalized to include dynamic and transient assemblies of interacting components (i.e., *interactons*) only in the mid- to the late-20th century, here called SOWAWN machines. And yet we now realize that living systems may have been utilizing SOWAWN machines from their very inception, that is, for over 3.5 billion years!

Organisms can be viewed as networks of SOWAWN machines made out of smaller SOWAWN machines. As already indicated, SOWAWN machines are dissipative structures carrying both *free energy* and *genetic information* that are essential for self-organizing into dynamic and transient systems to effectuate specific functions including self-replication (see Eq. (2-56)). It should be pointed out that, although SOWAWN machines are dissipative structures, not all dissipative structures are SOWAWN machines. As accurately reflected in their acronym, SOWAWN machines are dynamic material systems that have evolved to possess the following characteristics:

1) Ability to self-organize (SO)
2) Ability to move/change in space and time (WAW), and

3) Ability to sense and meet the need (N) of themselves and others.

2.4.4 Hyperstructures and SOWAWN Machines

There are concepts and theories published in the literature that are closely related to SOWAWN machines, including *metabolons* (Srere 19870), *metabolic machines* (Hocombe 1982, Ji 1991, pp. 44-49), *cytosociology* (Smith and Welch 1991), *modules* (Hartwell et al. 1999), *IDSs*, or *intrtascellular dissipative structures* (see Section 3.1.2 and Chapter 9) (Ji 1991), and *hyperstructures* (Norris et al. 1999, 2007a,b). The last concept is especially interesting because it is highly detailed and supported by strong experimental data originating from microbiology. Therefore it may be instructive to compare SOWAWN machines and hyperstructures as shown in Table 2-14. In constructing Table 2-14, it became necessary to make a distinction between "self-organization" and "self-assembly", the former implicating dynamic steady states far from equilibrium and the latter implicating " an approach-to-equilibrium". Norris et al. (1999) also distinguish "nonequilibrium" or "dissipative" and "equilibrium" forms of hyperstructures. It should be noted that Table 2-14 lists both the similarities and differences between hyperstructures and SOWAWN/SAWAWN machines. The most important difference may be the differential kinetic behaviors specified for SOWAWN vs. SAWAWN machines (see Row 6) whereas no such differential behaviors were specified for active and passive hyperstructures.

Table 2-14 A classification of *hyperstructures* based on the dissipative structure theory of Prigogine. SOWAWN = Self-Organzing-Whenever-And-Wherever-Needed; SAWAWN = Self-Assembling-Whenever-And-Wherever-Needed.

	Hyperstructures	
	Active	Passive
1. Alternative Names	SOWAWN machines	SAWAWN machines
2. Self-organizing	Yes	No
3. Self-assembling	Yes	Yes
4. Equilibrium structure	No	Yes
5. Dissipative structure	Yes	No
6. Kinetics of the formation-degradation cycle ($t_{1/2}$)	Rapid (mseconds?)	Slow (minutes ~ hours?)

2.4.5 Micro-Macro Correlations in Bionetworks

Organisms, from the unicellular to multicellular levels, cover a wide range of sizes and temporal scales, which may be conveniently divided into three levels as shown in Table 2-15. What is common to these three levels of organization is the phenomenon of *long-range correlations*, namely, the influence of molecules on the behaviors of cells and multicellular systems exerted over distance scales varying by 10, time scales by 22, and volume ratios by 30 orders of magnitude as indicated in the second, third and fourth rows, respectively.

Table 2-15 The three levels of characteristic spatiotemporal scales of organisms (or living systems).

	Microscopic	Mesoscopic	Macroscopic
Examples	Enzymes	Cells	Animals & Plants
Distance scale (nm)	$1 – 10$	$10 – 10^4$	$10^4 – 10^{10}$
Volume scale (nm^3)	$1\text{-}10^3$	10^3 - 10^{12}	10^{12} - 10^{30}
Time scale (second)	$10^{-12} – 1$	$1 – 10^6$	$10^6 – 10^{10}$
Order parameter	Degree of coincidence of (or correlation between) amino acid residues at the active site	Degree of coincidence of (or correlation between) intracellular events	Degree of coincidence of (or correlation between) intercellular events

The spatiotemporal correlations over these scales may be expressed quantitatively in terms of "order parameter", the concept borrowed from condensed matter physics (Domb 1996), unique to living systems, which may be defined as the *degree of correlation* (e.g., *coincidence* or *synchrony* in the time dimension) *among critical structures or events* (see the last row in Table 2-15). In physics and chemistry, the adjective, 'critical', refers to the value of a measurement, such as temperature, pressure, or density, at which a physical system undergoes an abrupt change in quality, property, or state. For example, at the *critical* temperature of 0° C, water changes from the liquid (disordered) to solid (ordered) states, passing through the *critical state* or *phase* where both ordered and disordered states of water coexist. The biological systems may exist in states resembling such a *critical state*, in that ordered and non-ordered processes can coexist in cells and multicellular systems.

It may be necessary to distinguish between two levels of order-disorder transitions – at the molecular and organismic levels. At the molecular level, biologists can employ the same opposite pairs, *order* vs. *disorder*, to describe, say, protein structures, just as

physicists use such an opposite pair to describe physical states on either side of a critical point. At the organismic (i.e., cellular or higher) levels, it may be necessary to adopt another opposite pair such as *life* vs. *nonlife* (or *live* vs. *dead)*. Thus, in biology, we may have a duality of opposite pairs: i) *order* vs. *disorder* on the molecular and subcellular levels, and ii) *life* vs. *nonlife* that is applicable to cells and multicellular systems.

It may well turn out that cells are constantly at a critical point in the sense that both ordered and disordered states of subcellular constituents coexist as a means to effectuate long-range interactions over micro- and meso-scopic scales, and such interactions may be an essential condition for the *living state* of the cell (see Section 16.7 for a related discussion). If this view turns out to be correct, what is unique about the phenomenon of life would be micro-macro correlation (e.g., the body movement driven by molecular motors utilizing the free energy of ATP hydrolysis) mediated by cells to couple micro- to meso-scale structures and processes. In this sense, we may view cells as the effector or the agent of micro-macro correlations (or coupling) under varied environmental conditions conducive to life, which conditions may be referred to as 'bio-critical points' (see Section 15.12 for a related discussion).

Micro-meso correlations/interactions/couplings are evident in the theoretical model of the cell known as the Bhopalator proposed in (Ji 1985a). This model is reproduced in Fig. 2-11. The Bhopalator model appears to be the first comprehensive molecular model of the living cell proposed in the literature. Two novel concepts are embedded in the Bhopalator: i) The ultimate form of the expression of a gene is a dynamic structure called "dissipative structure" (or *dissipation*) defined as any spatiotemporal distribution of matter produced and maintained by dissipation of free energy (Section 3.1 and Chapter 9), and ii) enzymes are molecular machines driven by conformational strains (i.e., conformons) generated from chemical reactions and localized in sequence-specific sites. The arrows, both solid and dotted, represent molecular processes mostly catalyzed by enzymes (which are viewed as elementary coincidence-detectors (see Section 7.2.2.) that are organized in space and time to produce coherent behaviors of cells at the meso-scopic level. For example, the binding of a ligand to a cell surface receptor can influence what happens in the center of the nucleus 5-10 microns away, suggesting that *correlation lengths* in cells at critical points can be 5-10 microns, which is much longer than the persistence length (i.e., the length over which mechanical forces can be transmitted owing to stiffness) of biopolymers, typically less than 0.1 microns (Bednar et al. 1995). The Bhopalator model of the cell suggests that there are three possible mechanisms for effectuating the micro-meso correlations or couplings –

i) Mechanical mechanisms mediated by the cytoskeleton as has long been advocated by Ingber and his group (1998),
ii) Chemical mechanisms mediated by diffusible molecules and ions as are well established in signal transduction pathways (Kyriakis and Avruch 2001) and the actions of transcription factors, and
iii) Electromagnetic field mechanisms as evident in various membrane potential-dependent processes such as voltage-gated ion-channel openings and closings.

Unlike in condensed matter physics where long-range correlations (e.g., snow crystal formation (Libbrecht 2008)) are driven solely by the free energy of interactions among

molecular components, the long-range correlations seen in cells are driven by both *free energy* and *genetic information*, because both of these factors are essential in the operation of enzymes as catalysts (see information-energy complementarity in (Ji 2002b, 2004a,b)). Thus it may be concluded that the role of enzymes are what distinguishes biotic and abiotic critical phenomena exhibited, for example, by living cells.

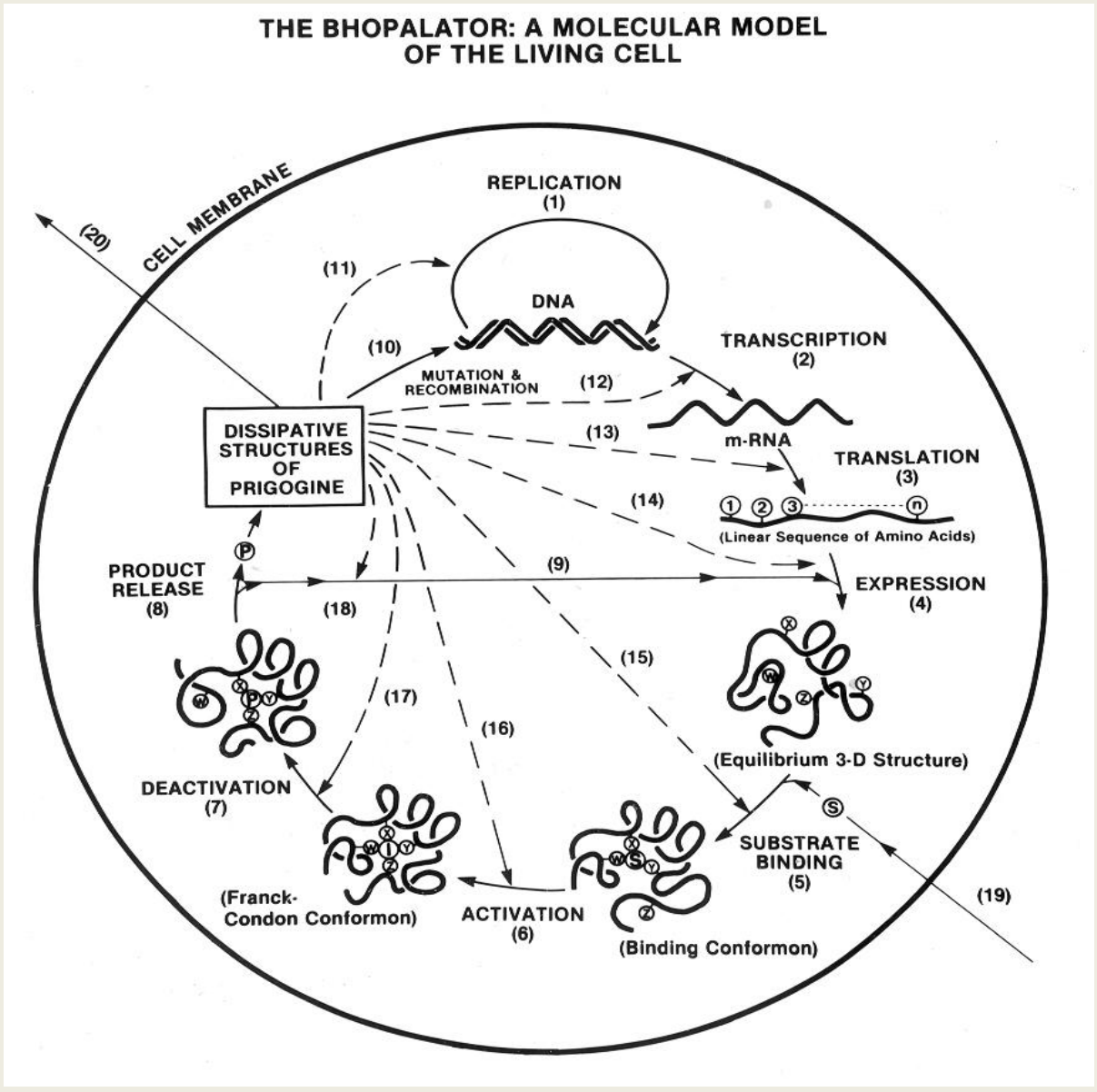


Figure 2-11 The Bhopalator - A molecular model of the living cell. Reproduced from (Ji 1985a,b). The cell can be treated as the physical system wherein micro-meso correlations occur under a wide variety of environmental conditions supported by free energy utilizing enzymes acting as *coincidence detectors* (see Section 7.2.2). The Bhopalator consists of a total of 20 major steps: 1 = DNA replication; 2 = transcription; 3 = translation; 4 = protein folding; 5 = substrate binding; 6 = activation of the enzyme-substrate complex; 7 = equilibration between the substrate and the product at the metastable transition state; 8 = product release contributing to the formation of the intracellular dissipative structure (IDS); 9 = recycling of the enzyme; 10 = IDS-induced changes in DNA structure; 11 through 18 = feedback interactions mediated by IDS; 19 = input of substrate into the cell; and 20 = the output of the cell effected by IDSs, which makes cell function and IDSs synonymous (see Section 10.1 for more details).

2.5 The Theory of Finite Classes

Bohr thought that biologists should accept the *functions of living systems* as a given, just as physicists accept *quantum of action* as an irreducible unit of physical reality at the microscopic level. This is the essence of the *holism* in biology that Bohr suggested 7 decades ago. This seminal idea was further developed and elaborated on by W. Elsasser from the 1960's through the 1990's, laying the logical foundation for Bohr's intuitive grasp of the essence of the phenomenon of life. Hence we may well consider Bohr and Elsasser as the originators of *holistic* or *systems biology* that has been gaining momentum in recent years (Hartwell et al. 1999, Bechtel 2010).

Elsasser dedicated the last three decades of his life to the theoretical research aimed at defining the basic difference between physics and biology. He maintains that the class of the objects studied in physics is *homogeneous* in kind and *infinite* in size (in the order of Avogadro's number, $\sim 10^{23}$), whereas the class of objects studied in biology is *heterogeneous* in kinds (the number of different kinds in this case being in the order of $10^{10\wedge 9}$, the number of all possible strings that can be constructed out of the different kinds of deoxyribonucleotides, one billion units long, as found in the human genome) and *finite* in size (less than $\sim 10^{6}$ molecules). According to Elsasser, the traditional mathematical equations used in physics and chemistry cannot be applied to biology because they do not converge when applied to finite classes (Elsasser 1998). Wolfram (2002) reached a similar conclusion from a different direction.

To distinguish between *homogeneous* and *heterogeneous* classes, it may be useful to represent a class, C, as a 2-tuple:

$$C = (m, n) \tag{2-62}$$

where m is the number of different kinds of the elements of a class, and n is the number of copies of each kind in a class. It should be noted here that m in Equation (2-62) can be characterized further in terms of M, the number of components of a living system, and N, the number of particles in each component as done by Mamontove et al. (2006). Variables m and n can have two ranges of values -- large and small. When m is small we can refer to the class as homogeneous; when m is large, heterogeneous. Likewise, when n is large, the class can be referred to as infinite; when small, finite:

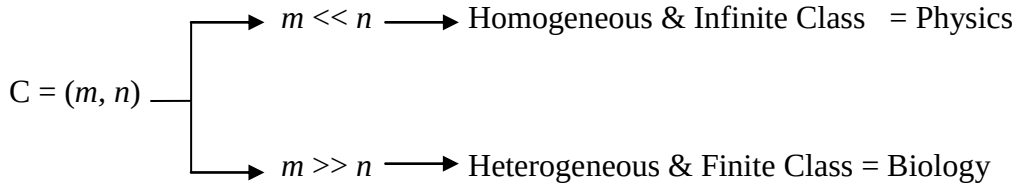


Figure 2-12 A diagrammatic representation of the homogenous and heterogeneous classes, the former being the primary object of study in physics and the latter in biology, according to Elsasser (1998).

One important conclusion that Elsasser arrived at, based on the recognition of the two classes of objects, is that *reductionist scheme works only for homogeneous classes but not for heterogeneous ones*. For the latter, the principle of holism is essential. This conclusion, when applied to the cell, a prototypical example of the objects belonging to the heterogeneous class, is that *the property or phenomenon we call life belongs to the class as a whole and not to any members of the class*. This is the same conclusion that Bohr arrived at based on the analogy between the cell and the atom (Bohr 1933) and is consonant also with the concept of the bionetwork in the sense that life belongs to the cell (a network), not to component molecules (i.e., nodes) such as enzymes and DNA.

The author found the following quotations from (Elsasser 1998) helpful in understanding Elsasser's theory of holistic biology:

" There has been in the past a tendency to apply the successful methods of physical science more or less blindly to the description of organism; reductionist reasoning being one of the results of this tendency. Here, we shall try to deal with the difference between living and dead material in terms of a closer analysis that consists, as already indicated, in suitable generalizations of the logical concept of classes. This gets one away from the exclusive use of purely quantitative criteria, which use is a remnant of the uncritical transfer of the methods of physical sciences to biology. Instead of this we shall find a more subtle use of the class concept." (pp. 22-23).

"The basic assumption to be made in our interpretation of holism is that an organism is a source (or sometimes a sink) of causal chains which cannot be traced beyond a terminal point because they are lost in the unfathomable complexity of the organism." (p. 37).

"Drawing on the idea of generalized complementarity interpreted here as mechanistic vs. holistic properties, we have strongly emphasized the holistic aspects . . . . " (p. 148).

Consistent with the holism advocated by Bohr (1933) and Elsasser (1998), I concluded in (Ji 1991) that, to account for the functional stability (or robustness) of the metabolic networks in cells in the face of the randomizing influence of thermal fluctuations of molecules, it was necessary to postulate the existence of a new kind of force holding molecules together in functional relations within the cell (and hence called the *cell force* mediated by 'cytons'), just as physicists were forced to invoke the concept of the strong force (mediated by gluons) as the agent that holds together nucleons to form stable nuclei against electrostatic repulsion (Ji 1991, pp. 110-113).

2.6 Synchronic vs. Diachronic Causes

It appears to be the Swiss linguist Ferdinand de Saussure (1857-1913) who first distinguished between the *synchronic* study of language (i.e., the study of language as it is practiced *here* and *now*, without reference to *history*) and the *diachronic* study (i.e., the study of language *evolution*) (Culler 1991). (This distinction may be analogous to the distinction between *space* and *time* in nonrelativistic physics.)

The main purpose of this section is to suggest that the linguistic concepts of *synchronicity* and *diachronicity* can be extended to all of the sciences, both natural and human, including biology. It is possible that linguistic principles in general are as important as the principles of physics (and chemistry) in helping us understand the Universe, including the phenomenon of life and the workings of organisms at the fundamental levels (Pattee 1969, 2001, Ji 1997a,b, 1999, 2001, 2002b). So it seems logical to suggest that there are two kinds of causalities – here called the 'synchronic causality' widely discussed in physics (which dominates the thinking of most contemporary molecular biologists) and the 'diachronic causality' derived from linguistics and other historical sciences, including sociology. Table 2-16 summarizes the characteristics of these two kinds of causalities.

Table 2-16 Two kinds of causalities operative in the material universe. When two objects or events, A and B, are correlated, A and B may interact directly (i.e., synchronically) by exchanging material entities, C (e.g., photons, gravitons, gluons, etc. (Han 1999)), or indirectly (i.e., diachronically) through the historical sharing of a common entity, C, which preceded A and B in time.

	Causality	
	Synchronic	**Diachronic**
1. Interaction mediated by	Synchronic agent (e.g., photons, gravitons, gluons)	Diachronic agent (e.g., entangled phases of wave functions, DNA)
2. Interaction speed limited by the speed of light	Yes (i.e., local)	No (i.e., non-local)
3. Mathematics needed for description	Analytical functions (e.g., differential equations, probability wave functions)	Algorithms (e.g., cellular automata)
4. Phenomena explained	A-historic phenomena	Historic phenomena (e.g., cosmogenesis, origin of life, biological evolution, EPR paradox (Herbert 1987))
5. Alternative names	Energy-based causality Local causality Luminal causality	History-based causality Non-local causality Superluminal causality

If the content of the above table is right, we will have access to two (rather than just one) kind of causalities with which to explain and understand what is going on around us--including cosmogenesis, the origin of life, biological evolution, the working of the living

cell, and the relation between the mind and the brain (Amoroso 2010).

CHAPTER 3

Chemistry

3.1 Principle of Self-Organization and Dissipative Structures

The phenomenon of spontaneous generation of spatial patterns of chemical concentration gradients was first observed in a purely chemical system in 1958 (see Figure 3-1) (Babloyantz 1986, Kondepudi and Prigogine 1998, Kondepudi 2008) and inside the living cell in 1985 (see Figure 3-2) (Sawyer et al. 1985). These observations demonstrate that, under appropriate experimental conditions, it is possible for chemical reactions to be organized in space and time to produce *oscillating chemical concentrations, metastable states, multiple steady states, fixed points* (also called *attractors*), etc., all driven by the free energy released from exergonic (i.e., $\Delta G < 0$) chemical reactions themselves. Such phenomena are referred to as *self-organization* and physicochemical systems exhibiting self-organization are called *dissipative structures* (Prigogine 1977, Babloyantz 1986, Kondepudi and Prigogine 1998, Kondepudi 2008). It has been found convenient to refer to *dissipative structures* also as *X-dissipatons*, X referring to the function associated with or mediated by the dissipative structure. For example, there is some evidence (Lesne 2008, Stockholm et al. 2007) that cells execute a set of *gene expression pathways* (GEPs) more or less randomly in the absence of any extracellular signals until environmental signals arrive and bind to their cognate receptors, stabilizing a subset of these GEPs. Such mechanisms would account for the phenomenon of the *phenotypic heterogeneity* among cells with identical genomes (Lesne 2008, Stockholm et al. 2007). Randomly expressed GEPs are good examples of *dissipatons*, since they are dynamic, transient, and driven by dissipation of metabolic energy. Ligand-selected GEPs are also dissipatons. All living systems, from cells to multicellular organisms, to societies of organisms and to the biosphere, can be viewed as evolutionarily selected *dissipatons*. As indicated above, attractors, fixed points, metastable states, steady states, oscillators, etc. that are widely discussed in the non-linear dynamical systems theory (Scott 2005) can be identified as the mathematical representations of *dissipatons*.

The theory of dissipative structures developed by Prigogine and his coworkers (Prigogine1977, Nicolis and Prigogine 1977, Prigogine 1980, Kondepudi and Prigogine 1998, Kondepudi 2008) can be viewed as a thermodynamic generalization of previously known phenomena of *self-organizing chemical reaction-diffusion processes* discovered independently by B. Belousov in Russia (and by others) working in the field of chemistry and by A. Turing in England working in mathematics (Gribbins 2004, p. 128-134). That certain chemical reactions, coupled with appropriate diffusion characteristics of their reactants and products, can lead to symmetry breakings in molecular distributions in space (e.g., the emergence of concentration gradients from a homogenous chemical reaction medium; see Figure 3.2) was first demonstrated mathematically by A. Turing (1952, Gribbins 2004, pp. 125-140). Murray (1988) has shown that the Turing reaction-diffusing models can account for the colored patterns over the surface of animals such as leopards, zebra, and cats.

Prigogine suggested that the so-called "far-from-equilibrium" condition is both necessary and sufficient for *self-organization*, but the general proof of this claim may be lacking as already pointed out. Nevertheless, Prigogine and his group have made important contributions to theoretical biology by establishing the concept that structures in nature can be divided into two distinct classes – *equilibrium* and *dissipative structures* and that organisms are examples of the latter. It should be noted that these two types of structures are not mutually exclusive, since many dissipative structures (e.g., the living cell) require equilibrium structures as a part of their components such as phospholipid bilayers of biomembranes (which last much longer than, say, action potentials upon removing free energy supply).

One of the characteristic properties of all *self-organizing systems* is that the free energy driving them is generated or produced within the system (concomitant to self-organization), most often in the form of exergonic chemical reactions, either catalyzed by enzymes (e.g., see Figure 3.2) or uncatalyzed (Figure 3.1). In contrast, there are many organized systems that are driven by forces generated externally, such as the Bernard instability (Prigogine 1980) which is driven by externally imposed temperature gradients and paintings drawn by an artist's brush. To describe such systems, it is necessary to have an antonym to 'self-organization', one possibility of which being 'other organization'. It is unfortunate that, most likely due to the lack of the appropriate antonym, both self-organized (e.g., the flame of a candle) and *other-organized* entities (e.g., a painting, or the Bernard instability) are lumped together under the same name, i.e., *self-organization*.

Dissipative structures are material systems that exhibit non-random behaviors in space and/or time driven by irreversible processes. Living processes require both *equilibrium* and *dissipative structures*. Operationally we may define the *equilibrium structures* of living systems as those structures that remain, and *dissipative structures* as those that disappear, upon removing free energy input. Some *dissipative structures* can be generated from *equilibrium structures* through expenditure of free energy, as exemplified by an acorn and a cold candle, both *equilibrium structures*, turning into an oak and a flaming candle, *dissipative structures*, respectively, upon input of free energy:

$$\text{Equilibrium Structures} \xrightarrow{\text{Free Energy}} \text{Dissipative Structures} \qquad (3\text{-}1)$$

The flame of a candle is a prototypical example of dissipative structures. The pattern of colors characteristic of a candle flame reflects the space- and time-organized oxidation-reduction reactions of hydrocarbons constituting the candle that produce transient chemical intermediates, some of which emit photons as they undergo electronic transitions from excited states to ground states. From a mechanistic point of view, the flame of a candle can be viewed as high-temperature self-organizing *chemical reaction-diffusion systems* in contrast to the Belousov-Zhabotinsky reaction (Figure 3-1) which is a low-temperature self-organizing *chemical reaction-diffusion system.*

3.1.1 Belousov-Zhabotinsky Reaction-Diffusion System

The Belousov-Zhabotinsky (BZ) reaction was discovered by Russian chemist, B. P. Belousov, in 1958 and later confirmed and extended by A. M. Zhabotinski (Babloyantz 1980, Gribbin 2004, pp. 131-34). The spatial pattern of chemical concentrations exhibited by the BZ reaction results from the chemical intermediates formed during the oxidation of citrate or malonate by potassium bromate in acidic medium in the presence of the redox pair, Ce^{+3}/Ce^{+4}, which acts as both a catalyst and an indicator dye. Ce^{+4} is yellow and Ce^{+3} is colorless. The BZ reaction is characterized by the organization of chemical concentrations in space and time (e.g., oscillating concentrations). The spatial patterns of chemical concentrations can evolve with time. 'Patterns of chemical concentrations' is synonymous with 'chemical concentration gradients'. The organization of chemical concentration gradients in space and time in the BZ reaction is driven by free energy-releasing (or exergonic) chemical reactions. The BZ reaction belongs to the family of oxidation-reduction reactions of organic molecules catalyzed by metal ions. The mechanism of the BZ reaction has been worked out by R. Field, R. Noyes and E. Koros in 1972 at the University of Oregon in Eugene. The so-called FNK (Field, Noyes and Koroso) mechanism of the BZ reaction involves 15 chemical species and 10 reaction steps (Leigh 2007). A condensed form of the FNK mechanism still capable of exhibiting spatiotemporally organized chemical concentrations is known as the *Oregonato*r. A simplified mathematical model of the BZ reaction was formulated in 1968 and is known as the *Brusselator* (Babloyantz 1986, Gribbin 2004, pp. 132-34).

Figure 3-1 The Belousov-Zhabotinsky (BZ) reaction. The most intensely studied chemical reaction-diffusion system (or dissipative structure) known.

3.1.2 Intracellular Dissipative Structures (IDSs)

Living cells are formed from two classes of material entities that can be identified with Prigogine's *equilibrium structures* (or *equilibrons* for brevity) and dissipative structures (or *dissdipatons*) (Section 3.1). What distinguishes between these two classes of structures is that *equilibrons* remain and *dissipatons* disappear whern cells run out of free energy. Dissipatons are also theoretically related to the concept of 'attractors' of nonlinear dynamical systems (Scott 2005).

All of the cellular components that are *controlled* and *regulated* are dissipatons referred to as Intracellular Dissipative Structures (IDSs) (Ji 1985a,b, 2002b). One clear example of IDSs is provided by the RNA trajectories of budding yeast subjected to glucose-galactose shift that exhibit pathway- and function-dependent regularities (Panel a in Figure 12-2), some of which was found to obey the blackbody radiation-like equation (see Panels a through d in Figure 12-25). The main idea to be suggested here is that IDSs

constitute the immediate causes for all cell functions (Ji 1985a,b, 2002b). In other words, *IDSs* and *cell functions* are synonymous:

IDSs constitute the internal (or endo) aspects and cell functions (3-2)
constitute the external (or exo) aspects of the living cell.

The concepts of *dissipative structures* or *self-organizing chemical reaction-diffusion systems* is not confined to abiotic (or inanimate) systems, but can be extended to biotic (or animate) systems such as intracellular chemical reaction-diffusion processes, was first demonstrated experimentally in chemotaxing human neutrophils by Sawyer, Sullivan and Mendel (1985) (see Figure 3-2). What is interesting about the findings of these investigators is that the direction of the intracellular calcium ion gradient determines the direction of the chemotactic movement of the cell as a whole. This is one of the first examples of *intracellular dissipative structures* (IDSs) i.e., intracellular calcium gradients in this case, that are observed to be linked to cell *functions*. Figure 3-2 offers two important take-home messages – i) *dissipative structures* in the form of ion gradients can be generated inside a cell without any membranes (see Panels F, I, and L), and ii) IDSs determine cell functions.

There are three major differences to be noted between the dissipative structures in the Belousov-Zhabotinsky (BZ) reaction shown in Figure 3-1 and the dissipative structures shown in Figure 3-2: i) The boundary (i.e., the reaction vessel wall) of the BZ reaction is fixed, and
ii) The boundary of IDSs (such as the intracellular calcium ion gradients) is mobile, and
iii) The BZ reaction is a purely chemical reaction-diffusion system, while the intracellular dissipative structures in Figure 3-2 are chemical reactions catalyzed by enzymes which encode genetic information. Hence the cell can be viewed as dissipative structure regulated by genetic information or as a 'genetically informed dissipatons (GIDs)".

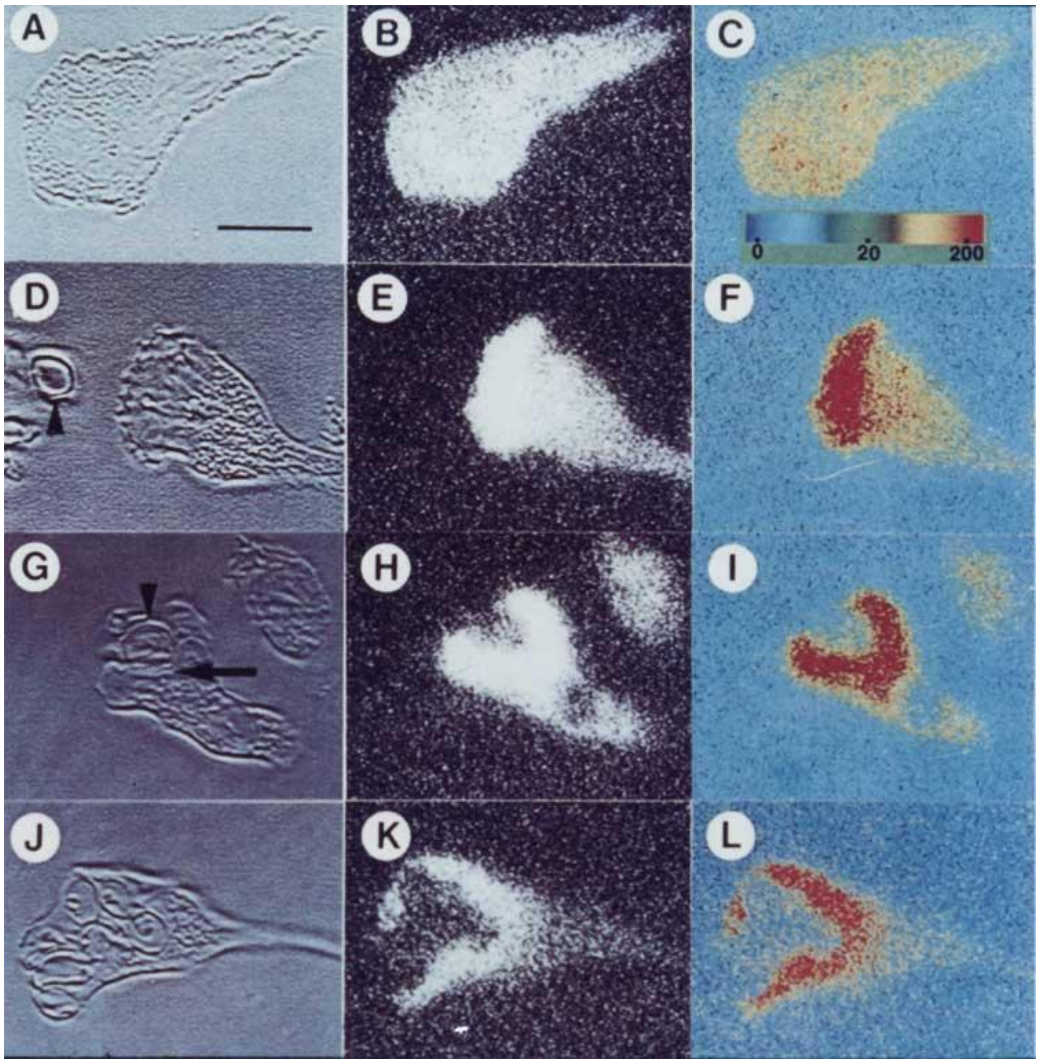


Figure 3-2 Intracellular Ca^{++} ion gradients generated in the cytosol of a migrating human neutrophil. The intracellular Ca^{++} ion concentration was visualized using the Ca^{++}-sensitive fluorescent dye, Quin2. The pictures in the first column are bright-field images of a human neutrophil, and those in the second column are fluorescent images showing intracellular calcium ion distributions (white = high calcium; gray = low calcium). The pictures in the third column represent the color-coded ratio images of the same cell as in the second column. Images on the first row = unstimulated neutrrophil. Images on the second row = The neutrophil migrating toward an opsonized particles, 'opsonized' meaning "being treated with certain proteins that enhance engulfing" by neutrophils. Images on the third row = the neutrophil with pseudopods surrounding an opsonized particle. Images on the fourth row = the neutrophil after having ingested several opsonized particles. Before migrating toward the opsonized particle (indicated by the arrows in Panels D & G), the intracellular Ca^{++} ion concentration in the cytosol was about 100 nM (see Panel C), which increased to several hundred nM toward the advancing edge of the cell (see Panel F). Reproduced from Sawyer, Sullivan and Mandell (1985).

4.2 Molecular Machines, Motors, and Rotors

The living cell can be viewed as space- and time-ordered systems (or networks) of *molecular machines* (Alberts 1998), proteins that can utilize the free energy of chemical reactions such as ATP hydrolysis to carry out goal-directed or teleonomic molecular motions (Ishii and Yanagida 2000). The molecular mechanisms responsible for such goal-directed molecular motions of biopolymers are postulated to be provided by *coformons*, conformational strains resident in sequence-specific sites within biopolymers that are generated from chemical reactions based on the generalized Franck-Condon principle (Sections 8.2) (Green and Ji 1972, Ji 1974a, 1979, 2000, 2004a).

Concept of molecular machines (McClare 1971, Ji 1991, Alberts 1998, Ishii and Yanagida 200, 2007, Xie and Lu 1999, Xie 2001) is one of the most important contributions that biology has made to our understanding of how the living cell works. Like macroscopic machines, molecular machines must exert forces on their environment during their work cycle and this means that molecular machines must possess mechanical energies stored in them, since energy is required to generate forces. Such stored internal energies of molecular machines have been referred to as *conformons* (Green and Ji 1972a,b, Ji 1974a,b, 1991, 2000). Molecular machines that perform work on their environment without utilizing internally stored mechanical energy (e.g., conformons) violate the First and Second Laws of Thermodynamics (McClare 1971).

Most metabolic processes inside the cell are catalyzed by combinations of two or more proteins that form functional units through noncovalent interactions. Such protein complexes have been variously referred to as metabolons (Srere 1987), modules (Hartwell et al. 1999), hyperstructures (Norris et al. 1999, 2007a,b). The number of component proteins in complexes varies from two to over 50 (Aloy and Russell 2004). More recent examples of the protein complexes that involve more than 50 components include eukaryotic RNA polymerases, or *transcriptosomes* (Halle and Meisterernst 1996), *spliceosomes* (catalyzing the removal of introns from pre-mRNA), *molecular chaperones* (catalyzing protein folding), and *nuclear pore complexes* (Blobel 2007, Dellaire 2007, Dundr and Misteli 2001). These protein complexes are theoretically related to dissipaticve structures of Prigogine (1877, 1980) and SOWAWN machines discussed in Section 2.4.4. Therefore it may be convenient to view them as members of the samne class of molecular machines called “dissipatons” defined in Section 3.1.5.

4.3 What Is Information?

The concept of information is central not only to computer scicence (Wolfram 2002, Lloyd 2006), physics (Wheeler 1990) and biology (e.g., this Section) but also to philosophy and theology (Davies and Gregersen 2010). Molecular machines require both *free energy* and *genetic information* to carry out goal-directed molecular work processes. The definition of free energy is given in Section 2.1.2. In this section, the term *information* is defined, primarily within the context of molecular and cell biology. The

dictionary definitions of *information* include the following (except the last two items that are my additions):

1) Knowledge obtained from investigation, study, or instruction.
2) Intelligence, news, facts, data.
3) The attribute inherent in and communicated by one of two or more alternative sequences or arrangements of something (such as the nucleotides in DNA and RNA or binary digits in a computer program) that produce specific effect.
4) A quantitative measure of the uncertainty in the outcome of an experiment to be performed.
5) A formal accusation of a crime made by a prosecuting officer as distinguished from an indictment presented by a grand jury.
6) Anything or any process that is associated with a reduction in uncertainty about something.
7) Information is always associated with making a choice or a selection between at least two alternatives or possibilities.

It is generally accepted that there are three aspects to information (Volkenstein 2009, Chapter 7) –

i) *amount* (How much information can your USB store?),
ii) *meaning* (What is the meaning of this sequence of nucleotides? What does it code for?), and
iii) *value* (What practical effects does this nucleotide sequence have on a cell?).

All of these aspects of information play important roles in biology, but only the quantitative aspect of information is emphasized by Shannon (1916-2001) (1949) who proposed that information carried by a message can be quantified by the probability of the message being selected from all possible messages as shown in Eq. (4-2):

$$H = - K\sum_{i=1}^{n} p_i \log_2 p_i \qquad (4\text{-}2)$$

where H is the Shannon entropy (also called the information-theoretic entropy or *intropy*) of a message source, n is the total number of messages, and p_i is the probability of the i^{th} message being selected for transmission to the receiver. The meaning of H is that it reflects the average *uncertainty* of a message being selected from the message source for transmission to the user. When the probabilities of the individual messages being selected are all equal H assumes the maximum value given by Eq. (4-3), which is identical to the Hartley information (see Fgirue 4-1):

$$H = \log_2 n \qquad (4\text{-}3)$$

According to Klir (1993), there are two types of information – the *uncertainty-based* and *algorithmic* informations (see Figure 4-1). The amount of the uncertainty-based information, I_X, carried by a messenger, X, can be calculated using Eq. (4-3) leading to the following formula:

$$I_X = H_{before} - H_{after} = \log_2 n - \log_2 n' = \log_2 n/n' \quad \text{bits} \qquad (4\text{-}4)$$

where H_{before} and H_{after} are the Shannon entropies before and after the selection process, respectively, and n' is the number of messages selected out of the initial n. Evidently, I_X assumes a maximal numerical value when n' = 1 or $H_{after} = 0$. That is, when the selected message, X, reduces the uncertainty to zero.

It is possible to view Shannon entropy, H, as characterizing the property of the *sender* (i.e., the message source) while Shannon information, I, characterizes the amount of the information received by the *user* (Seife 2006). If there is no loss of information during the transmission through the communication channel, H and I would be quantitatively identical. On the other hand, if the channel is noisy so that some information is lost during its passage through the channel, I would be less than H. Also, according to Eq. (4-4), information, I_X, and Shannon entropy of the message source, H_{before}, become numerically identical under the condition where H_{afer} is zero (i.e., under the condition where the number of the message selected is 1). It is for this reason that the term "information" and "Shannon entropy" are almost always used interchangeably or synonymously in the information theory literature, leading to the following general statement:

"*Shannon entropy of a message source and the information content of a message selected from it is numerically identical if and only if the channel is noiseless and the number of messages selected is 1.*" *(4-5)*

Statement (4-5) may be referred to as the "non-identity of information and Shannon entropy (NISE) thesis". There are two types of information – *algorithmic* and *uncertainty-based* (Figure 4-1). Algorithmic (also called descriptive) information is measured by the shortest possible program in some language (e.g., the binary digital language using 0's and 1's) that is needed to describe the object in the sense that it can be computed. Thus algorithmic information is *intrinsic* to the object carrying the information. It is quantitated by the number of bits necessary to characterize the message. Uncertainty-based information is *extrinsic* to the object carrying information, since extrinsic information belongs to the property of the set to which the message belongs rather than to the message itself. Uncertainty-based (or uncertainty-reducing) information is measured by the amount of the uncertainty reduced by the reception of a message (see Eq. (4-4)).

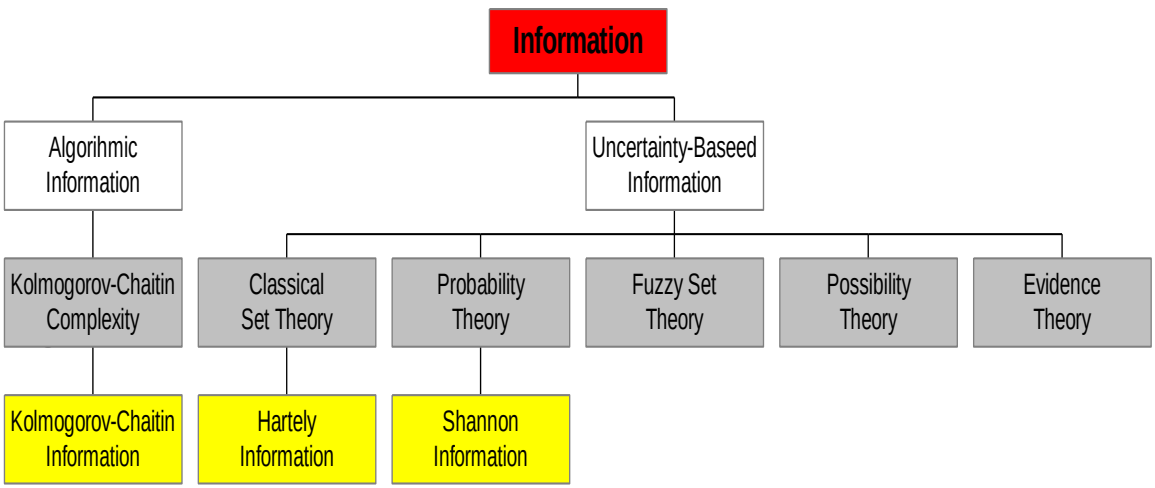


Figure 4-1 A classification of information based on the quantitative aspect of information (Klir 1993).

When the probability of occurrence is equal for all of the messages in a message source, we are dealing with the *Hartley information* (see Eq. (4-3)), while, when the probabilities of occurrences are uneven (i.e., p_i's in Eq. (4-2) are not the same), we are dealing with the *Shannon information*. Consider an object or a message consisting of a string of 10 deoxyribonucleotides:

TGCTTAGCCT (4-6)

which can be represented as a string of 0's and 1's as

11 01 10 11 11 00 01 10 10 11 (4-7)

by adopting the following code (or convention),

A = 00 (4-8)
C = 10
G = 01
T = 11.

Thus, the algorithmic (also called Kolmogorov-Chaitin) information content of the 10-nucleotide message in String (4-6) is 20 bits, since the shortest program that can characterize the message contains 20 binary digits (as evident in Expression (4-7)).

The Hartley information content of the same 10-nucleotide message can be calculated if we knew the "cardinality" (i.e., the size) of the set out of which the message was selected. The cardinality of the set involved is $6^{10} = 6.0466 \times 10^7$, if we assume that each of the 10 positions in the 10-nucleotide message can be occupied by any one of the six nucleotides, A, C, G, T, A' and T', where A' and T' are covalently modified nucleotides. Hence the Hartley information content of the message would be $\log_2 (6^{10}) = 10 \log_2 6 = 10 \times 2.6 = 26$ bits. That is, if the above decanucleotide (deca = 10) is chosen out of all possible decanucleotides formed from the 6 elements, A, C, G, T, A' and T', then the amount of information that can be carried by the decanucleotide (or by any one of the rest of the set, including, say, TTTTTTTTTT or AAAAAAAAA) is 26 bits. Because Hartley information or Shannon information cannot distinguish between individual messages, they are unable to convey any meaning of a message.

Turvey and Kugler (1984) made the interesting suggestion that there are two kinds of information – i) the orthodox information (also called the *indicational/injunctional information*), often associated with symbol strings, that *indicates* and *instructs* (e.g., stop signs, genes), and ii) the 'Gibsonian' information (also called the *specificational information*), not expressible in terms of symbol strings, that provides *specifications* (e.g., visual information from surrounds guiding a driver to stop at a desired location at a desired time). 'Information' is akin to 'compounds' in chemistry. Although all compounds are made out of one or more of the slightly more than 100 elements in the periodic table, the kinds of compounds found on this planet alone is astronomically large ($10^9 – 10^{12}$?), and chemists have come up with rational methods for denoting and classifying them. It is clear that the number of the kinds of information that we can conceive of is probably similarly large. Just as there are many ways of classifying chemical compounds (e.g., natural vs. synthetic, organic vs. inorganic, acid vs. base, biological vs. abiological, stable vs. unstable, toxic vs. nontoxic, monomers vs. polymers, volatile vs. nonvolatile, solid, liquid vs. gas, etc.), there should be many ways of classifying information. The ones suggested in Figure 4-1 and by Turvey and Kugler (1984) may represent just the tip of the iceberg of information.

The information concept plays a fundamental role in biology akin to the role of energy in physics and chemistry. The pivotal role of information in biology is illustrated by the following list of information-related expressions widely used in biology:

1) Genetic information.
2) The *sequence information* of proteins, RNA, and DNA
3) Functional vs. structural information of biopolymers.
4) The *control information* carried by transcription factors.
5) The *regulatory information* encoded in the promoter regions of DNA.
6) DNA carries genetic information.
7) Hormones carry regulatory information.
8) Protein shapes carry the *information* specifying their target ligands or receptors.
9) Intracellular dissipative structures (or dissipatons) carry *genetic information* (called the Prigoginian form of *genetic information* (Ji 1988)).
10) Amino acid residues of protein domains carry *information* (Lockless and Ranganathan 1999, Süel et al. 2003, Socolich et al. 2005, Poole and Ranganathan 2006).

4.4 The Chemistry and Thermodynamics of Information

The concept of information in computer science is heavily influenced by the Shannon information theory (Shannon and Weaver 1949) and by symbol strings such as Expression (4-7). *Biological information*, however, may be too rich and deep to be adequately captured by the *quantitative theories of information* developed so far, including that of Shannon. The statement made by Prigogine (1991) two decades ago still holds:

"Traditional information theory was too vague, . . . , because (4-9)

it is not deeply enough rooted in physics and chemistry . . . "

The connection among i) irreversible thermodynamics, ii) chemistry, and iii) information production was illustrated by Prigogine (1991) using a simple example. He considered a chemical system containing two monomers X and Y which can polymerize whenever the concentration of one of them exceeds some critical level. If the system is at equilibrium, the concentrations of these monomers would fluctuate randomly, obeying the Poisson law, leading to the production of a random or disordered polymer as shown in Reaction (4-10). However when the system is under nonequilibrium conditions and exhibits irreversible dynamics with some regularity, the resulting polymer can encapsulate these regularities into nonrandom monomer sequences. One such sequence is shown in Reaction (4-11) which exhibits a long-range correlation among the trimeric units **XYX** whose correlation distance increases with time.

Reversible Processes ---------- > **XXYXYYYXYXYYXXXYXX** (4-10)

Irreversible Processes ---------- > **XYXYXYXYYXYXYYYXYX** (4-11)

Process (4-11) illustrate what Prigogine means when he states that:

". . . chemistry plays a very specific role. . . . it may "encapsulate" irreversible time into matter. . . . . In this way, irreversible processes may be made more permanent and transmitted over longer periods of time. This is of special importance for us, as we should be able to describe in these terms a world where the very existence of biological systems implies some recording of irreversible processes in matter . . . . . .chemical molecules produced under non-equilibrium conditions keep some memory of the deviations from equilibrium which exists at the moment of their production." (4-12)

Process (4-11) together with Statement (4-12) maybe viewed as defining a novel principle in nature which may be referred to as the *Principle of Encoding Time into Matter* or alternatively the *Principle of Encoding Dissipatons into Equilibrons* (PEDE), since the left-hand sides of the arrows in Processes (4-10) and (4-11) can be identified as equilibrium structures (*equilibrons*) and dissipative structures (*dissipatons*), respectively (Section 3.1). The PEDE may be re-stated as follows:

"It is possible for some non-equilibrium chemical systems to encode *dissipatons* into *equilibrons*." (4-13)

Viewing species as dissipative structures (Brooks and Wiley 1986, p. 40) and genomes as equilibrium structures, Statement (4-13) can logically be interpreted as the *thermodynamic principle of biological evolution* (TPBE), i.e., the thermodynamic

principle that *allows* the biological evolution (Chapter 14) to occur spontaneously on this planet, in analogy to the Second Law which is the thermodynamic principle that *disallows* the existence of the perpetual motion machines of the second kind (Atkins 2007).

Molecular biology is replete with examples of the processes that support the reverse of Statement (4-13), namely, the decoding of equilibrons (e.g., DNA sequences) into dynamic patterns of concentration changes of molecules, i.e., dissipatons (e.g., RNA trajectories in Figure 12-2). This allows us to formulate another principle to be called the Principle of Decoding Equilibrons into Dissipatons (PDED):

"It is possible for some non-equilibrium chemical systems to decode *equilibrons* into *dissipatons*." (4-14)

Statements (4-13) and (4-14) can be combined into what may be termed the "Principle of Dissipaton-Equilibron Transduction (PDET)":

"It is possible for some non-equilibrium chemical systems to interconvert *equilibrons* and *dissipatons*." (4-15)

It seems logical to view Statement (4-15) as the *thermodynamic principle of organisms* (TPO), since organisms are the only non-equilibrium thermodynamic systems known that are equipped with mechanisms or molecular devices to carry out the interconversion between equilibrons and dissipatons.

Since organisms can both *develop* and *evolve*, it is possible to derive Statements (4-16) and (4-17) as the corollaries of Statement (4-15):

"Biological *evolution* results from non-equilibrium systems encoding dissipatons into equilibrons." (4-16)

"Biological *development* results from non-equilibrium systems decoding equilibrons into dissipatons." (4-17)

4.5 Synchronic vs. Diachronic Information

It is clear that the symbol string generated in Process (4-11) carries two kinds of information which may be referred to as *synchronic* and *diachronic information* in analogy to the *synchronic* and *diachronic* approaches in linguistics (Table 4-1) (Culler 1991). Synchronic information refers to the totality of the information that can be extracted from the symbol string *here* and *now* without having to know neither how it was generated in the past nor how it may be related to other symbol strings with similar functions. For example, the linear sequences of amino acid residues of proteins often carry sufficient 'synchronic' information that allows proteins to spontaneously fold into the secondary structures such as α-helices and β-sheets, if not into their tertiary structures (see Section 11.1). In contrast, 'diachronic' information refers to the information embodied in a symbol string that cannot be extracted or decoded from the structure of the

string alone but must take into account its past history as left behind or recorded in the form of the correlations found among the symbol strings having similar or related functions. A good example of "diachronic information" is provided by the information buried in amino acid sequences of proteins belonging to a given family, e.g., the WW domain family studied by Ranganathan and his group (Lockless and Ranganathan 1999, Poole and Ranganathan 2006, Socolich et al 2005, Süel et al 2003). *Diachronic information* can be extracted if and only if multiple sequences of proteins belonging to a given family are compared and the frequencies of occurrences of their amino acid residues are measured at each position. The studies carried out on the WW domain family proteins by the Ranganathan group using the *statistical coupling analysis* (SCA) have revealed that only about 20% of the 36 amino acid residues constituting the WW domain proteins has coevolved, thus carrying evolutionary information (Lockless and Ranganathan 1999). Table 4-1 and its footnotes summarize the characteristics of *synchronic* and *diachronic* information in a self-explanatory manner, except for what is here referred to as the "Law of Requisite Information (LRI)" which can be stated as follows:

"It is impossible to solve any problem without the requisite prior information." (4-18)

An example of the operation of LRI is provided by the well-known fact that an algebraic equation with *n* unknowns cannot be solved without knowing the numerical values of the (*n-1*) unknowns. For example, the intracellular concentration of an RNA molecule (z) is determined by the balance between two opposing rate processes – the transcription (x) and the transcript degradation rates (y) (Section 12.3):

$$z = x - y \tag{4-19}$$

However, many workers in the DNA microarray field erroneously assumed that x can be determined directly by measuring z alone (Section 12.6) (Ji et al. 2009a), which can be said to violate LRI: The information on z is not sufficient to solve Eq. (4-19) for x, because the information on y is also required.

Another example that illustrates the operation of LRI may be the cosmogenesis (Table 4-2). Just as the amino acid sequences of proteins analyzed above, the physical structure of the Universe that is observable by the astronomers of the 21st century may contain two kinds of information –i) *synchronic information* that can be extracted from our own Universe here and now, and ii) the *diachronic information* that is buried in (or hidden under) the structure of our observable Universe but not recognizable until and unless the structure of our Universe is compared with the possible structures of other Universes that might have been formed in parallel at $t = 0$ ((Bacciagaluppi and Valentini 2009).

We can divide the history of the genesis of our Universe into two phases – i) the initiation (singularity) phase at $t = 0$, also called the Big Bang, and ii) the post-Big Bang phase. The totality of the information carried by or encoded in the observable Universe of ours can be identified with the synchronic information. The information about those features of our Universe that correlate with similar features found in other possible Universes generated at $t = 0$ along with our Universe (but is too distant for our Universe

to communicate with) can be defined as diachronic information. Since the interaction between our Universe and other possible Universes is not allowed by the laws of physics and chemistry operating in our current Universe, the diachronic aspect of our Universe transcends the laws of physics and chemistry, allowing for the possibility of non-locality, for example (see Table 4-2).

Table 4-1 The Definitions of synchronic and diachronic information

	INFORMATION	
	SYNCHRONIC	**DIACHRONIC**
1. Refers to	Phenomena here and now	Phenomena long past
2. Meaning	Apparent in the structure of the message	Hidden behind the structure of the message
3. Laws Obeyed	a) Laws of physics and chemistry b) 'Law of Requisite Information' (LRI)'[1] c) 'Synchronic laws'[2]	a) Laws of physics and chemistry b) 'Law of Requisite Information (LRI)'[1] c) 'Diachronic laws'[3]
4. Philosophy	a) Causality b) Dyadic relation[5] c) Deterministic[7] d) Knowable[9] e) Orthogonal to diachronic information[10]	a) 'Codality'[4] b) Triadic relation[6] c) Arbitrary[8] d) Unknowable[9] e) Orthogonal to synchronic information[10]
3. Alternative Names	a) Deterministic b) Ahistorical c) Physical d) Law-governed e) Objective	a) Non-deterministic b) Historical c) Evolutionary d) Rule-governed e) Arbitrary

[1]In analogy to the Law of Requisite Variety (Section 5.3.2) (Heylighen and Joslyn 2001) which mandates that a certain minimum level of variety in the internal state of a machine is required for the machine to perform a complex task, so the proposed *Law of Requisite Information* states that no problem (machine) can be solved (output) without inputting the minimum amount of requisite information (input).

[2]The laws in physics and chemistry that have been recognized or abstracted from empirical observations here and now without having to rely on any historical studies. Most laws of physics and chemistry currently dominating natural sciences appear to be of this nature.

[3]The regularities of nature that are revealed only when historical records are taken into account such as the evolutionarily conserved nucleotide sequences of genes belonging to different species.

[4]'Codality' is a new word that I coined to indicate the 'code-mediated' interactions such as the interactions between hormones and their target genes or between symbols and their meanings understood by human mind, in contrast to 'causality' which is 'cause-mediated' interactions including force- or energy-mediated interactions in physics. 'Codality' is related to what Roederer (2003, 2004) refers to as "information-based interactions" while causality is related to his "force-driven interactions".

[5]The relation between *two* entities, e.g., the electron being attracted by the proton, and two cars colliding at an intersection, etc.

[6]The relation among three entities, e.g., a membrane receptor interacting with an ion channel mediated by a G-protein, and a Korean communicating with an Italian through a Korean-Italian interpreter.

[7]For example, the physicochemical properties of protein domains are more or less completely *determined* by their amino acid sequences.

[8]For example, the 3-dimensional structures of certain proteins are arbitrary from the point of view of physics and chemistry since they cannot be completely predicted solely based on the principles of physics and chemistry.

[9]When we say that we know something, we usually mean that we can explain that something in terms of a set of principles, laws and/or theories. When there are no such principles, laws or theories that can be used to explain something, we say that that something is *unknowable*. For example, the beginning (or the origin) of the Universe is *unknowable* from the point of view of the current laws of physics and chemistry because there is no guarantee that such laws were extant at t = 0.

[10]The *orthogonality* means that synchronic information can vary independently of diachronic information and *vice versa*, just as the x-coordinate of a point on a 2-dimensional plane can vary independently of its y-coordinate, and *vice versa*.

It is clear that molecular biological phenomena carry both *synchronic* and *diachronic* informations as explained in Table 4-2. It may well be that quantum mechanical phenomena also carry *synchronic* and *diachronic* informations, but physicists might have been slower in recognizing this fact than biologists, possibly due to the paucity of clear experimental data indicating the effects of history. Table 4-2 summarizes some of the evidence supporting the roles of synchronic and diachronic informations in biology and physics.

Table 4-2 The synchronic vs. diachronic information in biology and physics.

	INFORMATION	
	SYNCHRONIC	**DIACHRONIC**
BIOLOGY	a) amino acid sequence of proteins b) enzymic catalysis	a) co-evolving subsets of amino acid residues of proteins b) allosterism

	c) *causal* interactions between ligands and receptors	c) *encoded* interactions between primary and secondary messengers
PHYSICS	a) traditional physics b) hydrodynamics c) Copenhagen interpretation	a) quantum weirdness (e.g., non-locality) b) cosmogenesis c) Einstein-de Broglie-Bohm-Bell-(EDBB) interpretation*

*John S. Bell is included here because he mentioned the biological evolution as a metaphor for understanding the nonlocality in his lecture delivered at Rutgers several years before he passed away in 1990.

If the content of Table 4-2 is right, it may be necessary to divide biology and physics into two branches -- *synchronic* and *diachronic*, just as the linguistics is so divided (Culler 1991). One consequence of such a division in physics may be the reconciliation between Bohr's and Einstein's long-standing debate (Plotnitsky 2006, Murdoch 1987) about the completeness (or the lack thereof) of quantum mechanics thus:

As Einstein claimed, quantum mechanics is incomplete because it does not address the diachronic aspect of the reality. As Bohr claimed, quantum mechanics is complete because it provides complete explanations for all synchronic phenomena in the Universe. (4-20)

4.8 The Minimum Energy Requirement for Information Transmission

In addition to Eq. (4-2) that defines what was later referred to as the Shannon entropy, H, Shannon derived another important equation, the *channel capacity equation*, Eq. (4-29):

$$C = W \log_2 (1 + P/N) \quad \text{bits/sec} \tag{4-29}$$

where C is the channel capacity or the capacity for a communication channel to transmit information in unit time, W is the bandwidth of the channel or the range of frequencies (also called the "degee of freedom") used in communication, P is the power or the rate of energy dissipation needed to transmit the signal, and N is the thermal noise of the channel.

According to Eq. (4-29), when no power is dissipated, i.e., when P = 0, the channel capacity C is zero, indicating that no information can be transmitted through the channel. Calculations show that the amount of energy needed to transmit the minimum amount of information, i.e., 1 bit, is 0.6 Kcal/mole or 2.4 Jules/mole (Pierce 1980). Therefore, it is possible to formulate the following general statement which may be referred to as the *Principle of Minimum Energy Dissipation for Information Transmission* (PMEDIT):

"*It is impossible to transmit information without dissipating energy*." (4-30)

4.9 Info-Statistical Mechanics and the Gnergy Space

Traditionally, the dynamics of any N-particle systems in statistical mechanics is completely described in terms of the 6-dimensional *phase space* consisting of the 3N positional coordinates and 3N momenta, where N is the number of particles in the system (Tolman 1979, Prigogine 1980). Unlike the particles dealt with in statistical mechanics which are featureless and shapeless, the particles of importance in biology have characteristic shapes and internal structures that determine their biological properties. In other words, the particles in physics are completely described in terms of energy and matter (in the phase space) but the description of the particles in living systems require not only the energy and matter of the particle but also the genetic information carried by the particle, consistent with the information-energy complementarity (or gnergy) postulate discussed in Section 2.3.2. Thus, it seems necessary to expand the dimensionality of the traditional phase space to accommodate the *information* dimension, which includes the three coordinates encoding the *amount* (in bits), *meaning* (e.g., recognizability), and *value* (e.g., practical effects) of information (see Section 4.3). Similar views have been expressed by Bellomo et al. (2007) and Mamontov et al. (2006). Thus the expanded "phase space" would comprise the 6N phase space of traditional statistical mechanics plus the 3N information space entailed by molecular biology. Therefore, the new space (to be called the "gnergy space") composed of these two subspaces would have 9N-dimension as indicated in Eq. (4-31). This equation also makes contact with the concepts of *synchronic* and *diachronic* informations discussed in Section 4.5: It is suggested that the traditional 6N-dimensional phase space deals with the *synchronic information* defined in Section 4.5 and thus can be alternatively referred to as the *Synchronic Space* while the 3N-dimensional information space is concerned with the consequences of history and evolution encoded in each particle and thus can be referred to as the *Diachronic Space*. The resulting space will be called the *gnergy space* (since it encodes not only *energy* but also *information*) and represented diagrammatically as shown in Figure 4-2.

Gnergy Space = **6N-D Phase Space** + **3N-D Information Space** (4-31)
(*Synchronic Space*) (*Diachronic Space*)

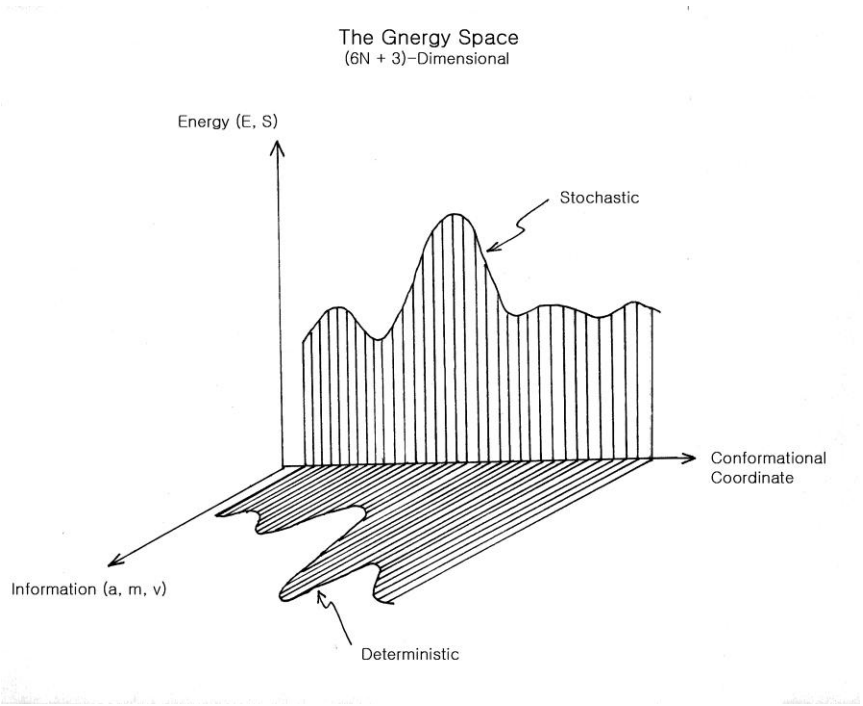


Figure 4-2 *The gnergy space*. The gnergy space comprises two complementary subspaces – the 6N-dimensional phase space (or the *synchronic space*) and the 3N-dimensional information space (or the *diachronic space*). Energy here refers to free energy, which is a function of both *internal energy* E and system *entropy* S. Here physical entropy S is presumed to be fundamentally different from Shannon's entropy, H, in agreement with Wicken (1987) but in contradiction to the information theory of Brillouin (1953, 1956) (see Table 4-3). For a review of this controversial field, see (Leff and Rex 1990) and (Ji 2006d). Information has three dimensions: a = amount, m = meaning, and v = value. Only the quantitative aspect of information, namely, a, is captured by Shannon entropy (see Section 4.3). The time evolution of an N-particle system traces out what may be referred to as a semi-stochastic trajectory in the gnergy space which projects a stochastic shadow onto the phase space and a deterministic shadow onto the information space. It should be noted that the trajectories shown above represent the averages of their corresponding ensembles of trajectories (Prigogine 1980). "Stochastic" processes are the apparently randmon processes that exhibit regularities although not predictable. Deterministic processes exhibit properties that are predictable.

Figure 4-2 depicts the independence of *genetic information* from *free energy*, which is equivalent to the assertion that that genetic information is not reducible to the laws of physics and chemistry (see **Exclusivity** in Section 2.3.1 and Statements (4-25) and (4-26)). There are many other ways of expressing the same concept, just as there are many equivalent ways of stating the Second Law of Thermodynamics, including the following:

i) The genetic information vs. free energy orthogonality,
ii) The independent variations of free energy and genetic information (Statements (4 25) and (4-26)), and
iii) The genetic information vs. free energy complementarity.

It is suggested here that, to study the dynamics of living systems such as genome-wide kinetics of mRNA levels measured with DNA microarrays (Watson and Akil 1999), treated as N-particle systems, it is necessary to employ the gnergy space. Since living systems trace out trajectories that are both *stochastic* and *deterministic* (see the legend to Figure 4-2 for the definitions of "stochastic" and "deterministic"), the study of living processes in the gnergy space has been referred to as the *info-statistical mechanics* (Ji 2006a)

The orthogonality between *information* and *free energy* depicted in Figure 4-2 may be described in yet another way, using the photosynthetic process as an example. Figure 4-3 shows the complex interactions among *light*, *chemical reactions*, *heat*, *evolution*, and *catalysis* in producing the phenomenon of life.

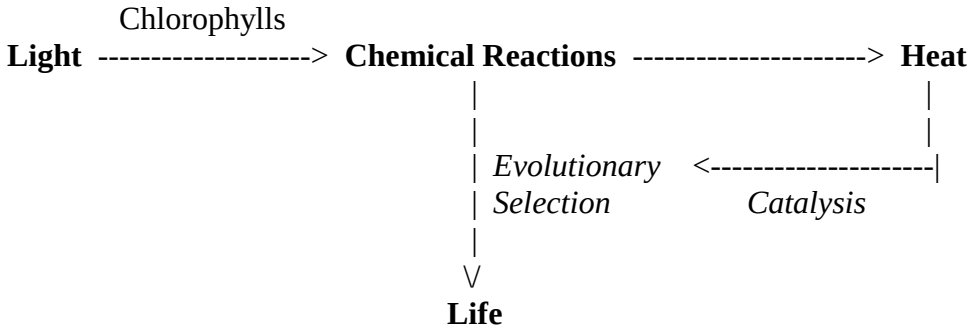


Figure 4-3 A bionetwork representation of the interactions among *light, chemical reactions, heat, biological evolution*, and *catalysis*. Chemical reactions driven by *free energy* occur along the horizontal arrows (i.e., in the synchronic space) while the evolutionary selection process controlled by or producing *genetic information* occurs along the vertical arrow (i.e., in the diachronic space), which supports the notion that *free energy* and *genetic information* are orthgonal.

All living processes ultimately depend on the absorption of light by chlorophyll molecules in the leaves of plants or in photosynthetic bacteria. The photons absorbed by chlorophylls activate and drive the endergonic (i.e., free energy requiring) chemical reactions leading to the synthesis of carbohydrates and oxygen, starting from carbon dioxide and water, as summarized in Reaction (4-32). In the process, most of the light energy is converted to thermal energy or heat (see the top horizontal arrows in Figure 4-3). Living systems then utilize glucose and oxygen (or other electron acceptors such as sulfur) to synthesize ATP which provides most of the thermodynamic driving force for living processes.

$$nH_2O + nCO_2 \xrightarrow[Heat]{Light} C_nH_{2n}O_n + nO_2 \qquad (4\text{-}32)$$

The evolution of life and the attendant genesis of biological information depended on a set of chemical reactions that has been selected (through the action of enzyme-mediated catalysis) out of all possible reactions allowed for by the laws of physics and chemistry under prevailing environmental conditions, through the process of natural selection, which is represented by the vertical arrow in Figure 4-3. Let us recall that any selection process implicates information (either as used or as produced). One important point to notice in Figure 4-3 is the postulate that natural selection (generating genetic information) favors those systems that can utilize *even* the waste product of chemical reactions, namely, *heat*, as indicated by the bent arrow labeled 'Catalysis', without violating the Second Law (see Section 2.1.4.). As is well known, the Second Law prohibits using heat to do any useful work without temperature gradients. In (Ji 1974a), I proposed one possible molecular mechanism by which enzymes might be able to utilize thermal energy (i.e., heat) without violating the Second Law, and this mechanism was in part based on the generalized Franck-Condon principle imported from the chemical kinetics literature as pointed out in Section 2.2.3.

Because the physico-chemical processes (or *energy processes*) occur along the *horizontal* direction (or in the synchronic space) and the biological evolution (i.e., *information processings*) occurs along the *vertical* direction (or in the diachronic space), Figure 4-3 well illustrates the notion of the 'genetic information - free energy orthogonality', or the 'information-energy complementarity' (Ji 1991). In other words, Figure 4-3 depicts the paradox between physics/chemistry (in the synchronic space) and biology (diachronic space): They are *orthogonal*, or mutually exclusive, in the sense of the Bohr's complementarity (see Section 2.3).

Biology is more complex than physics and chemistry, primarily because it implicates components that are the products (e.g., enzymes) of *biological evolution* and hence encodes the history (or memory) of the interactions between biological systems and their environment. These elusive environmental influences derived from the past can only be described in the language of the *information theory* that accommodates at least three degrees of freedom -- *amount, meaning*, and *value* of information as indicated in Section 4.3. Thus, the theory of life, taking these mutually exclusive components into account, may be referred to as 'info-statistical mechanics', or 'informed statistical mechanics' (Ji 2006a). The 'info-' component is associated with the vertical arrow and the 'statistical mechanics' component with the horizontal arrows in Figure 4-3. 'Info-statistical mechanics' is compared with *traditional statistical mechanics* in Table 4-4. Info-statistical mechanics discussed here may share a common ground with ‘info-dynamics’ discussed by Weber and Depew (Salthe 1996).

Table 4-4 A comparison between the postulated 'info-statistical mechanics' of life and the traditional statistical mechanics of abiotic physicochemical processes.

	Heat	**Life**

1. Parent science	Thermodynamics	Molecular & cell biology
2. Microscopic theory	Statistical mechanics	Info-statistical mechanics
3. Landmark event	1877 Boltzmann's equation* $S = k_B \ln Q$	1953 Watson & Crick's DNA; genetic code Conformons as packets of genetic information and mechanical energy
4. Field named	1884 (W. Gibbs, Yale University)	2006 (The 96th Statistical Mechanics Conference, Rutgers University) (Ji 2006a)
5. Key concepts	Energy & entropy (Synchronic information)	Energy, entropy & information (Synchronic & diachronic informations)
6. Laws	1st and 2nd laws of thermodynamics	4th law of thermodynamics (?) (see Figure 2-2 and Table 14-9)
7. Theoretical tools	6N-dimensional *phase space*	9N-dimensional *gnergy space* (Figure 4-2)

*S = thermodynamic entropy; k_B = the Boltzmann constant; Q = the number of microstates of a thermodynamic system underlying the observed microstates of the system.

Just as statistical mechanics is the *microscopic theory* of thermodynamics, so *info-statistical mechanics* may be viewed as a microscopic *theory* of molecular and cell biology (see the first two rows). And yet the traditional molecular and cell biology, although often couched in the concepts of information, does not, in the real sense of the word, involve any information theory at all (as attested by the fact that no major biochemistry or molecular biology textbooks currently in print, to the best of my knowledge, define what *information* is!). Thus traditional molecular cell biology can be regarded mostly as an applied field of chemistry and physics (i.e., a synchronic science, the science dealing with *synchronic information*; see Section 4.5), devoid of any truly *information-theoretical* contents (i.e., diachronic science, the science dealing with *diachronic information*). Linguists distinguish between *synchronic* (i.e., ahistorical) and *diachronic* (i.e., historical) studies of language (Culler 1991). Similarly it may be assumed that traditional molecular biology can be viewed as the synchronic study of life on the molecular level (which is indistinguishable from physics and chemistry) and info-statistical mechanics as both synchronic and diachronic studies of life. One of the landmark developments in statistical mechanics is the mathematical derivation by Boltzmann of the formula for entropy. The comparable event in info-statistical mechanics may be suggested to be the discovery of the double helical structure of DNA in 1953, that is here postulated to be the carriers of *molecular information* and

mechanical energy, namely, conformons (Benham 1996a,b, 2004a, Ji 1985, 2000) (see Section 8).

4.11 What Is Gnergy?

The concept of gnergy may be related to the concept of the *substance* discussed by Socrates, Aristotle, and Spinoza. According to the theory of hylomorphism (from Greek roots 'hylo-' meaning 'wood, matter', and '–morph-' meaning 'form') which originated with Socrates, substance is composed of matter and form or form inheres in matter. Aristotle believed that matter and form are real and exist in substance. This view is known as Aristotelian realism. Hylomorphism may be diagrammatically represented as shown in Figure 4-4, where the triangle symbolizes the inseparability of substance, matter and form, and the H in the center of the triangle symbolizes the philosophical perspective of hylomorphism.

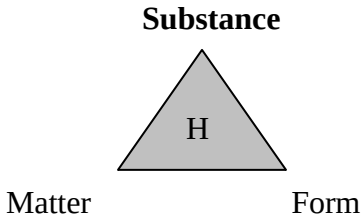


Figure 4-4 A diagrammatic representation of the philosophy of hylomorphism (H) of Socrates and Aristotle.

The concept of gnergy as the complementary union of information and energy (see Section 2.3.2) can be conveniently depicted using the same triangular scheme as shown in Figure 4-4. One feature added to Figure 4-5 is the designation of two levels of philosophy – *ontology*, the study of being or what is, and *epistemology*, the study of how we know about the being. Gnergy transcends the level of energy and information since gnergy is what is or exists (i.e., ontic or ontological) regardless of whether we, *Homo sapiens* are here to observe it or not, while energy and information are about how we, Homo sapiens, know what is (i.e., epistemic or epistemological).

Energy Information <--- *Epistemology*

Figure 4-5 A diagrammatic representation of the concept of gnergy in the context of the philosophy of complementarism (C) (Ji 1993, 1995).

As can be seen, the nodes of Figures 4-4 and 4-5 are very similar (i.e., Substance ~ Genergy, Matter ~ Energy, and Form ~ Information), and the two triangle can be made identical (or symmetric) by equating *hylomorphism* with *complementarism*. If this analysis is right, we may regard hylomorphism of Greek philosophers as the forerunner of complementarism of Bohr (Pais 1991) and his followers (Ji 1993, 1995). Biology played an important role in both theorizings, and the difference between *hylomorphsism* and *complementarism* may be traced to the difference between the biology of the ancient Greece and that of the 20th and 21st centuries.

It can be readily recognized that Figure 4-5 contains two kinds of complementarities:

i) the 'horizontal' (H) complementarity between *energy/matter*, and *information*, and
ii) the 'vertical' (V) complementarity between *ontology* and *epistemology*.

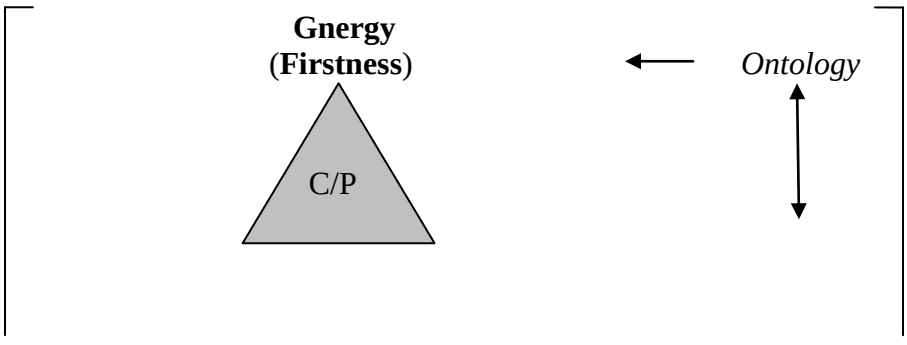
This would be natural if the principle of complementarity is universal, as Bohr seemed to have believed when he inscribed on his coat of arms the following dictum (Pais 1991):

"*Contraries are complementary*." (4-33)

Figure 4-5 contains two pairs of contraries -- the energy~information pair, and the ontology ~ epistemology pair, and, if Bohr is right, it may be anticipated that, associated with these two pairs, there should be two kinds of complementarities -- H and V, as indicated above. Thus it may be permitted to name these complementarities as follows:

i) Horizontal (H) complementarity = *Energy-information complementarity*, and
ii) Vertical (V) complementarity = *Ontic-epistemic complementarity*.

If this analysis is right, *reality* may be associated with the complementary union of two kinds of complementarities, H and V, reminiscent of recursivity in computer science (see Section 5.2.4). In other words, the principle of complementarity may be both *universal* and *recursive,* satisfying the principle of closure (see Section 6.3.2), and underlies the ultimate reality. These ideas are organized into a coherent system of thoughts utilizing the geometry of a triangle inspired by the metaphysics of C. S. Peirce (see Section 6.2) as depicted in Figure 4-6. For the sake of convenience, we may refer to the complex system of ideas depicted in Figure 4-6 as the *triadic theory of reality* (TTR).



Energy (**Secondness**) | **Information** (**Thirdness**) ⟵ *Epistemology*

Figure 4-6 The *Triadic Theory of Reality* (TTR). A diagrammatic representation of the relations among *reality, ontology, epistemology, energy/matter, information, and substance,* based on the Bohr's principle of complementarity (C) and Peircean metaphysics (P) (Firstness = Substance; Energy/Matter = Secondness; Information = Thirdness). The right-hand portion of the figure symbolizes the *transcendental relation* (symbolized by the double-headed vertical arrow) between ontology and epistemology.

4.12 Two Categories of Information in Quantum Mechanics

The First Postulate of Quantum Mechanics (QM) (Morrison 1990) states that:

> "Every physically-realizable state of a system is described in quantum mechanics by a single state function Ψ that contains all accessible physical information about the system in that state." (4-34)

The First Postulate of QM may be viewed as the definition of the "information" concept as used in physics. It is clear that there are *two categories of information* in quantum mechanics, symbolized by Ψ and Ψ^2, the former given by Statement (4-34) and the latter related to measurement or observation (Herbert 1987, Morrison 1990). The relation between these two categories of physical information may be diagrammatically represented as:

$$\underset{(1)}{\Psi} \xrightarrow[\text{(2)}]{\text{Measurements}} \underset{(3)}{\Psi^2} \qquad (4\text{-}35)$$

Applying Peircean triadic metaphysics (Section 6.2), it appears reasonable to suggest that Ψ belongs to or is associated with Firstness (1); Measurement with Secondness (2); and Ψ^2 is by default left to pair with Thirdness (3), which category including theories, knowledge, and representations. Thus Eq. (4-35) can be graphically represented as shown in Figure 4-7.

Firstness
Potentiality

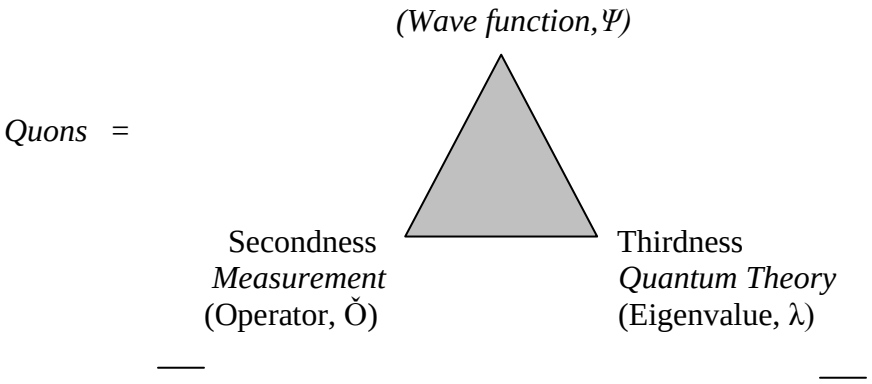


Figure 4-7 A semiotics-based metaphysics of quantum theory.
Quons are material entities exhibiting quantum properties such as wave-particle duality, nonlocality, and entanglement (Herbert 1987). Reproduced from Figure 1 of the NECSI (New England Complex Systems Institute, Boston) post entitled "quantum mechanics and semiotics" dated August 11, 2005 (see Appendix XI). *An exact copy of this figure appears in an article by Prashant Singh published in arXiv:physics/0605099v2 [physics.gen-ph] entitled "Quantum Semiotics: A Sign Language for Quantum Mechanics", submitted on May 12, 2006 and last revised on January 11, 2007, without referring to the original publication reproduced in Appendix XI.*

The contents of Eq. (4-35) and Figure 4-7 agree well with the results obtained through somewhat different routes as described in the next section.

4.13 Information-Energy Complementarity as the Principle of Organization

For the purpose of discussing living processes, it appears sufficient to define 'organization' as the nonrandom arrangement of material objects in space and time. I have long felt that both *energy* and *information* are required for any organization, from the Belousov-Zhabotinsky reaction-diffusion system (Section 3.1.1) to the living cell (Figure 2-11) and higher structures. This vague feeling may now be given a more concrete expression by asserting that 'organization' is the *complementary union* of *information* and *energy* or that *information* and *energy* are the complementary aspects of organization (Figure 4-8). In other words, the *information-energy complementarity* may well turn out to be the elusive physical principle underlying all organizations not only in living systems but also nonliving systems including the Universe Itself (see Table 4-5 and Figure 15-12). *Organization* in living systems require intra-system and intersystem communications, and communications require transferring information in space (through waves) and time (through particles) obeying a set of rules embodied in a language, thus implicating both language and the wave-particle duality or complementarity (Table 4-5). Since no information can be transferred without utilizing energy, according to Shannon's channel capacity equation (see Section 4.8), communication necessarily implicate the information/energy complementarity. I assume that any organization has a purpose or

equivalently that systems of material components organize themselves (i.e., self-organize) to accomplish a purpose or a goal, the final cause of Aristotle.

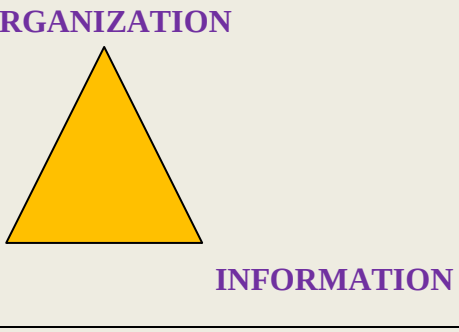


Figure 4-8 Information and energy as the complementary aspects of organization. Since gnergy is the complementary union of informationa and energy, organization and gnergy may be viewed as synonymous.

Table 4-5 The information/energy complementarity as the ultimate principle of organization.

Energy	**Information**	**Organization**
Mattergy (Matter-Energy) ($E = mc^2$; Matter as a highly condensed form of energy)	'Liformation' (Life-Information; Life as a highly condensed form of information) (Table 2-5)	Self-organization (Section 3.1)
Force	Structure	Control, regulation
Space	Language	Law of requisite variety
Time	Communication, purpose	Curvature of spacetime
The Principle of Complementarity (Wave/Particle & Information/Energy Complementarities)		

4.14 The Quantization as a Prelude to Organization

Quantization (or discretization) may be essential for any organization, since organization

entails selection and selection in turn requires the existence of discrete entities to choose from. In Sections 11.3.3 and 12.12, experimental evidence is presented that indicates that biological processes such as single-molecule enzymic activities (Lu, Xun and Xie 1998, Ji 2008b), whole-cell RNA metabolism (Ji and So 2009d), and protein folding (Ji 2012) are quantized because they all obey mathematical equations similar in form to the blackbody radiation equation (see Table 4-6) that was discovered by M. Planck in physics in 1900 which led to the emergence of *quantum mechanics* two and a half decades later (Herbert 1987, Kragh 2000, Nave 2009).

To make the blackbody radiation data fit a mathematical equation, Planck had to assume that the product of energy and time called "action" is quantized in the unit later called the Planck constant, *h*, which has the numerical value of 6.625×10^{-27} erg·sec. This quantity seems too small to have any measurable effects on biological processes which occur in the background of thermal fluctuations involving energies in the order of kT, where k is the Boltzmann constant, 1.381×10^{-16} erg/degree and T is the absolute temperature. The numerical value of kT is 4.127×10^{-14} ergs at room temperature, T = 298 °K, which is thirteen orders of ten greater than *h*. Thus it appears reasonable to assume that biological processes are quantized in the unit of k rather than in the unit of h as in physics, which leads me to suggest that

"The Boltzmann constant *k* is to biology what the Planck constant *h* is to physics." (4-36)

Thus by combining the evidence for the quantization of biological processes provided by Table 4-6 and Statement (4-36), it appears logical to conclude that

"Biological processes at the molecular and cellular levels are quantized in the unit of the Boltzmann constant k." (4-37)

Table 4-6 Blackbody radiation law-like equation (BRE) is obeyed by 1) blackbody radiation, 2) single-molecule enzymic activity of cholesterol oxidase, 3) whole-cell RNA metabolism in budding yeast, and 4) protein stability data (see Sections 11.3.3 and 12.12 for more details).

Process	$\mathbf{y = a(Ax + B)^{-5}/(e^{b/(Ax + B)} - 1)}$						
	a	**b**	**A**	**B**	**a/b**	**y**	**x**
1. Blackbody radiation	5×10^{-15}	4.8×10^{-13}	1	0	1.04×10^{-2}	Spectral intensity	Wavelength
2. Single-molecule enzymic catalysis	3.5×10^{5}	2.0×10^{2}	1	0	1.75×10^{3}	Frequency of occurrences	Waiting time[1]
3. Distances between RNA	8.8×10^{8}	50	2.23	3.21	1.7×10^{7}	Frequency of	Phenotypic similarity

pairs in the concentration space; catalysis by *enzyme complexes*[2]						occurrences	classes[3]
4. Protein stability/unfolding	$1.8x10^{10}$	300	14	18	$6.0x10^{7}$	Frequency of the occurrence of ΔG	Δ G, i.e., the Gibbs free energy of the native conformation of a protein

[1]The time an enzyme waits until it begins its next cycle of catalysis. The longer the waiting time, the slower the catalytic rate constant. See Rows 6 and 7 in Table 1-9.
[2]The parameter a in BRE may reflect the number of enzymes forming an *enzyme complex*. If this conjecture is right, transcriptosomes and degradosomes together may contain over 10^2 individual enzymnes, just as a quantum dot contains 10^2-10^3 individual atoms (see Table 4-7).
[3]The classes (or bins) of the quantitative measure of the similarity between two RNA trajectories.

Statement (4-37) may be referred to as the "Boltzmann Quantization of Biological Processes" (BQBP). If Statement (4-37) turns out to be true, we will have two types of quantizations in nature – i) the *Planck quantization* in the unit of h and ii) the *Boltzmann quantization* in the unit of k. These two types of quantizations are compared in Table 4-7, the fifth row of which suggests the *final cause* of the two types of quantizations, and the last row suggests that the Planck quantization is to Boltzmann quantization what atos are to quantum dots (more on this in Section 4.15).

Table 4-7 Two types of quantizations in nature**.**

	Planck Quantization	**Boltzmann Quantization**
1. Symbol of quantum	h	k
2. Unit of quantization	erg·sec	erg/degree
3. Numerical value	$6.625x10^{-27}$	$1.381x10^{-16}$
4. Name of quantum (dimensions)	action (energy x time)	entropy (energy/temperature)
5. Final cause for (or is prelude to)	Physical organization	Biological organization

6. Analogy	Atoms	Quantum dots (?)

The relation between the *Planck quantization* and the *Boltzmann quantization* postulated in Row 5 may be summarized as in Statement (4-38) and schematically represented in Figure 4-10:

"Quantization precedes organization." (4-38)

Statement (4-38) may be referred to as the "Quantization before organization (QBO) hypothesis".

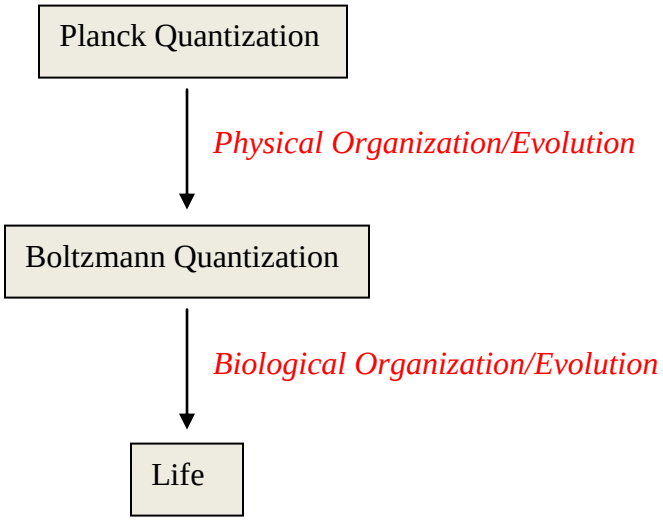


Figure 4-9 A schematic representation of the "quantization before organization" postulate.

Two recent developments may support the QBO hypothesis:

(1) Gilson and McPherson (2011) demonstrate that Boltzmann's constant k (= 1.3805×10^{-16} ergK^{-1}) is quantized in terms of cosmological scale quantities according to the formula $k = N_B k_q$ where $N_B = 10^{13}$, thus indicating that the concept of quantization first introduced by Plank in 1900 need not be confined to the microscopic scale characterized by the Planck constant, h (= 6.6252×10^{-7} ergsec).

(2) When 10^2-10^3 atoms form a nanoparticle (nano = 10^{-9} m), they can exhibit electronic properties that are intermediate between those of individual atoms (typically 10^{-10} m in diameter) and those of bulk semiconductors (http://en.wikipeia.org/wiki/Quantum dot). Such nanoparticles are called "quantum dots" because they possess new quantum mechanical properties that are determined by the shape and the size of the particle as a whole. For example, as the size of the quantum dot increases, the frequencies of light emitted after excitation of the dot decreases leading to

a shift of color from blue to red. This indicates that the electronic energy levels of the quantum dot are quantized in a new way reflecting the shape and size of the quantum dot unlike the quantization of individual atoms whose energy levels are largely determined by the internal structure of atoms. For this reason, quantum dots are also called "artificial atoms".

5.2.3 Two Kinds of Complexities in Nature – *Passive* and *Active*

We can recognize two kinds of 'complexities' in nature -- *active* and *passive*, in analogy to *active* and *passive* transport. For example, snowflakes (Figure 5-3) exhibit *passive* complexity or complexification, while living cells (see the book cover) exhibit *active* complexity in addition to passive complexity. Unlike passive complexity, active complexity is exhibited by living systems utilizing free energy, and organisms with such a capability is thought to be more likely to survive *complex* environment than those with passive complexity only. The According to the Law of Requisite Variety (LRV) (Section 5.3.2), no simple machines can perform complex tasks. Applying LRV to cells, it can be inferred that

"No simple cells can survive complex environment." . . . . . (5-10)

If this conjecture is true, it is not only to the advantage of cells (both as individuals and as a lineage) but also essential for their survival to complexify (i.e., increase the complexity of) their internal states.

One strategy cells appear to be using to complexify their internal states is to vary the amino acid sequences of a given enzyme or of the subunits of an enzyme complex such as ATP synthase and electron transfer complexes, each containing a dozen or more subunits. This strategy of increasing the complexity of sequences may be forced upon cells because they cannot increase, beyond some threshold imposed by their physical dimensions, the variety of the spatial configurations of the components within their small volumes. In other words, it is impossible to pack in more than, say 10^9, enzyme particles into the volume of the yeast cell, about 10^{15} m^3, but the yeast cells can increase the variety of their internal states by increasing the variety of the amino acid sequences of their enzymes and enzyme complexes almost without limit, as a simple combinatorial calculus would show. For example, there would be at least $2^{100} = 10^{33}$ different kinds of 100-amino-acid-residue polypeptides if each position can be occupied by one of at least two different amino acid residues. This line of thought led me to infer that there may be a new principle operating in living systems, here referred to as the "Maximum Variation Principle (MVP)" or the "Maximum Complexity Principle (MCP)", which states that:

"The variety of the internal states of living systems increases with evolutionary time." . . . . . (5-11)

or

"The complexity of the internal states of living . . . . . (5-12)

systems increase with evolutionary time."

Statement (5-12) resembles that of the Second Law ("The entropy of an isolated system increases with time."), which may lead conflating MVP with the Second Law unless care is taken. MVP cannot be derived from the Second Law, because MVP embodies the evolutionary trajectories (or contingencies) of living systems (i.e., slowly changing environmental variations encountered by rapidly changing short-lived organisms during evolution) just as the shapes of snowflakes (see Figure 5-2) cannot be derived or predicted from the Second Law because these embody the trajectories (or a series of boundary conditions of Polanyi (1968)) traversed by incipient snowflakes through the atmosphere, the information about which being lost to the past, except whatever is recorded in snowflakes.

Although all snowflakes exhibit a 6-fold symmetry due to the unique structure of the water molecule (see the lower panels in Figure 5-3), no two snowflakes look alike, and this phenomenon has now been well understood as the result of experimental works on artificial snowflakes produced in laboratories (see Section 15.1) (Libbrecht 2008): No two snowflakes look alike because no two snowflakes traverse the same trajectories from the atmosphere to the ground as they evolve from the incipient clusters of a few water molecules formed high up in the atmosphere to the final macroscopic snowflakes fseen on the ground (see the left-hand panel in Figure 5-3). Similarly, no two RNA trajectories measured from the yeast cell undergoing the glucose-galactose shift look exactly alike (see the bottom of the right-hand panel in Figure 5-3), most likely because i) no two RNA polymerases inside the nucleus and ii) no two RNA molecules in the cytosol experience identical microenvironments (see the RNA localizations in Drosophila embryios, Figure 15-3). Consequently no two RNA molecules are associated with identical rates of production (through transcription) and degradation (catalyzed by RNases or ribonucleases). In analogy to the 6-fold symmetry exhibited by all snowflakes reflecting the geometry of the water molecule, all RNA trajectories share the a common feature of being above the zero concentration levels reflecting the fact that the yeast cell is a dissipative structure, continuously dissipating free energy to maintain its dynamic internal structures, including RNA trajectories. Most of the discussions on complexity in the past several decades in the field of computer science and physics concern "passive complexity" which was taken over by biologists *apparently* without realizing that living systems may exhibit a totally new kind of complexity here dubbed "active complexity". The time- and space-dependent heterogeneous distributions of RNA molecules observed in developing *Drosophila* embryo (see the cover of this book and Figure 15-1) provide a prototypical example of "active complexity", since depriving energy supply to the embryo would certainly abolish most of the heterogeneous RNA distributions.

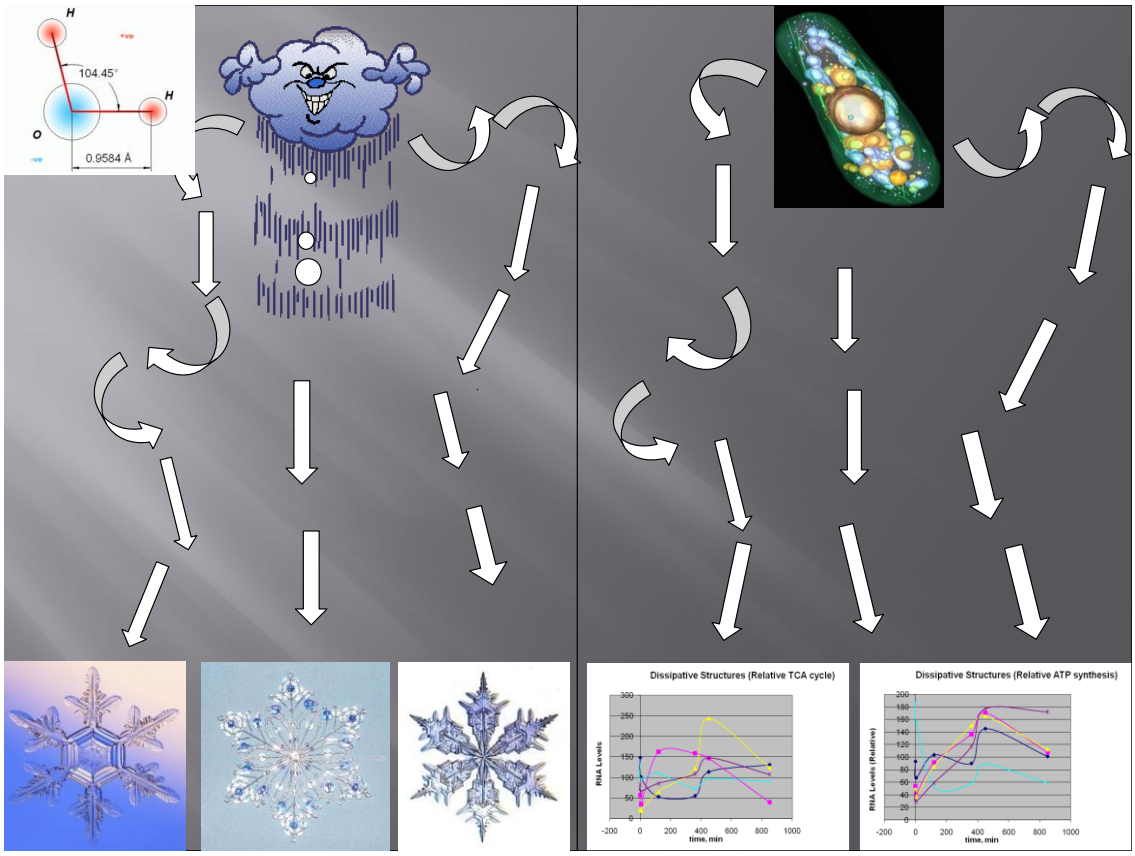


Figure 5-3 Just as the shape of snowflakes reflect their trajectories through the atmosphere, so the different RNA trajectories measured from yeast cells are postulated to reflect the different microenvironmental conditions (see Figure 12-28) under which RNA molecules are synthesized in the nucleus and degraded in the cytosol. Snowflakes are *equilibrium structures* or *equilibrons* whose 6-fold symmetry are determined by the geometry of the water molecule, while RNA trajectories are *dissipative structures* or *dissipatons* (Section 3.1) whose shapes reflect the fact that cells are themselves *dissipative structures* maintaining their dynamic internal structures (including RNA trajectories) by continuously dissipating free energy. For the experimental details concerning the measurement of the RNA trajectories shown above, see Section 12.2. (figure 5-3 was drawn by one of my undergraduate students, Ronak Shah, in April, 2009).

5.2.4 The Principle of Recursivity

A "recursive definition", also called "inductive definition", defines something partly in terms of itself, i.e., *recursively*. A clear example of this is the definition of the Fibonacci sequence:

$$F(n) = F(n - 1) + F(n - 2) = 1, 1, 2, 3, 5 , , \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (5\text{-}13)$$

where n is a natural number greater than or equal to 2. As can be seen, Eq (5-13) defines the (n +

1)th Fibonacci number in terms of two previous Fibonacci numbers. A linguistic example of recursivity is provided by the acronym GNU whose definition implicates itself: "GNU is not Unix". A biological example of *recursivity* may be suggested to be the self-relication of the DNA double helix, since it implicates replicating the DNA double helix using the original DNA as the template: Self-replication of the DNA double helix is *self-referential*, or *recursive*. The growth of an organism from a fertilized egg cell can be viewed as recursive process in the sense that the fertilized egg serves as a template to form its daughter cell, the daughter cell in turn serving as the template for the production of the next-generation cell, etc. The cell division is recursive or results from a series of recursive actions. On the basis of these analyses, it may be concluded that life itself is recursive.

Many physical, chemical, biological, engineering and logical principles are mutually *inclusive* and *intertwined* in the sense that it is impossible to separate them completely. This principle is represented in the familiar Yin-Yang symbol of the Taoist philosophy (Figure 5-4): The dot of the Yin (dark) is embedded in the sea of the Yang (light) and the dot of the Yang is embedded in the sea of the Yin. The embededness of the Yin in Yang (and *vice versa*) is reminiscent of the embeddedness of a sentence within a sentence in human language or the embededness of an algorithm within an algorithm in computer programming, both of which exemplifying the *recursivity* (or the recursion and self-similarity) widely discussed in computer science (Hofstadter 1980).

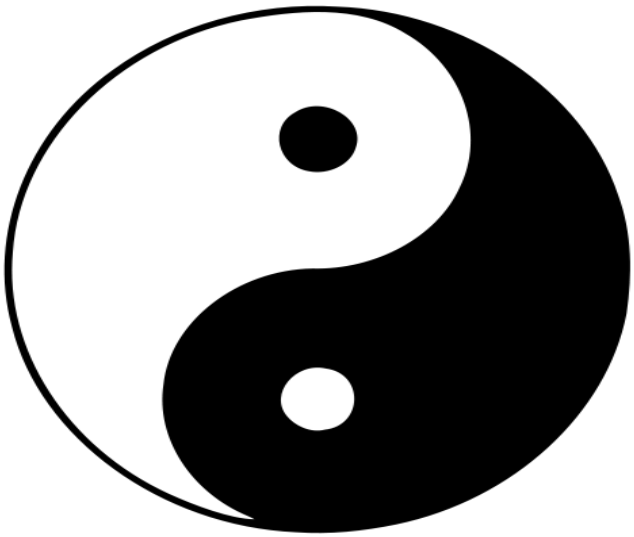


Figure 5-4 The Yin-Yang symbol visualizing the concept of *embeddedness* (i.e., the black dot in the white background, and the white dot in the black background) and the *intertwining* (between the white and black tear-drop shapes)**.**

http://commons.wikimedia.org/wiki/File:Yin_yang.svg

The complementarity principle of Bohr seems to embody the principle of recursivity as the following argument shows. As is well known, Bohr in 1947 inscribed on his coat of

arms the following motto:

"*Contraria sunt complementa*." or (5-14)

"*Contraries are complementary*." (5-15)

It is interesting to note that Statement (5-15) can be interpreted as either of the following two contrary statements, P and not-P:

"*All contraries are complementary*." (5-16)

"*Not all contraries are complementary*." (5-17)

Statement (5-17) is synonymous with (5-18):

"*Only some contraries are complementary*." (5-18)

Statement (5-16) reflects the views of Kelso and Engström (2006) and Barab (2010) who list over one hundred so-called "complementary pairs" in their books. I favor Statements (5-17) and (5-18) based on the complementarian logic discussed in Section 2.3.3.

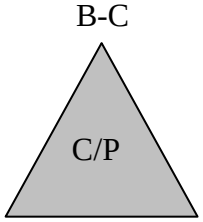
Since (5-16) and (5-17) are contraries, they must be COMPLEMENTARY to each other according to (5-15). That is, defining the relation between (5-16) and (5-17) as being complementary entails using Statement (5-15). This, I suggest, is an example of "recursive definition", similar to the definition of the Fibonacci sequence, (5-13). To rationalize this conclusion, it appears necessary to recognize the three definitions of complementarities as shown below (where B, KE, and J stand for Bohr, Kelso and Engstrom, and Ji, respectively):

B-Complementarity (B-C) = "Contraries are complementary." (5-19)

KEB-Complementarity (KEB-C) = "All contraries are complementary." (5-20)

J-Complementarity (J-C) = "Not all contraries are complementary." (5-21)

Since, depending on whether or not the complementarian logic is employed, the B-complementarity can give rise to either the KEB-or the J-complementarity, respectively, it appears logical to conclude that the KEB- and J-complementarities are themselves the complementary aspects of the B-complementarity. This idea can be represented diagrammatically as shown in Figure 5-5.



KEB-C J-C

Figure 5-5 A diagrammatic representation of the complementarity of complementarities, or the "recursive complementarity".

After formulating the idea of the "recursivity of complementarity", I was curious to find out if anyone else had a similar idea. When I googled the quoted phrase, I was surprised to find that Sawada and Caley (1993) published a paper entitled "Complementarity: A Recursive Revision Appropriate to Human Science". This paper may be viewed as an indirect support for the conclusion depicted in Figure 5-5. However, upon further scrutiny, there is an important difference between the perspective of Sawada and Caley (1993) and mine: Sawada and Caley believe that, in order to introduce the idea of recursivity to complementarity, Bohr's original complementarity must be revised (by taking the observer into account explicitly). In contrast, my view is that Bohr's original complementarity is intrinsically recursive, due to its ability to generate two contrary statements, P and not-P, i.e., Statements (5-16) and (5-17).

Finally, it should be pointed out that, if not all contraries are complementary (as I originally thought in contrast to the views of Kelso and Engstrom (2006) and Barab (2010)), there must be at least one other relation operating between contraries. In fact, there may be at least three non-complementary relations operating between contraries:

1) SUPPLEMENTARITY = C is the sum of A and B (e.g., energy and matter).

2) DUALITY = A and B are separate entities on an equal footing (e.g., Descartes' *res cogitans* and *res extensa*).

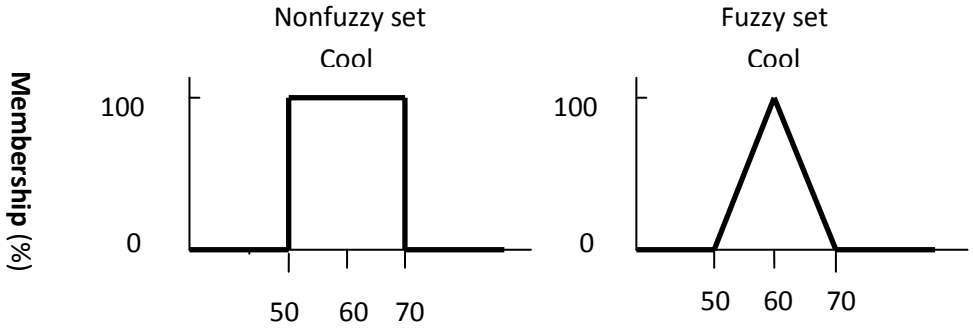
3) SYNONYMY = A and B are the same entity with two different labels or names (e.g., Substance and God in Spinoza's philosophy; the Tao and the Supreme Ultimate in Lao-Tzu's philosophy).

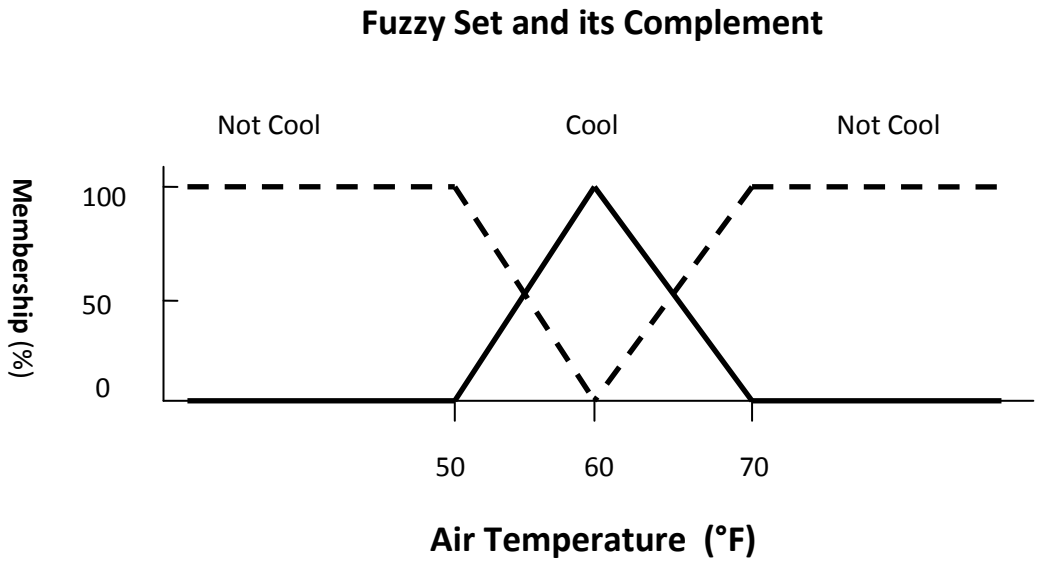
5.2.5 Fuzzy Logic

There are two kinds of logic -- *classical* (also called Aristotelian, binary, or Boolean) *logic* where the truth value of a statement can only be either *crisp* yes (1) or no (0), and *multivalued logic* where the degree of truthfulness of a statement can be *vague or fuzzy* and assume three or more values (e.g., 0, 0.5 and 1). Fuzzy logic is a form of multi-valued logic based on fuzzy set theory and deals with approximate and imprecise reasoning. In fuzzy set theory, the set membership values (i.e., the degree to which an object belongs to a given set) can range between 0 and 1 unlike in crisp set where the membership value is either 0 or 1. In fuzzy logic, the truth value of a statement can range continuously between 0 and 1. The concept of fuzziness in human reasoning can be traced back to Buddha, Lao-tze, Peirce, Russell, Lukasiewicz, Black, Wilkinson (1963),

and others (Kosko 1993, McNeill and Freiberger 1993), but it was Lotfi Zadeh who axiomatized fuzzy logic in the mid-1960's (Zadeh 1965, 1995, 1996a).

Variables in mathematics usually take numerical values, but, in fuzzy logic, the non-numeric *linguistic variables* are often used to express rules and facts (Zadeh 1996b). Linguistic variables such as age (or temperature) can have a value such as young (warm) or old (cold). A typical example of how a linguistic variable is used in fuzzy logic is diagrammatically illustrated in Figure 5-6.





Adopted from http://www.fortunecity.com/emachines/e11/86/fuzzylog.html

Figure 5-6 Diagrammatic representations of *binary logic* and *fuzzy logic*. In standard logic, objects belong to a set completely (100%) or not at al. (0 %) (see top left). In fuzzy logic, objects belong to a fuzzy set only to some degree (top right) and to the complement of the set to some other extent (bottom), the sum of the partial memberships always summing up to unity. For example, the air temperature of 50 °F is 0% cool and 100% not cool; 55°F is 50% cool and 50% not cool; 60 °F is 100% cool and 0% not cool; 65 °F is 50% cool and 50% not cool; and 70 °F is 0% cool and 100% not cool.

5.2.6 Fuzzy Logic and Bohr's Complementarity

In Section 5.2.4, it was shown that the principle of Bohr's complementarity embodies the principle of recursivity as well, which may be seen as an example of the *intertwining among principles* as symbolized by the dark and white objects in the Yin-Yang diagram (Figure 5-4). Bohr's complementarity exhibits fuzziness. According to fuzzy/vague/multivalence theorists, including Peirce, Russell, Black, Lukasiewicz, Zadeh, and Kosko (1993), words are fuzzy sets. The word 'young' is an example of the fuzzy set. I am neither 'young' (0) or old (1) but both young (to a degree of say 0.2) and old (to a degree of say 0.8). In other words I am both 'young' and 'not-young' (i.e., old) at the same time to certain degrees. Similarly, it can be suggested that the word 'complementary' or 'complementarity' is also a fuzzy set, since what is complementary to some scholars may not be complementary to others. For example, Kelso and Engstrøm list hundreds of complementary pairs in their book, *The Complementary Nature* (2006). Although their complementary pairs do satisfy Bohr's definition of complementarity, Statement (5-16), they certainly do not satisfy the definition of complementarity given in Section 2.3.3 which is based on three criteria of the complementarian logic:

1) *Exclusivity* (A and B are mutually exclusive),
2) *Essentiality* (A and B are both essential to account for C), and
3) *Transcendentality* (C transcends the level where A and B have meanings).

Thus, some of the complementary pairs of Kelso and Engstrøm satisfy only one and some two of the above three criteria, and only a small number of them satisfy all of the three criteria. We may designate these complementary pairs as the 0-, 0.3-. 0.6-. and 1.0-complementary pairs, respectively, the fractions indicating the degree of membership to the complementary set (see the dotted lines in Figure 5-7 calculated as the ratio of the number of the criteria satisfied over the total number of the criteria. Some examples of complementary pairs having different degrees of complementarities are listed in Table 5-3.

Degree of Membership

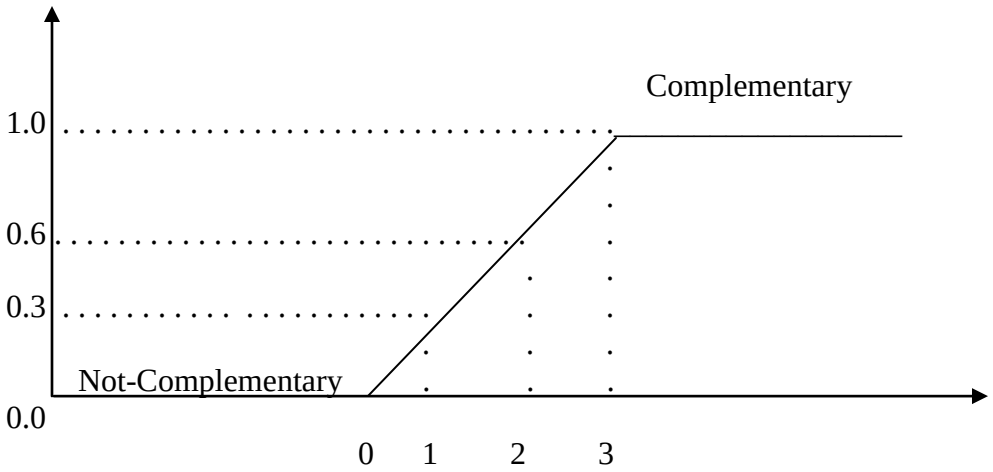


Figure 5-7 The concept of complementarity as a fuzzy set.

Table 5-3 Some examples of the complementary pairs of Kelso and Engstrøm whose degree of complementarity has been calculated on the basis of the three criteria of the complementarian logic discussed in Section 2.3.3. (These calculations are somewhat subjective.)

Complementary Pairs of Kelso and Engstrøm	**Criteria of the Complementarian Logic**			**Degree of Complementarity**
	Exclusivity	**Essentiality**	**Transcendentality**	
wave ~ particle	+	+	+	1.0
information ~ energy	+	+	+	1.0
energy ~matter	-	+	-	0.3
energy ~ time	+	+	-	0.6
space ~ time	+	+	+	1.0
mind ~ body	+	+	+	1.0
object ~ subject	+	+	+	1.0
abrupt ~ gradual	-	+	-	0.3
even ~ odd	-	+	-	0.3
perception ~	-	+	-	0.3

action				
vitalism ~ mechanism	+	-	+	0.6

5.2.7 The Knowledge Uncertainty Principle (KUP)

The first line of the Taoist text, The Lao-Tze, states that

"The Tao, once expressed, is no longer the permanent Tao." (5-22)

which in Chinese can be written with just six characters that read in Korean thus:

"Doh Gah Doh, Bee Sahng Doh."

We may refer to Statement (5-22) as the 'Principle of Ineffability', probably one of the most important principles of the Taoist philosophy.

The purpose of this section is to formulate an 'algebraic geometric' version of the Principle of Ineffability, which will be referred to as the 'Knowledge Uncertainty Principle (KUP)' in analogy to the Heisenberg Uncertainty Principle (HUP) in quantum mechanics. For the purpose of the present discussion, I will differentiate "knowledge" from "information" as follows: *Knowledge* refers to actuality and *information* to potentiality, just as physicists differentiate between the probability wave function Ψ symbolizing "possible information" and its square Ψ^2 referring to measured information or probability (Herbert 1987, Morrison 1990). It may well turn out that KUP subsumes HUP as suggested by Kosko (1993). The KUP is based on the following considerations:

1) All human knowledge (including scientific knowledge) can be represented as sets of answers to N binary questions (i.e., questions with *yes* or *no* answers only), where N is the number of questions that defines the universe of discourse or the system plus its environment under observation/measurement. This resonates with Wheeler's "It from bit" thesis (1990) that *information* is as fundamental to physics as it is for computer science and that humans participate in producing all scientific information by acquiring the *apparatus-elicited answers* to yes-or-no questions as in *the game of 20 questions* (Section 4.15). Recently Frieden (2004) has claimed that all major scientific laws can be derived from maximizing the Fisher information of experimental data.

2) As shown in Table 5-4, each answer in 1) can be represented as a string of N 0's and 1's, for example, (0, 1, 1, . . ., 0) for Answer #1, and (1, 0, 0, . . . , 0) for Answer #3, etc.

Table 5-4 The Question and Answer (QA) matrix. 1 = Yes; 0 = No.	
Answers	**Binary Questions**

	1	2	3	. . .	N
1	0	1	1	. . .	0
2	0	0	1	. . .	1
3	1	0	0	. . .	0
. . .	. . .	. . .	. . .	. . .	. . .
2^N	0.	0	0	. . .	1

3) There will be a total of 2^N *N-bit strings* as the possible answers to a set of N questions (see the last row in Table 5-4).

4) The *N-bit strings* in Table 5-4 can be represented geometrically as the vertices of an N-dimensional hypercube (Kosko 1993, p. 30). An N-dimensional hypercube is a generalization of an ordinary cube which can be viewed as a 3-dimensional hypercube (see Figure 5-8). A square (e.g., one of the 6 aspects of a cube) can be treated as a 2-dimensional hypercube. To generate a cube from a square, it is necessary only to move a square in a new direction (i.e., along the z-axis) perpendicular to the pre-existing axes, the x- and y-axes in the case of a square. This operation can be repeated to generate an N-dimensional hypercube from an (N - 1)-dimensional one, where N can be any arbitrarily large number.

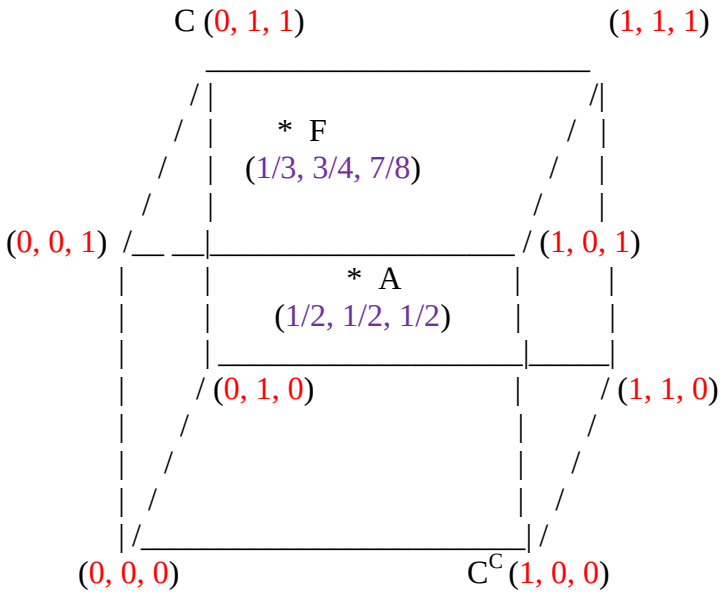


Figure 5-8 A 3-dimensional hypercube. One of the 8 vertices is arbitrarily located at the origin (0, 0, 0) of the (x, y, z) coordinate system. Point A denotes the center of the hypercube. The closest vertex to point F is C(0, 1, 1), whose complement is vertex C^C(1, 0, 0).

5) According to the principle of excluded middle, also called *the Aristotelian logic* or *crisp logic* (McNeill and Freiberger 1993, Kosko 1993), an answer is either true (1) or false (0), and no answer can have any truth values intermediate between 0 and 1. That is, no 'crisp' answer can reside in the interior or on the edges of the hypercube, only on the vertices.

6) In contrast, the theory of fuzzy sets or the fuzzy logic (Zadeh 1965, 1995, 1996a,b, Kosko1993) allows the truth value of an answer to be any positive number between 0 and 1, inclusive. For example, an answer with a truth value (i.e., the degree of membership to a set of true answers) of 3/4 is more true (1) than false (0); an answer with a truth value of 1/2 is both true and not-true at the same time, etc. The unit of fractional truth values is referred to as "fits" or "fuzzy units" (Kosko 1993).

7) Based on **5**) and **6**), we can conclude that 'crisp' answers (expressed in bits) reside at the vertices or nodes of an N-dimensional hypercube, while fuzzy or vague answers (expressed in fits) reside in the interior or on the edges of the N-dimensional hypercube. For example, a fuzzy answer with a truth value of (1/2, 1/2, 1/2) will be found at the center of the cube (see point A in Figure 5-8), whereas a fuzzy answer with truth value of (1/3, 3/4, 7/8) will be located at point F in Figure 5-8.

8) It is postulated here that when the human mind is challenged with a set of N questions, it generates a fuzzy answer (say, F in Figure 5-8) *unconsciously* (guided by intuition and previous experience), but, in order to communicate (or articulate) it to others, the human mind *consciously* search for the *nearest vertex*, say, (0,1, 1) in Figure 5-7. Thus *articulated* or *represented* crisp answers can be assigned degrees of *truthfulness* or *certainty* measured as a ratio of two numbers, i.e., D_1/D_2, where D_1 is the distance between the fuzzy answer (located at coordinate F) in the N-dimensional hypercube) and its nearest vertex located at C and D_2 is the distance between F and the vertex, C^C, that is irreconcilably opposites to C. (C^C is called the *complement* of C.) The bit values of crisp C^C are obtained by subtracting the corresponding bit values of C from 1. For example, the complement of C(1,0,1) is C^C (1-1, 1-0, 1-1) or C^C (0, 1, 0). The distance, D_{AB}, between the two points, A (a_1, a_2, a_3, . . ., a_k) and B (b_1, b_2, b_3, . . . , b_k), can be calculated using the Pythagorean theorem:

$$D_{AB} = [(a_1 - b_1)^2 + (a_2 - b_2)^2 + (a_3 - b_3)^2 + \ldots, + (a_k - b_k)^2]^{1/2} \qquad (5\text{-}23)$$

Applying Eq. (5-23) to points C and F, and C^C and F in Figure 5-8, the ratio of D_1 over D_2 can be calculated, which Kosko referred to as *fuzzy entropy* (Kosko 1993, pp. 126-135), one of many fuzzy entropies defined in the literature. For convenience, we will refer this ratio as the *Kosko entropy*, denoted by S_K , in recognition of Kosko's contribution to the science of fuzzy logic. S_K now joins the list of other well-known *entropies* in physics and mathematics -- the Clausius (which may be denoted as S_C),

Boltzmann (as S_B), Shannon (as S_S), Tsalis entropies (as S_T), etc. The Kosko entropy of a fuzzy answer is then given by:

$$S_K = D_{CF}/D_{FC}^{c} \qquad (5\text{-}24)$$

where D_{CF} is the distance between crisp point C and fuzzy point F and D_{FC}^{c} is the distance between crisp point C^C and fuzzy point F. Formally, Eq. (5-24) constrains the numerical values of S_K to the range between 0 and 1:

$$1 \geq S_K \geq 0 \qquad (5\text{-}25)$$

However, both the Principle of Ineffability, Statement (5-22), and the Einstein's Uncertainty Thesis, Statement (5-38) (see below), strongly indicate that S_K cannot be equal to 1 or to zero, leading to Inequality (2-26):

$$1 > S_K > 0 \qquad (5\text{-}26)$$

According to Inequality (5-26), the maximum value of S_K is less than 1 and its minimum value is greater than 0. If we designate the minimum uncertainty that no human knowledge can avoid with *u* (from uncertainty) in analogy to the Planck constant *h* below which no *action* (i.e., the energy integrated over time) can exist, Inequality (5-26) can be re-written as:

$$1 > S_K \geq u \qquad (5\text{-}27)$$

where u is a positive number whose numerical values probably depend on the measurement system involved.

9) The Kosko entropy of fuzzy answer F in Figure 5-28 is given by:

$$S_K(F) = [(0\text{-}1/3)^2 + (1\text{-}3/4)^2 + (1\text{-}7/8)^2]^{1/2}/[(1\text{-}1/3)^2 + (0\text{-}3/4)^2 + (0\text{-}7/8)^2]^{1/2}$$

$$=[(2/3)^2 + (1/4)^2 + (1/8)^2]^{1/2}/[(2/3)^2 + (-3/4)^2 + (-7/8)^2]^{1/2}$$

$$=[4/9 + 1/16 + 1/64]^{1/2}/[4/9 + 9/16 + 49/64]^{1/2}$$

$$= [0.4444 + 0.0625 + 0.016]/[0.4444 + 0.5625 + 0.7656]$$

$$= 0.5229/1.7725$$

$$= 0.2950 \qquad (5\text{-}28)$$

10) As evident in **8**) and **9**), it is possible to calculate the numerical value of the *Kosko entropy* of any fuzzy answer F, $S_K(F)$. But what is the meaning of $S_K(F)$? It is here suggested that the Kosko entropy, S_K, of fuzzy answer F is a *quantitative measure of the uncertainty* that F is C (or C is F, for that matter). By multiplying $S_K(F)$ with 100, we can express this uncertainty in the unit of %:

$S_K(F)$ x100 = The percent uncertainty that F is C (or C is F) (5-29)

Applying Eq. (5-29) to the result in Eq. (5-28), we can conclude that

"It is 29.5% certain that fuzzy answer located at (1/3, ¾, 7/8) is equivalent to (and hence can be represented by) the crisp answer located at (0, 1, 1)." (5-30)

If we assume that

"All crisp answers are approximations of their closest fuzzy answers" (5-31)

we can re-express Statement (5-30) as follows:

"The uncertainty of crisp answer C (0,1,1) is (100 - 29.5) = 70.5 %." (5-32)

11) Statements (5-31) and (5-32) would gain a strong support if we can associate the interior of the N-dimensional hypercube defined in Table 5-4 with *reality* or the source of the apparatus-elicited answers of Wheeler (1990) and its vertices with possible, theoretical, or represented answers. The apparatus-elicited answers may have two aspects – the "registered" aspect when artificial apparatuses are employed and "experienced" aspect when living systems are involved as measuring agents. Frieden (2004) associates the former with *Fisher information* (I) and the latter with what he refers to as "bound information" (J), i.e., the algorithmic information needed to characterize the "source effects" that underlie registered data or crisp answers. In the case of Frieden (2004), it seems clear that the registered answers (carrying Fisher information, I) belong to the vertices of the N-dimensional hypercube and the "experienced" answers or "bound information", J, belong to the interior of the N-dimensional hypercube. If these identifications are correct, the following generalizations would follow:

"*All crisp answers are uncertain*." (5-33)

"All crisp answers have non-zero Kosko entropies." (5-34)

"*No crisp answers can be complete*." (5-35)

"*Reality cannot be completely represented*." (5-36)

"*The ultimate reality is ineffable*." (5-37)

12) Einstein stated (cited, e.g., in Kosko 1993, p. 29) that

"As far as the laws of mathematics refer to reality, they are not certain; (5-38)

and as far as they are certain, they do not refer to reality."

Since Statement (5-38) is very often cited by physicists and seems to embody truth, it deserves to be given a name. I here take the liberty of referring to Statement (5-38) as the *Einstein's Uncertainty Thesis* (EUT).

EUT can be accommodated by the Knowledge Uncertainty Principle (KUP) as expressed in Statements (5-33) through (5-38), if *we identify the volume or the interior of the N-dimensional hypercube with 'reality'* as already alluded to in **11**) *and its surface (i.e., some of its vertices) as the 'laws of mathematics'*. Again, we may locate crisp articulations of all sorts (including mathematical laws and logical deductions) on the vertices of the N-dimensional hypercube and the 'ineffable reality' in the interior or on the edges of the hypercube. If this interpretation is correct, at least for some universes of discourse, we may have here a possible *algebraic-geometric (or geometro-algebraic) rationale* for referring to the *N-dimensional hypercube* defined in Table 5-4 as the "reality hypercube (RH)" or as "a N-dimensional geometric representation of reality", and Inequality (5-27) and Statement (5-38) as the keystones of a new theory that may be called the "Algebraic Geometric Theory of Reality (AGTR)". It is hoped that RH and AGTR will find useful applications in all fields of inquiries where uncertainties play an important role, including not only physics (see **13**) below) but also biology, cognitive neuroscience, risk assessment, pharmacology, and medicine (see Chapter 20), epistemology, and philosophy, by providing an objective and visual theoretical framework for reasoning.

13) The wave-particle duality of light (see Section 2.3.1) served as a model of the complementarity pair in the construction of the philosophy of complementarity by N. Bohr in the mid-1920's (Plotnitsky 2006, Bacciagaluppi and Valentini 2009), although it was later replaced with the more general 'kinematics-dynamics complementarity pair' (Murdoch 1987). Assuming that the wave-particle duality of light embodies an uncertainty principle (in addition to a complementarity principle to a certain degree), it will be analyzed based on the Knowledge Uncertainty Principle, Eq. (5-29). The analysis involves the following steps:

(1) *Classical concepts*: The concepts of *waves* and *particles* have been well established in human language, having developed over thousands of years as a means to facilitate communication among humans about physical processes.
(2) *Observations*: Light has been found to exhibit the dual properties of both waves and particles, depending on the measuring apparatus employed, which cannot be readily combined into one picture.
(3) *Binary questions*: The paradoxical observation in (2) can be summarized in the form of two binary questions.

Is light wave ?	Yes = 1, No = 0
Is light a particle?	Yes = 1, No = 0

(4) *The QA matrix*: The binary questions (Qs) have a finite number of possible answers (As) suggested by existing knowledge which can be represented as a QA matrix defined in **2**):

Table 5-5 The QA matrix for the wave-particle duality of light. N = the number of questions.		
Possible Answers (N^2)	Binary Questions (N = 2)	
	1	2
[1]	0	0
[2]	0	1
[3]	1	0
[4]	1	1

(5) *N-Dimensional hypercube*: The QA matrix can be transformed into an N-dimensional hypercube (Figure 5-9), where N is the number of the binary questions related to the wave-particle duality of light. That is, the QA matrix and its associated N-dimensional hypercube are *isomorphic* in the sense that they obey the same set of common logical principles, including the principle of fuzzy logic (Kosoko 1993).

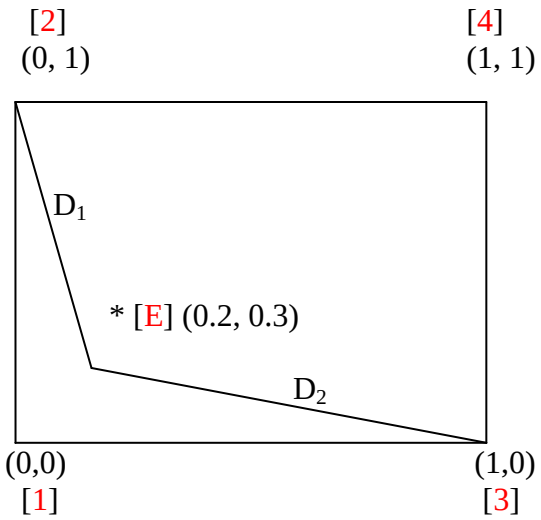


Figure 5-9 The N-dimensional hypercube (where N = 2) representation of the QA matrix concerning the wave-particle duality of light.

(6) *Apparatus-elicited answers (AEAs)*: To choose among the theoretically possible answers, experiments are designed and carried out to register AEAs, i.e., the answers provided by nature (including the observer which, with Bohr, is thought to comprise a part of the experimental arrangement and the registering device). Three AEAs are indicated in Figure 5-9, two of which are well established and the third is

hypothetical:

Photoelectric experiment = [2]
Two-slit experiment = [3]
A novel experiment = [E] (0.2, 0.3)

(7) Kosko entropy, S_K: The Kosko entropy, defined in **8**) above, of the fuzzy answer [E] can be calculated from the coordinates given in the 2-dimensional hypercube, Figure 5-9:

$$S_K(E) = D_1/D_2 \qquad (5\text{-}39)$$
$$= \{(0 - 0.2)^2 + (1 - 0.3)^2\}^{1/2}/\{(1-0.2)^2 + (0 - 0.3)^2\}^{1/2}$$
$$= \{4x10^{-2} + 49x10^{-2}\}^{1/2}/\{ 64x10^{-2} + 9x10^{-2}\}^{1/2}$$
$$= (0.53^{1/2})/(0.73^{1/2})$$
$$= 0.726^{1/2} = 0.852$$

(8) *Uncertainties of crisp (or nonfuzzy) statements*: Applying Eq. (5-29) to crisp answers [2] and [3], the associated uncertainties, defined in **10**), can be calculated as:

$$S_K([2])\ x100 = 0.85 \times 100 = 85\% \qquad (5\text{-}40)$$
$$S_K([3])\ x100 = (1- 0.85) \times 100 = 15\% \qquad (5\text{-}41)$$

Eqs. (5-40) and (5-41) indicate that crisp answers [2] and [3] are 85% and 15% uncertain, respectively, relative to the apparatus-elicited answer [E].

Applying Eqs. (5-29) to the Airy experiment (AE), two calculations are possible: The Airy pattern is an experimental evidence that light is both waves and particles, i.e., crisp answer [4] (1,1), supporting the de Broglie equation, $\lambda = h/p$:

$$S_K([4]) = 0 \qquad (5\text{-}42)$$
$$\text{Uncertainty } ([4]) = 0\ \% \qquad (5\text{-}43)$$

The Airy pattern demonstrates that light is particles when observed over a short time period and waves when observed over a long period of time:

$S_K(AE) = 1$, since $D_1 = D_2$, and

$$\text{Uncertainty} = S_K(AE)x100 = 1 \times 100 = 100\% \qquad (5\text{-}44)$$

Eq. (5-44) indicates that the Airy experimental result is 100% uncertain as to whether light is wave or a particle. In other words, the crisp answers [2], [3] and [4] are all 100% uncertain with respect to the question whether they are true relative to the Airy experimental data.

14) In Section 2.3.4, the logical relation between the Heisenberg Uncertainty Principle (HUP) and Bohr's Complementarity Principle (BCP) was substantially clarified based on a geometric argument which may be viewed as a species of the so-called *table method* (Ji 1991, pp. 8-13). The result is that

"The Heisenberg uncertainty principle (HUP) presupposes Bohr's complementarity principle (BCP) and BCP can give rise to uncertainty principles including HUP." (5-45)

Statement (5-45) may be referred to as the *non-identity of the uncertainty and complementarity principles* (NUCP).

5.2.8 The Universal Uncertainty Principle

Although the quantitative form of the uncertainty principle was discovered by Heisenberg in physics in 1926 (Lidley 2008), the essential notion behind the uncertainty principle appears to be more general. Theoretical support for such a possibility can be found in the so-called 'spectral area code' (Herbert 1987, pp. 87-89),

$$\Delta W \times \Delta M > 1 \qquad (5\text{-}46)$$

where ΔW and ΔM are the spectral widths (or bandwidths) of conjugate waves W and M, respectively. A spectral width is defined as the number of waveforms into which a wave can be decomposed. The size of a bandwidth is inversely related to the closeness with which a wave resembles its component waveforms. Inequality (5-46) is called the "spectral area code", since the product of two numbers (i.e., bandwidths ΔM and ΔW) can be viewed as an area (*vis-à-vis* lines or volumes). When wave X is analyzed with the W prism (or software), a particular bandwidth ΔW of the output W waveforms is obtained, which is an inverse measure of how closely the input wave X resembles the members of the W waveform family. Similarly, when X is is analyzed with the M prism, another bandwidth ΔM is obtained, which is an inverse measure of how closely the input wave X resembles the members of the M waveform family. Since W and M are mutual conjugates (i.e., polar opposites), it is impossible for wave X to resemble W and M both. Hence there exists some restriction on how small these two spectral widths can get for the same input wave. Such a restriction is given by Eq. (5-46).

To relate the *spectral area* code to the Universal Uncertainty Principle, it is necessary to make two additional assumptions: (i) All human knowledge can be quantitatively expressed in terms of waves (each wave having three characteristic parameters, amplitude, frequency, and phase) and (ii) The *Fourier theorem* and its generalization known as the *synthesizer theorem* (Herbert 1987, pp. 82-84) can be used to decompose any wave, either physical or nonphysical, into a sum of finite set of component waveforms. The difference between the 'physical wave' such as water waves and 'nonphysical wave' such as quantum wave is this: The square of the amplitude of a *physical wave* is proportional to energy, whereas the square of the amplitude of *nonphysical wave* is proportional to the *probability* of the occurrence of some event.

Herbert (1987, pp. 87-89) provides an example of the spectral area code in action, namely the complementary abilities of analog and digital synthesis techniques. An analog synthesizer can construct a sound wave X out of a range of sine waves with different frequencies k. Each wave X, depending on its shape, requires a certain spectral width Δk of sine waveforms for its analog synthesis. The sine wave's conjugate waveform is the impulse wave, which is the basis of digital music synthesis. A digital

synthesizer forms a wave X out of a range of impulse waves with different values of position x. Each wave requires a certain spectral width Δx of impulse waves for its digital synthesis. According to the spectral area code, Eq. (5-46), the product of the spectral bandwidth of sine waves ant that of impuse waves must satisfy the *spectral area code*, leading to:

$$\Delta k \times \Delta x > 1 \qquad (5\text{-}47)$$

Short musical sounds (such as from a triangle or a woodblock) have a narrow impulse spectrum. According to Inequality (5-47), to analog-synthesize such crisp sounds (i.e., with small Δx) requires a large range of sine waves (i.e., with large Δk). To synthesize an infinitely short sound, i.e., the impulse wave itself, requires all possible since waveforms. In contrast, musical sounds that are nearly pure tones such as from a flute, an organ, or a tuning fork have a narrow sine spectrum. To digitally synthesize such pure tones, the spectral area code requires a large range of impulse waves. The spectral area code informs us that *analog* and *digital* music synthesizers are *complementary*: One is good for synthesizing long waveshapes, the other for short ones. Analogously, it may be stated that the *photoelectric effect devices* and *optical interference devices* are complementary to each other: One is good for measuring the particle nature of light, the other is good for measuring the wave nature of light. Thus it may be concluded that the complementarity principle of Bohr is a natural consequence of the *spectral area code*, Inequality (5-46).

These considerations based on the *synthesizer theorem* and the *spectral area code* provide theoretical support for the notion that there are at least three kinds of uncertainty principles in nature – i) the *Heisenberg Uncertainty Principle* in *physics* (see Inequalities (2-38) and (2-39)), ii) the *Cellular Uncertainty Principle* in *cell biology* formulated in the late 1990's based on the molecular model of the cell known as the Bhopalator (Ji 1985a, b, 1990, 1991, p.119-122) as explained in Figure 5-10 below, and iii) the *Knowledge Uncertainty Principle* in *philosophy* (see Section 5.2.7). One question that naturally arises is "What, if any, is the connection among these three uncertainty principles?" Is the Heisenberg Uncertainty Principle perhaps ultimately responsible for the other two uncertainty principles? I do not think so. Rather I think it is more likely that these three uncertainty principles are *mutually exclusive* and constitute special cases of a more general principle, here termed the *Universal Uncertainty Principle* that operates in the Universe, leading to the following assertion:

> "There exists a principle in this universe that manifests itself as the Heisenberg Uncertainty Prinicple, the Cellular Uncertainty Principle, or the Knowledge Uncertainty Principle, depending on whether the system under consideration is the *quantum object*, *the living cell*, or *the human brain*." (5-48)

Statement (5-48) will be referred to as the *Postulate of the Universal Uncertainty Principle* (PUUP). As already alluded to above, the ultimate basis for the validity of PUUP may be found in the *synthesizer thereom* and the *spectral area code* (Herbert 1987).

One utility of PUUP may be its ability to protect philosophers, literary critics, anthropologists, journalists, artists, and others from being criticized for invoking

Heisenberg's Uncertainty Principle to describe "uncertain" situations/scenarios encountered in their own fields of specializations. For example, Lindley (2008), in his otherwise insightful and informative book on the history of the uncertainty principle in physics, chastised one editorialist who invoked the Heisenberg Uncertainty Prtinciple by claiming that "the more precisely the media measures individual events in a war, the more blurry the warfare appears to the observer". Had the editorialist under attack invoked the PUUP instead of Heisenberg's uncertainty principle, he would have avoided Lindley's criticism on a sound logical basis.

The Cellular Uncertainty Principle (CUP) mentioned above is derived as follows (Ji 1991, pp. 118-122). It is assumed that the complete characterization of life entails specifying the behavior of the smallest unit of life, the cell. The cell behavior is depicted as a curvy line denoted as **R** (from "river", the symbol of life) in Figure 5-10. The genetic program responsible for the cell behavior is indicated as the projection $\mathbf{R}^{g}$ of **R** onto the internal coordinate (or genetic information) space (see the vertical plane on the left in Figure 5-10). The projection of **R** onto the spacetime plane produces its spacetime trajectory denoted as $\mathbf{R}^{s}$.

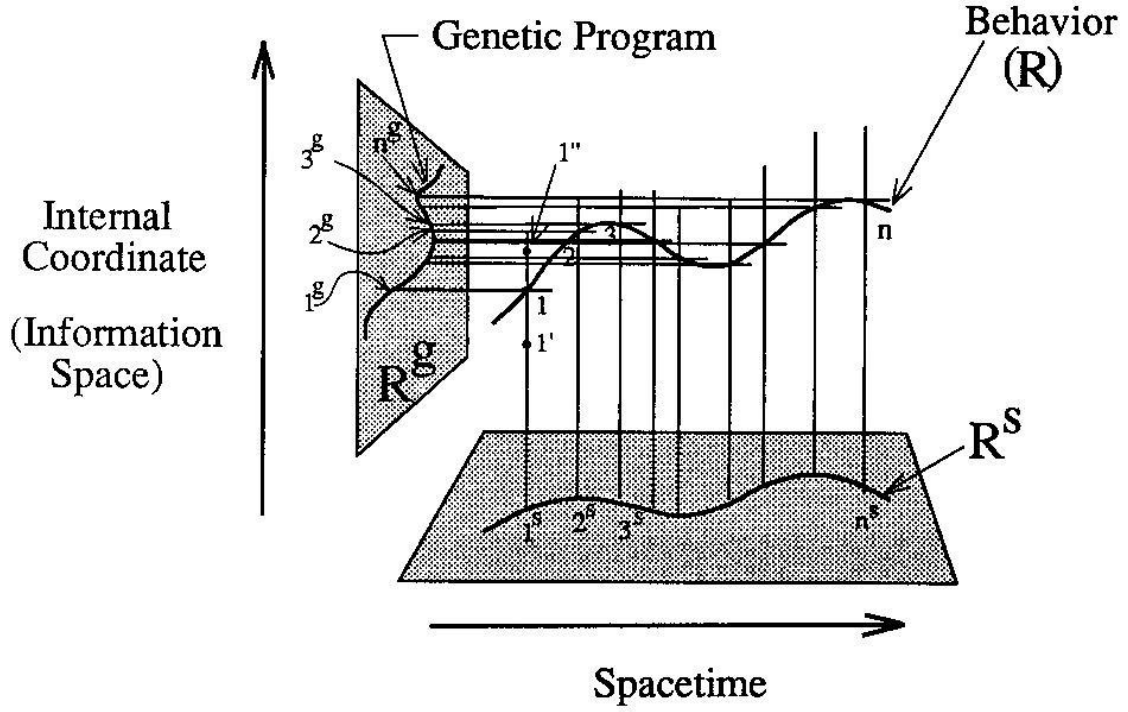


Figure 5-10 The cellular uncertainty principle derived from living processes represented in the 5-dimensional space, four dimensions of spacetime and one additional dimension for biological information. Reproduced from (Ji, 1991, p. 121).

The trajectory **R** is postulated to be composed of N sub-trajectories called "streams", where N is the number of biopolymers inside the cell. Each stream represents the behavior of one biopolymer inside the cell. The uncertainty about the behavior about the

cell cannot be less than the uncertainty about the behavior of one of the N biopolymers. The uncertainty about the behavior of a biopolymer inside the cell can be estimated as follows:

(1) There is a finite amount of uncertainty that is associated with the determination of the Gibbs free energy change underlying a given intracellular process catalyzed by a biopolymer. This uncertainty is designated as ΔG. Since driving any net biological process necessitates dissipating Gibbs free energy at least as large as thermal energies, kT, it would follow that the smallest uncertainty about the measurement of the Gibbs free energy change attending a biopolymer-catalyzed process inside the cell can be estimated to be

$$\Delta G \geq kT \quad \text{Kcal/mole} \tag{5-49}$$

(2) Due to ΔG, the cross-section of the behavior trajectory **R** of the biopolymer possesses a finite size. This leads to an uncertainty about the internal coordinate (i.e., the genetic information) of the biopolymer, since there are at least two internal coordinates that can be accommodated within the cross-section of **R** (see 1, 1' and 1'' and their projections, not shown, onto the information space). Therefore, the uncertainty concerning the genetic information associated with the biopolymer behavior is at least one bit:

$$\Delta I \geq 1 \quad \text{bit} \tag{5-50}$$

(3) Inequalities (5-49) and (5-50) can be combined by multiplication to obtain what was referred to as *the Cellular Uncertainty Principle* in (Ji 1991, pp. 119-122):

$$(\Delta G)(\Delta I) \geq kT \quad \text{bit Kcal/mole} \tag{5-51}$$

The three uncertainty principles discussed above are given in the first rows of Tables 5-6, 5-7 and 5-8, the first two of which are the modified forms of Tables 2-9 and 2-10 in Section 2.3. The two forms of the Heisenberg Uncertainty Principle are reproduced in the first row of Table 5-6, i.e., Inequalities (2-38) and (2-39). These inequalities are displayed in the table as the *horizontal* and *vertical* margins, respectively. As pointed out in Section 2.3.5, the *uncertainty relations are located on the margins of the table and the complementary relations such as the kinematics-dynamics duality are located in the diagonal boxes (or the interior) of the table*, suggesting that the uncertainty principles and the complementary principles belong to two different logical classes in agreement with Murdoch (1987, p. 67). Although the wave-particle duality is widely regarded as the empirical basis for Bohr's complementarity principle, this view is considered invalid since Bohr's complementarity principle has been found to be upheld in the so-called which-way experiments even when the Heisenberg Uncertainty Principle is not applicable (Englert, Scully and Walther 1994). Therefore the wave-particle duality must be viewed as valid only under some specified experimental situations such as the gamma-ray microscopic experiment (Murdoch 1987, p. 50) and not universally. Similarly, all of

the *complementary pairs* listed in the diagonal boxes of Table 5-6 may hold true only under appropriate experimental or observational situations and not universally.

Table 5-6 The relation between the *uncertainty principles* and *complementary relations* in physics, all thought to result from the numerical values of the critical parameters, h and c.

Physics $\Delta q \cdot \Delta p \geq h/2\pi$ . . . . . (2-38) $\Delta t \cdot \Delta E \geq h/2\pi$ . . . . . (2-39)		
h, c	Position (q)	Momentum (p)
Time (t)	1. wave 2. spacetime 3. kinematics 4. globality 5. continuity 6. group (or superposition)	
Energy (E)		1. particle 2. momenergy 3. dynamics 4. locality 5. discontinuity 6. individuality

If the Symmetry Principle of Biology and Physics (SPBP) described in Table 2-5 is valid, it may be predicted that the relation between the *uncertainty principle* and the *complementarity principle* as depicted in Table 5-6 may have a biological counterpart. One such possibility is shown in Table 5-7, which is almost identical with Table 2-7, except for the inclusion of the postulated uncertainty relations, Inequalities (5-51) and (5-52). In Inequality (5-51) which was derived on the basis of a geometric argument (Ji 1991, pp. 120-122), ΔG is the uncertainty about the measurement of the Gibbs free energy change accompanying an intracellular process at temperature T, ΔI is "the uncertainty about the biological significance of the cellular processes under study, e.g., the uncertainty about the "fitness" value of the cellular processes involved" (Ji 1991, p. 120), and k is the Boltzmann constant. It is assumed that the critical parameter in biology is the *thermal energy per degree of freedom*, i.e., kT, which is thought to be analogous to h (see Statement (4-36)). Again, in analogy to the canonical conjugates in physics (i.e., the q-p and t-E pairs), it is assumed in Table 5-7 that the canonical conjugates in biology are information-life (I-L) and energy and matter (E-m) pairs. If this conjecture is valid, we can derive another uncertainty relation in biology, namely, $\Delta L \cdot \Delta m \geq kT$, where ΔL is the uncertainty about whether the object under investigation is alive or death, and Δm is the uncertainty about the material constitution or configuration of the living object under consideration.

Table 5-7 The postulated relation between the *cellular uncertainty principle* and the *liformation-mattergy complementarity* in biology.

Biology

$$\Delta G \cdot \Delta I \geq kT \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(5-51)}$$
$$\Delta L \cdot \Delta m \geq kT \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(5-52)}$$

kT	Life (L)	Matter (m)
Information (I)	1. wave 2. kinematics 3. liformation 4. Structure	
Energy (E)		1. particle 2. dynamics 3. mattergy 4. Function

Finally, if the complementarity principle revealed in *physics* and *biology* can be extended to philosophy as envisioned by Bohr (1934) and myself (Ji 1993, 1995, 2004b), it should be possible to construct a table similar to Tables 5-6 and 5-7 that applies to philosophy. One possibility is shown in Table 5-8. Just as the extension of the uncertainty and complementarity principles from physics to biology entailed recognizing

Table 5-8 The extension of the principles of uncertainty and complementarity from physics and biology to philosophy. M = mind, B = body, S = soul, and P = personality. The symbol u denotes the postulated minimum uncertainty below which no human knowledge can reach.

Philosophy

$$\Delta M \cdot \Delta B \geq u \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(5-53)}$$
$$\Delta S \cdot \Delta P \geq u \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(5-54)}$$

u	Soul (S)	Personality (P)
Mind (M)	1. wave 2. liformation 3. fuzzy logic	
Body (B)		1. particle 2. mattergy 3. crisp logic

a new complementary pair (i.e., *liformation vs. mattergy* in Table 5-7), so it is postulated

here that there exists a novel kind of complementarity observable at the philosophical level, and that complementary pair is here suggested to be the *crisp vs. fuzzy logics* (see the diagonal boxes in Table 5-8).

Associated with the crisp vs. fuzzy logics *complementarity* are suggested to be *two uncertainty relations*, Inequalities (5-53) and (5-54), where ΔM is the uncertainty associated with defininingthe mind, ΔB is the uncertainty associated with defining the body, ΔS is the uncertainty about what constitutes soul, ΔP is the uncertainty about what determines one's personality, and u expressed in fits, the fuzzy units (Kosko 1993), is thought to be the minimum amount of uncertainty that necessarily accompanies all human knowledge and communication. 'Knowledge" is here defined simply as the ability to answer questions, and the amount of the knowledge a person possess can be measured by the number of questions that can be answered by a person possessing the knowledge. Inequality (5-53) may be interpreted as stating that the more precisely one determines what mind is in non-material terms, the less precisely can one define the role of the body in the phenomenon of mind. Similarly, the more precisely one determines what the body is from the biochemical and physiological perspectives, the less precisely can one determine what mind is from the psychological perspective. This complementarity-based view of mind appears to be consistent with the hologram-based theory of mind proposed by Pribram (2010). Inequality (5-54) may be interpreted to mean that the more precisely one determines what soul is, the less precisely can one determine what personality is. The more precisely one can determine what personality is, the less precisely can one determine what soul is. This conjecture was motivated by the statement made by a Japanese theologian in Tokyo in the mid-1990's to the effect *that it is relatively easy to know whether a human being has a personality but it is very difficulty* to know whether he or she has a soul.

The three kinds of the uncertainty principles described in Tables 5-6 through 5-8 are recapitulated in Table 5-9, along with their associated complementarity principles.

Table 5-9 The uncertainty principles in physics, biology, and philosophy.

	Uncertainty Principle		
	Heisenberg	**Cellular**	**Knowledge**
1. System (Volume, m^3)	Atom (10^{-30})	Cell (10^{-15})	Brain (1)
2. Uncertainty Inequality (Minimum Uncertainty)	$\Delta q \cdot \Delta p \geq h/2\pi$ $\Delta t \cdot \Delta E \geq h/2\pi$ ($\sim 10^{-27}$ erg sec)	$\Delta G \cdot \Delta I \geq \gamma^a$ ($\sim 10^{-14}$ erg)	$\Delta X \cdot \Delta Y \geq u^b$ ($\sim 10^{-2}$)

3. Complementary Pairs	Wave vs. particle Kinematics vs. dynamics Measuring instruments A vs. B	Linformation vs. mattergy Diachronicity vs. synchronicity[c] Structure vs. process	Fuzzy vs. crisp (*Kosko 1993*) Continuity vs. discontinuity Local vs. global Classical vs. nonclassical epistemology *(Plotnitsky 2006)*
4. Key Principles	Principle of the Quantum (or the Quantization of Action, i.e., Energy x Time)	Principle of Self-Organization Principle of the Conformon (or the Quantization of Biological Action) (*Ji 2000*)	Principle of Ineffability (Statement5-22) Einsteins' uncertainty Thesis (Statement 5-38) Principle of Minimum Uncertainty: i.e., $u > 0$ (see Inequality (5-27))
5. Quantum (Alternative names)	Action = h (**quons**, **ergons**[d])	Life = γ (conformons, gnergons[e])	Knowledge = u^f (gnons[f])
6. Concerned with (Discrete units)	Energy (Ergons)	Gnergy (Gnergons)	Information (Gnons)
7. Field of Study	Physics	Biology	Philosophy/Psychology

[a]The minimum size of the conformon postulated to be kT or 4.127×10^{-14} ergs (or 0.594 Kcal/mole) (Ji 1991, p. 32).

[b]To maintain the symmetry of the table, it is postulated that there exist one or more uncertainty pairs denoted as X and Y such that increasing the precision of describing X is possible if and only if the precision of describing Y is reduced proportionately so that their product is always greater than some minimum uncertainty symbolized by u . One example of X and Y may be suggested to be *natural language* and *mathematics*. The minimum uncertainty of human knowledge, u, may be represented in terms of the Kosko entropy, $S_{K,}$ that cannot be reduced to zero nor exceeds 1. The numerical value of *u* has been conjectured to be about 10^{-2}, which is about 12 orders of magnitude greater than *kT*, the minimum size of the cellular uncertainty, and about 25 orders of magnitude greater than *h*, the minimum size of quantum mechanical uncertainty.

[c]Cells are evolving systems whose current properties and processes have been selected by evolution and hence cannot be completely understood without taking into account their past history as recorded in their structures, e.g., DNA. In other words, cells can be described in two complementary ways—via the *diachronic* and the *synchronic* approaches (see Section 4.5).

[d]The energetic aspect of gnergy, the complementary union of information and energy (Section 2.3.2).

[e]The discrete unit of gnergy (Section 2.3.2).

[f]The symbol u refers to the *minimum uncertainty* in human knowledge which is equivalent to the *maximum human knowledge*, because it takes a maximum amount of information to minimize uncertainty.

[g]The informational aspect of gnergy (Ji 1991, pp. 1, 152 and 160).

Several features emerge from Table 5-9:

(1) Although the first mathematical expression of the uncertainty principle was discovered in physics by Heisenberg in 1926 (Lindley 2008), the qualitative concept of uncertainty in human knowledge is much older, going back to Lao-tse, for example (see Statement 5-22). The mathematical expressions for the uncertainty principle applicable to cell biology and psychology/philosophy are formulated for the first time in this book (see the first and second rows in Table 5-9).

(2) The intense discussions on Heisenberg's uncertainty principle in physics and philosophy of science during the past 7 decades (Murdoch 1987, Plotnitsky 2006, Lindley 2008) have created the impression that there exists only one overarching principle of uncertainty, namely, that of Heisenberg. But Table 5-9 suggests that there exists a multiplicity of uncertainty principles, each reflecting specific mechanisms of interactions among the components of the system under consideration, from the atom to the cell to the human brain. Just as the complementarity principle advocated by Bohr on the basis of quantum mechanical findings was postulated to have counterparts in fields other than physics (Bohr 1933, 1958, Pais 1991, Ji 1991, 1993, 1995, Kelso and Engstrøm 2006, Barab 2010), so it appears that the uncertainty principle first recognized in quantum mechanics has counterparts in fields other than physics.

(3) The uncertainty inequality differs from systems to systems as evident in the second row. The numerical value of the minimum uncertainty associated with a given system appears to increase approximately linearly with its material volume (compare the first two rows).

(4) The complementarity pairs associated with their associated uncertainty inequalities also vary depending on systems (see the second and third rows).

(5) The key principles underlying each uncertainty inequality and its associated complementarity pair depend on systems, the principle of self-organization for cells (discussed in Section 3.1) being a prime example (see the fourth row).

(6) Just as the *action* is quantized in physics, so it is proposed here that *life* and *knowledge* are quantized in cell biology and psychology/philosophy (see the fifth row).

(7) Somewhat simplifying, physics may be viewed as the study of *energy* (or ergons), cell biology as the study of *gnergy*, and philosophy/psychology as the study of *information* (or gnons) (see the sixth row).

(8) One of the most significant conclusions suggested by Table 5-9 is that there is no overarching uncertainty principle nor is there an associated complementarity principle but these principles are all *system-dependent*, giving rise to a multiplicity of uncertainty principles and complementarity principles:

"Uncertainty principles and complementarity principles are system-dependent." (5-55)

Statement (5-55) may be referred to as the System-Dependency of Uncertainty and Complemetnarity Principles (SDUCP).

(9) Table 5-9 strongly indicates that the principles of uncertainty and complementarity are not confined to physics but are universal. Since complementarism (Section 2.3.4) is a philosophical framework based on the universality of complementarity and since the principle of complementarity is in turn thought to be related to that of uncertainty (see the second and third rows, Table 5-9), the question naturally arises as to how complementarism may be related not only to uncertainties but also to other cognate terms such as information (or *liformation* more generally, Section 2.3.1), energy (or *mattergy* more generally), and measurement (Plotnitsky 2006). One possible way to characterize the multifaceted relations among these terms is suggested in Figure 5-11, utilizing the language of networks and the Peircean triadic template (see Figure 4-6) :

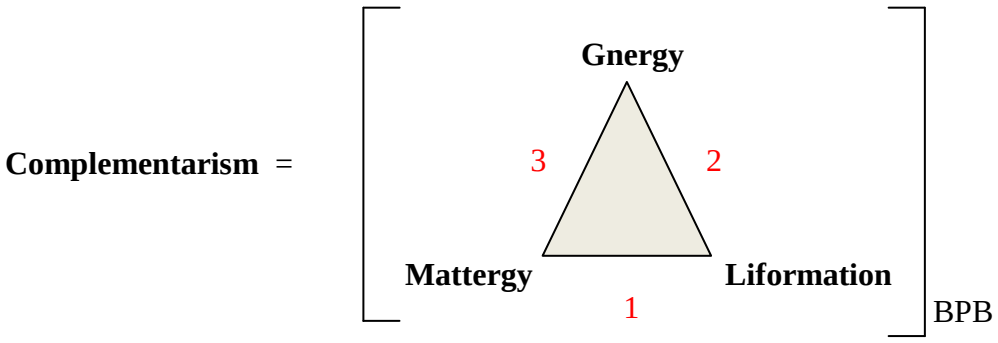


Figure 5-11 A 3-node network representation of *complementarism*.

In Figure 5-11, complementarism is suggested to be a network of three nodes-- Gnergy, Mattergy, and Liformation -- and 3 edges -- Complementarity (1), Uncertainty (2), and Measurement (3). BPB stands for the Bernstein-Polanyi boundaries (explained in Section 3.1.5) that provides the context of discourses or specifies the system-dependency entailed by Statement (5-55). Just as "*mattergy*" embodies the intimate relation between *energy* and *matter* through Einstein's special relativity theory (Shadowitz 1968), so "*liformation*" embodies the inseparable relation postulated to exist between *life* and *information* in the gnergy theory of biology (Ji 1991, 2004b). Thus, as first suggested in (Ji 2004b), it may be concluded that:

"*Just as matter is regarded as a highly condensed form of energy, so life can be viewed as a highly condensed form of information.*" (5-56)

Statement (5-56) may be referred to as the *information-life identity principle* (ILIP) just as $E = mc^2$ can be referred to as the *energy-matter identity principle* (EMIP).

5.3.2 The Law of Requisite Variety

One of the most useful laws to be imported from engineering into biology is what is known in cybernetics as the Law of Requisite Variety (LRV). There are many ways to state this law (Heylighen and Joslyn 2001) but the following definition adopted from Ashby (1964) is suitable for application to molecular and cell biology:

> "*When a machine (also called a system or a network) is influenced by its environment in a dominating manner (i.e., the environment can affect the machine but the machine cannot influence its environment to any significant degree), the only way for the machine to reduce the degree of the influence from its environment is to increase the variety of its internal states.*" (5-62)

The complexity of biological systems (or bionetworks), from enzymes to protein complexes to metabolic pathways and to genetic networks, is well known. One way to rationalize the complexity of bionetworks is to invoke the Law of Requisite Variety. We can express LRV quantitatively as shown in Eq. (5-63). If we designate the variety of the environment (e.g., the number of different environmental conditions or inputs to the system) as V_E and the variety of the internal states of the machine as V_M, then the variety of outputs of the machine, V_O, can be expressed as

$$V_O \geq V_E / V_M \tag{5-63}$$

One interpretation of Equation (5-63) is that, as the environmental conditions become more and more complex (thus increasing V_E), the variety of the internal states of the machine, V_M, must increase proportionately to maintain the number of outputs, V_O, constant (i.e., keep the system homeostatic). Another way to interpret this equation is that, in order for a bionetwork to maintain its functional homeostasis (e.g., to keep the numerical value of V_O constant) under increasingly complexifying environments (i.e., increasing V_E), the bionetwork must increase its variety or complexity, namely, V_M.

The term 'variety' appearing in LRV can be expressed in terms of either (i) the number of distinct elements, or (ii) the binary logarithm of that number. When variety is measured in the binary logarithmic form, its unit is the bit. Taking the binary logarithm to the base 2 of both sides of Inequality (5-63) leads to Inequalities (5-64) and (5-65):

$$\log V_O \geq \log (V_E / V_M) \text{ or} \tag{5-64}$$

$$\log V_O \geq \log V_E - \log V_M \tag{5-65}$$

which is identical with the equation for LRV used by F. Heylighen and C. Joslyn (2001), except that the buffering capacity of the machine, K, is assumed to be zero here, i.e., the machine under consideration is assumed to respond to all and every environmental

perturbations. Since $\log V_x$ is defined as Shannon entropy H_x (see Eqs. (4-2) and (4-3)), Inequality (5-65) can be transformed into a more convenient form:

$$H_O \geq H_E - H_M \quad (5\text{-}66)$$

where H_O is the Shannon entropy of the machine outputs, H_E is the Shannon entropy of the environmental inputs, and H_M is the Shannon entropy of the state of the machine or its controller. Two cautionary remarks are in order concerning Inequality (5-66):

i) The symbols for Shannon entropy, H, should not be confused with the symbol for enthalpy, H, in thermodynamics, and
ii) The same term 'entropy' is represented by H in information theory and by S in thermodynamics. In other words, there are two kinds of entropies – the *information-theoretic entropy* (referred to by some as 'intropy') and *thermodynamic entropy*. There are two schools of thought about the relation between intropy, H, and entropy, S (Section 4.7). One school led by Jaynes (1957a, b) maintains that H and S are in principle identical up to a constant factor, whereas the other schools represented by Wicken (1987), myself (Ji 2004c) and others assert that H and S are distinct and cannot be quantitatively related (see Sectgion 4.7).

Just as the Second Law of thermodynamics can be stated in many equivalent ways, so LRV can be expressed in more than one ways, including the following:

"*Simple machines cannot perform complex tasks.*" (5-67)

"To accomplish a complex tasks, it is necessary to employ complex machines." (5-68)

"Nature does not employ complex machines to accomplish simple tasks." (5-69)

"If the internal structure of a biological machine is found to be complex, it is very likely that the task performed by the machine is complex." (5-70)

Thus, LRV provides one way to explain the possible biological role of the complex biological structures such as signal transduction pathways, transcriptosomes, nuclear pore complexes, both of which can implicate 50 or more proteins (Halle and Meisterernst 1996, Dellaire 2007). For example, it is possible that nuclear pore complexes had to increase the variety of their internal states to maintain functional homeostasis (e.g., transport right RNA-protein complexes in and out of the nuclear compartment at right times and at right speeds) in response to increasingly complexifying environmental (e.g., cytoplasmic) inputs or perturbations. In other words, nuclear pore complexes (viewed as molecular computers or molecular texts) had to became complex in their internal structures so as to process (or carry out computations on) more and more complex input signals from their microenvironment, in order to produce the desired outputs without fail.

6.1.2 The Isomorphism between Cell and Human Languages: The Cell Language Theory

Human language can be defined as a system of *signs* obeying a set of rules that enables humans to communicate with one another. In other words, human language is a necessary condition for human communication. Similarly, there must be a language unique to living cells in multicellular (Ji 1997a,b) as well as unicellular (Stock et al. 2000) organisms, since cells must communicate among themselves in order to survive by carrying out their specialized biological activities in a coordinated manner. Such a language was named '*cell language*' in (Ji 1997a). Cell language was defined as "a self-organizing system of molecules, some of which encode, act as signs for, or trigger, gene-directed cell processes" (Ji 1997a). This definition of cell language was inspired by the definition of human language given by Saussure (Culler 1991): "The language is a system of signs that represent concept". The definition of cell language can be *formally* derived from that of human language given by Saussure by applying the following transformations: 1) replace 'signs' with 'molecules', 2) replace 'systems' with 'self-organizing systems'; and 3) replace 'concepts' with 'gene-directed cell processes' (see Figure 6-1).

"**The language is a system of signs that represent concept**."

1) *Signs* => *Molecules*
2) *Systems* => *Self-Organizing Systems*
3) *Concepts* => *Gene-Directed Cell Processes*

"The cell language is a self-organizing system of molecules, some of which encode, act as signs for, or trigger, gene-directed cell processes."

Figure 6-1 The 'formal' derivation of the definition of cell language from that of human language given by Saussure (Culler 1991, Ji 2002b).

Human and cell languages obey a common set of *linguistic* (or more generally *semiotic*) principles (Section 6.2), including *double articulation, arbitrainess of signs* (Section 6.1.4), *rule-governed creativity*, the *energy requirement* of information transduction, storage, and transmission (Section 4.6) ((Ji 1997a, 2001). Both human and cell languages can be treated as 6-tuples, $\{L, W, S, G, P, M\}$, where L is the alphabet, W is the lexicon or the set of words, S is a set of sentences, G is a set of rules governing the formation of sentences from words (called the *first articulation*) and the formation of words from letters (the *second articulation*), P is a set of physical mechanisms necessary

and sufficient to implement a language, and finally *M* is a set of objects or processes, both symbolic and material, referred to by words, sentences, and their higher-order structures (e.g., texts). In Table 6-3, cell and human languages are compared with respect to the components of the linguistic 6-tuple. Table 6-3 contains two important concepts, *conformons* and *IDSs*, which play fundamental roles in the *Bhopalator model* of the living cell (Ji 1985a,b, 1991, 2002b), the user of cell language, as discussed in Sections 8 and 9. It is convenient to refer to cell language as *cellese* and human language as *humanese* (Ji 1999b), and the science of *cell biology* may be viewed as the translation of *cellese* to *humanese.* To the best of my knowledge, the first concrete application of the cellese concept was made by Aykan (2007) in formulating his so-called "message-adjusted network (MAN) model of the gastro-enteropancreatic endocrine system.

Table 6-3 A *formal* comparison between human and cell languages (Ji 1997a, 1999b).

	Human Language (*Humanese*)	**Cell Language** (*Cellese*)
1. Alphabet (L)	Letters	4 Nucleotides (or 20 Amino acids)
2. Lexicon (W)	Words	Genes (or Polypeptides)
3. Sentences (S)	Strings of words	Sets of genes (or polypeptides) expressed (or synthesized) coordinately in space and time dictated by DNA folds[1] (cell states).
4. Grammar (G)	Rules of sentence formation	The *physical laws* and *biological rules* mapping DNA sequences to folding patterns of DNA (polypeptides) under biological conditions[2].
5. Phonetics (P)	Physiological structures and processes underlying phonation, audition, and interpretation, etc.	Concentration and mechanical waves responsible for information and energy transfer and transduction driven by *conformons*[3]and *intracellular dissipative structures* (IDSs)[4].
6. Semantics (M)	Meaning of words and sentences	*Codes* mapping molecular signs to gene-directed cell processes
7. First Articulation	Formation of sentences from words	Organization of gene expression events in space and time through *non-covalent interactions*[5] between DNA and proteins (or Space- and time-dependent non-covalent interactions among proteins, DNA, and RNA molecules). Thus,

		macromolecular complexes can be viewed as molecular analogs of sentences.
8. Second Articulation	Formation of words from letters	Organization of nucleotides (or amino acids) into genes (or polypeptides) through covalent interactions[6].
9. Third Articulation	Formation of texts from sentences	Organization of chemical concentration gradients in space and time called *dissipative structures* (Babloyantz 1986, Kondepudi and Prigogine 1998) or *dissipatons* (see Section 3.1.5) in order to 'reason' and 'compute'[7].

[1]Just as verbal sentences (as written) are strings of words arranged linearly in the Euclidean space, so the cell-linguistic (or molecular) sentences are visualized as series of gene expression events arranged in time leading to dissipative structures or dissipatons (Section 9).

[2]Of all the folds of DNA and polypeptides allowed for by the laws of physics and chemistry, only small subsets have been selected by evolution (thereby giving rise to *biological information*) to constitute the gernome of a cell.

[3]Sequence-specficific conformational strains that carry both free energy (to do work) and genetic information (to control work) (Ji 1974a, 2000) (Section 8). Conformons are thought to provide immediate driving force (or serve as the force generators) for all non-random molecular processes inside the cell. Experimental evidence for conformons is discussed in Section 8.3.

[4]Space- and time-specific intracellular gradients of ions, biochemicals, and mechanical stresses (e.g., of the cytoskeletal system) that serve as the immediate driving forces for all cell functions on the microscopic level (see Chapter 9).

[5]Also called "conformational" interactions which involve neither breaking nor forming covalent bonds and depend only on the rotation around, or bending of, covalent bonds. Non-covalent interactions implicate smaller energy changes (typically around 1 to 3 Kcal/mole) than covalent interactions which entail energy changes in the range of 30-100 Kcal/mole.

[6]Molecular interactions that involve changes in covalent bonds, i.e., changes in valence electronic configurations around nuclei of atoms within a molecule.

[7]This row is added to the original table published in (Ji 1997a,b). The *third articulation* (Ji 2005a) is a generalization and an extension of *second articulation*. Intercellular communication through chemical concentration gradients is well established in microbiology in the phenomenon of *quorum sensing* (Section 15.7) (Waters et al. 2008, Stock et al. 2000), whereby bacteria express a set of genes only if there are enough of them around so that they can combine and coordinate their efforts to accomplish a common task which is beyond the capability of individual bacteria. This phenomenon can be viewed as a form of *reasoning* and *computing* on the molecular level and the cell

therefore can be viewed as *the smallest computational unit* (Ji 1999a), which may be referred to as *the computon,* a new term used here for the first time.

Just as human language can be viewed as a *linear* network of letters forming words (i.e., *second articulation*), words forming sentences (i.e., *first articulation*), and sentences forming texts (i.e., *third articulation* (Ji 2005a, pp. 17-18)), so bionetworks (e.g., individual proteins or their networks known as metabolic networks) can be viewed as *multidimensional* generalizations of linguistic networks, where, for example, amino acids can be compared to letters, proteins to words, complexes of proteins to sentences, and network of complexes as texts (see Rows 7, 8 and 9 in Table 6-3). In addition to these structural or morphological similarities, there is a set of conventional/evolutionary rules and physical principles that is common to both human and cell languages, including the following:

i) The principle of self-organization (PSO) (6-10)
The phenomenon of self-organization was first observed in physical (e.g., Bernard instability (Kondepudi and Prigogine 1998, Kondepudi 2008)) and chemical systems (e.g., Belousov-Zhabotinsky reaction) as discussed in Section 3.1. Since the cell is an example of self-organized systems, it would follow that one of its functions, namely, communication with its environment including other cells (and hence cell language itself), must be self-organizing. Self-organization on the cellular level entails generating molecular forces from exergonic chemical reactions occurring internally. Also, since human communication is built upon (or presupposes) cell communication, it too must be an example of self-organizing processes. Therefore, it can be concluded that both cell and human languages are rooted in (or ultimately driven by) self-organizing chemical reaction-diffusion systems.

ii) The minimum energy requirement for information transmission (6-11)
Both human and cell languages can be viewed as means of transmitting information in space and/or time. All information transmission requires dissipating free energy as mandated by Shannon's channel capacity equation (see Section 4.8). For artificial communication systems, the requisite energy is provided *externally* (e.g., a power station); for natural communication systems such as cells, the needed energy is generated from chemical reactions occurring *internally* utilizing chemicals provided by their environment. This difference in the sources of energy may have profound role in determining the global differences between artificial and living systems (e.g., macro vs. micro sizes of system components).

iii) The complementarity between determinism and non-determinism (6-12)
The process of communication can be viewed as a complementary union of *determinism* and *nondeterminism.* The deterministic aspect of communication reflects both the energy requirement (e.g., PSO, MERIT) and the syntactic rules (e.g., grammar) inherent in the language employed in communication, and the non-deterministic aspect (e.g., the principle of the arbitrariness of signs (PAS), the principle of rule-governed creativity (RGC), both described in Section 6.1.4) reflects the freedom of choice available to

the sender of a message. Shannon's formula, Eq. 4-2, coupled with the definition of information given in Eq. (4-4), clearly indicates that, when there is no choice (i.e., no uncertainty), there is no information (Pattee 2008, p. 119), since 'no choice' means 'no selection', which in turn signifies 'no reduction' in uncertainty.

To summarize, cell and human languages are *symmetric* with respect to at least 5 principles. Thus, to borrow the idioms of the group theory in mathematics, it may be stated that cell and human languages are the members of a *symmetry group* that has five 'symmetry operators', here identified with i) PSO, ii) MERIT, iii) CDN, iv) PAS, and v) RGC, and hence may be designated as SG(5), where S and G stand for symmetry and group, respectively, and the Arabic numeral indicates the number of the principles that remain unchanged (or invariant, or symmetric) when one language is replaced by the other. In other words, cell and human languages may be said to belong to a linguistic symmetry group with 5 symmetry operators, i.e., the SG(5) group.

The set of the 5 rules common to cell and human languages may be divided into two complementary subsets – i) *physical laws* (to be denoted as the P set), and ii) *linguistic* or *semiotic principles* (to be denoted as the L set) (See Section 6.2). It is clear that PSO and MERIT belong to the P set, and that the members of the L set include the principles of triple articulation as indicated in Table 6-3, the principles of the *arbitrariness of signs* and *rule-governed creativity* that are discussed next. These results agree with the matter-symbol complementarity thesis of Pattee (1969, 2008) and the basic tenets of the semantic biology advocated by Barbieri (2003, 2008a,b).

6.1.3 The Complexities of the *Cellese* and the *Humanese*

One of the most useful results that can be derived from the *cellese-humanese isomorphism* thesis is our ability to estimate the complexity (or the information content per symbol) of the cellese based on our experience with the humanese (see Table 6-4). The maximum *complexity* (viewed from the perspective of the message source) or the maximum information content (viewed from the receiver's perspective) (Seife 2006) of an English text can be estimated using the simplified version of Shannon's formula (see Eq. 4-3), i.e.,

$$I = cbd \log_2 a \qquad (6\text{-}13)$$

where a is the number of letter in an alphabet, b is the number of letters in a word, c is the number of words in a sentence and d is the number of sentences in a text. In other words, Eq. (6-13) is based on the *principle of triple articulations* (PTA), denoted as 1, 2 and 3 as shown in Scheme (6-14):

$$\textbf{Letters} \xrightarrow{1} \textbf{Words} \xrightarrow{2} \textbf{Sentences} \xrightarrow{3} \textbf{Texts} \qquad (6\text{-}14)$$

The *cellese hypothesis* (Ji 1997a, 1999b) assumes that PTA, Eq. (6-14), applies to the molecular processes occurring in the living cell and identifies the three levels of articulations of the cellese as shown in Scheme (6-15):

$$\text{Monomers} \xrightarrow{1} \text{Biopolymers} \xrightarrow{2} \text{Compexes} \xrightarrow{3} \text{Networks} \qquad (6\text{-}15)$$

We will refer to Scheme (6-15) as the principle of the *triple articulations of the cellese* (TAC).

Table 6-4 An estimation of the average information content, I, or the complexity, H, of a linguistic text or a metabolic pathway based on the *cellese-humanese isomorphism* thesis and the simplified version of Shannon's formula, Eq. (4-3). The cellese is postulated to consist of two sub-languages -- DNese and proteinese**.**

Language	Letters in alphabet (a)	Letters in a word (b)	Words in a sentence (c)	Sentences in a text (d)	Complexity[1] of a text (H or I, in bits)
English	26	~10	~10	~10	~ $4.7\text{x}10^3$
DNese	~60 (Nucleotide triplets)	~100 (Genes)	~10 (Genes co-expressed)	~10 (Genes working as a pathway)	~$5.9\text{x}10^4$
Proteinese	20 (amino acids)	~100 (Polypeptide)	~10 (Complexes/ Metabolons)	~10 (Metabolic pathways)	~$4.3\text{x}10^4$

[1]The complexity of a linguistic system (viewed from the perspective of the message source) is measured in terms of Shannon's entropy, H, i.e., Eq. (4-3), which is equivalent to information, I, when viewed from the receiver's point of view (Seife 2006).

It is interesting to note that the complexities of linguistic and molecular texts (see the last column of Table 6-4) are the same within one order of magnitude. The *cellese* can be viewed as the *formal* aspect of the living cell whereas the set of physicochemical principles and laws embodied in '*biocybernetics*' (Ji 1991) represents the *physical* (i.e., energetic/material) aspect of the living cell. In other words, it may be stated that

> "The *cell language theory* (Ji 1991, 1999b) and *biocybernetics* (Ji 1991) are the complementary aspects of the Bhopalator, the molecular model of the living cell. (6-16)

6.1.4 Double Articulation, Arbitrariness of Signs, and Rule-Governed Creativity

Of the 13 design features of human language described by Hockett (1960), three of them stand out in terms of their possible application to biology. These are i) *double articulation* (extended to the triple articulation described in Table 6-3, ii) *arbitrariness of signs*, and iii) *rule-governed creativity* (see Table 6-6). It will be shown below that these features have molecular counterparts in cell language and may be necessary to maximize the channel capacity of biological communication systems (Ji 1997a), thereby facilitating biological evolution itself.

In Table 6-3, cell and human languages are compared from a formal (i.e., linguistic) point of view. In contrast, Table 6-5 compares cell and human languages from a physical point of view.

Table 6-5 A *physical (or material)* comparison between human and cell languages

	Human Language (*Humanese*)	**Cell Language** (*Cellese*)
1. Scale	Macroscopic	Microscopic
2. Signifier	Words	Molecules
3. Signified	Concepts	Gene-directed molecular processes
4. Rules wrought by	Social conventions	Biological evolution
5. Information Transmission by	Sounds & light (i.e., sound and electromagnetic waves)	Conformons[1] & IDSs[2] (i.e., mechanical and concentration waves)
6. Maximum Information Principle made possible by	Arbitrariness of signs with respect to their objects or referents	Arbitrariness of molecular signs with respect to their target functions

[1]Conformational strains of biopolymers localized in sequence-specific sites (Chapter 8).
[2]Intracellular Dissipative Structures such as gradients of ions, metabolites, proteins, etc. inside the cell (Chapter 9).

One of the design features of the human language, *arbitrariness of signs*, states that there is *no inevitable link* between the signifier (also called signs or representamen) (see Figure 6-2) and the signified (object or referent) (Lyons 1993, p.71). The arbitrary nature of signs in human language contributes to the flexibility and versatility of language, according to linguists. In addition, the author suggested that the arbitrariness of signs maximizes the amount of the information that can be transmitted by a sign, which idea being referred to as the *Maximum Information Principle* (Ji 1997a, pp. 36-37). Since cell language is isomorphic with human language, both belonging to the symmetry group,

SG(5) (see Section 6.1.2), the *arbitrariness of signs* should apply to molecular signs in cell language, leading to the following inference:

> *"Just as the link between signs and their objects is arbitrary in human language, so the relation between molecular signs and their objects (or referents) are arbitrary, likely because such arbitrariness is necessary to maximize the amount of the information transmitted through or carried by molecular signs."* (6-17)

For convenience, we will refer to Statement (6-17) as the *principle of the arbitrariness of molecular signs* (PAMS). Some experimental data supporting PAMS will be discussed in Section 12.10, where yeast RNAs are found to be divided into two distinct groups called the *cis*- and *trans-regulatory groups*, based on their genotypes, the former being less arbitrary (and thus carrying less genetic information) than the latter by a factor of about 3.

The *principle of arbitrariness of molecular signs* may be viewed as an aspect of the more general principle of *rule-governed creativity* (Ji 1997a). Both these principles appear to apply to multiple levels of biological organizations (as indicated in Table 6-6), from protein folding (Row 1a) to other processes on the molecular (Row 1b, 1c and 1d) and cellular (Rows 2 and 3) levels.

Table 6-6 The principles of the arbitrariness of molecular signs, rule-governed creativity, and constrained freedom in action at various levels of living systems

Levels		**Sign (Rule, Constraints)**	**Object/Function (Creativity, Freedom)**
1. Molecules	a. Protein Folding	Amino acid sequences	3-Dimensional shapes or folds
	b. Catalysis	Protein shape	Chemical reaction catalyzed
	c. Allostery	Allosteric ligand	Chemical reaction regulated
	d. Binding	Transcription factor	Structural genes expressed
2. Cell-Extracellular Interactions		Intercellular messengers	Signal transduction pathways
3. Cell-Intracellular Interactions		Genome	Morphology, physiology

The arbitrary relation between amino acid sequence and the 3-dimensional shape of a protein (see Row 1a in Table 6-6), which in turn determining its function, has already

been pointed out in Tables 6-1 and 6-2 and is further discussed in Section 11.1. But protein folds are not entirely independent of amino acid sequences or completely dependent on them either, which may therefore be more accurately described as "quasi-deterministic" (Ji et al. 2009b). Although point mutations have been demonstrated to alter the shapes and functions of some proteins (but not all), it has also been found that an identical amino acid sequence can lead to more than one dominant conformations or folds, depending on the environmental conditions under which proteins fold. In fact, the Anfinsen's classic experiments with ribonuclease A carried out in 1954 clearly demonstrate how sensitively dependent ribonuclease A conformations are on the environmental conditions under which it folded. The refolding of the denatured ribonuclease A induced by the removal of urea followed by the removal of 2-mercaptoethanol led to the native conformation of the enzyme with the 100% recovery of its enzymic activity but, when the refolding was induced by removing the denaturants in the reverse order, i.e., removing 2-mercaptoethanol first followed by the removal of urea, the enzyme folded into non-native conformations with only 1% of its enzymic activity recovered. Thus, the Anfinsen experiment of 1954 supports the notion that *conformations of proteins are the functions of both i) amino acid sequences and ii) the environmental conditions under which proteins fold.* These dual conditions for protein folding constitute the core of the *unpredictability of the 3-D protein folds* (U3DPF) (see Statement 6-1). Thus the principle of arbitrariness of molecular signs (PAMS), Statement (6-17), may best regarded as reflecting an aspect of the molecular version of the principle of *rule-governed creativity* (*RGC*), another of the 13 design features of human language (Hockett 1960). RGC states that native speakers are able to produce an indefinitely large number of novel sentences based on finite sets of words and grammatical (or syntactic) rules and that these sentences can be understood by others in the linguistic community even though they never encountered them before (Lyons 1992, pp. 228-231, Harris 1993, pp. 57-58, 99-100). A *molecular version* of RGC may be stated as follows:

"Just as humans can produce an indefinitely large number of novel and meaningful sentences based on finite sets of words and grammatical rules, so living cells have evolved to produce an indefinitely large number of novel (i.e., unpredictable) functional molecular processes based on finite sets of molecules and physicochemical principles." (6-18)

Statement (6-18) may be referred to as the principle of rule-governed productivity, the principle of constrained freedom (PCF), or the principle of rule-governed molecular creativity. The principle of constrained freedom is symmetric or isomorphic with the principle of rule-governed creativity with respect to the following transformations –

i) replace "rule-governed" with "constrained", and
ii) replace "creativity" with "freedom".

These mutually replaceable elements in quotation marks may be considered to form a group comparable to the permutation group of Galois in his theory of polynomial equations (http://en.wikipedia.org/wiki/Galois_theory).

Just as it is impossible to predict the 3-D folds of a protein based on its amino acid sequence, so it is suggested in Row 1b in Table 6-6 that *it would be impossible to predict the nature of the chemical reaction that is catalyzed by an enzyme based solely on the 3-D shape (also called conformers, not to be confused with conformons of Chapter 8) of the enzymes alone, because the link between protein shape and the chemical reactions it catalyzes is not deterministic but arbitrary within physicochemical constraints (and hence quasi-deterministic),* reflecting the uncertainty about the environmental conditions under which biological evolution has selected the particular enzyme-catalyzed reaction.

The arbitrariness of the link between the shape of an allosteric ligand and the enzymic reaction it regulates (Row 1c) was pointed out by J. Monod (1971) who referred to it as 'gratuity'. Similarly, it is suggested in Row 1d that the link between the shape of a transcription factor and the nature of the structural gene whose expression it regulates is arbitrary within physicochemical constraints (i.e., *quasi-deterministic*), presumably to maximize the efficiency of the information transfer mediated by transcription factors (Ji 1997a).

Again in analogy to the unpredictability of the 3-D protein folds from amino acid sequences alone, so it is thought to be impossible to predict *a priori* the nature of the signal transduction pathways being activated based on the 3-D shape of intercellular messengers (Row 2) such as hormones, cytokines, and autoinducers.

Finally, Row 3 in Table 6-6 suggests that there may be no inevitable (i.e, deterministic) link between a genome and its phenotype, including the morphology and physiological processes of the organism involved. For example, human anatomy and physiology are arbitrarily related to and hence cannot be predicted from the human genome based on the laws of physics and chemistry alone. Again, to the extent that the link between a genome and its phenotype is arbitrary in the above sense, to that extent may the genome have been optimized to transfer information from one generation to the next which entails information transfer in space and time. The identical twin studies of the human brain cognitive functions using functional magnetic resonance imaging (fMRI) technique (Koten Jr. et al. 2009) indicates that brain functions such as memorizing and recognition are partly gene-dependent and partly gene-independent, i.e., quasi-deterministic with respect to genetic influence, consistent with the *principle of constrained freedom*.

6.2 Semiotics

Semiotics is the study of signs that dates back to ancient times when farmers predicted the weather from cloud patterns in the sky, or doctors diagnosed diseases based on the symptoms of patients. The American chemist-logician-philosopher Charles Sanders Peirce (1839-1914) has made a major contribution to establishing the field of modern semiotics which has been applied to a wide range of disciplines from linguistics, to art, to philosophy, and to biology (Sebeok 1990, Emmeche 2002, 2003, Hoffmeyer 1996, Barbieri 2008a,b,c, Fernández 2008). Since signs can be divided into two types – macroscopic (e.g., stop signs) and microscopic (e.g., DNA) -- based on their physical sizes, it would follow that semiotics itself can be divided into two branches – *macrosemiotics* and *microsemiotics* (Ji 2001, 2002a). Few biologists would deny that DNA molecules are *molecular signs,* since they encode (or refer to) RNA and protein

molecules that are different from themselves. Likewise few biologists would deny that the cell is the smallest physical system that can read and implement the genetic information/instructions encoded in DNA, leading to the following conclusions:

Molecular and cell biology constitute a part of *biosemiotics*, the study of living systems viewed as sign processors (Emmeche 2003), and, since the cell is arguably the smallest DNA-based physical system that can process molecular information and perform molecular computation in the sense of Wolfram (2002) (Ji 1999a) and since the cell is the smallest unit of all living systems, *microsemiotics* constitutes the foundation of *biosemiotics*, just as *statistical mechanics* underlies *thermodynamics*.

6.2.1 The Peircean Theory of Signs

According to Peirce,

> "A *sign*, . . . , is *something* which stands to *somebody* for *something* in some *respect* or *capacity*." (Buchler 1955, p. 99). (6-19)

Thus, 'apple' is a sign referring to a juicy spherical fruit to someone, E, who speaks English. But 'apple' is not a sign for a Korean, K, who does not understand English. For K, the sign, S, for the same object, O, is not 'apple' but 'sah-gwah'. So, it is evident that the definition of a sign, S, must include, in addition to O, a third element that Peirce referred to as *interpretant*, I, which is well characterized in the following paragraph quoted in (Houser et al. 1998):

> "A *sign* is a thing which serves to convey knowledge of some other thing, which it is said to *stand for* or *represent*. This thing is called the *object* of the sign; the idea in the mind that the sign excites, which is a mental sign of the same object, is called an *interpretant* of the sign." (6-20)

Thus, the interpretant is the effect that S has on the mind of its interpreter or as the mechanisms or processes by which the interpreter or the processor of S is made to connect O and S. That is, in order for a sign process to occur successfully, there must be interactions among three elements, S, O, and I, within the sign processor. It was Peirce who first recognized the necessity of invoking these three elements in the definition of a sign and their actions (which he called 'semiosis'). In other words, a sign, according to Peirce, is an irreducible triad of S, O, and I, which idea is often referred to as the "irreducibility of the sign triad" or the "triadicity of a sign." It is important to note that, in this definition of a sign, the term 'sign' has dual roles – as a *component* of the sign triad and as the *sign triad itself*. To distinguish between these two roles, Peirce coined the term 'representamen' to refer to the narrower sense of the term sign (Buchler 1955, p. 121). Thus, we may represent the Peircean definition of a sign diagrammatically as follows:

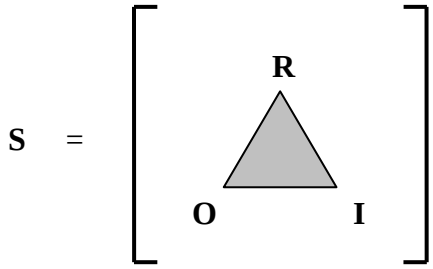


Figure 6-2 A diagrammatic representation of the *Peircean sign triad*. **S** = sign, **R** = representamen (also often called a *sign or a sign vehicle*), **O** = object, and **I** = interpretant. Unless pointed out otherwise, sign usually means **R**, a component of the irreducible sign triad. Also, it is important to note that the interpreter of **R** or the material system that process **R**, thereby implementing semiosis, is not explicitly discussed in semiotics literature but is assumed to be present. We may use the triangle itself to represent this interpreter, thus graphically distinguishing between *interpretant* (one of the three apexes or nodes) and *interpreter* (the triangle itself). It is important to note that the bracket symbolizes the *inrreducibility* of Peircean sign triad: i.e., none of the three elements can be replaced by any other.

Although the study of signs can be traced back to the beginning of the human history as already pointed out, the investigation of signs as a fundamental science did not begin until the Portuguese monk John Poinsot (1589-1644) and C. S. Peirce (apparently independently of Poinsot) undertook their comprehensive and systematic studies of signs (Deely 2001).

The definition of signs that Peirce formulated can be extended to molecular biology, although Peirce probably did not know that such a possibility existed because he died about four decades before Watson and Crick discovered the DNA double helix, that ushered in the era of molecular biology. Genes encoded in DNA fit the definition of the Peircean sign, because they encode and stand for their complementary transcripts, RNA molecules and their functions, which are evidently distinct from the molecular structure of DNA. One plausible candidate for the *interpretant* for DNA viewed as a molecular sign is the *state of the cell*, since whether a given gene encoded in DNA is transcribed to RNA or not depends on the state the cell is in, leading to the following diagrammatic representation of DNA as a sign (Ji 2002a).

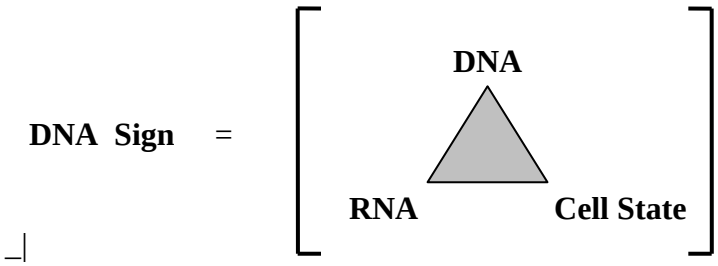


Figure 6-3 Genes encoded in DNA as an example of Peircean signs at the molecular level. The role of interpretant is suggested to be fulfilled by *cell states*, and the interpreter of DNA is postulated to be the *cell* itself represented by the triangle. This definition seems to be consistent with the finding that only a select set of genes are expressed in cells at any given time and under a given environmental condition depending on the internal state of the cell (Nishikawa, Gulbahce and Motter 2008).

Peirce distinguished between *semiotics* and *semiosis*. Semiotics is the systematic knowledge that human mind has created about semiosis based on empirical data, while semiosis refers to the totality of the natural and artificial processes whose occurrence requires the mediating role of signs. Thus, we may logically conclude that, *although semiotics depends on human mind, semiosis does not.* The causal relation between *semiotics* and *semiosis* may be represented diagrammatically as shown in Figure 6-4:

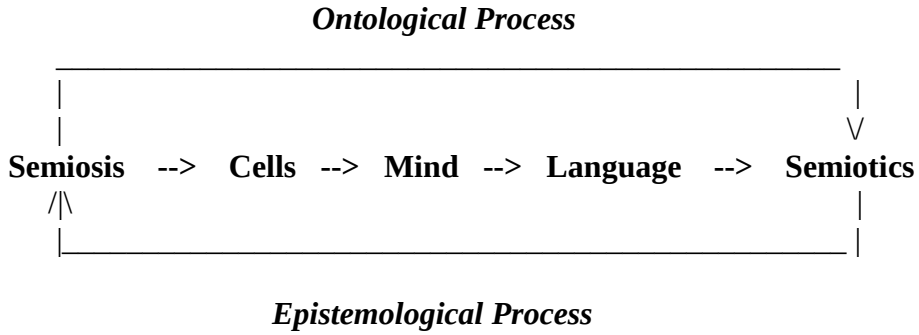


Figure 6-4 The cyclical, or reversible, relation between *semiosis* and *semiotics*. he expression 'A --> B' should be read as "B presupposes A" or "B cannot exist without A". The upper arrow from left to right indicates the *ontological* process in the Universe known as *evolution*, while the lower arrow from right to left signifies the *epistemological* causal relation resulting from the inferential activities of the human mind. It is assumed that ontological processes are independent of the human mind but epistemological processes are dependent on it. This figure is consistent with the principle of closure discussed in Section 6.3.2.

6.2.2 The Principle of Irreducible Triadicity: The Metaphysics of Peirce

According to the metaphysics of Peirce, all phenomena, material or mental, living or nonliving, comprise three basic elements or aspects – *Firstness* (e.g., quality, feeling, possibilities), *Secondness* (e.g., facts, actualities, reaction, interaction, brute force), and *Thirdness* (e.g., generality, laws, habit-taking, representation, reasoning). For example, in logic, there are three kinds of relations; C = monadic, A = dyadic, and B = triadic relation. We may represent this principle diagrammatically as follows:

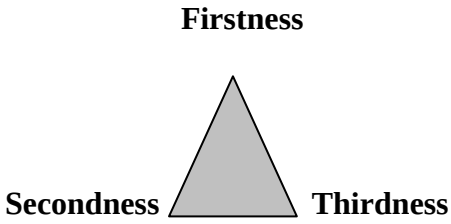


Figure 6-5 A diagrammatic representation of the principle of irreducible triadicity of Firstness, Secondness and Thirdness of Peirce (Goudge 1969, Hausman 1997, de Waal 2001, Sheriff 1994, Feibleman 1946).

The *Threeness* plays a fundamental role in the metaphysics of Peirce, metaphysics being the study of the most general traits of reality. *Reality is the object of the conclusions one cannot help drawing*. As pointed out by Pierce, "When a mathematical demonstration is clearly apprehended, we are forced to admit the conclusion. It is evident; and we cannot think otherwise." (Goudge 1969). Metaphysics studies "the kinds of phenomena with which every man's experience is so saturated that he usually pays no particular attention to them". One way to get a feel of the three metaphysical categories of Peirce is through some of the examples that Peirce gave of these categories throughout his career. These are collected in Table 6-7, which was adopted from (Debrock 1998). It is evident that the examples are not logically tight, and, indeed, they are "vague" or "fuzzy" (Section 5.2.5), and even contradictory in some cases, having some overlaps here and there and missing some examples as well. Nevertheless, it is possible to recognize (i) the unmistakable family resemblances among most of the items listed within each category (i.e., within each column), and (ii) distinct family characteristics present among the three categories (i.e., within each row).

Table 6-7 The evolution of Peirce's nomenclature of categories. Reproduced from [Debrock 1998] except items 8 and 9.

	Year (Peirce's age)	**Firstness**	**Secondness**	**Thirdness**
1	1867 (*28*)	quality	relation	representation
2	1891 (*52*)	first	second	third
3		spontaneity	dependence	mediation
4		mind	matter	evolution
5		chance	law	tendency to take habits
6		sporting	heredity	fixation of

				character
7		feeling	reaction	mediation
8	1894 (*55*)	-	-	learning
9		-	-	government
10	1896 (*57*)	quality	fact	law
11	1897 (*58*)	ideas of feelings	acts of reaction	habits
12		quality	shock/vividness	-
13		feeling	reaction	thought
14	1898 (*59*)	quality	reaction	mediation
15		first qualities/ ideas	existence/ reaction	potential/ continuity

6.2.3 Peircean Signs as Gnergons

One corollary of Figure 6-4 is that the elucidation of the connection between *semiotics* and *life* would be tantamount to elucidating the principles underlying *semiosis* itself (in agreement with Sebeok 1990), and this is because life (as exemplified by cells and mind) presupposes semiosis. Based on the information-energy complementarity principle discussed in Section 2.3.2, we can conclude that, like all fundamental processes in nature, *semiosis* must have two complementary aspects – the *energetic/material* (e.g., computer hardware, or ATP in cells) and the *informational* (e.g., computer software or genetic information encoded in DNA). Of these two aspects, the traditional semiotics as formulated by Peirce has emphasized primarily the *informational* aspect of semiosis, apparently ignoring the equally fundamental e*nergetic/ material* aspect. It was only with the advances made in both *experimental* and *theoretical* branches of molecular and cell biology during the past several decades that *the essentiality of the energy/material aspect of semiosis has come to light* (Ji 1974a,b, 1985, 1988, 1991, 1997a,b, 1999b, 2000, 2002a,b, 2004a,b). Thus it has been postulated that all self-organizing processes in the Universe, including semiosis, are driven by a complementary union *of information* and *energy,* i.e., *gnergy* (Sections 2.3.2 and 4.13 and Ji 1991, 1995). Since information can be alternatively called 'gnon' (from the Greek root *gnosis* meaning knowledge) and energy 'ergon' (from Greek root *ergon* meaning work or energy), the *gnergon*, the discrete unit of *gnergy*, can be viewed as the complementary union of the *gnon* and the *ergon*:

Gnergon = Gnon ^ Ergon (6-21)

where the symbol "^" denotes a *generalized complementarity relation as* defined in Section 2.3.3 (Ji 1991, 1995). That is, "C = A^B" reads as "A and B are complementary aspects of C", or "C is a complementary union of A and B". Since it has been postulated that Gnergy serves as the universal driving force for all self-organizing processes in this Universe (see Figure 4-8), including molecular processes in the living cell (Ji 1991), we can interpret Figure 6-4 as implying the following general statement:

"*Life* results from *semiosis* driven by *gnergy*." (6-22)

Those not familiar with Peirce's (1839-1914) semiotics may think of signs as synonymous with 'symbols' like stop signs and written words on printed pages. Such a view is frequently referred to as "glossocentric" or "language-centered". But the concept of signs according to Peirce is much more general and includes not only linguistic symbols, but also icons (e.g., portraits, statutes, maps, electronic circuit diagrams), and indexes (e.g., smokes, laughter, fever, weathervane). The generality of signs is in part due to the fact that we think in signs. As someone said: *Think of an elephant; do you have an elephant in your head?* The neuronal firing patterns associated with our thoughts are signs representing their objects, whatever they may be, because neuronal firing patterns are not identical with the objects that they stand for.

Peirce divides signs into a total of nine classes (Buchler 1955):

"Signs are divisible by three trichotomies; first, according to as the sign itself is a mere quality ('qualisign'; my addition)), is an actual existent ('sinsign'), or is a general law ('legisign'); secondly, according as the relation of the sign to its object consists in the sign's having some character in itself ('icon'), or in some existential relation to the object ('index'), or in its relation to an interpretant ('symbol'); thirdly, according as its interpretant represents it as a sign of possibility ('rheme') or as a sign of fact ('dicent sign') or a sign of reason ('argument')." (6-23)

The term 'interpretant' here can be understood as the effect that a sign has on the mind of an interpreter, or as "meaning", "significance" or "more advanced sign". The above classification of signs by Peirce is summarized in Table 6-8.

Table 6-8 The classification of signs based on the dual trichotomies –i) the ontological/material trichotomy (OT) (first row), and ii) the phenomenological/formal (PT) trichotomy (first column) (Ji 2002c).

OT / *PT*	**Firstness** (Potentiality)	**Secondness** (Facts)	**Thirdness** (Law)
Firstness (Sign)	*Qualisign*	*Sinsign*	*Legisign*

Secondness (Object)	*Icon*	*Index*	*Symbol*
Thirdness (Interpretant)	*Rheme*	*Dicent Sign*	*Argument*

Each of the nine types of signs appearing in the *interior* of Table 6-8 has dual aspects (reminiscent of the wave/particle duality of light) – i) the *ontological* (or *material*) aspect, and ii) the *phenomenological* (or *formal*) aspects, which appear on the *margins* of the table. The ontological/material aspect of a sign can be identified with *energy/matter* properties, while the phenomenological/formal aspect with *informational* properties. It is for this reason that the Peircean signs located in the interior of Table 6-8 can be viewed as examples of *gnergons*, the discrete units of gnergy postulated to be the ultimate cause of, or ground for, all self-organizing (or pattern-forming) processes in the Universe (Ji 1991, 1995). Since all sign processes (semiosis) can be viewed as species of self-organizing processes, ultimately driven by the free energy of exergonic chemical reactions (e.g., ATP hydrolysis or oxidation of NADH) or physical processes (e.g., heat flow, solar radiation, the Big Bang, etc.), it would follow that gnergons are the ultimate causes of semiosis (Ji 1995, 2002c) consistent with Figure 4-8.

Complementarism, a scientific metaphysics rooted in both contemporary biology and Bohr's complementarity (Section 2.3.4), states that the ultimate reality consists in a complementary union of *information* and *energy*, i.e., *gnergy*. Since signs are species of gnergons, it would follow that Peirce's semiotics falls within the domain of complementarism. This assertion may be supported by the following arguments:

1) Peirce's semiotics deals mainly with macroscopic signs, i.e., signs with macroscopic dimensions "perfusing" the Universe: Peirce dealt mainly with *macrosemiotics*. This is not surprising because Peirce died in 1914, about four decades before the discovery of DNA double helix that ushered in the age of molecular biology and *microsemiotics* (Ji 2001, 2002a).

2) Complementarism can be applied not only to Peirce's semiotics (as suggested above) but also to molecular and cell biology, as evident in the formulation of the theory of "microsemiotics" based on the gnergy concept (Ji 2002a,c). *Microsemiotics* can be regarded as synonymous with the twin theories of the living systems known as *biocybernetics* (Ji 1991) and *cell language theory* (Ji 1997a). Thus the following relation suggests itself:

Complementarism = *Macrosemiotics* + *Microsemiotics*

= Peirce's semiotics + Biocybernetics/Cell Language Theory (6-24)

Consistent with Peirce's triadic ontology, the principle of *complementarity* may itself be manifested in the Universe in three distinct modes:

Firstness = **Complementarity in metaphysics** (e.g., Yin and Yang as complementary aspects of the Tao of Lao-tze; Extension and Thought as the complementary aspects of Substance of Spinoza; Body and Mind as the complementary aspects of the Flesh of Merleau-Ponty (Dillon 1997))

Secondness = **Complementarity in physics** (e.g., the wave-particle duality of light)

Thirdness = **Complementarity in life sciences** (e.g., hysterical anesthesia of William James (Stephenson 1986)), physiology (i.e., the left-right hemispheric specialization (Cook 1986), and molecular and cell biology (e.g., the *information-energy complementarity* of *gnergy* (Ji 1991, 1995))

These ideas are schematically represented in Figure 6-6.

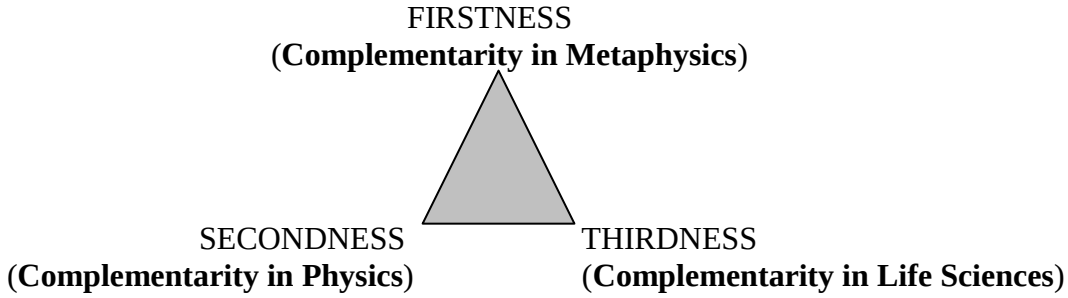


Figure 6-6 The three modes of being of the generalized complementarity (Ji 1995). This diagram suggests the possibility that *life sciences* as Thirdness may serve as the mediator between *metaphysics* and *physics. Life science* may be viewed as synonymous with *cognitive sciences, since all organisms are cognizant of and interact with their environment*. The three nodes of the triangle may also be interpreted diachronically (Section 4.5): Firstness gave rise to Secondness, which in turn gave rise to Thirdness.

If the ideas expressed in Figure 6-6 are correct, the separation and divergence of physics and metaphysics that are widely believed to have begun with Galileo's experiments with falling bodies in the 17th century may be expected to be reversed through the mediating role of the life sciences in the 21st century. In other words, the principle of information/energy complementarity manifested in *biology* (Ji 1991, 1995) may provide the theoretical framework for integrating *metaphysics* and *physics*.

6.2.4 Macrosemioticfs vs. Microsemiotics: The Sebeok Doctrine of Signs

As indicated in Section 6.2, we can divide semiotics into two branches – the *macrosemiotics* dealing with macroscopic signs such as written words and texts, and the *microsemiotics* concerned with molecular signs such as DNA, cytokines, and neurotransmitters, etc. Peirce did not have access to the empirical evidence that came to light only in the mid-20th century that semiotic processes are not confined to the macroscopic world (*macrosemiosis*) but also occur on the molecular level (*microsemiosis*). The possibility of extending Peircean semiotics from macroscale to microscale was clearly foreseen by Sebeok in 1968 when he wrote (as cited in Deely 1994):

> "*. . . the genetic code must be regarded as the most fundamental of all semiotic networks and therefore as the prototype for all other signaling systems used by animals, including man. From this point of view, molecules that are quantum systems, acting as stable physical information carriers, zoosemiotic systems, and, finally, cultural systems, comprehending language, constitute a natural sequel of stages of ever more complex energy levels in a single universal evolution. It is possible, therefore, to describe language as well as living systems from unified cybernetic standpoint . . . A mutual appreciation of genetics, animal communication studies, and linguistics may lead to a full understanding of the dynamics of semiotics, and this may, in the last analysis, turn out to be no less than the definition of life."*
>
> (6-25)

Elsewhere (Ji 2001), it was suggested that Statement (6-25) be referred to as the *Sebeok doctrine of signs* for convenience of reference.

The first full-length paper on microsemiotics was published in (Ji 2002a). Despite the enormous difference in the sizes of the sign processors involved in macro- and microsemiosis (see Table 6-9 below), it is surprising that there exists a set of principles that is common to the semiotic processes on both these levels as evidenced by the isomorphism found between human and cell languages (see Table 6-3) (Ji 1997a,b, 1999b, 2001, 2002a). This unexpected finding may be rationalized if we can assume that semiosis, the process of handling *information*, is scale-free, just as the process of handling *energy* are scale-free as evidenced by the universal applicability of the laws of energy and entropy to all structures and processes in the Universe from the microscopic to the cosmological, another evidence supporting *the information-energy complementarity* principle discussed in Section 2.3.2.

Table 6-9 A comparison between the physical dimensions of the *macrosemiotic* and *Microsemiotic agents*. Notice that the linear dimension of the human body is about five orders of magnitude greater than that of the cell. Adapted from (Ji 2001).

Parameters	**Macrosemiotics**	**Microsemiotics**
1. Sign Processor or Agent	Human Body	Cell

2. *Size* *Linear size (m)* *Volume (m^3)*	Macroscopic ~ 1 ~ 1	Microscopic ~ 10^{-5} ~ 10^{-15}
3. *Number of cells involved*	~10^{13}	1
4. *Signs used for communication* *Linear size (m)* *Volume (m^3)*	Words & sentences ~10^{-3} ~10^{-9}	Molecules ~ 10^{-8} ~10^{-24}
5. *Mechanics obeyed*	Classical	Classical and quantum
6. *Thermal stability at ~25° C*	Yes (i.e., rigid)	No (i.e., thermally fluctuating)
7. *Powered (or driven) by*	Chemical reactions	Chemical reactions

6.2.5 Three Aspects of Molecular Signs: Iconic, Indexical and Symbolic

If *macrosemiotics* and *microsemiotics* are isomorphic as asserted by the cell language theory (Ji 1997a, 2001), it may be inferred that the triadic aspects of macrosigns (i.e., signs with macroscopic sizes, Table 6-9), namely, the iconic, indexical, and symbolic aspects (Table 6-8), may also be found in microsigns (or molecular signs). As already indicated in Sections 6.2.1 and 6.2.3, (i) a *sign* stands for something (called *object or signified*) to someone (interpreter, receiver or sign processor) in some context (environmental contingencies), and ii) there are three kinds of signs – *iconic* signs (e.g., a statute) related to their objects by *similarity*, *indexical* signs (e.g., smoke) related to their objects by *causality*, and *symbolic* signs (e.g., words) related to their objects by *convention, rules*, and *codes* which are *arbitrary* from the standpoint of the laws of physics and chemistry.

Applying these concepts and definitions to the molecular information processing systems in the living cell, it may be conjectured (1) that DNA serves as the sign for RNA to cells during the transcription step catalyzed by *transcriptosomes*, RNA in turn serving as the sign for proteins during the translation step catalyzed by *ribosomes*, (2) that the relation between DNA and RNA during transcription is primarily iconic (due to Watson-Crick base paring) and indexical (requiring the mechanical energy stored in DNA as *conformons* (Ji 2000) to power orderly molecular motions), and (3) the relation between mRNA and protein synthesized during translation is *iconic* (owing to the complementary shapes of codons and anti-codons), *indexical* (requiring *conformons* in the ribosome to drive the orderly movement, or *translation*, of aminoacyl tRNA molecules along the mRNA track), and *symbolic* (due to the *arbitrariness of the relation* between the codons of mRNA and the corresponding amino acids carried by tRNA, i.e., the arbitrariness of the genetic code) (Barbieri 2003, 2008c).

If these conjectures prove to be correct in principle, it would be logical to conclude that biological information processing in the cell cannot be completely characterized in terms of the *laws* of physics and chemistry alone but requires in addition the *rules* (e.g., genetic codes) engendered by biological evolution, thus supporting the *von Neumann-Pattee principle of matter-sign complementarity* as applied to biological systems (Pattee 2001, 2008, Ji 1999). In other words, biology is best viewed not as an autonomous science separate from physics and chemistry as some evolutionary biologists assert but a *triadic* science based on *physics*, *chemistry*, and *semiotics* on equal footings.

6.2.6 Human and Cell Languages as Manifestations of *Cosmolanguage*

The proposition that the cell possesses its own language, 'the cell language', seems almost tautological in view of the fact that cells communicate, since *no communication would be possible without a language.* The natural question that then arises concerns the relation between human language and cell languages. There may be three possibilities:

1) Human language has evolved from cell language.
2) Both cell and human languages are different manifestations of a third language that exists independent of, and serves as the source of, them.
3) Possibilities 1) and 2) are not mutually exclusive but represent the *diachronic* and the *synchronic* manifestations, respectively, of the fundamental characteristics of the Universe we inhabit, namely, that *the final cause of our Universe is to know itself through Homo sapiens.* (Such a Universe was named *the Self-Knowing Universe* or *Universum sapiens* in (Ji 1991).)

The author is inclined to accept the third possibility. If this view is true, we are living in the *Self-Knowing Universe* where both cell and human languages exist as diachronic manifestations of a third language which may be referred to as the Cosmological language (or *Cosmolanguage*, for short). By invoking the existence of the cosmolanguage, I am in effect postulating that the *language principle* (or more generally *semiotic principles*) applies to all phenomena in the Universe. In (Ji 2002a), I expressed the same conclusion as follows:

> ". . . *the principles of language (and associated semiotic principles of Peirce, including rule-governed creativity and double articulation) are manifested* at two levels – at the material level in the external world as well as at the mental level in the internal world. We may refer to this phenomenon as the 'principle of the dual manifestations of language or semiosic principles', or the 'language duality' for short. Like the wave/particle duality in physics, this matter/mind duality may be a reflection of a deep-lying complementarity which may be identified with the following triad . . . ":
>
> (6-26)

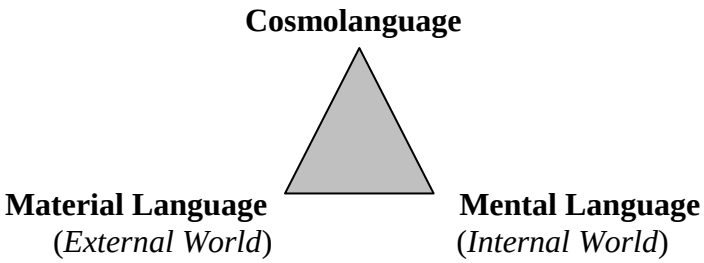


Figure 6-7 The postulate that the cosmolanguage is manifest in two ways – externally as material language (including cell language) and internally as mental language (exclusive to *Homo sapiens* ?).

Figure 6-7 can be read in two ways – diachronically (or ontologically) as indicating the evolution of the mental and material languages from the cosmolanguage, and synchronically (or epistemologically) as indicating that the material and mental languages are complementary aspects of the cosmolanguage. Both these interpretations are consistent with the model of the Universe called the Shillongator proposed in (Ji 1991). Figure 6-7 may be consistent with Wolfram's *Principle of Computational Equivalence* (Section 5.2.1) if we view language, communication and computation as fundamentlay related.

6.2.7 Semiotics and Life Sciences

S*emiotics* and the *science of life* (i.e., biology, agricultural science, and medicine) have had a long and venerable history of interactions (e.g., ancient physicians in both East and West diagnosed the diseases of patients based on symptoms; farmers used cloud patterns to predict weather, etc.), but the connection between *semiotics* and *life sciences* in general may have undergone a significant weakening when the reductionist scientific methodologies were imported into life sciences from physics and chemistry around the 19th century. The reductionist trend in physics began with the birth of the mathematically oriented physics following the successful experiments with falling bodies performed by Galileo in the 17th century. After over three centuries of domination of physical and biological sciences by reductionism, a new trend seems to be emerging in physics and life sciences that emphasizes *integration* and *holism*, without necessarily denying the fundamental importance of *reductionism* (Elsasser 1998, von Baeyer 2004, Emmeche 2002, Hoffmeyer 1966, Fernández 2008). As a concrete example of such a new trend, we may cite the isomorphism found between the cell language and the human language (see Table 6-3). One of the major goals of this book is to reveal the deep connection that exists between *life* and *semiosis*, thereby laying the foundation for a *semiotic theory of life*, or organisms viewed as systems of *molecular signs* and *sign processes* (Hoffmeyer 1996).

6.2.8 Semiotics and Information Theory

Table 6-10 Definition of signals, signs and symbols according to Nauta (1972, p. 159).

The study of information may not be successfully carried out without the aid of *semiotics.* This is because information is carried by *signs* (without signs, no information can be generated, transformed, stored or transmitted) and the study of signs in general is the domain of *semiotics*. Nauta (1972) states a similar view in greater details:

". . . Much work has been done in the field of pure information theory, but the problems concerning the meaning (i.e., semantics vis-à-vis syntactic; my addition) and application (i.e., pragmatics: my addition) of information have largely been neglected. In our opinion, these important problems can be tackled only from a semiotic point of view. (6-27)

The key to these problems will be the analysis of signals, signs and symbols." (Nauta 1972, p. 29)

"Semiotics, divided into transmission theory, syntactics, semantics and pragmatics, and subdivided into pure, descriptive, and applied semiotics, offers a general framework for the study of information processes and for the development of a universal theory of information. In its generalized form, semiotics encompasses the following fields: (6-28)

Logistics (artificial symbols)
Linguistics (symbols)
Semiotics in a narrower sense (signs)
Automatics, the study of automatic processes and pre-coded representations and mechanisms (signals)." (Nauta 1972, pp. 61-62)

Nauta distinguishes three information carriers -- "signals", "signs", and "symbols" (Table 6-10). He defines signals as carriers of *form* but not *meaning* nor *function*; signs as carriers of form and meaning but not of function; symbols as carriers of form, meaning and functions. This contrasts with Peirce's' division of signs into "iconic signs", "indexical signs", and "symbolic signs", each of which can have form, meaning, and function (Table 6-10).

	Form	Meaning	Function
Signals	+	-	-
Signs	+	+	-
Symbols	+	+	+

It is not clear to me why Nauta invoked his triad of information carriers rather than using Peirce's original sign triad, but it may be possible to represent Nauta's information carriers as linear combinations of Peirce's triadic signs. Writing Nauta's information carriers with capital letters and Peirce's signs with lower-case letters, we may construct a set of algebraic equations as shown below, where doubly indexed coefficients, a_{ij}, indicate the degree of contribution of Peircean signs to a given information carrier (IC) of Nauta:

$$\begin{aligned} \text{Signal} &= IC_1 = a_{11}\,\text{icon} + a_{12}\,\text{index} + a_{13}\,\text{symbol} \\ \text{Sign} &= IC_2 = a_{21}\,\text{icon} + a_{22}\,\text{index} + a_{23}\,\text{symbol} \\ \text{Symbol} &= IC_3 = a_{31}\,\text{icon} + a_{32}\,\text{index} + a_{33}\,\text{symbol} \end{aligned} \qquad (6\text{-}29)$$

In general, we may write:

$$\mathbf{A}x = b \qquad (6\text{-}30)$$

with

$$A = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}, \quad x = \begin{bmatrix} \text{icon} \\ \text{index} \\ \text{symbol} \end{bmatrix}, \text{ and } b = \begin{bmatrix} IC_1 \\ IC_2 \\ IC_3 \end{bmatrix}$$

Equation (6-30) may be viewed as an algebraic expression for the relation between *information theory* (as represented by b) and semiotics (as represented by x) and **A** as the rule of transforming the Peircean semiotics to the information theory according to Nauta (1972).

More recently Debrock (1998, pp.79-89) proposed a novel theory of information viewing information as *events* rather than as *entities* and suggested that such a dynamic approach to information may be consistent with the Peirce's theory of signs. Debrock's suggestion seems consistent with the postulate that Peircean signs are gnergons, the source of energy and information to drive all self-organizing processes, including informed events (see Section 6.2.3).

6.2.9 The Cell as the Atom of Semiosis

The following statement is often made as a useful metaphor:

The cell is the atom of life. (6-31)

In addition, it is asserted here that :

The cell is the atom of semiosis. (6-32)

The term 'semiosis' is defined as any physicochemical processes that are mediated by *signs* such as *communication, computation,* and DNA-directed *construction*. This triad of processes was referred to as *the C-triad* in (Ji and Ciobanu 2003).

One consequence of combining Statements (6-31) and (6-32) is the corollary that the *cell provides the physical basis and mechanisms for both living processes and semiosis.* A theoretical model of the cell, capable of achieving both these functions, was first proposed in 1983 in an international conference on the Living State held in Bhopal, India and hence was named the *Bhopalator* (Figure 2-11) (Ji 1985a,b, 2002b). One of the basic principles underlying the Bhopalator is that of *information-energy complementarity* as manifested in two ways – as *conformons* (conformational strains of biopolymers harboring mechanical energy in sequence-specific sites; see Chapter 8) and as *IDSs* (intracellular dissipative structures such as cytosolic calcium ion gradient; see Chapter 9).

6.2.10 The Origin of Information Suggested by Peircean Metaphysics

In this Section, the general problem of the origin of information (including biological and non-biological) is discussed based on Peirce's metaphysics (Section 6.2.2). As is evident in the following quotations, Peirce made a clear distinction between *possibility*, Firstness, and actuality, Secondness (see Table 6-7):

> "Possibility implies a relation to what exists."
> (Hartshorne and Weiss 1932, paragraph #531)

> ". . . a possibility remains possible when it is not actual"
> (Hartshorne and Weiss 1932, paragraph #42)

> ". . . possibility evolves the actuality"
> (Hartshorne and Weiss 1932, paragraph #453)

> "In order to represent to our minds the relation between the universe of possibilities and the universe of actual existent facts, if we are going to think of the latter as a surface, we must think of the former as three-dimensional space in which any surface would represent all the

facts that might exist in one existential universe."
(Hartshorne and Weiss 1933, Paragraph #514)

Feibleman (1946) summarized the essence of Peirce's' distinction between *possibility* and *actuality* as follows:

"Not all *possibles* can exist: *actualit*y is a selection of them."

When I read this statement, especially the term "selection", it occurred to me that Peirce's metaphysics might provide a philosophical foundation for the *origin of information* in this Universe, since information can be broadly defined as resulting from the *selection* of a set of objects, events, or entities from a larger set of them. The formalism is very simple. Let us designate the number of all possibilities (or *possibles* of Peirce) out of which this Universe originated as *p*, and the number of actual existents (which may be called 'actuals') as *a*. Then the primordial information associated with (or imparted on) this Universe, to be designated as I_C, where C means "cosmological", may be expressed simply as the binary logarithm of the ratio between these two numbers (assuming for simplicity that all *possibles* have equal probabilities of being actualized):

$$I_C = \log_2 (p/a) \quad \text{bits} \tag{6-33}$$

Although it is almost impossible to measure or determine *p* and *a* (and hence I_C), the mere fact that we can write down a mathematical expression relating these two quantities to the information content of the Universe may be significant.

Equation (6-33) describes only the informational aspect of the origin of the Universe. The energy aspect of the origin of the Universe appears adequately described by the Big Bang theory in physics. That is, the energy requirement for the selection process implicated in Equation (6-33) is met by the dissipation of free energy (or entropy production in this case, since the Universe is isolated) attending the expansion of the Universe:

$$p \xrightarrow{\text{Entropy Production}} a \tag{6-34}$$

where the arrow indicates that *a* actuals have been selected out of *p* possibles (i.e., $p > a$). In (Ji 1991), it was suggested that *p* might be identified with (all possible) *superstrings*, and hence *a* may now be identified with a subset of *p* reified into elementary particles constituting all the material entities extant in this Universe. The total number of particles in this Universe has been estimated to be approximately 10^{80}, which is known as the Eddington umber (Barrow and Tipler 1986, p. 225). These *a* actuals are thought to possess sufficient *information* and *energy* (i.e., *gnergy*) to evolve higher-order structures such as atoms and molecules, stars, planets, galaxies, the biosphere, and organisms including humans, under appropriate conditions emergent at specific epochs in the history of the Universe (see Figure 15-12). It is interesting to note that a similar view was recently put forward by a group of cosmologists (Kane, Perry and Zytkow 2000). The biological information encoded in living systems may be viewed as ultimately

derived from the Cosmological Information, I_C, through a series of information *transductions*, similar to the well studied phenomenon of signal transductions occurring in the living cell (Section 12.16). If this view of the origin of information is correct, a set of interesting inferences could be made:

1) What happens in this Universe cannot be completely random, including biological evolution. That is, biological evolution may be constrained (or directed) by the cosmological information, I_C , encoded in non-living material entities (i.e., abiotic matter).
2) All information associated with this Universe may be continuous with (or traced back to) the origin of the cosmological information at the time of and prior to the Big Bang.
3) *Possibles*, *Actual*s, and *Information* may reflect the ontological triad of Peirce:

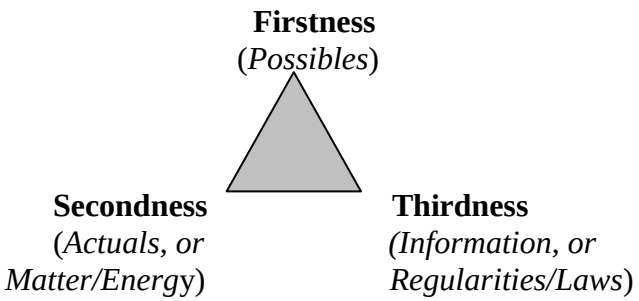


Figure 6-8 A postulated evolution (or reification) of *possibles* into *actuals* and associated *information* (*and laws*). The nodes are read in the counter clock-wise direction starting from the top node.

The similarity between Figures 6-8 and 4-5 may be significant. The similarity may be transformed into an identity simply by equating the Gnergy with the Possibles of Peircean metaphysics, leading to the following conclusions:

"*Gnergy is the source of possibles out of which all actuals in the Universe are derived."* (6-35)

6.2.11 The Triadic Model of Function

The notion of the *structure-function correlation* is widely discussed in biology. In fact, biology may be defined as the scientific study of the correlations between *structure* and *function* of living systems at multiple levels of organization, from molecules to the human body and brain (Polanyi 1968, Bernstein 1967, Kelso and Zanone 2002). The concept of *functio*n is not dichotomous or dyadic as the familiar phrase "structure-function correlation" may suggest but is here postulated to be *triadic* in the sense that a function involves three essential elements – *structure*, *processes*, and *mechanisms, all organized within an appropriate boundary or an environmental condition that constrains the processes to perform a function.* M. Polanyi (1891–1976) clearly realized

the fundamental role played by boundary conditions in effectuating living processes at the molecular, cellular, and higher levels (Polanyi 1968). A similar idea was expressed by N. Bernstein (1967) at the level of human body movement. Polanyi's and Bernstein's ideas may be expressed in the language of information theory:

$$I_X = \log_2 (w_0/w_x) \quad \text{bits} \qquad (6\text{-}36)$$

where I_X is the Shannon information (Section 4.3) associated with Function X, w_0 is the number of all possible processes allowed for by the laws of physics and chemistry, and w_x is the number of processes actually selected by the boundary conditions to perform Function X. Eq. (6-36) quantitatively expresses the idea that functions are processes selected (or constrained) by appropriate boundary conditions to perform Function X at a given level of biological organization. For the convenience of discussion, it is suggested that the boundary conditions that constrain and enable Function X to appear from the processes allowed for by the laws of physics and chemistry be referred to as the *Bernstein-Polanyi boundaries* and the information, I_X, embodied in (or needed to specify) such boundaries be referred to as the *Bernstein-Polanyi information*. The Bernstein-Polanyi boundaries (BPBs) reduce the degree of freedom of the components of the system so that they have no choice or freedom but to perform the motions or movements that constitute a function at a given level of organization. Thus, boundaries, constraints, and reduced degrees of freedom are all synonymous terms referring to a function (Polanyi 1968, Bernstein 1967). The triadic conception of function can then be diagrammatically represented as shown in Figure 6-9:

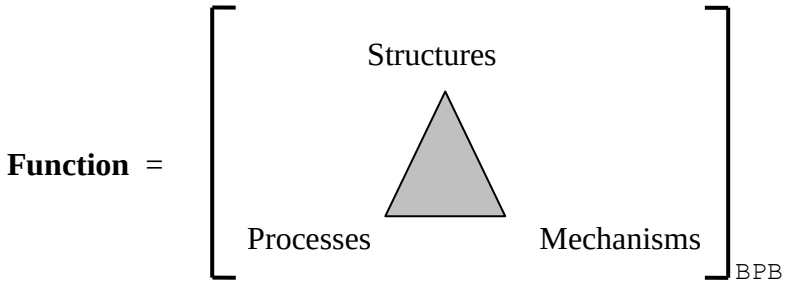


Figure 6-9 A diagrammatic representation of the triadic conception of function in biology. This diagram presents function as an irreducible triad *of structures, processes* and *mechanisms*. BPB stands for Bernstein-Polanyi boundaries. The boundary-sensitive mechanisms are thought to select only those dissipative structures that perform a desired function out of all possible processes permitted by the laws of physics and chemistry.

One advantage of Figure 6-9 is that it provides a geometric template to organize the four terms that are obviously related with one another, i.e., *function*, *structure*, *process*, and *mechanism.* It may be significant that the triadic definition of a function given in Figure 6-9 is isomorphic with the triadic definition of a sign given by Peirce (1839-1914) (see Figure 6-2) and consistyent with his metaphysics that all phenomena comprise three

basic elements (Section 6.2). Table 6-11 lists various examples of functions in biology and their triadic components

Table 6-11 Examples of various functions and their elements in biology.

Function	Structure	Process	Mechanism
1. Transcription	DNA template	RNA polymerization	RNA polymerase driven by conformons*
2. Translation	mRNA, tRNA, rRNA	Peptidyl transfer reaction	Directed movement of the ribosome components driven by conformons
3. Amino acyl tRNA synthesis	tRNA anti-codons	Amino acylation of tRNA	Allosteric control of amino acylation by tRNA anticodon
4. Protein folding	Amino acid sequence	Rate of translation	Environment-sensitive protein conformation
5. Enzymic catalysis	Protein folds	Chemical reactions	Conformon-driven regulation of the activation energy barrier
6. Semiosis	Representamen (or Signifier, Sign vehicle)	Object (or Signified, Referent)	Interpretant (or codemaking, mapping, habit-forming, evolution)

*Conformons are the mechanical energy stored in sequence-specific sites within biopolymers that are generated from exergonic chemical reactions and drive all orderly molecular motions inside the cell including enzymic catalysis, molecular motors, pumps, rotors and chromatin remodeling (see Section 8.1).

CHAPTER 8

The Conformon

Cells are examples of self-organizing chemical reaction-diffusion systems that have evolved to perform (or been selected because of their ability to perform) myriads of goal-directed (*purposive* or *teleonomic*) motions in space and time. The goal-directed molecular motions inside the living cell are carried out by biopolymers acting as molecular machines (Alberts et al. 1998), and each molecular machine is postulated to be driven by conformons. Conformons, sequence-specific mechanical strains of

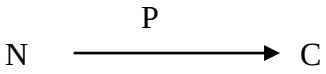
biopolymers, can be generated from the binding energy of ligands as in the Circe effect of Jencks (1975) or from the free energy of chemical reactions as in stress-induced duplex destabilizations (SIDDSs) in supercoiled DNA described by Benham (1992, 1996a, b, Benham and Bi 2004). The living cell can be represented as a system of molecular machines (e.g., myosin, kinesin, dynein, dynamin, RNA polymerase, DNA polymerase, topoisomerases, and ion pumps) that are organized in space and time in various combinations in order to carry out cell functions demanded by a given environmental condition.

Since the necessary and sufficient conditions for all self-organizations in the Universe are postulated to be the combination of free *energy* and control *information* referred to as *gnergy* (see Figure 4-8) (Ji 1991) (Section 2.3.2), the discrete units of which being referred to as *gnergons*, cells also must be driven by *gnergons*. Two classes of gnergons have been identified inside the cell so far that appear necessary and sufficient to account for cell functions – i) *conformons* (packets of conformational energy generated from substrate binding and chemical reactions and confined within biopolymers, and ii) *intracellular dissipative structures* (IDSs), i.e., the gradients of *translationally diffusible* chemicals such as glucose, pyruvate, ions, ATP, and RNA that reside *outside* biopolymers (Section 9). Using the piano as a metaphor, *conformons* can be compared to the packets of vibrational energies (or *phonons*) of strings and *IDSs* to the musical sounds generated by vibrating strings. Using the voice as another metaphor, *conformons* are akin to the vibrations of the vocal cord and *IDSs* to voice produced by vibrating vocal cord. Just as the vibrational motions of piano strings are responsible for generating sounds as the inevitable consequence of the laws of physics, so the oscillatory motions of biopolymers (i.e., conformons) are responsible to produce the *concentration waves* of diffusible molecular entities inside the cell, i.e., IDSs as a consequence of the laws of chemistry (Ji 1985a, b). These and other analogical relations are summarized in Schemes (8-1) and (8-2) and Table 8-1, where the difference between *sheet music* and *audio music* is introduced as a metaphor to differentiate between forms of genes (Ji 1988) – i) the *static form* of genes identified with nucleotide sequences, called the *Watson-Crick genes,* and ii) the *dynamic form* of genes identified with conformons and IDSs, referred to as the *Prigoginian genes*:

	Pianist		Physics		
Sheet Music	---------- >	*Phonons* (of Vibrating Strings)	---------- >	*Audio Music*	(8-1)
	Cell		Chemistry		
DNA (Watson-Crick genes)	---------- >	*Conformons* (Oscillating biopolymers; Lumry-McClare genes)	---------- >	*IDSs* (Prigoginian genes)	(8-2)

Alternatively, Process (8-2) can be expressed as follows:

(8-3)



where N is the nucleotide system (including DNA and RNA) that store the Watson-Crick form of genetic information, P is the protein system (including enzymes) that store the LUmry-McClare form, and C is the chemical system (including IDSs) stroing the Prigoginian form of genetic information, the three systems constituting the main components of the living cell. Scheme (8-3) incorporating the concept of the Lumry-McClare form of genetic information was formulated in my 02/03/2012 email to M. Burgin, the author of *The Theory of Information: Fundamentality, Diversity and Unification* (Burgin 2010) based on my 1989 abstract submitted to the Fifth FAOB (Federation of Asian and Oceanian Biochemists) Congress held in Seoul, Korea. I have taken the lierty of attaching the email to this book as Appedix N for the convenience of the readers.

Statement (8-3) is consistent with the definition of genes given in Rows 3, 4 and 5 in Table 8-1.

Table 8-1 The relation among *genes*, *conformons*, and *IDSs* (intracellular dissipative structures) suggested by the music-life analogy.

	Music	**Life**
1. Agent	Pianist	Cell
2. Energy Source (Chemical Reactions)	Pianist's fingers	RNA polymerase
3. Information Source (Equilibrium Structures)	Sheet music	Nucleotide sequences (Watson-Crick genes)
4. Periodic Motions (Dissipative Structures)	Vibrating strings (or Phonons)	Oscillating conformations of enzymes (or *Conformons***)** **(**Lumry-McClare form of genes**)**
5. Translational Motions (Dissipative Structures)	Audio music	IDSs (Prigoginian form of genes)
6. Evolutionary Selection acts on	Audio music	IDSs

In Table 8-1, the key analogical items are written in *italics*. Since both conformons and IDSs absolutely require free energy dissipation to exist and be maintained, they are examples of *dissipative structures* of Prigogine (see Rows 4 and 5) (also Section 3.1). Living cells must transmit information in both *space* (e.g., from cell membrane to the nucleus) and *time* (e.g., from a progenitor to its progeny, or from an embryo to its adult form) in order to carry out their functions both as individuals and as a member of a community. It was postulated in (Ji 1988) that i) traditional nucleotide sequences encoding proteins and regulatory information (called the Watson-Crick genes) transmit information in time and ii) dissipative structures consisting of dynamic gradients of all sorts (referred to as the Prigoginian genes) transmit information in space (see Row 3 in Table 8-2). Row 6 in Table 8-1 indicates that, just as music lovers choose their favorite songs through audio music (and rarely through sheet music), *so organisms are selected by evolution through their IDSs* (i.e., the Prigoginian form of genes), and not through their nucleotide sequences (i.e., the Watson-Crick form of genes). This claim is in good agreement with the 'phenotype first' postulate of evolution expressed by Waddington (1957) and others, including Kirschner and Gerhart (1998, 2005), West-Eberhard (1998), Jablonka (2006), and others.

As indicated in Rows 4 and 5 in Table 8-1, there are two types of dissipative structures operating in the living cell – *conformons* and *IDSs*. Any material systems that are endowed with the capacity to dissipate free energy to organize itself in space and/or time is conveniently referred to as *dissipatons* (Section 3.1.5). So defined, *dissipatons* are synonymous with *gnergons*, the discrete units of gnergy, and the postulated universal driving force for all self-organization in the Universe (Section 2.3.2) (Ji 1991). The difference between *gnergons* and *dissipatons* may be compared to the difference between *energy* and *force* in Newtonian mechanics (see Eq. (8-6)), the former pair (i.e., gnergons-dissipatons) referring to organized motions and the latter pair (i.e., energy-force) referring to any motions, whether organized or not. Thus conformons and IDSs are examples of *dissipatons*. Conformons are confined within biopolymers and IDSs propagate in space outside biopolymers. Another way to distinguish between *gnergons* and *dissipatons* is to view the former as the cause and the latter as consequences: i.e.,

"*Gnergons cause dissipatons*." (8-4)

To differentiate between *conformons* and *IDSs*, the two kinds of *dissipatons* active in the living cell, the terms "mechanical dissipatons" (denoted as *m-dissipatons*) and "concentration dissipatons" (denoted as *c-dissipatons*) have been introduced in Table 8-2 (see the second row), which compares the characteristics of these two types of dissipatons.

Table 8-2 The two types of the information-energy particles (or gnergons) responsible for self-organizing activities in the living cell and higher structures. Row 5 assumes that genes are not static as is widely believed but dynamic, storing both information (e.g., nucleotide sequences) and free energy (e.g., mechanical energy of supercoiled DNA). m-Dissipatons = mechanical dissipations (e.g., DNA supercoils; Section 8.3); c-dissipatons = concentration dissipatons (see text).

	Gnergons (or Dissipatons)	
	Conformons (or m-Dissipatons)	IDSs (or c-Dissipatons)
1. **Energy** stored in	Proteins, RNA, DNA (Section 8)	Concentration gradients of ions, small molecules (Section 9)
2. **Information** stored in	Amino acid and nucleotide sequences	Chemical structures of ions and molecules and the space- and time-dependent shapes of the gradients
3. Information transmission in	*Time* (via genes, biopolymer networks, neural networks)	Space (via intracellular ion gradients, membrane potentials, action potentials, sounds)
4. Mechanism of formation	Generalized Franck-Condon mechanisms (Section 2.2.3)	Triadic control mechanisms (Section 15.3)
5. Sheet music analog	Coding and non-coding regions of DNA	Coding and noncoding regions of DNA
6. Audio music analog (Types of motions)	Mechanical waves (Periodic motions confined within biopolymers; Local)	Concentration waves (Translational motions propagating in space; Global)

8.1 The Definition and Historical Background

Cells are organized systems of biopolymers (proteins, RNA, DNA) and small molecules and ions. Some of these biopolymers (e.g., kinesin, dynein, myosin) have enzymic activity and act as molecular motors (Alberts 1998) moving teleonomically, driven by exergonic chemical reactions such as ATP hydrolysis that they catalyze. In order for molecular motors to move in goal-directed manner, they must be able to produce requisite conformons from either substrate binding and the chemical reactions they catalyze (Ji 1974b, 2000, 2004a). Conformons can provide the necessary and sufficient conditions for goal-directed motions of molecular machines because conformons carry both energy (to generate force) and genetic information (to control the direction of motions). The energy stored in enzymes as conformational or mechanical strains can generate forces because energy and force are quantitatively related to each other through the Second Law of Newtonian mechanics and the definition of energy as the ability to do work. According to the Second Law of mechanics, force (***F***) equals mass (*m*) times acceleration (***a***):

$$\boldsymbol{F} = m\boldsymbol{a} \qquad (8\text{-}5)$$

where the bold letters are vectors having both a magnitude and a direction and regular letters indicate scalar quantities. Also energy is equivalent to the work performed by a mass when it is moved by force $\boldsymbol{F}$ along distance L:

$$\text{Energy} = \text{Work} = \boldsymbol{FL} = (\textbf{Force})(\textbf{Displacement}) \qquad (8\text{-}6)$$

Therefore, Eq. (8-6) guarantees that, given the requisite molecular mechanisms (i.e., the generalized Franck-Condon mechanism; see below), conformons can generate goal-directed molecular forces within biopolymers.

Proteins are unique among biopolymers in that they are the only macromolecules (except for some RNA molecules acting as ribozymes; see Section 11.4.4) that can utilize the free energy stored in chemical compounds through catalysis. That is, enzymes are the only molecules that can convert *chemical energy* into *mechanical energy* by generating molecular forces inside them. The precise molecular mechanisms by which proteins catalyze the chemical-to-mechanical energy conversion are not yet fully understood, despite intensive investigations over the past half a century. There are many competing theories to account for the so-called *force-generating mechanisms* in molecular motors and machines. These include the *molecular energy machine* theory (McClare 1971), *Brownian ratchet* hypothesis (Astumian, 2000, 2001), and a *non-equilibrium statistical thermodynamic model* (Qian 2006, 2007). The conformon theory of molecular machines first proposed in (Green and Ji 1972a,b) and further developed and elaborated on the basis of the generalized Franck-Condon principle (GFCP) (Ji 1974a,b, 1985a,b, 1991, 2000) is unique among these because i) it is the only theory providing a principled (i.e., based on GFCP) molecular and submolecular mechanism to couple chemical reactions to force generation within proteins (Ji 1974a,b, 2000, 2004a), and ii) it is consistent with and can accommodate all the other competing theories and hypotheses on the mechanisms of action of molecular machines and motors.

It is now generally accepted that molecular machines play fundamental roles in carrying out molecular processes inside the cell (Figure 8-1) (Alberts 1998, Baker and Bell 1998). Most recent evidence indicate that at least some motions of molecular machines are driven by conformational strains of biopolymers (see "DNA scrunching" or "DNA-scrunching stress' in (Kapanidis et al. 2006, Revyakin 2006)). However, the general mechanisms by which these molecular machines are powered and driven by exergonic (i.e., free energy-releasing) chemical reactions are not yet clear. One realistic possibility is provided by the *conformon theory of molecular machines* proposed over three decades ago (Green and Ji 1972a,b, Ji 1974b, 1991, 2000) (Chapter 8). The term 'conformon' was coined by combining two stems, 'conform-' indicating 'conformations' of biopolymers and '-on' meaning a mobile, discrete material entity. Conformons are defined as follows (Green and Ji 1972a,b, Ji 1974a, 1979, 1985a,b, 1991, 2000, 2004a):

> "*Conformons are sequence-specific conformational strains of biopolymers that carry mechanical energy and genetic information necessary and sufficient to effectuate any goal-oriented movement* (8-7)

of biopolymers inside the cell."

Although the concept of conformons was originally invoked to account for the mechanism of oxidative phosphorylation occurring in mitochondria (i.e., the coupling between the free energy-releasing oxidation of substrates and the free energy-consuming ATP synthesis from ADP and Pi; see below), the first experimental evidence for it was obtained in molecular biology, in the form of ATP-induced supercoiling of circular DNA double helix in bacteria observed under electron microscope in the mid-1960's (Stryer 1995, p. 795). The idea that biological properties of enzymes (and molecular machines, by extension) may depend on the mechanical (i.e., conformational) energy stored in proteins was first proposed by R. Lumry and others in the 1950's and 1960's (Lumry and Gregory 1986) (reviewed in (Ji 1974b, 2000)).

As indicated above, conformons were first invoked to explain the molecular mechanisms underlying free energy transfer from one protein (or chemical reaction) to another in mitochondria during energy-coupled process known as oxidative phosphorylation (or oxphos for short) (Ji 1974b). During oxphos, the enzyme systems located in (and on) the inner mitochondrial membrane synthesize ATP from ADP and inorganic phosphate, P_i, using the free energy supplied by the oxidation of NADH to NAD^+. The whole process is very complex and has not yet been completely elucidated in my opinion (Ji 1979), despite the fact that biochemistry textbooks around the world accept the assumption that *chemiosmosis* (i.e., the process of converting *chemical* energy of say NADH to the *osmotic* energy of the pH gradient across the inner mitochondrial membrane) is responsible for driving the synthesis of ATP from ADP and P_i (e.g., see Figure 21-22 on p. 545 in (Stryer 1995)). One glaring deficiency of the chemiosmotic hypothesis, for which P. Mitchell received the Nobel Prize in Chemistry in 1978, is a complete lack of any enzymologically realistic molecular mechanism that can convert chemical energy of NADH to the osmotic energy of the pH gradient and associated membrane potential. The chemiosmotic hypothesis can be represented as:

$$\text{NADH} + \tfrac{1}{2}\,O_2 \xrightarrow{\textit{Mechanism (?)}} NAD^+ + H_2O + \textit{Proton gradient} \qquad (8\text{-}8)$$

$$ADP + Pi \xrightarrow{\textit{Proton gradient}} ATP + H_2O \qquad (8\text{-}9)$$

To provide a chemically realistic molecular mechanisms underlying energy conversion in Processes (8-8) and (8-9), an alternative mechanism of oxphos, known as the *conformon hypothesis*, was proposed in 1972 (Green and Ji 1972a,b, Ji 1974a,b, 1976, 1977, 2000), according to which the free energy conversion involved proceeds through three main steps:

$$\text{NADH} + \tfrac{1}{2}\,O_2 + \textbf{ETC} \xrightarrow{\textbf{ETC}^{\ddagger}} NAD^+ + H_2O + \textbf{ETC*} \qquad (8\text{-}10)$$

$$(\textbf{ETC/TRU})^{\ddagger}$$

$$\textbf{ETC*} + \textbf{TRU} \text{ ----------> } \textbf{ETC} + \textbf{TRU*} \quad (8\text{-}11)$$

$$\text{ADP} + \text{P}_\text{i} + \text{TRU*} \xrightarrow{\textbf{TRU}^{\ddagger}} \text{ATP} + \text{H}_2\text{O} + \textbf{TRU} \quad (8\text{-}12)$$

where all the macromolecular systems (i.e., molecular machines) are written in bold letters, **ETC** stands for *electron transfer complexes* (of which there are three denoted as **I, III** and **IV**) located in the inner mitochondrial membrane, and **TRU** is an abbreviation for "tripartite repeating unit", the enzyme system consisting of (i) $\mathbf{F_0}$, (ii) the oligomycin-sensitivity conferring protein (**OSCP**), and (iii) $\mathbf{F_1}$, also called the **ATP synthase** or **Complex V** (see Figure 1 in (Ji 1976)).

It is to be noted that, in each step, the enzyme system involved plays a dual role – as a carrier of free energy denoted by the superscript * and as an enzyme lowering the energy level of the transition state denoted by the superscript ‡. Thus, a significant amount of the free energy generated from the oxidation of NADH is stored in **ETC*** in Process (8-10), which is thought to be transferred to **TRU*** in Process (8-11), which finally drives the free energy-requiring desorption of ATP from $\mathbf{F_1}$ in Process (8-12) (Boyer 2002). **ETC**‡ corresponds to the Franck-Condon state (see Section 2.2.3) that harbors *virtual* conformons symbolized by the superscript ‡, and **ETC*** is the energized state harboring real conformons symbolized by the superscript *. In other words, the superscripts ‡ and * denote the *virtual* and *real conformons*, respectively. *Virtual conformons are thermally derived and hence cannot be utilized to do work* (as discussed in Section 2.1.4), but *real* conformons are derived from free energy-releasing processes such as substrate binding or chemical reactions and hence can be utilized to do work. The conformon theory of molecular machines (Section 8.4) provides a reasonable and realistic mechanism for converting virtual conformons to real conformons based on the generalize Franck-Condon principle (Section 2.2.3).

According to the conformon hypothesis of oxidative phosphorylation, every key step in oxidative phosphorylation occurs inside the inner mitochondrial membrane and at no time is there any transmembrane proton gradient generated: *No chemiosmosis is required for oxidative phosphorylation*. However, the free energy stored in **TRU*** *can* be utilized to generate *transmembrane proton gradient*, if necessary, given appropriate experimental or physiological conditions, when the energy is transferred from **TRU*** to a hypothetical enzymic unit called the "proton transfer complex", **PTC**, yet to be discovered (Green and Ji 1972a,b, Ji 1979, 1985a,b). It has been postulated that the proton gradient formed across the inner mitochondrial membrane often observed under artificial experimental conditions is needed not for oxidative phosphorylation as assumed by Mitchell (1961, 1968) but i) mainly for the *communication between mitochondria and the cytosol* for the purpose of monitoring the ATP needs of the cell and ii) possibly for synthesizing ATP driven by the proton gradient generated by anaerobic glycolysis during anoxia (lack of oxygen) or ischemia (lack of blood flow) (Ji 1991, pp. 60-61). It is further postulated that when this mechanism of proton-mediated intracellular communication breaks down due to the permeability transition of the inner mitochondrial membrane, the cell undergoes a programmed cell death or 'apoptosis' (Crompton 1999).

8.2 The Generalized Franck-Condon Principle-Based Mechanism of Conformon Generation

In Process (8-10) above, it was assumed that a part of the free energy released from the oxidation of NADH was stored in the enzyme system, **ETC**, that catalyzes the exergonic reaction. One plausible mechanism that can accomplish this *chemical-to-mechanical energy conversion* is schematically shown in Figure 8-1. In passing it should be noted that the *chemical-to-mechanical energy conversion* is synonymous with the *chemical reaction-induced force generation*, because *force* and *energy* (or work) are related through the Second Law of Newtonian mechanics as indicated above (see Eq. (8-6)). In other words, energy and force are causally related, leading to the following dictum:

"Without energy no force can be generated; (8-13)
without force no energy can be stored."

For convenience, we may refer to Statement (8-13) as *the molecularized Second Law of Newtonian mechanics* (MSLNM), in analogy to the *molecularized Second Law of Thermodynamics* (MSLT) formulated by McClare (1971) and discussed in Section 2.1.4.

Since the key theoretical principle underlying the *chemical-to-mechanical energy conversion* mechanism described below is the generalized Franck-Condon principle (GFCP) discussed in Section 2.2.3, the mechanism shown in Figure 8-1 will be referred to as the *GFCP-based mechanism of conformon production*. GFCP is in turn related to (and consistent with) two other laws – MSLNM, i.e., Statement (8-13), and MSLT discussed in Section 2.1.4. Thus we have the following relations among the three theoretical entities implicated in the mechanism of the *chemical-to-mechanical energy conversion* to be presented.

$$\text{GFCP} = \text{MSLT} + \text{MSLNM} \tag{8-14}$$

The GFCP-based mechanism of conformon generation occurs through the following three key steps:

(1) **ETC** (or any molecular machines) can exist in two conformational states – the ground state (to be denoted as **ETC** and visualized as a relaxed spring in Figure 8-1 **a)** and the thermally activated or excited state (denoted as $\mathbf{ETC}^{\ddagger}$ and visualized as a cocked spring in Figure 8-1 **b)**. These two states are in thermal equilibrium, which can be represented as **ETC** < --- > $\mathbf{ETC}^{\ddagger}$. Due to the constraints of the molecularized Second Law of thermodynamics discussed in Section 2.1.4, the lifetime of $\mathbf{ETC}^{\ddagger}$ must be shorter than τ, the turnover time of **ETC**.

(2) In the ground-state **ETC**, the two substrate binding sites are thought to be located too far apart for AH_2 to react with B or for the electrons to be transferred from AH_2 to B. In other words, AH_2 and B are prevented from reacting with each other in the ground state.

(3) When the two sites on **ETC** that bind AH_2 and B are brought close together as a result of thermal fluctuations of **ETC** (see **a** --- > **b** in Figure 8-1), two electrons

are postulated to be transferred from A to B (through *quantum mechanical tunneling* in one or more elementary steps), resulting in the formation of two protons in the AH_2 binding site and two hydroxyl groups in the B binding site (see **c**), which stabilizes **ETC**‡ to produce the energized state, **ETC***. Due to the exergonic nature of the redox reaction catalyzed by **ETC**, the lifetime of **ETC*** is no longer constrained by the Second Law of thermodynamics and can be much longer than τ.

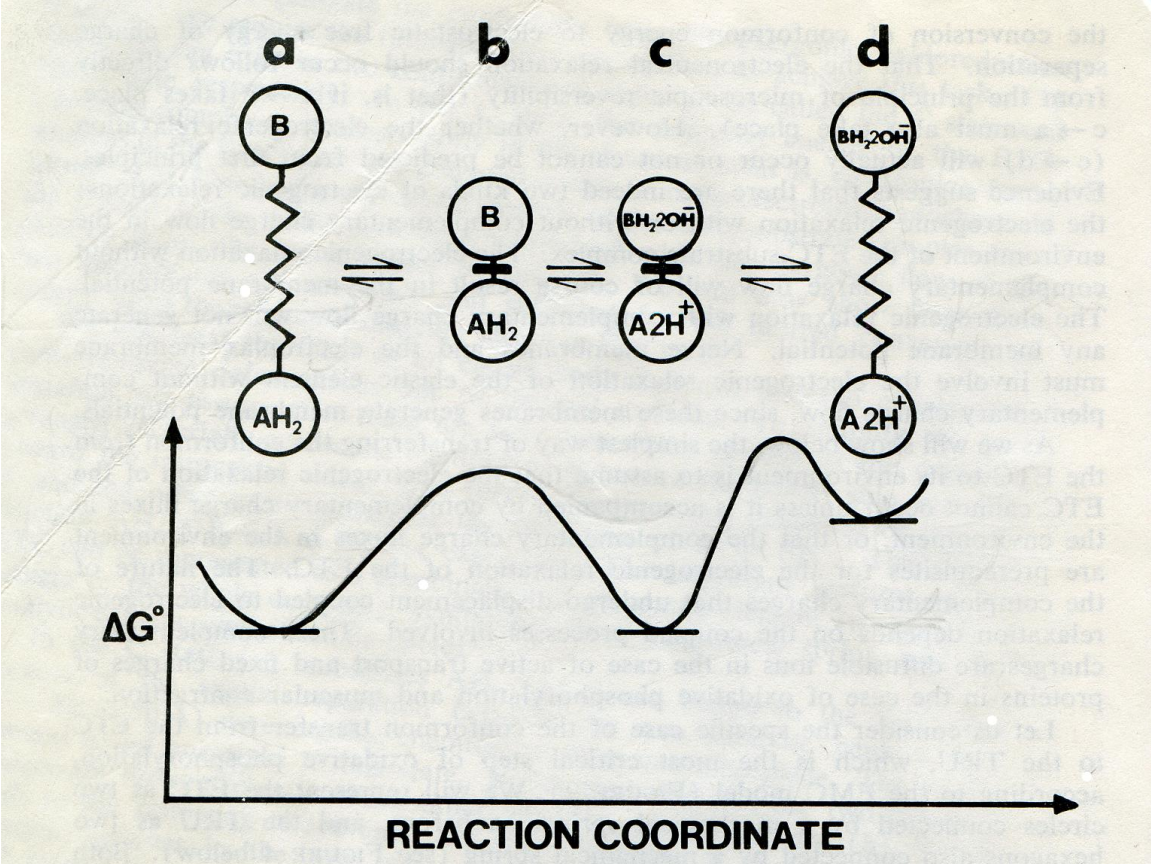


FIGURE 3. A proposed mechanism for the conversion of the chemical free energy of substrates (AH_2+B) to the elastic free energy of the enzyme (the conformon).

Figure 8-1 A mechanism for converting chemical energy to mechanical energy based on the generalized Franck-Condon principle (GFCP). Reproduced from (Ji 1974b). The spheres symbolize enzyme active sites and the spring symbolizes the conformational deformability of enzymes. The dumb-bell shaped objects are multisubunit enzymes embedded in the inner mitochondrial membrane. The first E·S complex (**a**) undergoes thermal fluctuations leading to the contraction and relaxation cycle of the 'spring' (**a** and **b**). When thermal motions bring the substrate-binding sites close together at the transition state, **b**, two electrons are thought to flow (or *tunnel*) from AH_2 to B, leading to (1)

generation of electrical charges and (2) the stabilization of the 'cocked' or energized spring via the electrostatic attraction between separated charges. The unstabilized cocked spring in **b** corresponds to the Franck-Condon state harboring *virtual conformons,* and the stabilized cocked spring in **c** corresponds to the mechanically deformed and energized state of the enzyme harboring *real conformons.* The **c** to **d** transition exemplifies the conformon-driven work processes, which in this case is charge separation across the mitochondrial inner membrane.

The intramembrane electron transfer reaction involved in Figure 8-1 can be described in greater detail as shown in Figure 8-2, taking into account both the generalized Franck-Condon principle (GFCP) (Section 2.2.3) and the principle of microscopic reversibility (PMR), which Hine (1962) describes as follows:

> "*. . . the mechanism of a reversible reaction is the same, in microscopic detail (except for the direction of reaction, . . .), for the reaction in one direction as in the other under a given set of conditions.* ' (8-15)

A close examination will reveal that the mechanism given in Figure 8-2 obeys PMR. Please note that, in the Franck-Condon state, (*b*), indicated by $[\ .\ .\ .]^{\ddagger}$, two electrons can be associated with either A or B with an equal probability. We assume that water molecules equilibrate rapidly within the enzyme active site, reacting with anion to form a hydroxide ion, OH^-, or with a cation to form a hydronium ion, H_3O^+, written simply as H^+

$$
\begin{array}{ccc}
\text{(a)} & & \\
AH_2{\cdot}B & \rightleftharpoons & [AH_2{\cdot}B]^{\ddagger} \\
 & & \uparrow\downarrow \\
 & & [AH_2^{+}{\cdot}\,B^{-}]^{\ddagger} \quad (b) \\
 & & \uparrow\downarrow \\
 & & [AH_2^{++}{\cdot}B^{--}]^{\ddagger} \rightleftharpoons [A{\cdot}2H^{+}{\cdot}BH_2{\cdot}2OH^{-}] \\
 & & \qquad\qquad\qquad\qquad (c)
\end{array}
$$

Figure 8-2 A general mechanism of redox reaction satisfying the generalized Franck-Condon principle and the Principle of Microscopic Reversibility.

8.3 Experimental Evidence for Conformons

The idea that biological properties of enzymes may depend on the mechanical (i.e., conformational) energy stored in proteins was first seriously considered by R. Lumry and others in the 1950's and 1960's (Lumry 1974, 2009, Lumry and Gregory 1986) (reviewed in Ji 1979, 2000), but the first direct experimental evidence for such a possibility did not emerge until the mid-1960's when the so-called "supercoiled" DNA

was observed under electron microscope (Stryer 1995, p. 795]. When a circular DNA duplex is cut through both strands and the resulting ends are twisted around the long duplex axis (called the helical axis) *n* times in the direction of increasing the distance between the paired bases (referred to as the negative direction) and then resealed, the circular form twists in space so that the helical axis itself coils into a helix, which phenomenon being known as "supercoiling'. To undo each helical turn, about 10 hydrogen bonds must be broken between the complementary base pairs along the DNA double helix, requiring a total of about 15 Kcal/mole of free energy. Thus, a circular DNA duplex which was negatively twisted around the helical axis, say, 20 times would store approximately 15 x 20 = 300 Kcal/mole of mechanical energy in the form of conformational deformations or strains. Therefore, a supercoiled DNA duplex can be interpreted as providing *a direct experimental evidence for the concept of conformons.* That is, the supercoiled DNA duplex stores conformons.

J. H. White derived a mathematical formula (known as *White's formula*; see pp. 795-796 in Stryer 1995) that specifies the relation among three parameters – (i) the *linking number*, *Lk,* the number of times the two strands are intertwined, (ii) *twist, Tw,* a number determined by the local pitch of the helix, and (iii) *writhe, Wr,* a number determined by the degree of the twisting of the helical axis in space (Bauer, Crick and White 1980):

$$Lk = Tw + Wr \tag{8-16}$$

A relaxed circular DNA duplex is characterized by the lack of any writhe, i.e., $Wr = 0$, and non-zero values for the other two parameters. As described above, *writhe* can be introduced into the circular DNA duplex by first cutting the two strands of a relaxed form and by turning counter-clock-wise *n* times before resealing the ends to regenerate the circular form, which can be spontaneously converted into supercoiled form. It is important to note that *Lk* can be altered only through the *cutting-twisting-resealing* operation, which are efficiently carried out by ATP-dependent enzymes known as *topoisomerases or DNA gyrase,* and that the remaining two parameters, *Tw* and *Wr*, can change in a mutually compensating manner. If the linking number of a relaxed circular DNA duplex is denoted as Lk_0 and the corresponding number for a supercoiled circular DNA duplex as *Lk*, then the *linking number difference* (symbolized as α) can be expressed as:

$$\begin{aligned} \alpha &= Lk - Lk_0 = (Tw + Wr) - (Tw_0 + Wr_0) \\ &= (Tw - Tw_0) + (Wr - Wr_0) \\ &= \Delta Tw + \Delta Wr \end{aligned} \tag{8-17}$$

Inside the cell, DNA molecules are commonly maintained by topoisomerases in negatively supercoiled states, making their linking number *Lk* smaller than their relaxed values Lk_0 so that $\alpha = Lk - Lk_0 < 0$. Therefore, α can be interpreted as a quantitative measure of *conformons* embedded in circular DNA (Ji 2000).

Linking number difference α can be viewed as a quantitative measure of the free energy stored in supercoiled DNA introduced by the *nicking-twisting-resealing* operation

on the circular DNA duplexes. Interestingly this mechanical energy can be distributed either in the twist (ΔTw) or write (ΔWr) of the supercoiled DNA duplex as indicated in Eq. (8-17). The former represents the mechanical energy stored in local deformations, while the latter indicates the same energy distributed over the whole circular DNA duplex, and these two different states of mechanical energy distributions may actually fluctuate between them due to Brownian motions, thus supporting the concept that *conformons* are mobile mechanical energy stored in biopolymers. It can be imagined that *such conformons will visit all possible local sites within a circular DNA duplex and a transcription factor will bind to DNA if and only if its resident conformons happen to "collide" with the transcription factor.* We will refer to this concept as the *transcription factor-conformon collision hypothesis* (TFCCH) *or mechanism* (TFCCM) underlying the transcription factor binding-induced gene expression. Similar ideas have been proposed by others (Volkov 1996, Hisakado 1997, Cuevas et al. 2004, Alvarez et al. 2006). The TFCC hypothesis provides a rational explanation for the well-known phenomenon that a circular DNA duplex must exist in a supercoiled state before its genes can be transcribed or replicated (Benham 1996a,b).

In the early 1990's, C. Benham developed a statistical mechanical equation to describe the dynamics of the mechanical strains introduced in circular DNA duplexes (Benham 1996a,b, Benham and Bi 2004). His computational results indicated that the so-called "stress-induced duplex destabilizations (SIDDs) (equivalent to $\alpha < 0$) were not randomly distributed along the circular DNA duplex but were localized mainly to the 5' and 3' ends of RNA coding regions. Three examples of SIDDs are shown in Figure 8-3 (see the directed arrows), where the down-ward deflections indicate the decrease in the Gibbs free energy needed for strand separation due to the localized destabilization induced by mechanical strains. Thus, both the *sequence-specificity* and the *mechanical energy* stored in DNA make SIDDs excellent examples of the more general notion of *conformons* invoked two decades earlier and restated in Statement (8-7) (Green and Ji 1972a,b, Ji 1974b, 2000).

A more direct experimental evidence for the production of conformons from ATP hydrolysis was recently reported by Uchihashi et al. (2011, Junge and Müller 2011) who visualized the propagation of the conformational waves of the β subunits around the isolated F_1-ATPase stator ring (see Section 7.1.5).

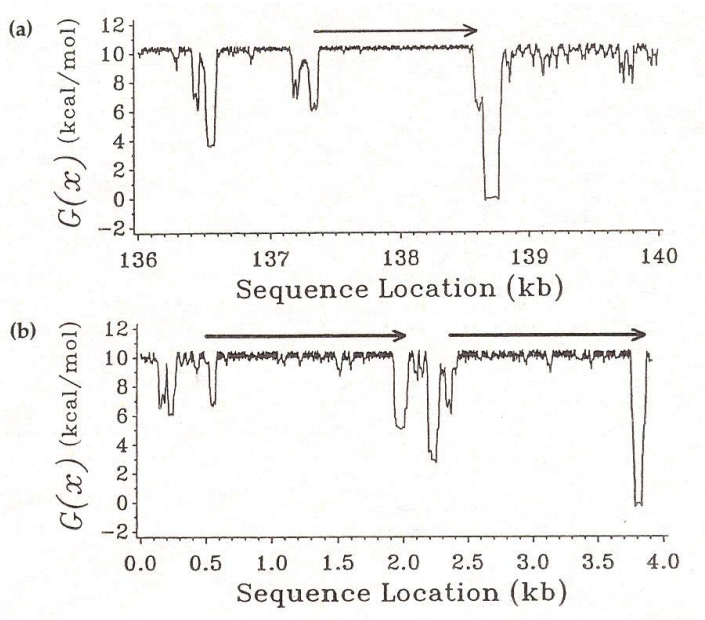


Figure 8-3 Mechanical strains of DNA localized at sequence-specific sites within circular DNA duplexes. The x-axis records the nucleotide positions along the DNA duplex and the y-axis records the Gibbs free energy required to separate the based pairs located at position x along the DNA duplex chain. Notice that the base pairs located near the 3'-end (i.e., the right-hand end of the arrow) of some genes are already completely separated (see position 138.7 in (a) and 3.56 in (b)).

Functional (as compared to non-functional) DNA molecules carry not only genetic information but also mechanical energy in the form of supercoils. The mechanical energy stored in supercoiled DNA is known to be essential for transcriptional activities in *E. coli* (Benham 1996a,b), leading to the conclusion that *conformons are necessary for DNA functions*. More recently, Ebright and his coworkers (Revyakin et al. 2006, Kapanidis et al. 2006) provided direct molecular dynamics evidence, obtained using a fluorescence resonance energy transfer (FRET) technique, that conformational strain energies stored in deformed DNA strands (called 'DNA scrunching' (Cheetham and Steitz 1999)) may play a critical role in transcription initiation in bacterial RNA polymerase. What these authors call *DNA scrunches* can be identified with the *conformon of* Green and Ji (1972a,b) and Ji (2000), and the *SIDDs* of Benham (1996a,b).

8.4 Conformons as Force Generators of Molecular Machines

It is the basic postulate of the conformon theory that all molecular machines are driven by conformons. The sarcoplasmic/endoplasmic reticulum calcium ion pump (i.e., the SE Ca^{++} ATPase) is one of the simplest molecular machines known with a molecular weight of 110,000 Daltons and 994 amino acid residues (Toyoshima et al. 2000). This protein can catalyze the hydrolysis of ATP and use the free energy of this reaction to transport

two calcium ions across sarcoplasmic/endoplasmic reticulum membranes (Myung and Jencks 1995, MacLennan and Green, 2000). The 3-dimensional structure of this ion pump was determined by X-ray crystallography by Toyoshima et al. (2000). Their structure is reproduced in Figure 8-4.

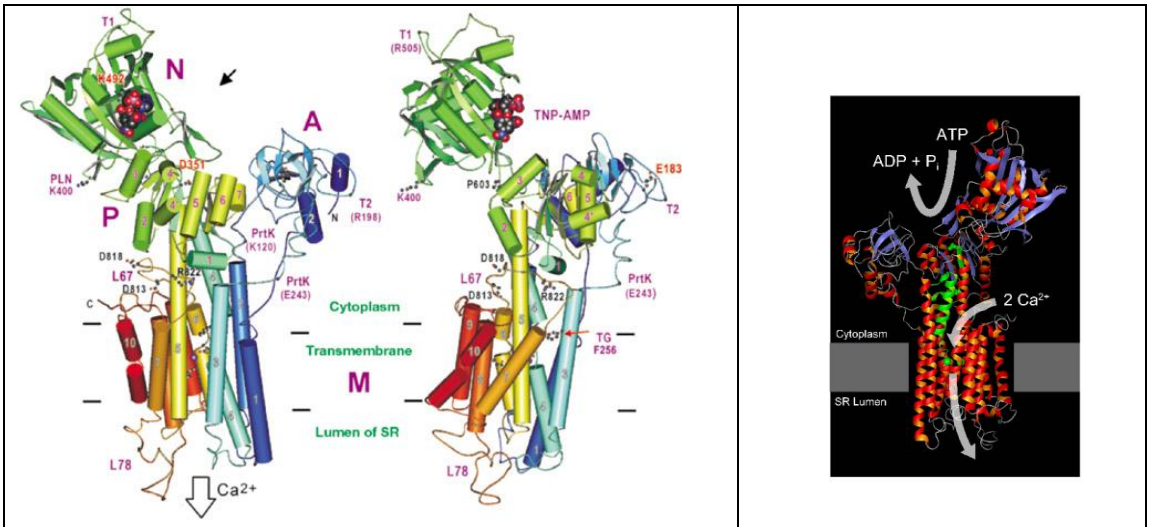


Figure 8-4 The 3-dimensional Ca^{++} ATPase of muscle sarcoplasmic reticulum determined by X-ray crystallography at 2.6 Å resolution (Toyoshima et al. 2000). (**Left**) The enzyme has 4 structural domains – i) the nucleotide-binding domain denoted as **N**, ii) the phosphorylation site-containing domain, **P**, iii) the actuator domain, **A**, and iv) the calcium-binding **M** domain. Blue indicates the N terminus and red the C terminus. Transmembrane helix M5 is parallel to the plane of the paper. The model on the right is rotated by 50° around M5. (**Right**) Reproduced, by permission of Andreas Barth, from **http://w3.dbb.su.se/~barth/Struktur/atpase.jpg,** which regenerated the ion pump shown in the left panel using the program **MolMol.**

In Figure 8-4 the first three domains of the calcium ion pump are on the cytoplasmic side of the membrane and the **M** domain (with its 10 transmembrane helixes symbolized as M1 through M10) spans the membrane. ATP bound to the **N** domain donates a phosphoryl group to aspartic residue 351 located on the P domain, across a distance of about 25 Å. Two calcium ions are bound to two separate binding sites (see the two circles side by side in the membrane domain) located in parallel at about the mid-section of the membrane, separated by 5.7 Å from each other. One of the two calcium ion binding sites is surrounded by helixes M5, M6 and M8, while the other site is associated mainly with helix M4. The distance between the aspartic acid residue 351 in the **N** domain that is phosphorylated by ATP and the calcium binding sites in the **M** domain is estimated to be about 50 Å (Toyoshima et al. 2000).

The X-ray structure of Ca^{++} ATPase determined by Toyoshima et al. (2000) provides new information that complement the dynamic properties of the pump determined by

biochemical and kinetic experiments carried out over more than four decades since the enzyme was discovered in 1962 (Toyoshima et al. 2000, MacLennan and Green 2000). The new X-ray structural data combined with the related biochemical and kinetic data summarized by Myung and Jencks (1995) and by MacLennan and Green (2000) can be integrated with the theoretical concept of the conformon (Sections 8.1 and 8.2) to construct a detailed and molecularly realistic mechanism of the action of the Ca^{++} ion pump as shown in Figure 8-5.

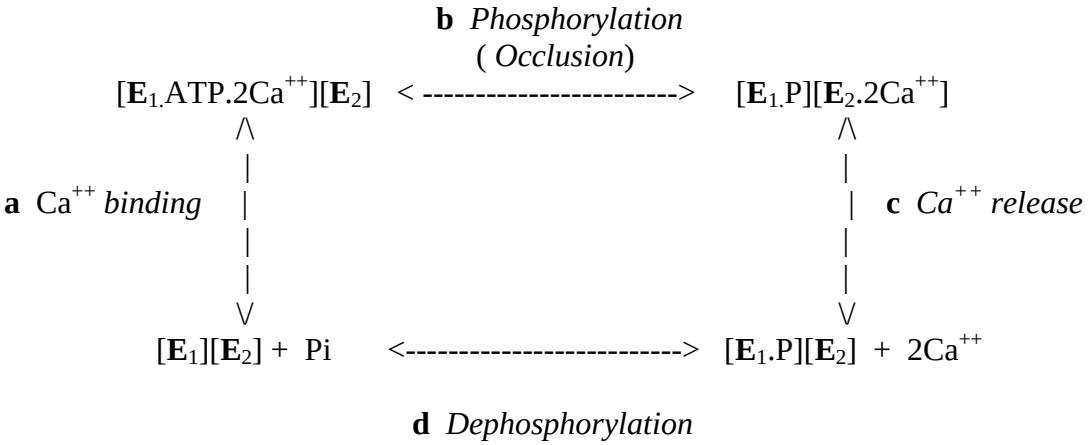


Figure 8-5 The conformon-based mechanism of action of the sarcoplasmic/ endoplasmic reticulum Ca^{++} ion pump. The ion pump proteins are written in bold letters. This mechanism has many features that have been adopted from the models of Ca^{++} ion pump proposed by MacLennan and Green (2000) and by Myung and Jencks (1995) but is distinct from these models in several important ways as explained in the text.

The mechanism in Figure 8-5 postulates that the ion pump can be divided into two structural domains, denoted as $\mathbf{E}_1$ and $\mathbf{E}_2$, both enclosed in a square bracket marking their boundaries. $\mathbf{E}_1$ has a high affinity for Ca^{++} and is accessible only from the cytosplasmic side of the membrane, and $\mathbf{E}_2$ has a low Ca^{++} affinity and is accessible only from the luminal side. In step **a**, two calcium ions and one molecule of ATP bind to $\mathbf{E}_1$ from the cytoplasmic side. In step **b**, $\mathbf{E}_1$ is phosphorylated causing it to be occluded from the cytoplasmic side and the two Ca^{++} ions are postulated to be translocated from $\mathbf{E}_1$ to $\mathbf{E}_2$ domains (probably involving a decease in the Ca^{++} binding affinity of $\mathbf{E}_1$ and an increase in that of $\mathbf{E}_2$, driven by appropriate conformons). In step **c**, $\mathbf{E}_2$ opens toward the luminal side and the Ca^{++} binding affinity of $\mathbf{E}_2$ decreases (again presumed to be driven by conformons), thus releasing Ca^{++} ions into the lumen. In step **d**, $\mathbf{E}_1$ is dephosphorylated to regenerate the original $\mathbf{E}_1$ and $\mathbf{E}_2$. It should be pointed out that the $[\mathbf{E}_1.P][\mathbf{E}_2.2Ca^{++}]$ state is thought to be ADP-sensitive (i.e., this complex can transfer the phosphoryl group to ADP added from the cytoplasmic side, leading to the formation of ATP (consistent with the observations made by Myung and Jencks (1995)) but the $[\mathbf{E}_1.P][\mathbf{E}_2]$ state is not.

There are three main features that are unique to the mechanism proposed in Figure 8-5:

1) The Ca^{++}-binding affinity of the $\mathbf{E}_2$ domain is not constant but depends on the structural state of the ion pump as a whole (including the $\mathbf{E}_1$ domain). That is, the model assumes that the binding affinity of the Ca^{++}-binding sites in the $\mathbf{E}_2$ domain undergoes transitions among three states – high (H), intermediate (I), and low (L).

2) The accessibility of the Ca^{++}-binding sites in the $\mathbf{E}_2$ domain is also not constant but depends on the structural state of the ion pump as a whole. There are three possible accessibilities – open to the cytoplasmic (C) side only, occluded from both the cytoplasmic and luminal (L) sides, and open to the luminal side only.

3) The two calcium-binding sites are postulated to be positioned vertically relative to the plane of the membrane, separated by less than 40-50 Å, the thickness of the membrane. The X-ray crystal structure of Toyoshima et al. (2000) indicates that the two Ca^{++} ion binding sites are located side by side horizontally in the interior of the membrane contrary to what is postulated here. The reasons for this discrepancy is not clear but may include the possibility that the horizontal arrangement of the Ca^{++} ions seen by Toyoshima et al. (2000) is an artifact of protein crystallization.

Characteristic features 1) and 2) are combined and represented as in Scheme (8-18):

H (Open to C side) <---> **I** (Occluded) <----> **L** (Open to L side) (8-18)

All of the three characteristics of the proposed mechanisms of the Ca^{++} ion pump can be visualized as shown in Figure 8-6. The formation of the occluded state is probably coincident with the phosphorylation of the C domain.

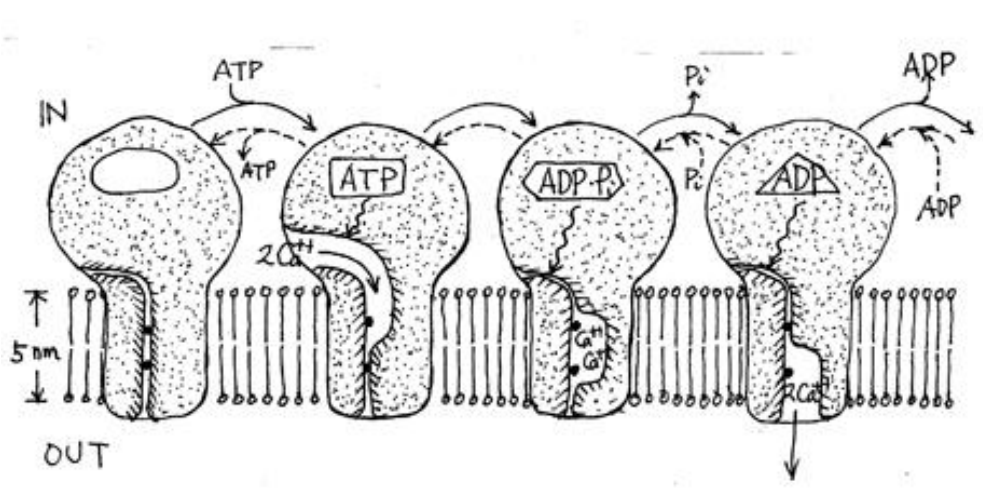


Figure 8-6 A proposed mechanism of the action of the Ca^{++} pump based on the conformon theory of molecular machines (Ji 1974b, 1979, 2000). The model assumes that the pump molecule can be divided into two domains—the catalytic or **C** (also called $\mathbf{E}_1$) domain (see the upper portion of the pump molecule) and the transport or **T (**also called $\mathbf{E}_2$**)** domain (see the channel in the lower portion of the pump). Both the **C** and **T** domains undergo coordinated conformational changes amidst thermal fluctuations as schematized in the form of the changing shapes of the domains. Conformons can drive any directional motions (including Ca^{++} movement across the membrane) because they

carry both *free energy* (in the form of conformational strains which act as the force generator) and *genetic information* (associated with the local amino-acid sequences entrapping conformational strains). Conformons are thought to be generated in the **C** domain and 'effectively' (i.e., directly or indirectly) transported to the **T** domain as symbolized by the wiggly arrows connecting the **C** and **T** domains, obeying the generalized Franck-Condon principle or the *pre-fit mechanisms* as discussed in Section 2.2.3. Molecular mechanisms to generate and transport conformons in enzymes have been presented Figure 8-1 and in (Ji 1974b, 1979, 2000).

8.5 A Bionetwork Representation of the Mechanisms of the Ca^{++} Ion Pump

The mechanism of the operation of the calcium ion pump proposed in Figure 8-5 can be represented using the language of bionetwork as shown in Figure 8-7. The two domains of the Ca^{++} ion pump are represented as **C**(. . .) and **T**(. . .) connected by **~** which symbolizes the structures that couple these two domains mechanically (see Figures 8-6 and 8-7) . Each domain is divided into two compartments separated by a backward slash, /. The **C** domain has the ATP (or ADP) and Pi binding sites, and the **T** domain has two calcium ion biding sites whose accessibility to, and binding affinity for, calcium ions obey a set of rules. The pump system is postulated to exist in four distinct states denoted by **I** through **IV**:

1) In State **I**, both the **C** and **T** domains are closed to their ligands.

2) In State **II**, the adenine nucleotide binding site in **C** is accessible from the cytoplasmic side and the Ca^{++}-binding site in **T** binds Ca^{++} with high affinity.

3) In State **III**, the **C** domain is phosphorylated and the Ca^{++}-binding site becomes inaccessible from either the cytoplasmic or luminal side and the calcium-binding affinity of the **T** domain decreases.

4) In State **IV**, the **C** domain releases ADP leaving the phosphoryl group covalently bound to **C** while the **T** domain opens towards the luminal side, releasing Ca^{++} by lowering its Ca^{++}-binding affinity.

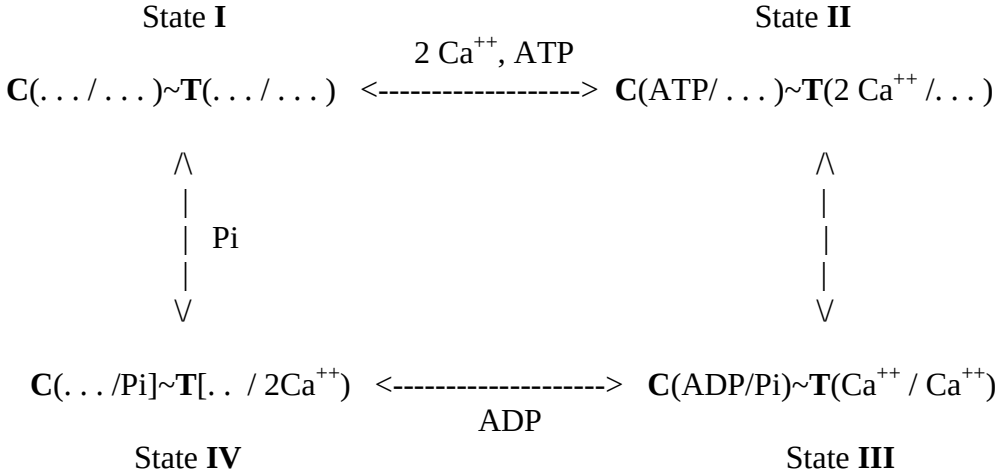


Figure 8-7 The molecular mechanism of the action of the ATP-driven calcium ion pump of sarcoplasmic reticulum represented as a *bionetwork* consisting of four nodes and four edges. The nodes of the network represents the structural and chemical states of the **C** and **T** domains of the pump (that are mechanically coupled as indicated by ~) and the edges represent the state transitions and associated movements of ligands in and out of their binding sites.

There are two basic factors operating in Figure 8-7 that control the activity of the calcium ion pump (and all other molecular machines for that matter). One is the *thermodynamic* factor that determines the direction of the net ion movement across the membrane, from a high free energy to the low free energy states, leading to a net free energy decrease, and the other is the *kinetic* factors controlling the activation free energy barriers that ions must overcome in order to move through the membrane and hence the rates of transmembrane ion movement. Either factors alone are insufficient to drive the ion movement; both conditions must be satisfied for ion movement (or the motion of any goal-directed or purposive molecular machines). We may refer to the first as the 'thermodynamic requirement' and the second as the 'kinetic requirement'. It is postulated here that the *thermodynamic* requirement is met by the Gibbs free energy associated with the concentration gradients of ATP or Ca^{++} ion and the *kinetic* requirement is satisfied by the *conformon-driven structural changes* of the Ca^{++} ATPase that modulate the local activation energy barriers for catalysis in **C** domain and ion transport through the **T** domain. This view can be state as follows:

> "*The direction of ion movement is determined by global thermodynamics of the exergonic chemical reactions or physical processes, and the rate of ion movement is determined by conformons generated in enzymes locally through ligand-binding processes*." (8-19)

Statement (8-19) is consistent with the view that the primary role of enzymes and molecular machines is to control *timing* or to effect *temporal structures* (see Section 7.2.3.). For future references, we may refer to Statement (8-19) as the "Dual Control Hypothesis of Active Transport". It is possible to generalize Statement (8-19) so that it can be applied to both a machine (viewed as a network of the components of a machine) as well as to the network of molecular machines themselves. Thus we may formulate what may be referred to more generally as the "Dual Control Hypothesis of Molecular Machines" (DCHMM) as follows:

> "*The direction of movement of molecular machines (or their components) is determined by thermodynamics through free energy changes and their speed or timing by kinetics implemented by conformons."* (8-20)

Statement (8-20) may be represented using the concept of vectors. There are three key elements in Statement (8-20) --- i) molecular machines, ii) the direction of motion of the

machines, and iii) the speed or timing of machine motions. We may compare i) with the coordinates of the origins of vectors, ii) with the angle of the vectors, and iii) with the lengths of vectors.

8.6 Ion Pumps as Coincidence Detectors

Since enzymes can be viewed as coincidence detectors (see Section 7.2.2) and since the Ca^{++} ATPase is an enzyme, it is natural to view the ATP-driven active transport of Ca^{++} ion shown in Figure 8-6 as an example of an enzyme-catalyzed coincidence-detecting event as explained in Figure 8-8.

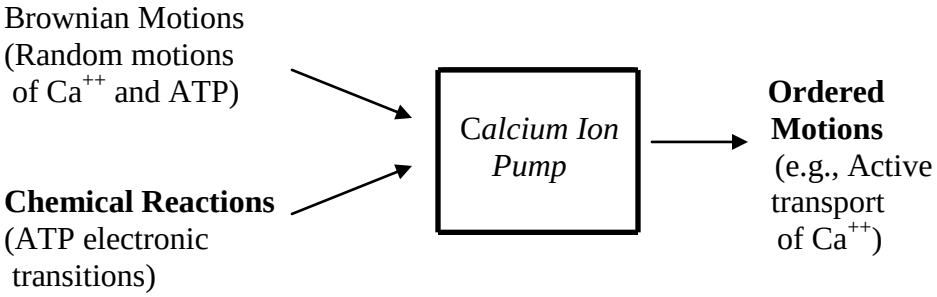


Figure 8-8 Conformon-driven calcium ion pumping viewed as a coincidence-detecting event catalyzed by the Ca^{++} ATPase. This figure represent the application of the general enzymic mechanisms, Figure 7-6, to the case of the calcium ion pump. See text for details.

Here, we identify the chemical processes of ATP hydrolysis within the **C** domain and the physical processes of Ca^{++} ion movement across the membrane through the **T** domain as the two events that are *synchronized* or *correlated* by the ion pump, and the set of all the space- and time-ordered motions of the molecular entities necessary to couple the **C** domain and **T** domain is treated as the co-incident events or long-range molecular correlations (to use the terminology of the physics of critical phenomena (Domb 1996)). The calcium ion pump, being a *coincidence detector*, is postulated to execute an orderly movement of catalytic amino acid residues located in the **C** and **T** domains in such a manner as to hydrolyze ATP if and only if Ca^{++} ions move through the requisite binding sites in the **T** domain in the right direction, namely, from the cytoplasmic to the luminal side when the ATP in the cytosol provides the thermodynamic driving force and in the reverse direction when the high luminal Ca^{++} ion concentration relative to that in the cytosolic side provides the thermodynamic driving force.

The essence of the model shown in Figures 8-7 and 8-8 is the *synchronization* (or long-range correlations) of the fast ATP hydrolytic electronic transitions occurring in the **C** domain with the slow Ca^{++} ion positional changes that occur within the **T** domain separated from the **C** domain by at least 40-50 Å (Toyoshima et al. 2000). One way to avoid the *action-at-a-distance* problem that plagued Newtonian mechanics is to postulate that these two events are coupled through the *transfer of conformons* from the ATP

processing sites in the **C** domain to the Ca^{++} binding sites in the **T** domain through the structural link that connects these two domains (symbolized by "~ " in Figure 8-7), again obeying the generalized Franck-Condon principle implemented by the *pre-fit mechanisms* (Section 7.1.3). In other words, the two domains of the calcium ion pump are correlated or coupled via conformon exchanges just as quarks in hadrons (i.e., protons, neutrons and pions) are coupled through the exchange of gluons (Han 1999). Conformons can be generated in the Ca^{++} binding sites in the **T** domain which are then transferred to the ATP-processing sites in the **C** domain, when the thermodynamic driving force is provided by the Ca^{++} ion gradient, high in the luminal side and low in the cytosolic side. This conclusion is mandated by the principle of microscopic reversibility, Statement (8-15) (Hine 1962).

8.7 The Conformon Hypothesis of Energy-Coupled Processes in the Cell

The cell is composed of three main classes of material entities – *biopolymers* (i.e., DNA, RNA proteins, etc.), *metabolites* (e.g., glucose, pyruvate, NADH, ATP, O_2, CO_2, H_2O, etc.) and *inorganic ions* (e.g., H^+, Na^+, K^+, Ca^{++}, etc.). The interior space of the cell is so crowded with these molecular entities that changing the concentration of any one component at a given locus within the cell may affect the chemical activities of other components in distant locations due to the so-called "crowding effects" or "macromolecular crowding effects" (Minton 2001, Pielak 2005, McGuffee and Elock 2010) (see Figure 12-28).

All these intracellular molecular entities are in constant motions under physiological temperatures, and these motions can be divided into three categories—i) *up-hill motions*, also called energy-requiring or *endergonic processes* (e.g., ion pumping, molecular motor movement, synthesis of ATP); ii) *down-hill motions*, also called energy-dissipating or *exergonic processes* (e.g., diffusion of ions across a membrane along their concentration gradients, ATP hydrolysis under physiological conditions; and iii) *random* (or *stochastic*) *motions* (e.g., thermal fluctuations or Brownian motions of biopolymers and collisions among molecules). Random motions lack any regularity but stochastic motions can exhibit regularities although they are not predictable. In order for the cell to carry out its functions such as growth, chemotaxis, cell cycle, cell differentiation, and apoptosis (i.e., programmed cell death) in interaction with its environment through its various receptors (both membrane-bound and cytosolic), many up-hill reactions must be carried out (driven by conjugate down-hill reactions resulting in non-random motions) in thermally fluctuating environment without violating the laws of thermodynamics. Such coupled processes are often referred to as "energy-coupled" processes, meaning that the free energy released from the down-hill reaction is partially 'transferred' to the coupled up-hill reaction in such a manner that the net free energy change accompanying the overall process remains negative. Examples of energy-coupled processes include respiration-driven ATP synthesis (i.e., *oxidative phosphorylation*), ATP- or respiration-driven active transport of protons across the mitochondrial inner membrane, and ATP-driven molecular motors and rotors, and the formation and destruction of hyperstructure or SOWAWN machines (Section 2.4.3). The conformon theory of molecular machines (Green and Ji

1972a, b, Ji 1974b, 2000) maintains that all such coupled processes proceed through the production and consumption of *conformons* (the mechanical energy stored in sequence-specific sites within biopolymers that acts as force-generator). This idea can be represented schematically as shown in Figure 8-9.

(Chemical Reactions) ----> (Conformons) ----> (Coupled Processes)

Figure 8-9 The conformon hypothesis of coupled processes in the cell.

The coupled processes include 1) oxidative phosphorylation, 2) active transport, 3) muscle contraction, 4) intracellular molecular trafficking, 5) signal transduction, 6) gene expression, 7) DNA repair, 8) cell cycle, 9) space- and time-dependent production and destruction of hyperstructures or SOWAWN machines, 10) intercellular communication, 11) cell migration, and 12) cell shape changes.

When the mechanistic scheme shown in Figure 8-9 is applied to mitochondria which carry out at least two coupled processes, namely, respiration-driven ATP synthesis (i.e., oxidative phosphorylation) and respiration-driven proton extrusion, we can construct the following scheme:

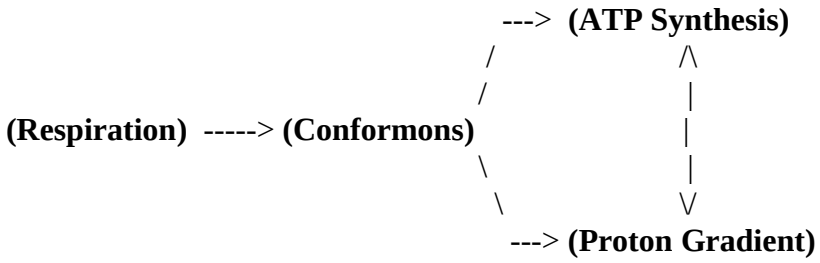


Figure 8-10 The conformon-based mechanisms of mitochondrial energy coupling (Ji 1974b, 1979). The double headed vertical arrow symbolizes both the ATP-driven proton extrusion from the matrix to the cytosol and the proton gradient-driven ATP synthesis.

As will be discussed in Section 11.6, the chemiosmotic hypothesis of P. Mitchell (1961, 1968) assumes that respiration directly generates the proton gradient across the mitochondrial inner membrane which subsequently drives the synthesis of ATP from ADP and Pi. In contrast, the conformon hypothesis shown in Figure 8-10 assumes that respiration first produce conformons (via the detailed mechanism discussed in Sections 8.2 and 11.5) which then drives either the synthesis of ATP from ADP and Pi or the extrusion of protons from the matrix to the cytosolic space. Since the chemiosmotic mechanism absolutely depends on the presence of biomembrane, it cannot mediate the coupling of non-membrane-dependent processes such as gene expression, muscle contraction, and molecular trafficking in the cytosol. Of the 12 coupled processes cited above that can be driven by conformons, only Process 2) (and possibly Process 1)) are membrane-dependent and hence can be driven by the chemiosmotic mechanism of P. Mitchell. Thus, it appears that the conformon mechanism is superior to the chemiosmotic

mechanism on two counts – i) the universality (i.e., applicable to both membrane-dependent and non-membranous processes), and 2) the realistic mechanism of generating conformons from chemical reactions based on the generalized Franck-Condon principle (Section 2.2.3).

CHAPTER 9

Intracellular Dissipative Structures (IDSs)

9.1 Experimental Evidence for IDSs

According to I. Prigogine (1917-2003) (1977, 1980), there are two fundamental classes of structures in nature – *equilibrium structures* that can exist without any dissipation of free energy (e.g., crystals, a stick of candle, purified proteins) and *dissipative structures* whose maintenance requires free energy dissipation (Section 3.1) (Kondepudi and Prigogine 1998, Babloyantz 1986, Kondepudi 2008). For convenience, the former has been referred to as *equilibrons* and the latter as *dissipatons* (Section 3.1.5). The Bhopalator model of the living cell (Ji 1985a,b, 2002b) (to be discussed in Section 10.1) postulates that the dissipative structures present inside the living cell (hence called IDSs, or Intracellular Dissipative Structures) play a fundamental role in determining cell functions. The first direct evidence supporting this postulate was provided by the intracellular calcium ion waves observed in chemotaxing human neutrophils using a calcium ion-sensitive fluorescent dye (Sawyer et al. 1985) (see Figure 3-2 in Section 3.1.2.).

The most recent evidence for IDSs is supplied by the genome-wide RNA (i.e., transcript) levels measured with DNA microarrays invented in the mid-1990's (Pease et al. 1994, Schena et al. 1995, Watson and Akil 1999). Using this technique, Garcia-Martinez et al. (2004) measured simultaneously both the transcript levels (TL) and transcription rates (TR) of more than 6,000 genes in budding yeast undergoing glucose-galactose shift. The nucleotide sequence structures of genes coding for transcripts are examples of *equilibrons* and the patterns of time-varying transcript levels are examples of *dissipatons*. Not distinguishing between these two types of structures can lead to Type I (false positive) and Type II (false negative) in analyzing DNA array data (Ji et al. 2009a).

The data reported by Garcia-Martinez et al. (2004) indicate (i) that the maintenance of the concentration levels of most of the mRNAs of the yeast cells is dependent on energy supply since they decreased toward zero levels when yeast cells are deprived of their energy source (see Figure 9-1 below), and (ii) that mRNA levels of yeast cells are function-dependent so that, upon replacing glucose with galactose, the levels of the mRNA molecules encoding the enzymes needed to catalyze glycolysis (converting glucose to ethanol) decline while those of the mRNA molecules encoding the enzymes needed to catalyze respiration (converting ethanol to carbon dioxide and water) and galactose metabolism increase (see Figures 9-2 and 12-4). The first observation supports the notion that mRNA levels are *dissipatons*, since their maintenance requires free energy supply, and the second observation supports the concept that the *patterns of the changes in* (or *trajectories of*) *mRNA levels* reflect (or can be identified with) cell functions as postulated in the Bhopalator model of the cell (Section 10.2) (Ji 1985a,b, 2002b).

Any concentration gradients present inside the cell qualify to be called *dissipatons* or *dissipative structures*. Since there are many chemical species in the cell, small molecules such as ATP, inorganic phosphate, and various ions and macromolecules such as proteins, RNA and DNA that can form gradients, it would be necessary to distinguish

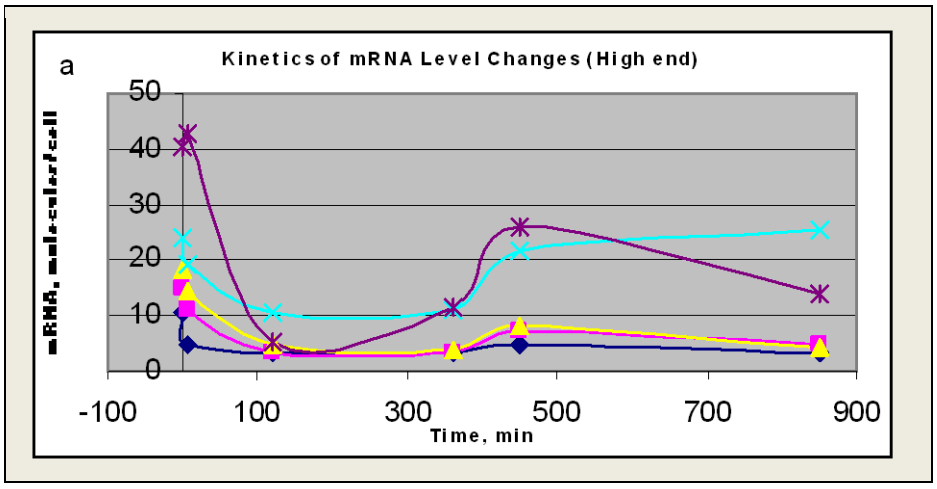
their dissipatons with appropriate adjectives. Thus the *X dissipaton* (e.g., RNA dissipatons) will denote the *dissipaton* consisting of the concentration gradient of X. An X dissipaton comprises two aspects -- i) the *static* structure of X which is an equilibrium structure, and ii) the *dynamic* aspect of X which is a process derived from or rooted in i). These two aspects of X form the two of the three elements constituting a function, the third element being the mechanism of producing dynamic processes from static structures (see Figure 6-9). Furthermore, it is here recommended that, whenever convenient, the term 'ribons' be used to refer to *RNA dissipatons, the term 'ribons' being derived from 'ribonucleic acid'*. Unlike *equilibrons* (e.g., genes defined as sequences of nucleotides) which are stable enough to be isolated, purified and sequenced, *dissipatons* are dynamic and ephemeral in the sense that, whenever attempts are made to isolate them, they disappear, just as the flame of a candle disappears if attempts are made to capture it. The main objective of this section is to describe and use the software known as ViDaExpert to characterize and classify *RNA dissipatons* or *ribons* in cells. The computational method presented in this book (see Sections 18 1nd 19) should be applicable to studying other kinds of *dissipatons*, including pericellular and extracellular concentration gradients (e.g., gradients of morphogens and cheomoattractants in tissues and hormones in blood), EEG patterns, and many other time-series data, since they are undoubtedly instances of dissipative structures (or dissipatons), their existence being dependent on free energy dissipation.

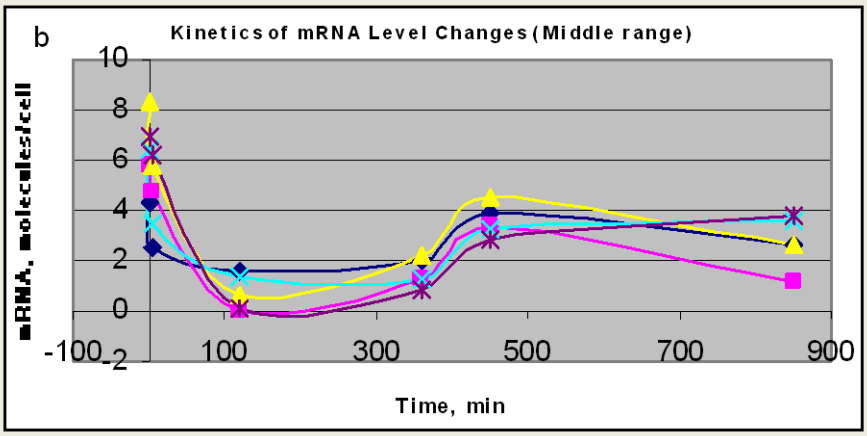
The software *ViDaExpert* was developed in (Zinovyev 2001, Gorban and Zinovyev 2004, 2005) and is freely available at http://bioinfo-out.curie.fr/projects/vidaexpert/ . The term ViDaExpert derives from "the **vi**sualization of multidimensional **da**ta **Expert** " program. It is a tool for visualizing high-dimensional data on a lower-dimensional space for easy visual examination and analysis of their spatiotemporal patterns and regularities. The main technique implemented in ViDaExpert is the method of elastic maps, an advanced analogue of the method of self-organizing maps. In addition it embodies many other methods of data analysis such as principal component analysis, various clustering methods, linear discriminate analysis, and linear regression methods (Gorban and Zinovyev 2004, 2005).

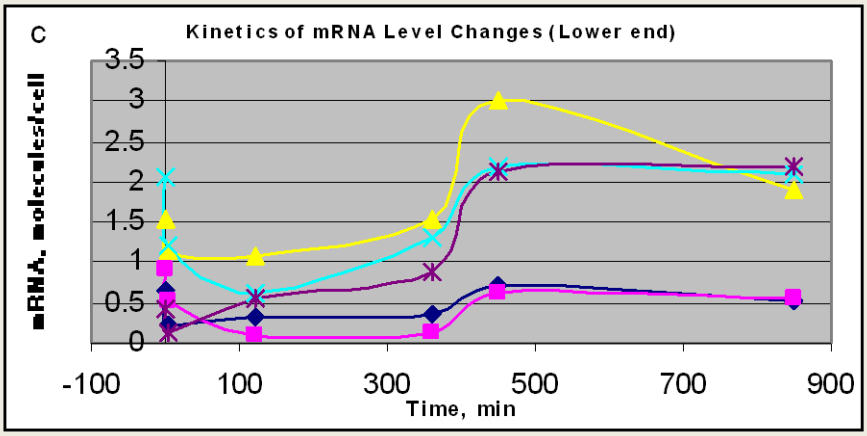
The RNA kinetic data can be displayed in an abstract 6-dimensional mathematical space wherein each point is associated with 6 numbers, each representing the concentration of an RNA molecule (or RNA equilibron) measured at one of the 6 time points 0, 5, 120, 360, 450, and 850 min measured after switching glucose to galactose (Garcia-Martinez et al. 2004). ViDaExpert was used to visualize the 6-dimenisional kinetic data of the genome-wide RNA levels of budding yeast on a 2-dimensional principal grid with n^2 nodes where n is the dimensionality of the grid which was varied from 2 to 15. The elastic coefficients, i.e., stretching coefficient λ and bending coefficient μ, were also varied from 0 to 50, but, having found no significant improvement in clustering behaviors of the data points, these elastic coefficients were kept constant at 0 for most analysis.

In the presence of glucose, budding yeast turns on those genes coding for the enzymes needed to convert glucose to ethanol (which phenomenon known as *glucose induction*) and turns off those genes needed for galactose metabolism (which is known as *glucose repression*) (Kuhn et al. 2001, Johnston 1999, Ashe, De Long and Sachs 2000, Jona, Choder and Gileadi 2000). The detailed molecular mechanisms underlying these

phenomena are incompletely understood at present and under intensive studies (Gasch 2002, Winderrick et al 2002). When glucose is depleted, *S. cerevisiae* increases its rate of metabolism of ethanol to produce ATP via the Krebs cycle and mitochondrial respiration (Gasch 2002, Ronne 1995). This metabolic control is exerted by reversing (or dis-inhibiting) the glucose repression of the genes encoding the enzymes required for respiration (i.e., oxidative phosphorylation), and this process is known as *glucose de-repression* (Gasch 2002). The glucose-galactose shift caused massive metabolic changes in budding yeast characterized by rapid decreases in most RNA levels within the first 5 minutes, continuing to decrease up to about 2 hours after which they generally increased (Figure 9-1), presumably due to the induction of enzymes capable of metabolizing galactose to generate ATP (see Figure 12-3). The kinetic behaviors of the yeast transcripts under this nutritional shift are complex in detail (see Figures 9-1a through 9-1c) but reveal a set of regular patterns, including the fact that the average glycolytic transcripts decreased between 5 and 360 minutes, whereas the average respiratory transcripts increased in the same time period (Figure 12-2(a)). These opposite changes reflect the anticipated metabolic transitions from glycolysis (i.e., fermentation) to respiration induced by the glucose removal (leading to *glucose de-repression* mentioned above). This observation provides a concrete evidence to support the hypothesis that the dynamic patterns of the changes in RNA levels (i.e., *RNA dissipatons*, RNA trajectories, or RNA waves) in living cells can serve as indicators or molecular markers for cell functions (see the IDS-Cell Function Identity Hypothesis described in Section 10.2).







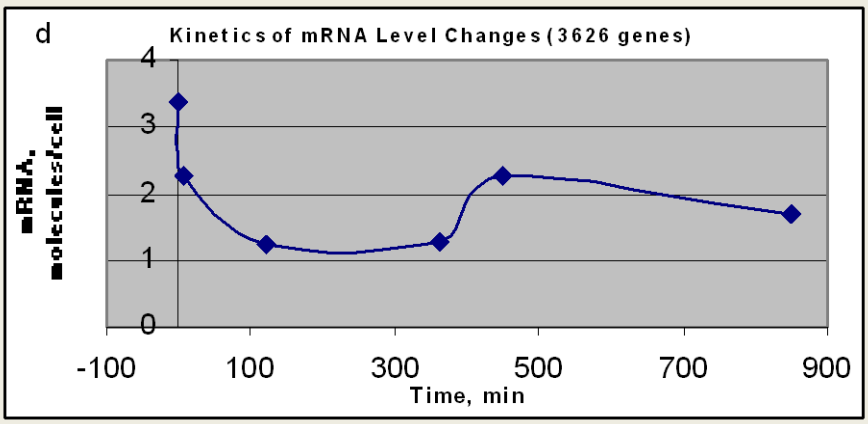


Figure 9-1 The time series of mRNA levels of budding yeast measured with DNA arrays after switching glucose to galactose (Garcia-Martinez et al. 2004). Figures 9-1a through 9-1c are individual examples randomly selected from 3,626 genes with no missing values. Figure 9-1d is the average kinetic behavior of the 3,626 transcript levels. Data from Ji et al. (2009a).

9.2 The p53 Network as a Multidimensional 'Hypernetwork'

Just as atoms consist of two types of particles, *hadrons* (i.e., heavy particles including protons and neutrons) and *leptons* (i.e., light particles including electrons), so the cell can be viewed as consisting of two types of physical objects --- *equilibrium structures* or *equilibrons* (e.g., ground-state molecules such as ATP, proteins, RNA, and DNA, and their complexes) and *dissipative structures* or *dissipatons*, including ion gradients across the cytosol or cell membranes, mechanical stress gradients in supercoiled DNA and the cytoskeleton, and cyclically turning-over molecular machines). It appears reasonable to conclude that the interactions among select sets of *equilibrons* and *dissipatons* that are organized in space and time can account for all cellular functions (i.e., phenotypes), just as the interactions among hadrons and leptons are known to account for all atomic structures and their properties in physics (except perhaps the phenomenon of entanglement (Albert and Galchen 2009)). We may refer to these phenotypes (e.g., chemotaxis, morphogenesis, cell cycling) as 'phenons' to go with 'equilibrons' and 'dissipatons'. Employing these new terms, we can describe the cell in two distinct ways – i) *phenomenologically* as a set of phenons, or ii) *mechanistically* as a set of spatiotemporally organized *equilibrons* and *dissipatons*. The phenomenological method of describing the living cell represents the traditional cell biology that prevailed before the emergence of the Mendelian gene as a unit of inheritance and before the mechanism-based way of describing the cell began to appear in the early decades of the 20th century, especially after the discovery of the double helical structure of DNA by Watson and Crick in 1953. Interestingly the concepts of *equilibrons* and *dissipatons* that are postulated to be the building blocks of all molecular mechanisms underlying life appear to be closely related to what Darden (2006) refers to as 'entities' and 'activities' in her dualistic theory of biological mechanisms.

The abstract concepts of *equilibrons* and *dissipatons* introduced in this book can be given some concreteness by illustrating their roles in the mechanism of action of p53. The p53 protein was discovered in 1979 but its function was not established until 1989. It suppresses tumors under normal conditions, and when mutated, loses its ability to suppress tumors, leading to cancer (Vogelstein, Lane and Levine 2000). About one half of all human tumors are known to be caused by (or associated with) mutated p53. In the so-called p53 network described by Vogelstein et al. (2000), the p53 protein plays the role of a *hub* having at least 5 incoming links and 18 outgoing ones. Additionally, the synthesis of p53 protein requires a set of other proteins to catalyze the translation step and the presence of p53 mRNA as the template. The synthesis of p53 mRNA in turn requires another set of about 50 proteins (in the form of a *transcriptosome*, a term coined by Halle and Meisterernst (1996)) to catalyze transcription and transcript processing using the p53 gene as the template. Finally, the p53 protein acts as a transcription factor for several dozens of genes by binding to specific sequences in DNA, thereby activating the transcription of target genes (Vogelstein et al. 2000).

To represent all these complex mechanisms of interactions of p53 with other ligands (DNA, RNA, proteins, and most likely some inorganic ions) and its biological functions, it is almost mandatory to use the *language of networks* (Barabasi 2002). Vogelstein et al.

(2000) used a 2-dimensional network for this purpose, but it became obvious to me that the dimensionality of the network should be expanded to at least 8. The 8 dimensions include the traditional space and time coordinates (x, y, z , and t) for localizing p53 molecule inside the cell at time t, three network-related dimensions of *n*, *l* and *f* (where *n* stands for *nodes*, *l* for *links* or *edges*, and *f* (or p) for *functions* (or *properties*) (Section 2.4.1), and the 8th dimension to characterize the higher-order organization (here called 'stacking') of the five traditional networks to form what may be referred to as a 'hypernetwork' or cell 'interactome', the term 'interactome' being defined here as the totality of molecular interactions in living systems (cf. Wikipedia.org/wiki/Interactome). Thus, the 8-dimensional hypernetwork (or *interactome*) of p53 can be graphically represented in terms of the following elements and procedures (see Figure 9-2):

1) The 2-dimensional network of genes (denoted by dots on the planes and the edges omitted for simplicity) centered on the p53 *gene* acting as a hub (see 1 on Plane A or the Gene Space),

2) the 2-dimensional network of mRNA molecules (denoted by dots) centered on the *p53-coding mRNA* acting as the hub (see 2 on Plane B, the RNA Space),

3) the 2-dimensional network of proteins (denoted by dots) centered on the *p53* protein acting as the hub (see 3 on Plane C, the Protein Space),

4) the 2-dimenional network of chemical reactions (denoted as dots in Plane D or the Chemical Space) catalyzed by one or more proteins (e.g., see the inverted circular cone labeled 17 that connects the Protein Space and the Chemical Reaction Space),

5) the network of *functions* (denoted as dots) associated with one or more proteins including the p53-mediated functions (see 5 on Plane E or the Function Space), and

6) Stacking of the above five 2-dimensional networks into a 3-dimensional network at each time point, t, to form "hypernetworks" or "supernetworks".

The gray circular cones in Figure 9-2, both straight and curved, represent the biochemical analog of "renormalization" in condensed matter physics (Section 2.4) (Domb 1996) and hence may be referred to as "renormalization cones". A renormalization cone can be viewed as a geometric representation of a group of biological entities (be they genes, RNA, proteins, or chemical reactions) located on the base of the cone acting as a unit to catalyze a process (represented by the apex of the cone).

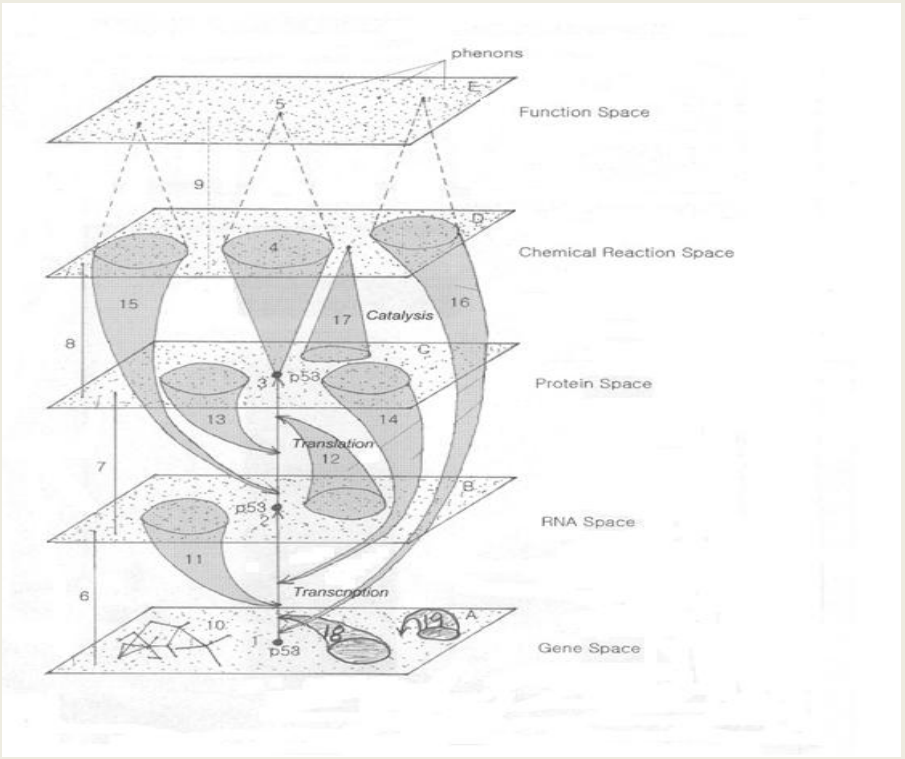


Figure 9-2 An 8-diemsnional representation of the "cell hypernetwork" or "cell interactome" that focuses on p53. The figure consists of five spaces or five traditional networks (depicted as planes) each consisting of elements (denoted by dots) that belong to the five classes of the entities indicated on the right-hand-side of the figure. *Dissipatons* = dissipative structures (section 3.1); *equilibrons* = equilibrium structures; *phenons* = phenotypes.

Most of the dots in each plane in Figure 9-2 are probably linked to form networks, one of which is explicitly shown as a small network in the Gene Space (see 10). The best known example of such in-plane networks is the protein-protein interaction network known as the protein interactome (Ito et al. 2001, Stumpf et al. 2008, Suter et al. 2008). There are two kinds of links (depicted as straight lines) in Figure 9-2 – the *horizontal* links belonging to a plane (e.g., network 10) and *vertical* links spanning two or more spaces (see lines labeled 6, 7, 8, and 9). All the points in one space should be connected to their counter parts in adjacent spaces via vertical lines, if one gene codes for one RNA (see line 6), which in turn codes for one protein (line 7), which catalyzes one reaction (line 8). It is well-known that a group of about 50 proteins acts as a unit to catalyze the transcription process in eukaryotes (which is indicated by Cone labeled 14), and another group of a similar size catalyzes translation (see Cone 13). As indicated above, such a process of grouping of a set of proteins into a functional unit (called a SOWAWN machine or a hyperstructure) is reminiscent of "renormalization" in statistical mechanics (Section 2.4.4) (Fisher 1998, Barabasi 2002, Domb 1996). Abundant experimental data indicate that some RNA molecules participate in regulating not only transcription and translation as represented by Cones labeled 11 and 12 but also transcript degradation (not

shown) (Mattick 2003, 2004, Harmon and Rossi 2004) are represented by Cones labeled 11 and 12. As indicated by Cones 15 and 16, chemical reactions can influence the rates of transcription and translation, e.g., *directly* by covalently modifying DNA and RNA or *indirectly* by changing the pH, metal ion concentrations, or membrane potentials of the microenvironment inside the cell. Thus, Cones 15 and 16 can provide molecular mechanisms for epigenetic phenomena which are emerging as important topics in both developmental and evolutionary biology (West-Eberhard 1998, 2003, Riddihough and Zahn 2010, Bonasio, Tu and Reinberg 2010). Whereas Cones 11, 12, 13, 14, 15, 16 and 17 involve many-to-one renormalizations, we have to invoke a renormalization that involves a one-to-many transitions as well (see Cone 4) to represent the fact that p53 proteins participate in numerous functions (Vogelstein et al. 2000).

Cone18 represents all the DNA regions that affect transcription and replication by acting either as templates (i.e., as 'structural genes') or as regulatory regions (i.e., as promoters, enhancers, or silencers). As will be discussed in Section 12.11, we have recently obtained the microarray evidence that some structural genes in budding yeast can co-regulate their own transcript levels in conjunction with regulatory genes (Ji, Davidson and Bianchini 2009c). Cone 18 in Figure 9-2 was not present in my original drawing of the figure but was later added at the suggestion of one of my undergraduate students at Rutgers, Julie Bianchini, and hence is referred to as the *Bianchini cone* .

Cone 19 indicates self-replication. The existence of Cone 19 is supported by the simple fact that DNA acts as the template for DNA synthesis catalyzed by DNA polymerase which makes a physical contact with the original DNA. The concept of Cone 19 is also consistent with the hypothesis that the DNA molecule as a whole can be viewed as a gene (called the d-gene in Section 11.2.4). It is important to note that d-genes carry not only *genetic information* but also *mechanical energy* in the form of SIDDSs (stress-induced duplex destabilizations) (see Section 8.3) or conformons (Chapter 8), thus enabling d-genes to act as *molecular machines to perform goal-directed molecular motions* such as strand separations or chromatin remodeling, very similar to protein molecular machines (Section 7.2.1). Since genes constitute parts of a DNA molecule, and since genes appear to act as molecular machines (Ji, Davidson and Bianchini 2009c), it is probably inevitable that a DNA molecule itself should act as a molecular machine. Also, since according to the conformon theory, all molecular machines are driven by conformons (Chapter 8) (Ji 2000), the following general statement may be made:

"DNA is a coformon-driven molecular machine." (9-1)

Statement (9-1) will be referred to the "DNA-as- Molecular-Machine (DMM) Hypothesis".

There are two types of networks in general -- *equilibrium* and *dissipative*. *Equilibrium networks* are those molecular systems that are at equilibrium, requiring no dissipation of any free energy, whereas *dissipative networks* are those molecular systems whose nodes can interact with one another if and only if requisite free energy is available and dissipated (as in SOWAWN machines; see Section 2.4.4). Examples of the former would include aggregates of heterogeneous proteins in the cytosol or protein-DNA complexes constituting chromatins in the nucleus, and those of the latter include sets of activated proteins catalyzing a metabolic process such as glycolysis, respiration, or gene expression

which are destroyed without continuous dissipation of free energy through, for example, phosphorylation and dephosphorylation reactions catalyzed by kinases and phosphoprotein phosphatases.

There are two types of connections in Figure 9-2 that link one plane to another – i) *catalysis* where a set of objects in one plane cooperates (or acts as a unit) to catalyze the coupling between one plane and another (as exemplified by Cones 4 and 11 through 17) and ii) what may be called *identity* as exemplified by the networks in the Chemical Reaction Space which are deemed *identical* with corresponding dots on the function plane (e.g., see apex 5 of the dotted cone whose base is labeled 4 in the Chemical Reaction Space). In *catalysis*, something A allows something else B to happen and hence A can be said to *cause B*. In contrast, when two entities A and B are connected by an *identity* relation, they represent two different manifestations of one and the same entity and so no causal relations can be found between A and B. Thus, *chemotaxis* in the Function Space is a phenotype or a *phenon* exhibited by a living cell under certain environmental conditions, whereas the set of intricate molecular mechanisms underlying chemotaxis that has so far been characterized on the levels of chemical reactions (Chemical Reaction Space), protein dynamics (Protein Space), gene expression (RNA Space) and genetic mutations (Gene Space) represents the inner workings of the cell that performs chemotaxis. We may represent the *identity relation* between chemotaxis and its molecular mechanisms graphically as shown in Figure 9-3 Because it is believed that the identity relation can be thought of as belonging to the relation type known as

supplementarity, symbolized as ⊥ in Section 2.3.1, this symbol is employed here to represent the identity relation:

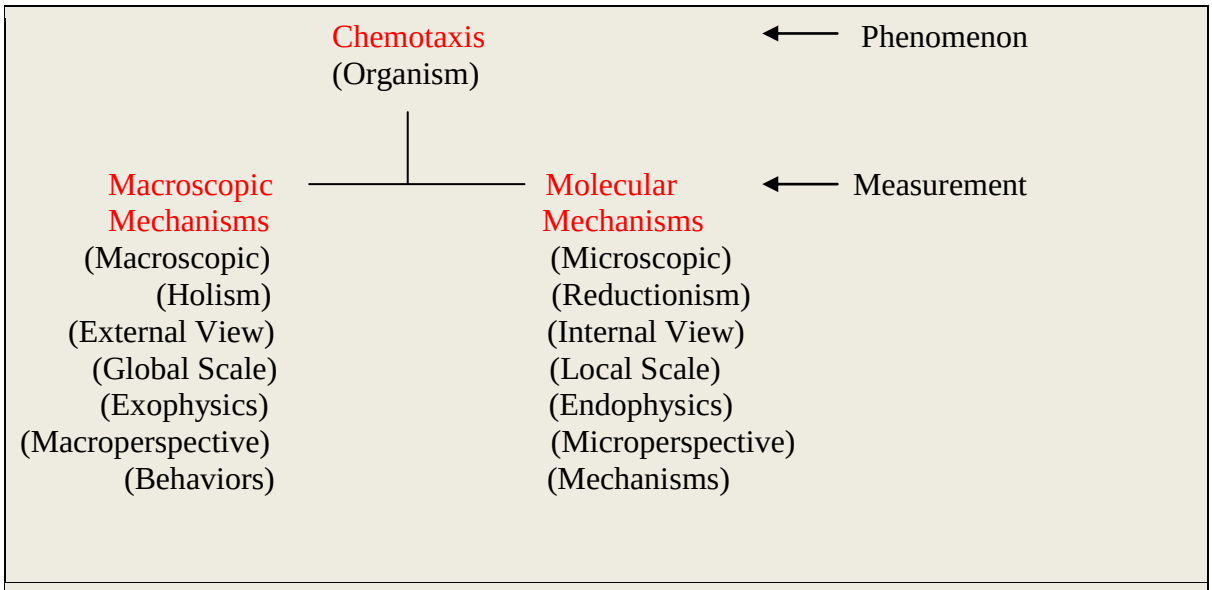


Figure 9-3 A diagrammatic representation of the postulated *identity relation* between *chemotaxis* and its underlying *mechanisms.*

The key point of Figure 9-3 is that the *phenomenon* of chemotaxis can be *observed* (or measured) in two contrasting ways - from *outsid*e of the organism on a macroscopic or mesoscopic scale and from *inside the organism* at the microscopic one (e.g., by artificially separating the working components of the organism and studying them in isolation at the molecular level). The results of the measurements so obtained are very different, giving rise to various dichotomous pairs descriptive of their differences, including *holism* vs. *reductionism*, *external* (or exo) vs. *internal (or endo)* views, *global* vs. *local* views, *exophysics* vs. *endophysics*, macroviews vs. *microviews*, and *behaviors* vs. *mechanisms*, etc. The identity relation symbolized as an inverted T in Figure 9-3 (as compared the complementarity relation symbolized by ^ in Equation (2-32)) may be viewed as an example of the *supplementarity relation* discussed by Bohr (1958) and in Section 2.3.1 in the sense that it is an *additive* relation (i.e., the top node of the inverted T is equal to the sum of the two lower nodes) unlike the complementarity relation which is *non-additive* (Ji 1995). Thus, just as when a large number of quanta are concentrated into a small volume matter emerges, so when a large number of molecular mechanisms (which can be viewed as examples of 'dissipatons' since their operations require dissipating free energy) are spatiotemporally organized inside the cell through the mechanism of evolution (i.e., a complex of coupled processes between the variation of genotypes and the selection of the fittest phenotypes by environmental conditions), living processes (including chemotaxis) emerge. If this interpretation is correct, emergence of living processes from molecular mechanisms (i.e., material processes) can be viewed as a *token* of the supplementarity relation viewed as a *type* reified over the spatiotemporal scales appropriate for the *biological evolution*. In a similar manner, the emergence of the collective properties of matter such as rigidity, fluidity, superconductivity, superfluidity, etc. of non-living matter may be looked upon as a *token* of the supplementarity relation *type* that has been instantiated or reified over the spatiotemporal scales appropriate for macroscopic and cosmological processes.

In Section 2.4.1, a biological network (or bionetwork) was defined in terms of three parameters, i.e., nodes (n), edges (e), and functions or emergent properties (f) (see Eq. (2-56)). The complexity of the structure and function of the living cell as depicted in Figure 9-3 entails expanding the definition of a bionetwork given by Eq. (2-56) by including two more parameters, namely, the dimensionality, d, of the network and the level, l, of the of the hypernetwork under consideration:

$$BN = (n, e, d, l, f) \tag{9-2}$$

The *cell hypernetwork* characterized Eq. (9-2) as a 5-dimensional hypernetwork is further detailed in Table 9-1. As indicated in Table 9-1, the *cell hypernetwork* can be alternatively referred to as the *cell interactome* which highlights the complex molecular interactions underlying the cell hypernetwork.

Table 9-1 The cell interactome as a 5-dimenional hypernetwork. Cis-interactions occur through direct physical contact between interaxcting entities, whereas trans-interactions occur through the mediation of diffusible molecules.

d	n (**node**)	e (**edge**)	f (**function**)
1	Genes	cis-Interactions trans-Interactions	Preservation and evolution of genetic information
2	RNAs	cis-Interactions trans-Interactions	Transfer of information from DNA to proteins Complexification of genetic information
3	Proteins	cis-Interactions trans-Interactions	Execution of genetic information by catalyzing those chemical reactions selected by genetic information
4	Chemical reactions	cis-Interactions trans-Interactions	Source of free energy needed for life Mediators of trans-interactions
5	Functions	tras-Interactions	Survival Evolution

9.3 Interactomes, Bionetworks, and IDSs

Since the yeast two-hybrid (Y2H) method of measuring protein-protein interactions was introduced by Fields and Song (1989), a variety of derivative methods has been devised to study protein-protein and protein-drug interactions in many different species of organisms, leading to the emergence of the field of *interactomes* (Ito et al. 2001, Suter, Kittanakom and Stagljar 2008). The term *interactome* was coined by French scientists Bernard Jacq and his colleagues in 1999 to indicate the whole set of molecular interactions that go on in living cells. The term is a natural extension of *genome* (the whole set of genes in an organism), *transcriptome* (the whole set of RNAs encoded in a genome), *proteome* (the whole set of proteins encoded in a genome), '*chemoreactome'* (the whole set of chemical reactions catalyzed by enzymes in a cell), and '*phenome'* (the whole set of phenotypes exhibited by a cell). Since the cell is a hierarchically organized system of genome, transcriptome, proteome, chemoreactome, and phenome, we can represent the cell interactome algebraically as:

Interactome = Genome + Transcriptome + Proteome + Chemoactome + Phenome (9-3)

Of the 5 subcellular interactomes appearing in Eq. (9-3), the protein interactome (also called *interative proteome*) has been best studied because of the availabilityof the Y2H method that allows biologists to measure protein-protein interactions directly. Table 9-2 summarizes the current knowledge of the protein-protein interactomes from several species (Stumpf et al. 2008).

Table 9-2 The estimated protein-protein interactome sizes of various organisms (Stump et al. 2008).

Organisms	**Nodes**	**Edges**	**Interactome Size***
1. S. cerevisiae	4,959	17,229	25,229
2. *D. melanogaster*	7,451	17,226	74,336
3. *C. elegans*	2,638	3,970	24,0544
4. *H. sapiens*	1,085	1,346	672,918

*The total number of the edges of the whole protein-protein interactome theoretically predicted based on the data obtained from partial or sub-interactomes.

The cell interactome can be graphically represented as a multi-layered hypernetwork such as the p53 hypernetwork shown in Figure 9-2. 'Interactome' defined as the totality of molecular interactions in cells (*http://en.wikipedia.org/wiki/Interactome*) and higher organisms has a significant overlap in meanings with bionetworks (Section 2.4.1). Bionetworks emphasizes the *static connections* among the nodes while interactomes focus on the *dynamic interactions* among nodes. The relation between *bionetworks* and *interactomes* may be akin to the relation between *kinematics* and *dynamics* in physics (Section 2.3.5) and hence Bohr's kinematics-dynamics complementarity may be applicable to both physics and biology as indicated in Table 9-3. In other words,

> "Bionetworks and interactomes are the complementary aspects of *life* just as kinematics and dynamics are the complementary aspects of *motion*." (9-4)

We may refer to Statement (9-4) as the *principle of the bionetwork-interactome complementarity* (PBIC), the biological counterpart of the *principle of kinematics-dynamics complementarity* in physics first articulated by N. Bohr in the 1930's to account for the wave-particle duality of light and quantum objects in general (Plotnitsky 2006). Statement (9-4) asserts that the *kinematics-dynamics complementarity principle* discovered in non-living systems applies to living systems as well, or that biology and physics are symmetric/isomorphic with respect to the principle of the kinematics-dynamics complementarity.

Table 9-3 *The Bohr's principle of kinematics-dynamics complementarity* (Murdoch 1987, Plotnitsky 2006) in action in physics and biology.

	Description

	Static	**Dynamic**
1. Motions	*Kinematics*	*Dynamics*
2. Life	*Bionetworks* *Hyperstructures* (Norris et al., 2007a,b), *Hypernetworks,* *Renormalizable Bionetworks* (Section 2.4)	*Interactomes* *IDSs* (Ji 1991), *SOWAWN machine* (Section 2.4)

It is also interesting to note that there are a set of closely related, almost synonymous terms for each of the complementary aspects of life as indicated below bionetworks and interactomes in Table 9-3. On the other hand, the *cell language theory* (Section 6.1.2) (Ji 1997a) cannot be readily relegated either to *bionetworks* alone or to *interacrtomes* alone but comprises both these complementary aspects, leading to the conclusion that cell language may best be viewed as the *complementary union* of bionetworks and interactomes as depicted in Figure 9-4.

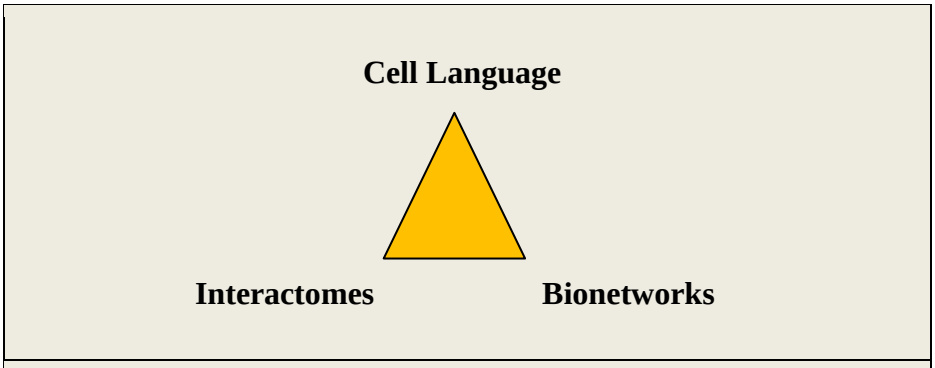


Figure 9-4 A diagrammatic representation of the hypothesis that *cell language* is the complementary union of *interactomes* and *bionetworks* or that interactomes and bionetworks are the complementary aspects of cell language.

Bionetworks and *interactomes* can be classified into cellular and multicellular bionetworks and interactomes, solely based on size considerations without regard to whether or not free energy dissipation is implicated. In addition, bionetworks and interactomes can be divided into equilibrium and dissipative bionetworks and interactomes solely based on energy (or force) considerations regardless of their sizes. The size (or geometry in general) of a network is related to *kinematics* and the energy dissipation by networks is related to *dynamics,* thus providing yet another example

illustrating the operation of the *principle of the kinematics-dynamics complementarity* in biology. Thus we can divide bionetworks into *equilibrons* and *dissipatons*, depending on whether or not free energy dissipation is needed to maintain their existence. In other words, we can recognize two classes of bionetworks – 'equilibrium bionetworks' and 'dissipative bionetworks'. The nodes and edges of equilibrium bionetworks do not dissipate free energy but those of dissipative bionetworks do (or are dissipation-dependent) (Table 9-4). That is, the nodes and edges of equilibrium bionetworks remain intact while the nodes and edges of dissipative bionetworks disappear when free energy supply is interrupted.

Table 9-4 Examples of *equilibrial* and *dissipative* nodes and edges in bionetworks.

	Equilibrial	Dissipative
Nodes	Proteins, RNAs, DNAs	a) ATP hydrolysis, NADH oxidation b) activated G protein c) supercoiled circular DNA
Edges	protein-protein, protein-RNA, protein-DNA interactions, etc. (see Table 9-5).	a) proton-motive force (the chemiosmotic theory), conformational energy (the conformon theory) b) binding to adenylate cyclase c) activation of select gene exprerssions

Another way of characterizing bionetworks or interactomes is in terms of the three fundamental building blocks of living cells, namely, proteins (p), RNA (r), and DNA (d), leading to a 3x3 table shown in Table 9-5. In the absence of clear evidence suggesting otherwise, it is here assumed that the interactions appearing in Table 9-5 are "directional" in the sense that, for example, the interaction, p-r, is not the same as the interaction r-p. In other words, Tsable 9-5 is asymmetric with respect to the diagonal.

Table 9-5 The nine classes of interactomes in living cells predicted on the basis of the three classes of nodes.

	Protein (p)	RNA (r)	DNA (d)
Protein (p)	p-p	p-r	p-d
RNA (r)	r-p	r-r	r-d
DNA (d)	d-p	d-r	d-d

Applying Prigogine's classification scheme of structures into *equilibrium* and *dissipative structures* (Section 3.1) to Table 9-5, we can generate a system of 18 classes of interactions as shown in Table 9-6. The examples shown in Table 9-6 for each of these 18 classes of interactions reflect my limited knowledge and may need to be replaced with better ones in the future but the structure of the table itself may remain valid, reminiscent of the periodic table in chemistry. Hence we may refer to Table 9-6 as the *periodic table of interactomes*. A similar table was suggested for molecular machines in Section 11.4.4. It is interesting to note that both these tables have 18 cells or entries, and it is not known whether the equality of the dimension of the tables is a pure coincidence or a consequence of some deep connection between *interactomes* and *molecular machines*.

Table 9-6 Examples of the 9 classes of interactomes predicted in Table 9-5. P = protein, r = RNA, and d = DNA.

Interactomes	**Examples**	
	Equilibrium	*Dissipative*
1. p-p	Multisubunit protein complexes, e.g., hemoglobin, cytochorme C oxidase, ATP synthase	Interaction between two or more metabolic pathways, e.g., between glycolysis and oxidative phosphorylation during glucose-galctose shift (see Table 12-1)
2. p-r	RNA binding proteins without any catalytic activity, e.g., Maxi-KH, PUF (Lee and Schedl 2006).	RNA binding proteins with catalytic activity, e.g., DEAD/DEAH box, Zinc knuckle (Lee and Schedl 2006), RNA polymerases, RNases, spliceosomes
3. p-d	Transcription factors	DNA polymease, transposase, DNA ligase, DNA recombinase
4. r-p	Same as p-r (?)	RNA guide component of RNA-protein complex catalyzing posttranscriptional gene silencing (PTGS) (Grishok et al. 2001)
5. d-p	Mutant structural gene-protein	Mutant regulatory gene-protein complex (?)

	complex	DNA supercoil-induced protein binding (see the *TF-conformon collision hypothesis*, Section 8.3).
6. r-r	Double stranded micro RNAs (Grishok et al. 2001)	Ribozymes (Kruger et al. 1982, Wochner et al. 2011, Tang and Breaker 2000)
7. r-d	Riboswitches without catalysis	Ribozymes
8. d-r	Same as r-d (?)	DNA supercoil-induced RNA binding or *RNA-conformon collision hypothesis* (?) akin to the *TF-conformon collision hypothesis* described in Section 8.3
9. d-d	Double stranded DNA	Conformon-conformon interactions within DNA superstrcutres such as supercoils (?)

CHAPTER 10

The Living Cell

The living cell is the unit of life. Therefore, without knowing how the cell works on the molecular level, it would be difficult to understand how embryos develop or how species evolve (Waddington 1957, Gerhardt and Kirschner 1997, West-Eberhard 2003). Most experimental data on the living cell have been obtained from "dead" cells, since living cells must be destroyed in order to isolate their components for purification and analysis (Section 3.1.5). To determine how living cells (*dissipatons*) work based on the experimental data measured from 'dead' cells (*equilibrons*), however complete, is not an easy task, just as reconstructing musical melodies from sheet music would not be easy if one does not know the rules of mapping sheet music to audio music or does not have the ability to sing from sheet music. It is probably fair to say that, despite the massive amount of experimental data on the cell that has accumulated in the literature and on the World Wide Web as of the first decade of the 21st century, we still do not understand how the myriad structural components of the cell interact in space and time to exhibit the dynamic phenomena we recognize as life on the cellular level. The major goal of this book is to propose, in the form of a model of the living cell called the Bhopalator (Figure 2-11), the theoretical concepts, molecular mechanisms, and physicochemical laws and principles that may facilitate uncovering the rules that map cell structures to cell functions.

10.1 The Bhopalator: a Molecular Model of the Living Cell

Although it had been known since the mid-19th century that the cell is the smallest unit of the structure and function of all living systems (Swanson 1964), it was apparently not until 1983 that the first comprehensive theoretical model of the cell was proposed (Ji 1985a,b, 2002b). In that year, a theoretical model of the living cell called the *Bhopalato*r (Figure 2-11) appeared in which both the *energetic* and *informational* aspects of life were integrated on an equal footing, based on the supposition that life is driven by *gnergy*, the complementary union of *information* and *energy* (Section 2.3.2). The name Bhopalator reflects the fact that the cell model was born as a result of the two lectures that I presented at the international conference entitled *The Seminar on the Living State*, held in Bhopal, India in 1983. The suffix, "-ator" indicates that the model is based on the postulate that the cell is a *self-organizing chemical reaction-diffusion systems* (i.e., a dissipative structure or a dissipaton) (Sections 3.1 and 9.1).

The Bhopalator model of the cell consists of a set of *arrows* (i.e., *directed edges*) and *nodes* enclosed within a 3-dimensional volume delimited by the cell membrane (Figure 2-11). The system is thermodynamically open so that it can exchange matter and energy with its environment (see Arrows 19 and 20) (Section 2.1.1). The arrows indicate the directional *flows of information* driven by free energy dissipation. The solid arrows indicate the flow of information from DNA to the final form of gene expression postulated to be the *dissipative structures* theoretically investigated by Prigogine and his schools (Babloyantz 1986, Kondepudi and Prigogine 1998, Kondepudi 2008). These

dissipative structures are in turn assumed to exert feedback controls over all the solid arrows, as indicated by the dotted arrows (Figure 2-11).

One of the most distinct features of the Bhopalator is the role assigned to *dissipative structures* of Prigogine. Thus, IDSs (intracellular dissipative structures) (Section 3.1.2) are assumed to be both the *final form* of gene expression and the *immediate or proximal causes* for cell functions. Another novel feature of the Bhopalator model of the cell is the assertion that all non-random (or goal-directed) motions of biopolymers and associated small molecules in the cell are driven by *conformons*, the packets of mechanical energy and control information embedded in biopolymers (Chapter 8). Although there was no direct empirical evidence for IDSs or conformons when the Bhopalator was first proposed in 1983, the experimental data supporting these molecular entities emerged in the mid-1980's and throughout the 1990's as reviewed in Sections 8.3 and 9.1.

An updated version of the Bhopalator is presented in Figure 10-1 using the formalism of a bionetwork (Section 2.4). All of the 12 edges or steps shown in this figure are present in the original version of the Bhopalator (Figure2-11), except Steps 8, 9, 10 and 11. The unidirectional arrows indicate the direction of information flow driven by appropriate conformons (i.e., packets of gnergy) which are not shown explicitly. The symbol, A ----> B, can be interpreted to mean that A *affects*, *influences*, *causes* or *gives rise to* B. IDSs are any structures inside the cell that require the dissipation of free energy into heat to be maintained and hence disappear upon the cessation of free energy supply to the cell (e.g., membrane potential, RNA levels, ATP levels).

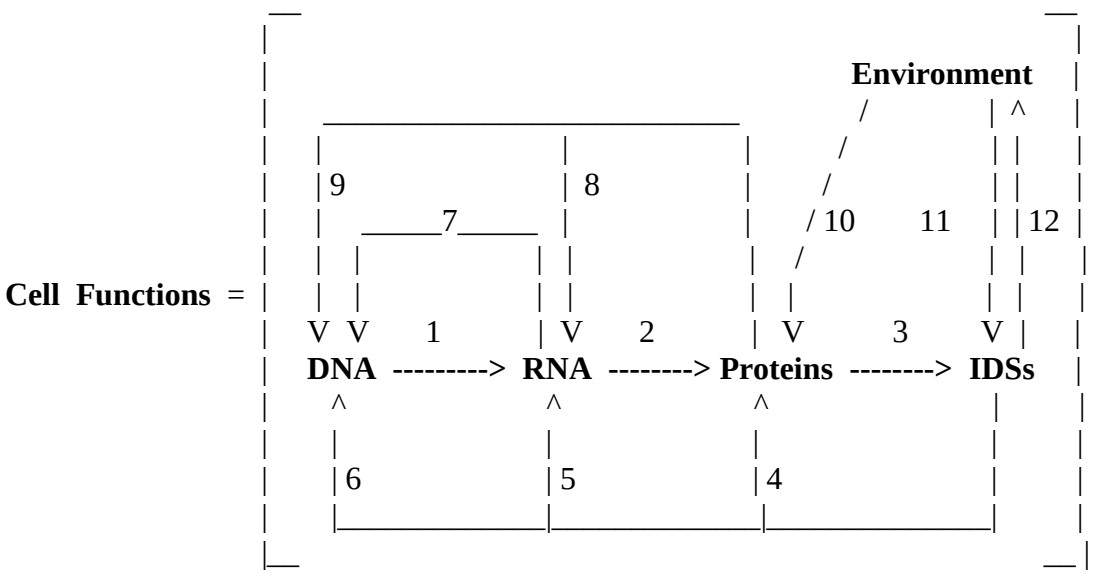


Figure 10-1 The Bhopalator 2011: A bionetwork version of the Bhopalator model of the living cell (Section 2-11). Not shown in the figure are the *biochemicals* that serve as the free energy source for generating the mechanical energy packets called *conformons* (Section 8.4) which drive all goal-directed motions of biopolymers, the most fundamental characteristics of life at the cellular level.

In Figure 10-1, Steps 1, 2 and 3 represent the familiar processes -- *transcription*, *translation* and *catalysis*, respectively. Steps 4, 5 and 6 indicate the feedback controls exerted by IDSs on DNA, RNA and proteins. Step 12 implies that the cell affects its environment through IDSs; i.e., IDSs are the immediate causes of cell functions (Section 10.2), although cell functions do implicate, in addition, DNA, RNA, proteins, as symbolized by the large square bracket. Steps 7, 8, 9, 10 and 11, not included in the original version of the Bhopalator, represent the following unidirectional interactions:

7 = RNA control over DNA (e.g., siRNA, microRNA),
8 = protein control over DNA (e.g., transcription factors),
9 = protein control over RNA (e.g., RNA-binding proteins),
10 = receptor-mediated input of environmental information (e.g., hormones, cytokines, morphogens), and
11 = non-receptor-mediated interactions with environment (e.g., mechanical pressure, osmotic pressure, radiative damages)

Figure 10-1 provides a convenient *visual* summary of the complex molecular interactions and their properties that underlie life on the cellular level. The *text* version of these interactions and properties is given below:

(**1**) The ultimate form of expression of genes is not proteins (i.e., *equilibrons*) as is widely assumed but IDSs (*dissipatons*) (Section 3.1). To emphasize this point, IDSs are *prescinded* (Section 6.2.12) to formulate what I call the *IDS-cell function identity hypothesis* in Section 10.2.

(**2**) IDSs exert feedback controls over DNA (Step 6), RNA (Step 5), and proteins (Step 4).

(**3**) IDSs are postulated to be the sole agent through which the cell affects its environment as indicated by the unidirectional arrow 12 in Figure 10-1. This postulate is an alternative expression of the *IDS-cell function identity hypothesis*.

(**4**) Environment can affect DNA in two ways – through i) receptor-mediated mechanisms (see Steps 10 and 9), and ii) non-receptor-mediated mechanism (see Steps 11 and 6).

(**5**) Through the two mechanisms described in (**4**), the environment of the cell can cause the two types of changes in DNA – i) changes in nucleotide sequences (*genetics*), and ii) changes in the 3-dimensional structure of DNA including covalent modification of bases and DNA-binding proteins without changing its nucleotide sequence (*epigenetics*; Riddihough and Zahn 2010, Bonasio, Tu and Reinberg 2010).

(**6**) There are two types of environment-induced genetic and epigenetic changes described in (**5**) – i) *heritable* from one cell generation to the next, and ii) *non-heritable*. Heritable genetic changes are well-known in biomedical sciences (Mundios and Olsen 1997, Chu and Tsuda 2004). Environment-induced heritable epigenetic changes (EIHEC), well established experimentally, is known as Lamarckism or lamarckian (Ji 1991, p. 178, Jablonka 2006, 2009) and may play a fundamental role in both *phenotypic plasticity* and *evolution* itself (West-Eberhard 2003).

(**7**) There are two types of environment-induced heritable epigenetic changes (EIHEC) – i) *rapid* with the time constant τ, comparable to or less than the life span of organisms,

and ii) *slow* with the time constant τ ', comparable to the lifespan of species (say, 10^2 x τ or greater) and to geological times. The study of rapid EIHEC constitutes a major part of developmental biology and phenotypic plasticity, whereas the study of slow EIHEC is a newly emerging aspect of biological evolution (West-Eberhard 2003).

(**8**) The causes of cell functions, i.e., the factors that affect cell functions directly or indirectly, can be identified with the directed arrows in Figure 10-1, either singly or as groups of two or more arrows.

(**9)** The causes of cell functions divide into two types –i) *external causes* or environment (e.g., temperature, humidity, salinity, pressure, radiation, environmental chemicals including nutrients), and ii) *internal causes*, namely, DNA, RNA, proteins, and/or IDSs.

(**10**) The internal causes of cell functions may be divided into at least three groups – i) the proximal (IDSs in Figure 10-1), ii) the intermediate (proteins and RNA), and iii) the distal causes (DNA). The external causes of cell functions may be similarly divided. Thus, the living cell, as modeled in the Bhopalator 2011, embodies a complex web of both internal and external causes that interact with one another. Such complex systems of interactions may be difficult to analyze and discuss without the aid of the visual diagram provided by the Bhopalator 2011, i.e., Figure 10-1.

(**11**) The system of the unidirectional arrows constituting the Bhopalator model of the living cell symbolizes orderly, non-random motions/movements of biopolymers and their associated small molecules inside the living cell (e.g., active transport of ions across cell membrane mediated by membrane ion pumps, RNA polymerse movement along DNA, myosin movement along actin filament, kinesin and dynein movement along microtubules, chromosome remodeling, etc.). According to the Second Law of Thermodynamics (Section 2.1.4), no orderly motions such as these are possible without dissipating requisite free energy, and this free energy dissipation is postulated to be mediated by conformons, which provide the molecular mechanism for the chemical-to-mechanical energy conversion based on the generalized Franck-Condon principle (Chapter 8).

(**12**) Cell functions entail transmitting *genetic information* in space (e.g., from the nucleus to the cytosol; from the cytosol to the extracellular space) and time (e.g., from an embryo to its adult form; from one cell generation to the next) through what has been referred to as the Prigoginian and the Watson-Crick forms of genetic information, respectively (Ji 1988). The Bhopaltor model of the living cell identifies the Prigoginian form of genetic information with IDSs and the Watson-Crick form with DNA.

To recapitulate, the updated version of the Bhopalator shown in Figure 10-1 embodies the following key principles, theories, and concepts discussed in this book:

i) the *principle of self-organization* and dissipative structures (Section 3.1),
ii) the *gnergy principle* that all self-organizing physicochemical processes in the Universe are driven by gnergy (Figure 4-8), the complementary union of information (gn-) and energy (-ergy), the discrete units of which being referred to as gnergons which include *conformons* and *IDSs* (Section 2.3.2),
iii) the living cell is a *renomalizable bionetwork* of *SOWAWN machines* (Section 2.4.2),

iv) the cell function is an *irreducible triad* of *equilbrons*, *dissipatons*, and *mechanisms* (Section 6.2.11),

v) *the IDS-cell function identity hypothesis* (see Section 10.2) results from *prescinding* (Section 6.2.12) IDS from other more distal causal factors of cell functions,

vi) the Bhopalator can provide a common theoretical framework for effectuating both *development* (Section 15.8) and *evolution* (Section 14.7) through genetic and epigenetic mechanisms obeying the Principle of Slow and Fast Processes, also known as the *generalized Franck-Condon principle* (Section 2.2.3).

vii) Because of vi), the Bhopalator provides a sound theoretical basis for unifying *genetics* and *epigenetics* on the one hand and *evolutionary developmental biology* (EvoDevo) (Carroll 2006) and *developmental evolutionary biology* (West-Eberhard 2003) on the other.

10.2 The IDS-Cell Function Identity Hypothesis

As already pointed out in Section 10.1, IDSs in Figure 10-1 are the only node among the four nodes that is connected to cell's environment via a unidirectional arrow, implying that IDSs are the *most proximate causes* of cell functions (also called cell behaviors, phenotypes, or phenons). Thus IDSs are unique among the possible causes of cell functions that are at different distances from the effects or cell functions, DNA being most distant. The idea that IDSs are the immediate causes of cell functions will be referred to as the *IDS-cell function identity hypothesis* (ICFIH). It is clear that asserting ICFIH does not entail denying the causal roles for other cell constituents, namely, proteins, RNA, and DNA but emphasizes the immediacy of IDSs among the four possible causes of cell functions (see Section 12.5 for further details).

10.3 The Triadic Structure of the Living Cell

Dissipative structures are distinct from *covalent* and *conformational* (also called *noncovalen*t) structures in that they are 'far-reaching' or 'global' in contrast to covalent and noncovalent structures whose effects are localized within one (in the case of covalent structures) or a set of contiguous molecules in physical contact (in the case of noncovalent structures). The 'far-reaching' (or 'global') effects of dissipative structures inside the cell can be mediated by electric field (in the case of action potentials) or mechanical tensions (in the case of the cytoskeletons, the dynamics of interconnected microfilaments, intermediate filaments and microtubules, supported by ATP or GTP hydrolysis). Ingber (1998) and his colleagues have obtained direct experimental evidence showing that local perturbations of a living cell under mechanical tensions can propagate throughout the cell, which phenomenon these authors referred to as 'tensegrity', or *tensional integrity*. Thus, Ingber's *tensegrity* belongs to the class of intracellular dissipative structures (IDSs).

It is suggested here that dissipative structures are essential (along with covalent and noncovalent ones) for cell *reasoning* and *computing* because their 'far-reaching' effects

provide mechanisms to coordinate many physicochemical processes occurring at different loci inside the cell, just as the 'far-reaching' axons allow the physicochemical processes occurring within individual neurons to get coordinated and organized in the brain to effectuate human reasoning.

Table 10-1 Three categories of structures in the cell and the brain.
The third structure, which is built on the first two structures, is thought to be essential for reasoning/computing, or the ability of a physical system to respond to input stimuli according to a set of rules or programs.

	Peircean Categories*		
Level	**Firstness**	**Secondness**	**Thirdness**
Cell	*Chemical Reactions* (Covalent interactions)	Biopolymer-Biopolymer Interactions (Noncovalent interactions)	*Dissipative Structures* (Space- and time-dependent gradients)
Brain	*Gradient Structures* (e.g., membrane potentials)	*Information Transmission* (From one neuron to another)	*Neural Networks* (Connected via action potentials and neuro-transmitters; space- and time-dependent)

*See Section 6.2.2.

If these assignments are correct, the following conclusions may be drawn:

1) In agreement with Hartwell et al. (1999) and Norris et al. (1999, 2007a,b), it is suggested here that a new category of structures (i.e., dissipative structures or dissipatons) must be invoked before biologists can understand the workings of the *living cell* (e.g., metabolic regulations, signal transduction, mitosis, morphogenesis, etc.), just as physicists had to invoke the notion of *strong force* (in addition to *electromagnetic force*) before they could explain the stability of atomic nuclei or quantum dots (see Section 4.15) to explain size-dependent optical properties of nano particles (http://en.wikipedia.org/wiki/Quantum.dot).

2) Reasoning process is not unique to the human brain but can be manifested by cellular and abiotic systems meeting certain structural requirements in agreement with the ideas of Wolfram (2002) and Lloyd (2006) in the field of computer science. This conclusion seems in line with Wolfram's *Principle of Computational Equivalence,* according to which all natural and artifactual processes obeying a set of rules are equivalent to computation (Wolfram 2002, pp. 715-846). Also the postulated ability of the cell to reason seems consistent with the isomorphism thesis between cell and human languages (Ji 1997a, b, 1999, 2002b), since, without being 'rational', neither humans nor cells would be able to use a language for the purpose of communication.

3) Humans can reason (i.e., the *Thirdness* phenomenon exists in the human brain), only because cells and abiotic systems in nature in general behave rationally (and not randomly); i.e., the *Thirdness* phenomenon exists in Nature, independent of human mind. The universality of *Thirdness* asserted here may be closely related to what Rosen called *Natural Law* that guarantees the ability of the human mind to model nature (Rosen 1991).

15.12 Micro-Macro Coupling in the Human Body

The human body is arguably the most complex material system in the Universe (besides the Universe Itself) in both its *structure* and *behavior*. The human body consists of approximately 10^2 joints, 10^3 muscles, 10^3 cell types, and 10^{14} neurons, each with multiple connections to other neurons (Kelso 1995). In addition, the motions of these components are not random but *coordinated* so that the body can perform macroscopic tasks essential for its survival under prevailing einvironmental conditions. The purpose of this section is to apply the theoretical principles and concepts developed in this book to elucidating the possible mechanisms underlying the phenomenon of the micro-macro coupling we experience in *coordianated motions* of our body.

Coordination dynamics originated in the study of the *coordination* and *regulation* of the movements of the human body (Bernstein 1967, Kelso 1995, Kelso and Zanone 2002, Kelso and Engstrøm 2006, Kelso 2008, 2009) but its principles are *scale-free*, i.e., *scale-independent,* and *universal* in that they apply to all material systems at all levels, including microscopic and macroscopic levels, that have more than one components interacting with one another to accomplish observable functions, leading to the following definition:

"Coordination dynamics is the study of the space-, time- and task-dependent interactions among the components of a dynamic system." (15-21)

We may recognize three broad branches of coordination dynamics on the basis of the distance scale over which coordination processes take place –

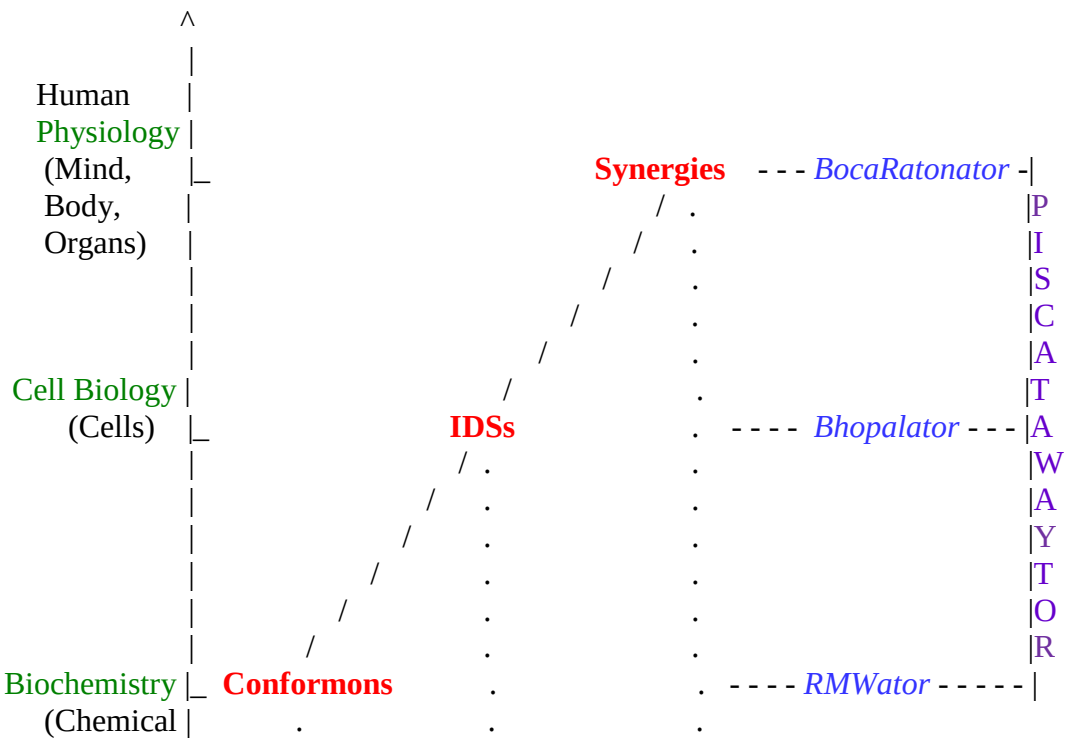
i) *Macroscopic Coordination Dynamics* (MacroCD) = the study of coordinated motions of the components of a system at the macroscopic scale (e.g., coordinated motions of left and right limbs, coordinated motions among the fingers of a hand),

ii) *Mesoscopic Coordination Dynamics* (MesoCD) = the study of coordinated motions of the components of a system at the mesoscopic scale (e.g., morphogenesis; see Section 15.1), and

iii) *Microscopic Coordination Dynamics* (MicroCD) = the study of coordinated motions of the components of a system at the molecular level (e.g., coordinated motions of the ATP-binding and Ca^{++}-binding domains of the Ca^{++} ion pump; see Figures 8-6 and 8-7).

The human body movement depends on the successful coordination of all the components of the body on these three distance scales. The physicochemical systems embodying coordination dynamics at the three scales are distinct as schematically shown in Figure 15-16. The theoretical concepts (*conformons*, *IDSs*, and *synergies*) that have been invoked as the mechanisms enabling the coordination dynamics at the three distance scales are indicted in Figure 15-16, along with the suggested names of the associated dynamical systems (*RMWator*, *Bhopalator*, and *BocaRatonator*). *RMWator* and *BocaRatonator* are the two names used here for the first time, and the rationale for coining them are given in the legend to Figure 15-16 and in Footnotes 24 and 26 to Table 15-10. The theoretical model of the human body as a whole that is based on the *principle of self-organization* was referred to as *the Piscatawaytor* in (Ji 1991) (see Figure 15-20). The various *ators* appearing in Figure 15-16 are related as shown in Eq. (15-22) where CD stands for coordination dynamics:

$$\text{Piscatawaytor} = \underset{(MicroCD)}{\text{RMWator}} + \underset{(MesoCD)}{\text{Bhopalator}} + \underset{(MacroCD)}{\text{BocaRatonator}} \qquad (15\text{-}22)$$



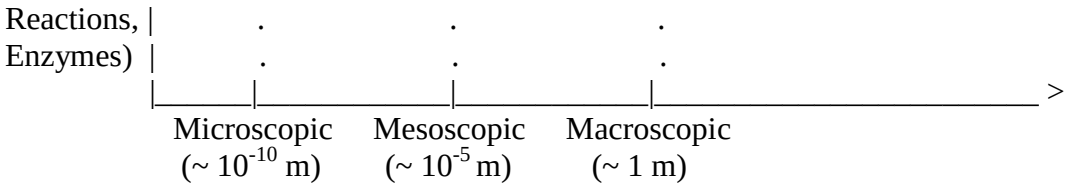


Figure 15-16 Conformons, IDSs (Intracellular Dissipative Structures) (Section 3.1.2), and synergies as *microscopic*, *mesoscopic*, and *macroscopic* manifestations of *gnergons* (Section 2.3.2) or *dissipatons* (Section 3.1.2). The gnergon-based model of human behavior is here referred to as the 'BocaRatonator' to acknowledge the seminal contributions made by Kelso and his colleagues at the Florida Atlantic University at Boca Raton, Florida. The term 'RMWator' derives from **R** (Richland, to acknowledge Xie and his colleagues for their measurement of single-molecule enzymic activity of cholesterol oxidase while at The Pacific Northwest National Laboratory in Richland, WA), M (Minneapolis, to acknowledge Rufus Lumry and his colleagues' fundamental contributions to enzymology at the University of Minnesota at Minneapolis), and W (Waltham, to acknowledge the seminal work on enzyme catalysis carried out by William Jencks and his group at the Brandeis University in Waltham, Mass).

In December, 2008, Professor Kelso visited Rutgers for three days and gave informative and inspiring seminars on *coordination dynamics* and the philosophy of *complementary pairs* to both my General Honors Seminar students and a University-wide audience. During his visit at Rutgers, we had an opportunity to compare the results of our researches over the past several decades in our respective fields of specialization and it did not take too long for us to realize that we have been studying the same forest called the human body albeit from two opposite ends – Kelso and his coworkers from the *macroscopic end* of human body movements and I from the *microscopic end* of molecular and cell biology. The similarities and differences between these two approaches and the results obtained are summarized in Table 15-9. Evidently, between us, we have covered the whole spectrum of *the science of the human body*, from "*molecules to mind*" (as Kelso poetically put it over breakfast one morning). One way to visualize how Kelso's poetic vision might be realized in material terms is shown in Figure 15-17, the essence of which can be stated as follows:

"*Mind controls cells; cells control molecules; molecules control energy supply and thereby cells and mind.*" (15-23)

Statement (15-23) reminds us of the *reciprocal causality* or *cyclic causality* where A affects B which then affects A back, etc. (Kelso and Engstrøm 2006, pp. 115,191). We may refer to Statement (15-23) as the 'Reciprocal Causality of Mind and Molecules' (RCMM). It may be significant that the source of *control information* and that of *free energy* are located at the two opposite ends of the diagram, reflecting the fact that control information originates in the mind and the energy needed to implement the control instruction can come only from the chemical reactions catalyzed by enzymes.

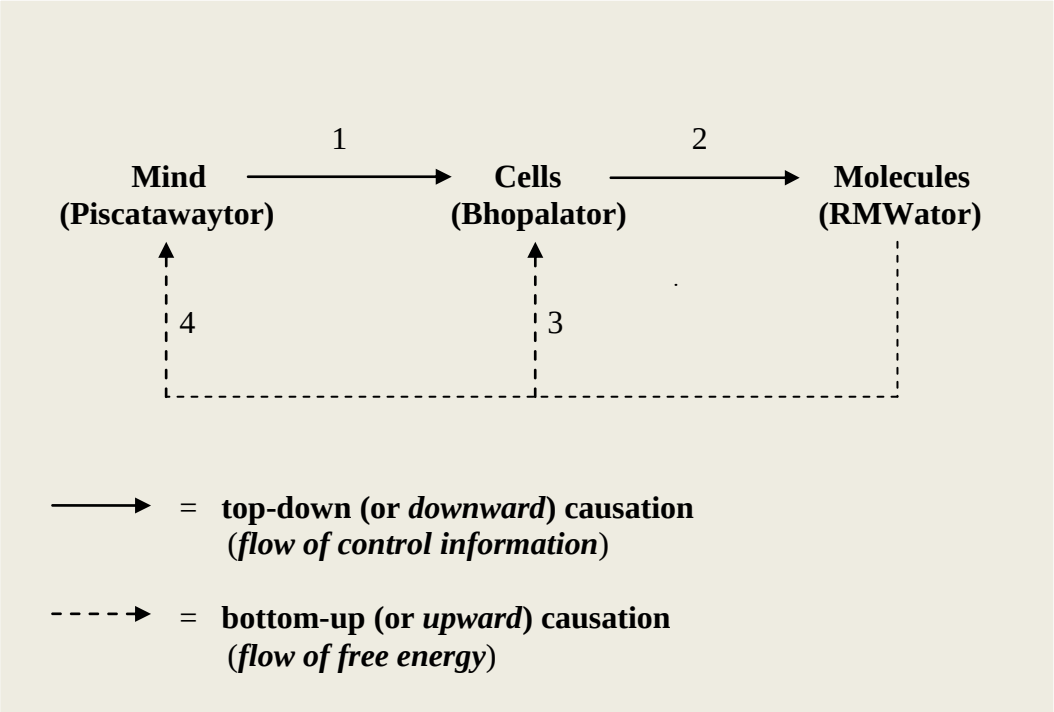


Figure 15-17 The *Principle of the Reciprocal Causality of Mind and Molecules (RCMM)* mediated by *cells*, or more briefly *the Principle of Mind-Molecule Coupling (PMMC).* Step **1** represents the action of mind on cells, as when I decide to lift a cup by activating neurons in my motor cortex which in turn activate the muscle cells in my arm and fingers. Step **2** represents the action potential-triggered activation of the myosin ATPase molecules in muscle cells that catalyze the hydrolysis of ATP, the source of free energy. The free energy released from ATP hydrolysis in muscles and the brain powers all the motions in muscle cells (Step **3**) and neurons in the body which constitute the mind (or the brain) (Step **4**). *It will be shown in Footnote 26 below that this figure embodies what is referred to as the First Law of Coordination Dynamics (FLCD). Mind* (viewed as a part of the human body), *cells*, and *enzyme molecules* in action are examples of dissipative structures (or *dissipatons*) and hence can be named as X-ators, where X is the name of the city where the most important research is done on a particular 'ator'. The acronym RMW stands for Richland, Minneapolis and Waltham (see Footnote 27 in Table 15-10).

Table 15-9 The similarities and differences between the biological theories developed by J. A. S. Kelso and S. Ji.

	Kelso (1984, 2008)	**Ji** (1974a,b, 2000, 2004a)
1. System studied	Human Body	Molecular Machines
2. Methods	Cognitive Neuroscience Nonlinear Dynamics	Chemistry Molecular Mechanisms
3. Principles invoked	Synergies Biological Information Self-Organization Complementarity	Gnergons* Biological Information Self-Organization Complementarity
4. Direction of generalization	Macro → Micro	Micro → Macro
5. Philosophical Generalization	Complementary Nature (Kelso & Engstrøm 2006)	Complementarism (Ji 1993, 1995)

*Gnergons are discrete units of gnergy, the complementary union of *energy* and *information* (Section 2.3.2). Gnergons are thought to be necessary and sufficient for all self-organizing, goal-directed motions in all physical systems including the cell and the human body. Examples of gnergons include cnformons (Chapter 8) and IDSs (Chapter 9).

Table 15-10 characterizes the three branches of coordination dynamics operating within the human body in detail and situates the works of Kelso and mine within the triadic framework of coordination dynamics. As Row 1 indicates, the human body can be viewed as an excellent example of a *renormalizable bionetwork* discussed in Section 2.4. That is, the human body is a network of cells, each of which is a network of biopolymers, and biopolymers are networks of atoms. It is interesting to note that each bionetwork is characterized by a unique mechanism of interactions among its nodes – short-range *covalent interactions* among atoms to form biopolymers; medium-range *noncovalent interactions* among biopolymers to form cells; and long-range *messenger-mediated interactions* among cells to form the human body. Extensive footnotes are attached to most of the items appearing in Table 15-10, often with their own tables and figures (reminiscent of nested networks of self-similarity).

Table 15-10 Coordination dynamics at three distance scales.

		Coordination Dynamics at 3 Scales		
		Macroscopic (~ 1 m)	Mesoscopic (~ 10^{-5} m)	Microscopic (~ 10^{-10} m)
1. Renormaliz-	Node	cells	biopolymers	atoms

able bionetwork[1]	Edge	intercellular messenger-mediated cell-cell interactions[2]	noncovalent interactions[3]	covalent interactions[4]
	Bio-network	human body	cells	biopolymers
2. Experimental Data	Kelso	e.g., lip and jaw movement in speech production		
	Ji	a) human anatomy[5] b) pain pathways[6] c) brain reward system[6]	a) metabolic pathways[7] b) genome-wide microarray data[8]	a) DNA supercoils[9] b) single-molecule enzymology[10]
3. Methods	Kelso	a) biomechanical[11] b) nonlinear dynamical[12]		
	Ji	a) anatomical[5] b) physiological[5] c) pharmacological[13]	a) molecular biological[14] b) cell biological[15]	a) physical[16] b) chemical[17] c) singe-molecule enzymological[18]
4. Key concepts	Kelso	synergiese[19]	(synergies)[20]	(synergies)[20]
	Ji	renormalizable bionetworks[1] (dissipatons, SOWAN machines, or gnergons)[21]	IDSs[21] (dissipatons, SOWAN machines, or gnergons)[21]	Conformons[22] (dissipatons, SOWAN machines, or gnergons)[21]
5. Models based on PSO[23]	Kelso	BocaRatonator[24]		
	Ji	Piscatawaytor[25]	Bhopalator[26]	RMWator[27]

[1]Biological networks where a node can become a new network at a higher resolution and a network can become a node of another network at a lower resolution (see Section 2.4). For example, at the microscopic level, atoms (e.g., H, O, C, N, deoxyribonucleotides) are the nodes of a network known as a biopolymer (e.g., DNA); at the mesoscopic scale, biopolymers are the nodes of a network known as the cell; and at the macroscopic scale, cells constitute the nodes of a networks known as the human body.

[2]This type of interactions make it possible for long-distance interactions or communications between cells, over distances ranging from 0 (e.g., contact inhibition) to meters (e.g., hormone-mediated or axon-mediated connections).

[3]Relatively weak and ATP-independent interactions or bonds requiring only about 5 Kcal/mole to break.

[4]Relatively strong, enzyme-catalyzed, interactions or bonds requiring 50-100 Kcal/mole to break (Moore 1963, p. 57).

[5]According to the triadic definition of function (Section 6.2.11), *structures* (including anatomy; see Figures 15-19 and 15-20) are as important as *processes* (including physiology) and *mechanisms* to account for functions.

[6]Much is known about the neuroanatomy and neurophysiology underlying the effects of pain and pleasure on human body motions.

[7]Metabolic pathways encoded in a cellular genome are akin to the keys on a piano keyboard (*equilibrons*) and metabolic activities observed in living cells are comparable to the melodies (*dissipatons*) that a pianist produces by striking a select set of keys obeying the instructions given in a sheet music.

[8]The DNA microarray technology allows us to measure (hear) the dynamic changes (audio music) in RNA levels (or waves) occurring within a living cell in response to environmental perturbations. Microarrays make it possible to visualize the coordinated interactions among select RNA molecules in a living cell under a given environmental condition (see Figures 12-1 and 12-2).

[9]Visual evidence for the concept of conformons (see Section 8.3).

[10]Dynamic evidence for the concept of conformons (see Section 11.4.1).

[11]For example the continuous monitoring of the thumb movement in both hands (Kelso 1984).

[12]According to Kelso and Engstrøm (2006, pp. 90-91),

> *"Coordination dynamics, the science of coordination, is a set of context-dependent laws or rules that describe, explain, and predict how patterns of coordination form, adapt, persist, and change in natural systems. . . . Coordination dynamics aims to characterize the nature of the functional coupling in all of the following: (1) within a part of a system, as in the firing of cells in the heart or neurons in a part of the brain; (2) between different parts of the same system, such as between different organs of the body like the kidney and the liver, or between different parts of the same organ, like between the cortex and the cerebellum in the brain, or between audience members clapping at a performance; and (3) between different kinds of things, as in organism~environment, predator~prey, perception~action, etc. . . ."* (15-24)

Coordinatioin dynamics at the macroscopic level can be studied using the powerful tools and concepts provided by the mathematics of *nonlinear dynamics* (van Gelder and Port 1995, Scott 2005). A *coordination law* that has been found useful in analyzing real-life biological systems can be expressed as in Eq. (15-25) (Kelso and Engstrøm 2006, pp. 156-157):

$$d(cv)/dt = f(cv, cp, fl) \quad (15\text{-}25)$$

where d(cv)/dt is the rate of change of the *coordination variable* cv whose numerical value changes with the state of the system under investigation, cp is one or more *coordination parameters* that can affect the state of the system but are not affected by it, and fl is the noisy or thermal fluctuations experienced by the system.

It should be pointed out that a given mathematical idea or principle such as Eq. (15-25) can be represented in many equivalent ways. Some examples are shown below:

$$dx/dt = f(x, P, fl) \quad (15\text{-}26)$$

where x = cv, and P = cp in Eq. (15-25), or

$$dx/dt = f(cv, cp, fl), \text{ or} \quad (15\text{-}27)$$

"(rate of change in x) is a function of x, control parameter cp and fluctuation fl" , or most abstractly (15-28)

$$(\_\_\_\_\_)' = f(\_\_\_\_\_, \_\_\_\_\_, \_\_\_\_\_) \quad (15\text{-}29)$$

where (____)' indicates a time derivative of whatever is inside the parenthesis, f is a mathematical function, and the underlines represent "place holders" which can be filled with appropriate variables, numbers, or words. That is, although Equations (15-25) through (15-29) all look different, their meaning is the same, and this is because mathematics employs *signs* and signs are arbitrary (see Section 6.1.1).

Eq. (15-25) can be integrated with respect to time t, resulting in:

$$cv = F(t, cp, IC, fl) \quad (15\text{-}30)$$

where F is a new function different from f, t is time, and IC is the integration constant whose numerical value is determined by initial conditions. According to Eq. (15-30), the so-called trajectories (see 1) below) in *t-cv plots* depend on *initial conditions.*

Somme of the basic concepts and principles embodied in the coordination law, Eq. (15-25), can be visualized using the skateboarder as an analogy. The skateboarder moving up and down the walls of the empty swimming pool is a convenient metaphor to illustrate a set of important concepts in nonlinear dynamics:

1) *Coordination variable*, cv: The position of the skateboarder on the x-axis which varies with time, increasing (movement from left to right) or decreasing (movement from right to left) as the skateborader moves up and down the pool surface acted upon by gravity. The plot of cv against time, t, is known as *trajectories*. The shape of the trajectories differ (i.e., the trajectories evolve in time in different ways) depending on *initial condition* (i.e., the numerical value of cv at t=0) and the *control parameter* cp, which is in the present case the curvature of the pool surface.

2) *Stable fixed point* also called *attractor*: The skateboarder always returns to the bottom of the pool to minimize its gravitational potential energy.

3) *Unstable fixed point* also called *repeller*: The skateboarder resting on the top of the hill is *unstable* because he/she can be easily pushed off the peak position. If the skateboarder is unperturbed (e.g., by randomly fluctuating directions of wind), he/she can remain at the precarious position for ever.

4) *Potential landscape* often designated as the *cv-V plot* : The relation between the gravitational potential energy of skateboarder's body, V, and its position on the x-axis which fixes its z-axis due to the constraint imposed by the pool surface.

5) *Control parameter* designated as cp: The *curvature* of the wall of the pool, depending on which the skateboarder moves up and down with different speeds

6) *Bifurcation*: One becoming two. For example, the trajectory of the skateboarder at the top of the hill divides into two (if he/she is pushed off) -- either toward the right or the left.

[13]The study of the effects of drugs on human bodily motions provide insights into the mechanisms underlying human movement under normal conditions.

[14]Molecular interactions inside the cell are determined not only by *free energy* changes but also by the *evolutionary information* (Section 4.9) (Lockless and Ranganathan 1999) encoded in the structures of interacting partners.

[15]The cell is the smallest DNA-based molecular computer (Ji 1999a) and the unit of biological structure and function.

[16]Many physical principles including the Fracnk-Condon principle (Section 2.2), laws of thermodynamics and quantum mechanics provide guidelines for visualizing molecular interactions in the cell.

[17]Life is ultimately driven by chemical reactions and needs the principles of chemistry and chemical reactions to be understood at the fundamental level.

[18]For the first time in the history of science, it has become possible, since the mid-1990's, to observe enzymic reactions and molecular motor actions on the single-molecule level, providing new insights into the workings of biopolymers, including dynamic disorder (Row A, Table 11-10), molecular memory effects (Row C, Table 11-10) and coordinated motions between remote domains.

[19]Kelso (2008) defines a *synergy* as

> *". . . a functional grouping of structural elements (molecules, genes, neurons, muscles, etc.) which, together with their supporting metabolic networks, are temporarily constrained to act as a single coherent unit."* (15-31)

Thus defined a *syngergy* is more or less synonymous with a *SOWAWN machine* (Section 2.4) and a *dissipation* (Section 3.1.5), both of which being examples of *gnergons* (Section 2.3.2). *Hence synergies may be considered as a member of the gnergon class.*

[20]Although the concept of the synergy originated in macroscopic science of human body motions (Bernstein 1967), the concept was subsequently extended to cellular and molecular levels (reviewed in (Kelso 2008, 2009)).

[21]*Intracellular dissipative structures* were first invoked in the Bhoplator model of the cell (Ji 1985a,b) as the final form of the expression of genes and generalized in the form of *dissipatons* and *SOWAWN machines* that were suggested to be applicable to other levels of biological organizations (Sections 9.1 and 10. 1).

[22]Conformons were invoked in (Green and Ji 1972a,b) to account for the molecular mechanism underlying the coupling between respiration and phosphorylation reactions in mitochondria (Sections 8.1 and 8.7) and later generalized to formulate the concept of *gnergons* in (Ji 1991) which was postulated to apply to all levels of organization, both biotic and abiotic (Section 2.3.2).

[23]The Principle of Self-Organization (Section 3.1)

[24]The nonlinear dynamical model of the human body based on the Principle of Self-Organization. The name BocaRatonator is suggested here (as indicated earier) to acknowledge the contributions that J.A. S Kelso and his colleagues at the Florida Atlantic University in Boca Raton, Florida have made in advancing the field of the coordination dynamics of the human body. The Piscatawaytor (see below), in contrast, is best considered as the theoretical model of the human body that integrates, albeit qualitatively, the molecular (micro coordination dynamics), cellular (mesocoordination dynamics), and physiological (macrocoordination dynamics) descriptions of the human body (Figures 15-16 and 15-18).

[25]The theoretical model of the human body comprising 5 basic compartments (nervous, circulatory, endocrine, immune, and motor systems) dynamically interacting with one another based on the *Principle of Self-Organization* (Ji 1991) (see Figure 15-18).

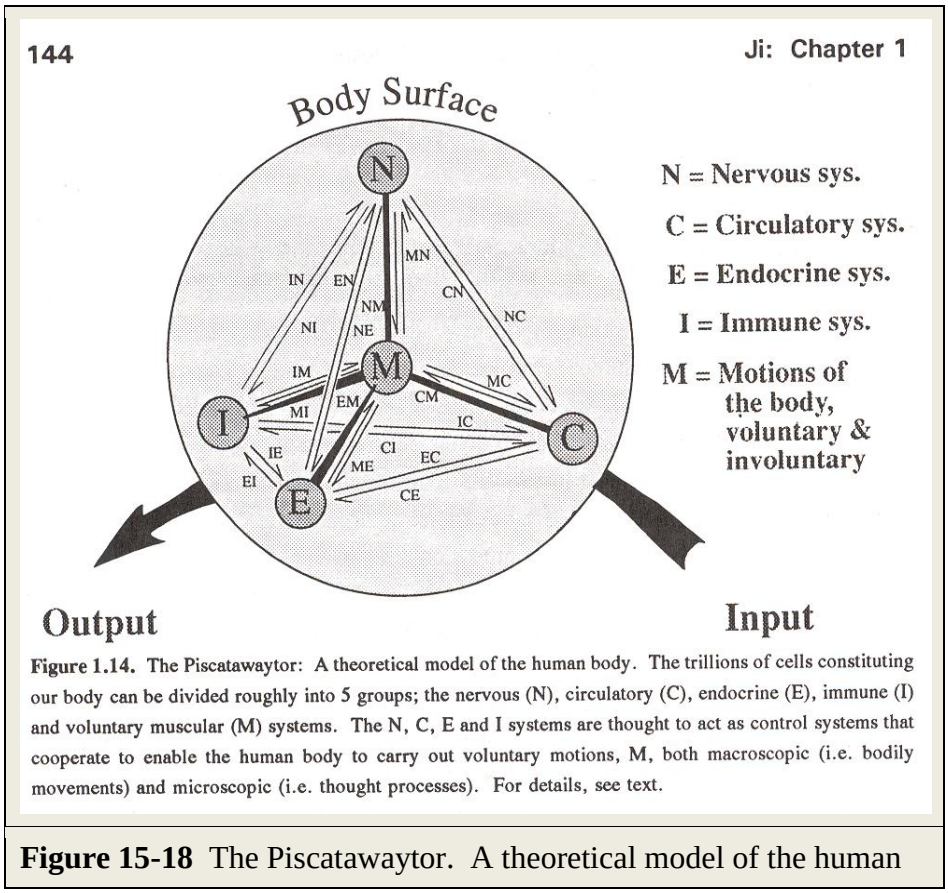


Figure 15-18 The Piscatawaytor. A theoretical model of the human

body based on the principle of self-organization described in Section 3.1.

As can be seen in Figure 15-18, the motor system (**M**) is placed at the center of the tetrahedron, the simplex of the 3-dimensional space (Aleksandrov et al. 1984), because motion is thought to constitute the most fundamental aspect of the human body as indicated in the following quotation from (Ji 1991, p. 144):

> *". . . the fact that the M system must be relegated to the center of the tetrahedron in order to effectuate the simultaneous contacts suggests the possibility that the most important biological function of the human body is voluntary motions, including thought processes (emphasis added). This conclusion places voluntary motions, which we all too readily take for granted, at the center of our biological being. Is it possible that there is some deep philosophical significance to this conclusion? Have we underestimated the fundamental biological and evolutionary significance of our voluntary bodily motions?"* (15-32)

The idea expressed in this paragraph appears consonant with the dynamical approach to cognitive science advocated in the book entitled *Mind as Motion* edited by Port and van Gelder (1995), which motivates me to suggest that the Piscataway tor may provide a

biologically realistic theoretical framework for *cognitive science* of the future that can not only integrates existing paradigms (e.g., computational vs. dynamical approaches) but also open up new possibilities of research.

[26]The Bhopalator model of the cell at the mesoscopic level (see Figure 2-11) may be essential in linking the microscopic and macroscopic worlds. That is,

"One of the fundamental roles of the living cell in biology is to provide the mechanistic framework for coupling exergonic microscopic processes and endergonic macroscopic processes in the human body." (15-33)

Statement (15-33) is consistent with or supported by Statements (15-34) and (15-35):

"It is impossible for the human body to perform macroscopic movement without driven by microscopic chemical reactions." (15-34)

"The free energy that is required for all macroscopic motions of the body can only be provided by exergonic chemical reactions catalyzed by enzymes at the microscopic level." (15-35)

Statements (15-33) through (15-35) are also in agreement with the *reciprocal causality of the human body* depicted in Figure 15-17, according to which the macroscopic events, i.e., *mind-initiated body motions*, and the *microscopic events, i.e., enzyme-catalyzed chemical reactions*, are coupled through the mediating role of *the living cell*. The fundamental role that the living cell plays in effectuating the bodily motions, therefore, may be more generally stated as a law:

"It is impossible to couple macroscopic bodily motions, either voluntary or involuntary, and microscopic chemical reactions without being mediated by the mesoscopic living cell." (15-36)

For convenience of discussions, Statement (15-36) may be referred to as the "First Law of Coordination Dynamics" (FLCD).

There are two mechanisms of coordinating two positions or points in the human body (and in muticellular organisms) –

i) the *static (rigid, equilibrium) coordination mechanism (SCM)* operating between the two ends of a bone, for example, that are connected to each other through a rigid body, and

ii) the *dynamic (flexible, dissipative) coordination mechanism (DCM) operating* between two points located in the opposite ends of a muscle, a muscle fiber or in two remote domains within a biopolymer, for example, that are connected through flexible, deformable bodies.

The principles underlying SCM are provided by the *Newtonian mechanics* while those underlying DCM derive from multiple sources including the i) *Newtonian mechanics*, ii)

thermodynamics, iii) *quantum mechanics*, iv) *statistical mechanics*, v) *chemical kinetics*, vi) *control theory*, and vii) *evolutionary biology* which are all implicated, although not always explicitly discussed, in what is known as *coordination dynamics* (Bernstein 1967, Kelso 1995, Turvey and Carello 1996, Jirsa and Kelso 2004, Kelso and Enstrøm 2006) .

When two objects A and B are coordinated via SCM, they are connected to a rigid body C so that A, B, and C form a mechanically coupled *simple machine* (to be called the *SCM machine*) and the movements of A and B are automatically coordinated. But when A and B are coordinated via DCM, they are connected to a deformable body C (to form what may be called the *DCM machine*) in such a manner that A, B and C are mechanically coupled system only when appropriate conditions are met. In other words, *the DCM machine is a much more complex and sophisticated than the SCM machine. In addition the DCM machine is synonymous with the SOAWN machine and the renormalizable network discussed in Section 2.4.*

The First Law of Coordination Dynamics (FLCD), Statement (15-36), is a phenomenological law similar to the laws of thermodynamics and does not provide any detailed mechanisms as to how the law may be implemented in real life. To the extent that empirical data can be marshaled to formulate realistic mechanisms to implement FLCD, to that extent FLCD will gain legitimacy as a law. Figure 15-17 provides an empirically based mechanistic framework for implementing FLCD and hence can be viewed as a diagrammatic representation of FLCD. According to Figure 15-17, FLCD consists of two causes – upward causes or mechanisms (Steps 3 and 4) and downward causes or mechanisms (Steps 1 and 2).

The *upward mechanisms* implementing FLCD implicates the hierarchical organization of material components of the muscle from the myosin molecule to the muscle attached to a bone, ranging in linear dimensions from 10^{-10} m to 1 m (see Figure 15-19). Figure 15-19 exposes the essential problem underlying the upward mechanism: *How can myosin molecules move the muscle?* For example, in order for our arm to move a cup of tea or an apple, the arm muscle must generate forces in the range of 1 Newton acting over distances in the range of 1 meter in less than 1 second (Figure 15-19). But a myosin molecule can generate forces only in the range of 1 pN (picoNewton, or 10^{-12} N) acting over distances in the range of 10^{-8} m. That is,

> *"In order for our body to move an object powered by chemical reactions, our body must (i) amplify the forces generated by individual myosin molecules from 10^{-12} N to 1 N (an increase by a factor of about 10^{12}), (ii) extend the active distance of the molecular force from 10^{-8} m to 1 m (an increase by a factor of about 10^{8}), and (iii) slow down processes from 10^{-9} s to abut 1 second (a factor of about 10^{9})."* (15-37)

We may refer to Statement (15-37) as *the FDT amplification requirement* (FDTAR) for the micro-macro coupling in the human body, F, D and T standing for *force*, *distance*, and *time*, respectively. Now the all-important question from the perspective of coordination dynamics is

> "*How is the FDTA requirement met in the human body?*" (15-38)

As a possible answer to Question (15-38), it is here suggested that there are two key principles to effectuate the FDT amplification in the human body:

i) The Chunk-and-Control (C&C) principle. This principle was discussed in Section 2.4.2, according to which the cell controls, for example, the replication of DNA by chuncking it into 6 different structural units (or chunks) ranging in size from 2 nm to 1,400 nm in diameter (see Figure 2-9). Similarly it is postulated here that the human body effectuates the FDT amplification by *chunking* the contractile system into 6 hierarchical structure ranging from 1) myosin molecules to 2) myofibrils to 3) sarcomeres to 4) muscle fibers (or muscle cell) to 5) fassicles, and to 6) skeletal muscle (Figure15-19).

Chunks are dissipative structures (or dissipatons) requiring continuous dissipation of free energy in order to maintain their functions. The chunks depicted in Figures 2-9 and 15-19 are the shadows of the functional chunks of DNA and the contractile system, respectively, that are projected onto the 3-dimensional space. Cells or the human body form their functional chunks so that they can more efficiently control the motions of DNA or the skeletal muscle, perhaps not unlike the human brain *chunking* symbols into *phonemes* (units of sound), *morphems* (units of meaning), *words* (units of denotation), *sentences* (units of judgment), *paragraphs* (units of reasoning ?), and *texts* (units of theory building?) to control the language.

ii) The Principle of Synchronization (PS) through the generalized Franck-Condon mechanism (Section 7.2.2). The synchronization of the actions of protein domains within an enzyme is thought to be needed for effectuating catalysis (see, for example, the synchronization of the amino acid residues 1 through 4 at the transition state in Figure 7-5). Synchronization is a non-random process and hence requires dissipation of free energy to be effectuated in order not to violate the laws of thermodynamics (see Section 2.1). The free energy required to synchronize amino acid residues in the catalytic cavity of an enzyme is postulated to be derived from substrate binding or the chemical reaction that the enzyme catalyzes. Organizing the catalytic residues at the enzyme active site is a relatively slow process compared to the fast electronic transitions accompanying chemical reactions that provide the needed free energy. To couple these two partial processes, the slow process must precede the fast one, according to the generalized Franck-Condon principle (GFCP) or the Principle of Slow and Fast Processes (PSFP) (Section 2.2). Thus, the following generalization logically follows:

"Slow and fast partial processes can be coupled or synchronized if and only if i) the fast process is exergonic and ii) the slow process precedes the fast process." (15-39)

Statement (15-39) may be viewed as a more complete expression of GFCP or PSFP than the previous version given in Statement (2-25) (Ji 1991, p. 53), because it specifies the source of free energy needed to drive the coupling or the synchronization of two partial processes, one slow and the other fast: *The free energy must be supplied by the fast, not the slow, partial process.*

The synchronization phenomenon has also been observed among neuronal firing activities in the brain which is known as *neuronal synchrony* (Woelbern et al. 2002, Anderson et al. 2006, Averbeck and Lee 2004). In analogy, we may refer to the synchrony underlying enzymic catalysis (see Figure 7-5 in Section 7.2.2) as the *protein domain synchrony*. Generalizing further, it is postulated here that the principle of synchrony can be extended to all *chuncked systems* in biology, including the contractile system depicted in Figure 15-19 and that, just as the *protein domain synchrony* is effectuated through the generalized Franck-Condon mechanism (GFCM) (see Figure 7-5), so all other '*chunk synchronies'* depend on GFCM in order not to violate the laws of thermodynamics. The essential role of GFCM in 'chunk synchrony' resides in making it possible for the synchronized system to pay for its free energy cost by coupling slow, endergonic processes to fast, exergonic process such as ATP hydrolysis or membrane depolarization triggered by action potentials. Based on these considerations, it appears reasonable to conclude that:

"The dynamic actions of the chunks in chunked systems in biology and medicine can be synchronized based on the generalized Franck-Condon mechanisms or the Principle of Fast and Slow Processes." *(15-40)*

We will refer to Statement (15-40) as the *principle of FDT amplification by increasing mass*, or *the FDTABIM (to be read as 'FDT-ah-bim') principle.* On the level of the contractile system of the human body, the FDTABIM principle appears to be satisfied because the size of the chunks increases by a factor of about 10^8 from myosin to muscle and because all the chunks can be activated simultaneously by the synchronous firing of the efferent neurons of the motor cortex (see Figure 15-20) that innervate the muscle cells. It is interesting to note that the FDTABIM principle is implemented by *nerve impulse* in the contractile system and by *thermal fluctuations* inside cells (Figure 7-6). We will refer to the former as the 'voltage-initiated' FDTABIM mechanism and the latter as the 'fluctuation-initiated' FDTABIM mechanism. (Since the *chunk synchronization* is a necessary condition for FDTABIM (see i) above), we can alternatively refer to these mechanisms as 'voltage-initiated' and 'fluctuation-initiated' chunk synchrony, respectively.) These two types of FDTABIM mechanisms are not independent of each other but hierarchically linked. Hence it can be predicted that the action of the skeletal muscle, for example, will depend on both the fluctuation- and voltage-initiated FDTABIM mechanisms, although the details are not yet known.

Size	**System**	**Time**	**Force**

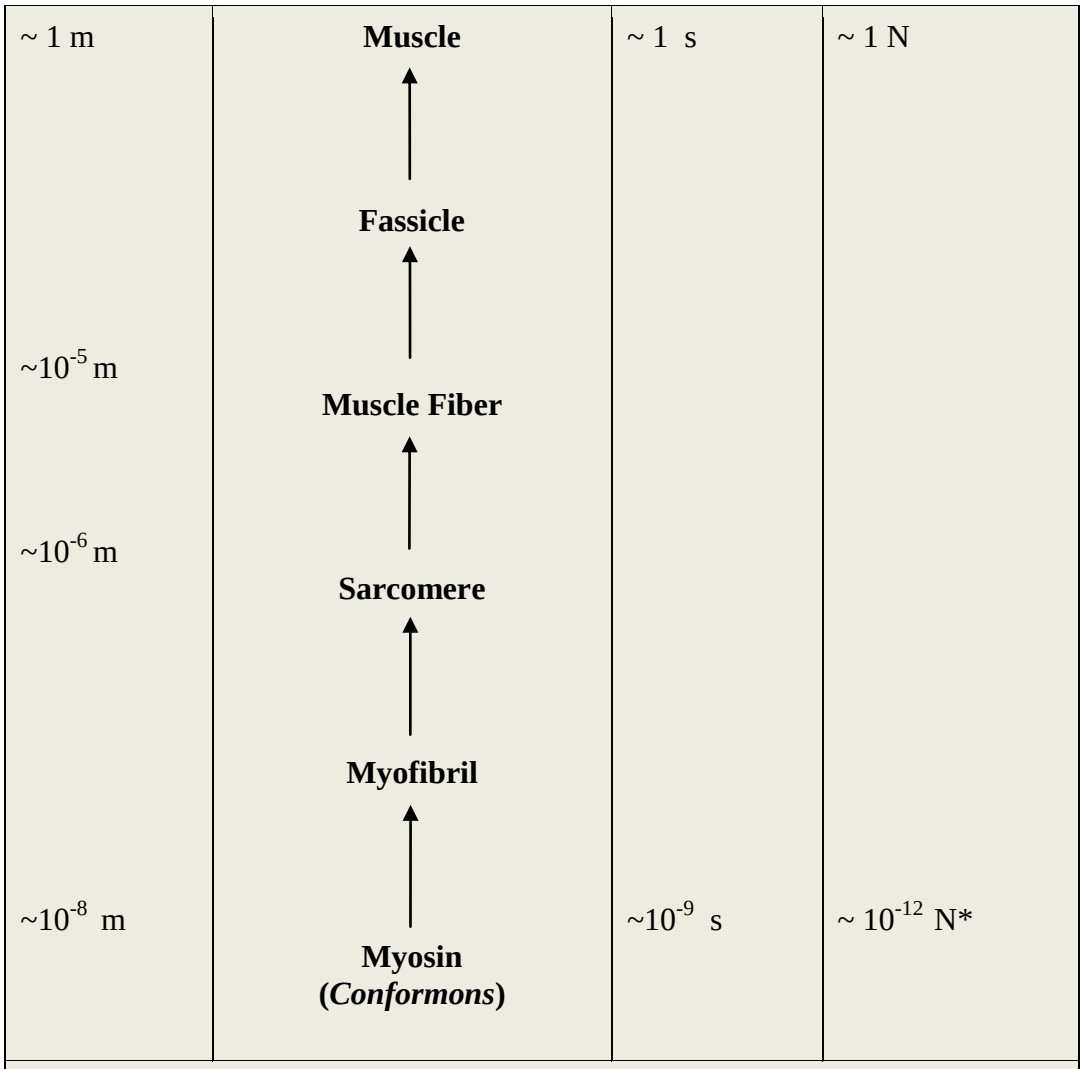


Figure 15-19 The upward arm of the mind-molecule coupling depicted in Figure 15-17. The macro-micro coupling in the muscle tissue by increasing the effective mass of contractile system. Myosin molecules generate mechanical energy packets known as *conformons* during the hydrolysis of ATP that myosin catalyzes (see Figure Panel (D) in Figure 11-34). *(Tominaga et al. 2003)

So far we have been discussing the mechanisms underlying the transmission of force from the myosin molecules to the skeletal muscle given the synchronous activation of the muscle cells involving neuronal synchrony, namely, through the *voltage-initiated FDTABIM mechanism*. That is, we have been focusing on the *upward arm* of the *reciprocal causation* underlying the mind-molecule coupling phenomenon (see Figure 15-17). We will now discuss the *downward arm* of the reciprocal causation of this mind-molecule coupling. The main idea here is that once the brain decides which muscle cells to activate to produce the desired bodily motions (a *slow process*), the brain fires the right number of the right neurons in the motor cortex (a *fast process*) innervating the right set of muscle cells that then generate the needed mechanical force to be subsequently amplified through the upward causal mechanism discussed above.

The brain consists of approximately 10^{12} neurons which are organized into functional cortical areas. For example, the motor cortex constitutes 6.3 % of the total cortical area of the human brain or about 100 cm^2 (Cook 1986, p. 69). There is experimental evidence (Cook 1986, pp. 61-73) that the neocortex is organized in terms of *column*-like structures arranged in grid-like formation, each consisting of ten to a hundred thousand neurons. The motor cortical column is about 500 μm in diameter and contains 30,000 pyramial cells, and there are a maximum of 10^6 such columns per cerebral heimisphere (Cook 1986, p. 63). Each cortical column is thought to possess a specific computational function, for example, the processing of the information from a specific whisker in a rat's mustache. Thus, the *cortical column* may be viewed as a *basic computational unit* of the cortex.

The *downward causation* of mind over molecule begins with somatic nerves that originate in the motor cortex and form the neuromuscular junctions (or end plates) on the surface of target muscle cells. Each muscle cell is innervated by one efferent somatic neuron and one such neuron can synapse with tens of thousands of muscle cells, an arrangement that seems ideal for *synchronizing* the activation of many muscle cells for the purpose of amplifying force and distance of myosin action. When activated these nerves release the neurotransmiter, acetylcholine (Ach), at the neuromuscular junction, causing the depolarization of the post synaptic muscle cells by opening their Na^{++} and K^+ ion channels in sequence which in turn leads to the release of intracellular Ca^{++} from the sarcoplasmic reticulum. The rise in the Ca^{++} concentration in muscle cells activates a series of intracellular events resulting in the generation of mechanical force in myosin molecules coupled to ATP hydrolysis, most likely through the conformon mechanism (see Chapter 8 and Figure 11-34). The downward arm of the reciprocal causation of mind and molecules (Figure 15-17) begins in the motor cortex and ends at the level of neuromuscular junction as schematically depicted in Figure 15-20. Strictly speaking the downward causation does not implicate any molecules directly but only indirectly through depolarized cells and hence should be referred to as mind-cell coupling rather than mind-molecule coupling which should be reserved for the upward causation. In other words, *the motor neurons in the motor cortex do not communicate directly with myosin molecules but only indirectly through muscle cells which control myosin and associated molecules involved in contraction.*

Size	**System**	**Time**
~ 10^{-1} m	**Cortex**	~ 1 s
~10^{-2} m	**Subcortical Regions**	

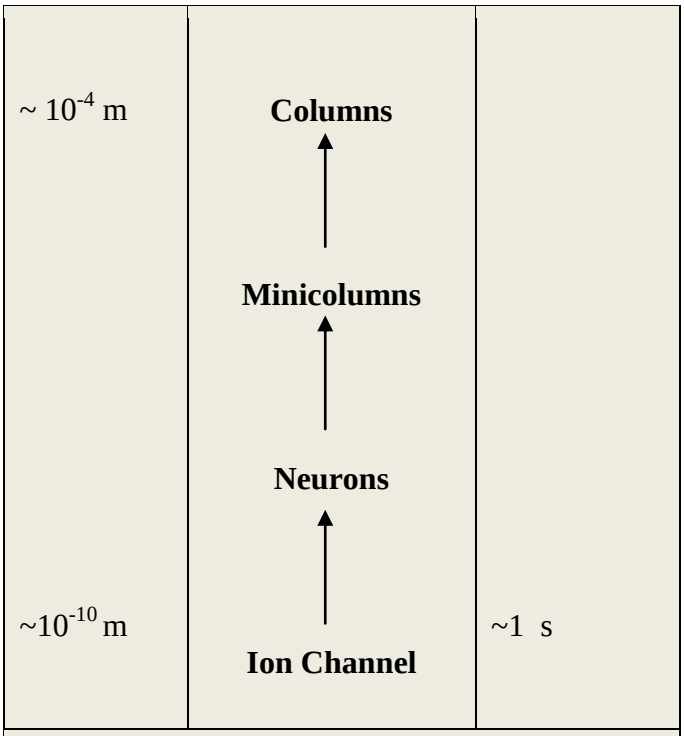


Figure 15-20 The downward arm of the *reciprocal causation of mind and molecule* depicted in Figure 15-17. The macro-micro coupling in the brain by increasing the effective mass of computing (or decision-making) system and hence the computational power.

As alluded to above, the downward causation also implicates coupling two partial processes – one *slow* and the other *fast*. It is here postulated that *the slow, endergonic partial process* underlying the downward causation is the thermal fluctuation-induced random and transient contact formation (or assembling) and detachment process (or disassembling) among cortical columns in the motor cortex and *the fast, exergonic partial process* is identifiable with membrane depolarization of assembled columns. *Here it is assumed that cortical columns possess structures (such as specific axon terminals) that can actively explore potential postsynaptic targets in their neighborhood by undergoing random fluctuations or Brownian motions*, just as molecules undergo Brownian motions or thermal fluctuations until they find their binding sites. But the 'seemingly' random motions postulated to be executed by axon terminals are active (in the sense that depolarized axon terminals are thought to be unable to undergo such explorative motions), while the random motions of molecules are passive since no free energy dissipation is involved. We will therefore refer to the seemingly random motions of axon terminals as ‚actively random', 'quasi-random', or 'quasi-Brownian' and the conventional Brownian motions of molecules as 'passively random', 'truly random', or just 'random'. Quasi-random processes may be slower than truly random processes.

As indicated above, there are approximately 10^6 cortical columns in the motor cortex per hemisphere (Cook 1986, p. 63). These motor columns may undergo *quasi-random interactions*, exploring all possible patterns of interactions or configurations, and when the right configuration is selected or stabilized by input signal to the brain, that particular set of motor cortical columns are thought to be activated (or depolarized) leading to an almost simultaneous activation of their target muscle cells which results in visual input-specific body motions. This series of postulated events are schematically represented in Figure 15-21. Using the language of *coordination dynamics*, we may conveniently describe the transition of the motor cortex from the state where cortical columns are undergoing quasi-random explorative motions to the state where the input signal-induced depolarization of a particular configuration of cortical columns has occurred in terms of the transition from *the metastable state* to *bi-table (or multi-stable) state*. This state transition is suggested to be the result of coupling the slow column rearrangement and the fast axonal depolarization obeying the generalized Franck-Condon principle or the Principle of Slow and Fast Processes (Section 2.2.3).

Based on the above mechanisms, it is possible to estimate the force generated in the muscle when one cortical column in the motor cortex is activated as the result of the input of some external stimuli such as visual signals (see Figure 15-21) through Steps i) through iv) described below:

i) The activation of the efferent motor neurons constituting a cortical column in the motor cortex causes an almost simultaneous activation of the muscle cells innervated by the motor neurons.

ii) The number of the muscle cells activated by one motor column is equal to nr, where n is the number of motor neurons contained in one motor column (estimated to be 10^4; see below) and r is the number of the muscle cells innervated by one motor neuron which is assumed to be 10^3, leading to nr = $10^4 \times 10^3 = 10^7$, the number of the muscle cells that can be activated synchronously by one column in the motor cortex.

iii) We assume that the number m of the myosin molecules contained in one muscle cell is approximately 10^4. Hence the number of myosin molecules activated by one motor column would be nrm or $(10^7)(10^4) = 10^{11}$.

iv) Since one myosin molecule can generate force f in the range of 10^{-12} N (see Figure 15-21), the force generated by activating one motor column would be nrmf = $(10^{11})(10^{-12}$ N) = 10^{-1} N.

v) The diameter of the cortical column is 5×10^{-6} m and the area of the motor cortex is 6,817 mm^2 (or approximately equal to a circle with 8×10^{-2} m in diameter) (Cook 1986, pp. 63-66). Hence the number of the columns contained in the motor cortex is approximately $[(8 \times 10^{-2})/(5 \times 10^{-6})]^2 = [1.6 \times 10^4] = 3 \times 10^8$.

vi) Therefore, the number of the motor columns that needs be activated synchronously to generate 1 N of force in the muscle to lift, say, a cup of tea or an apple (http://en.wikipedia.org/wiki/Newton) would be 1 N/(10^{-1} N) = 10, which is small compared to the total number of cortical columns present in the motor cortex of the human brain, 3×10^8.

The force (F), distance (D) and time (T) amplification by increasing mass (FDTABIM) is necessary for the upward causation of the mind-molecule coupling (Figures 15-17 and

15-19), ultimately because force originates at the molecular level and the objects to be moved are at the muscle level. But why is the FDTABIM necessary for the downward causation (Figures 15-17 and 15-20)? In other words, why is it necessary to amplify the molecular processes at the ion channel level to the macroscopic electrical activities at the level of cortical regions such as motor cortex (Figure 15-20)? One possible answer may be suggested as follows:

"Just as the FDTABIM is needed for the upward causation because the force originates at the molecular level in muscle cells and is finally needed at the macroscopic skeletal muscle level (Figure 15-19), so it may be that the FDTABIM is needed for the downward causation because *the control information originates at the molecular level in cortical neurons and the final control information is needed at the level of the macroscopic cortical regions* (Figure 15-20)." (15-41)

Statement (15-41) seems reasonable in view of the facts (i) that, just as force generation requires free energy, so does decision making (also called *reasoning*, *computation*, or *selecting* between 0 and 1, between *polarization* and *depolarization*), and (ii) that free energy is available only from enzyme-catalyzed chemical reactions or membrane depolarization (i.e., collapsing ion gradients) occurring at the ion channel level.

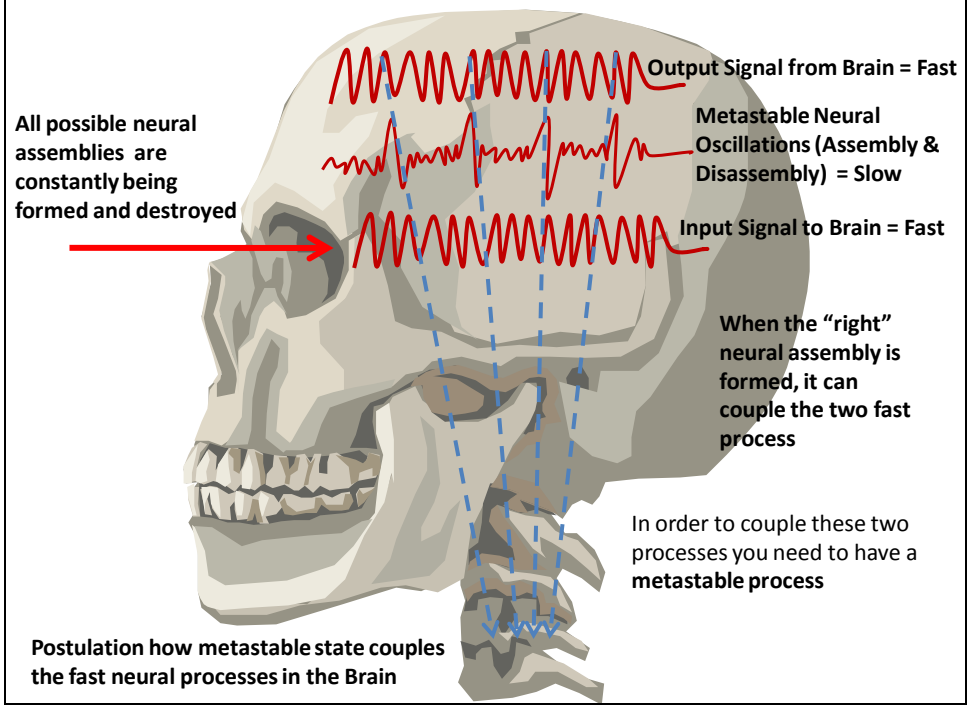


Figure 15-21 The generalized Franck-Condon principle postulated to underlie the coupling between i) *the cortical column assembling/disassembling* process essential for mental activities, and ii)

synchronous firings of muscle cells during the micro-macro coupling accompanying body motions. See text for details. (*I thank Julie Bianchini for drawing this figure in December, 2008*).

[27]Enzymes are molecular machines that are driven by chemical reactions that they catalyze. So the operation of an enzyme can be represented as a trajectory in a phase space (van Gelder and Porter 1995, p. 7) which would collapse when free energy supply is blocked. Therefore an enzyme in action is a dissipative structure or a *dissipation* and hence can be named as an X-ator, X being the name of the city where the most important research has been done to establish the mechanism of action of the dissipative structure under consideration. In the case of enzymology, there are three research groups, in my opinion, that have made major contributions to advancing our knowledge on how enzymes work – i) S. Xie (2001) and his group then at the Pacific Northwest National Laboratory, *Richland*, WA (by measuring the single-molecule enzymic activity of cholesterol oxidase analyzed in Section 11.3), ii) Rufus Lumry (1974, 2009) and his group at the University of Minnesota at *Minneapolis* (for establishing the role of mechanical processes in enzymic catalysis), and iii) William Jencks (1975) at the Brandies University in *Waltham*, MA for establishing the fundamental role of the substrate binding processes in enzymic catalysis which he referred to as the *Circe effect*. To acknowledge the contributions made by these three groups, enzymes have been named as *RMWators* in this book (see Figure 15-16).

CHAPTER 16

17.4 The Law of Requisite Variety and Biocomplexity

If forced to choose one principle that best accounts for the complexity of living systems, I would not hesitate to select the *Law of Requisite Variety* (LRV) as the most powerful candidate of all the laws and principles of biology discussed in this book. LRV (Section 5.3.2), when combined with the Second Law of thermodynamics (also called the Law of Maximum Entropy) (Section 2.1.4), can logically lead to the *Principle of Maximum Complexity* (LMC) (Section 14.3), according to which "*The active complexity of living systems increases toward a maximum"*, Statement (14-15), where "active complexity" is defined as the *complexity "created by living systems utilizing free energy in order to survive under complex environment".* Simply put, the reason surviving organisms increase the complexity of their internal states is because the complexity of their environment is constantly increasing due to the Second Law of thermodynamics and no simple organisms can survive complex environment, Statements (5-10) and (14-8).

17.5 Cybernetics-Thermodynamics Complementarity

Since cybernetics mainly deals with *control information* and thermodynamics with *free energy*, both of which being necessary and sufficient for producing complex living processes, it appears logical to conclude that *cybernetics* (including *informatics*) and *thermodynamics* (including *energetics*) are complementary sciences essential for a complete description of life and hence can be viewed as a complementary pair obeying the Principle of *Information-Energy Complementarity* or, more accurately, the *Liformation-Mattergy Complementarity* (Section 2.3.1). Just as the early 20th-century physics saw heated debates between the supporters of the particle- vs. the wave-views of light, which remains incompletely resolved (Plotnitsky 2006, Bacciagaluppi and Valenti 2009), I predict that biology, as it matures as a science, will experience similarly heated controversies surrounding the definition of life between two complementary views – the *cybernetic/informatic* (e.g., gene-centric) view of life and the *thermodynamic/energetic* (e.g., process-centric) view. Again just as the wave-view of light was dominant throughout the modern history of physics until the particle-view gained support from Einstein's theory of photoelectric effect published in 1905, the *gene-centric view* of life has been dominating molecular biology for over half a century now (since the discovery of the DNA double helix in 1953) with little or no attention given to the alternative *process-centric view*. The characteristics of the gene-centric view of biology is that most, if not all, biological phenomena can be satisfactorily accounted for in terms of genes, static nucleotide sequences in DNA (Section 11.2). In contrast, the process-centric approach to biology (e.g., see Section 10.2) maintains that *genes are necessary but not sufficient* to account for life and that genes and their RNA and protein products must be coupled to exergonic chemical reactions (processes) through thermal excitations (Section 12.12) and the Franck-Condon mechanisms (Section 2.2.3) before living phenomena can be completely explained (see Figure 14-7).

One example of the conflict between the *gene-centric* and *process-centric* views in biology is provided by the field of microarray data interpretation:

"*Most biologists believe that RNA levels in cells measured with microarrays can be used to identify the genes of interest. But careful analyses (Ji et al. 2009a) have revealed that these changes in RNA levels cannot be used to identify the genes of interest but reflect the different ways in which transcription and transcript degradation processes are coupled or interact in the cell."* (17-6)

Statement (17-6) is reminiscent of the famous *wave-particle debate or paradox* in physics in the early decades of the 20th century and hence may be viewed as a species of what may be referred to as the "*structure-process paradox in biology"* (SPPB) or the "*structure-process conflation in biology*" (SPCB). My students at Rutgers and I have examined over one hundred prominent papers reporting the results of DNA microarray experiments and found that over 90% of these papers have committed SPCB, i.e., the authors conflated *transcripts* (structures) and *transcription* (processes) rates (Section 12.6). The structure-process conflation may be related to the quality-quantity duality discussed in Section 17.7 below.

17.6 The Universal Law of Thermal Excitations and Biocomplexity

In Section 12.12, evidence was presented indicating that thermal excitations of biopolymers are implicated in single-molecule enzymology, whole-cell metabolism, and protein stability, thus establishing the fundamental role that *thermal motions* (also called Brownian motions or thermal fluctuations) play in living systems. But thermally excited states of biopolymers can last only briefly, in the order of 10^{-12} to 10^{-13} seconds, and hence very difficult to study unlike stable structures or ground-state structures or conformations (see nodes B and C in Figure 14-7). The transition from the ground-state conformation of a biopolymer to its excited state requires thermal excitation which corresponds to Step 2 in Figure 14-7. According to the generalized Franck-Condon principle (GFCP) (Section 2.2.3), the thermally excited states of proteins are necessary for catalyzing exergonic chemical reactions (Step 3 in Figure 14-7) which must release heat rapidly enough to pay back, within the lifetime of the excited states, the thermal energy "borrowed" by enzymes from their environment to reach excited states. When a sufficient number of thermally excited enzymic processes are coupled properly in space and time, self-organized processes are thought to emerge called Intracellular Dissipative Structures (IDSs) or dissipatons, capable of carrying out specific intracellular functions (Step 4 in Figure 14-7). One of the major sources of *biocomplexity* can be identified with the many-to-one mappings between the lower nodes and their higher counterparts in Figure 14-7. For example, many different amino acid sequences of proteins (node A) are known to fold into similar 3-dimensional conformations (node B), leading to what is known as the "designability of a structure", defined as the number of sequences folding

into the same structure (Zeldovich and Shakhnovich 2008). There are almost infinite number of amino acid sequences for a finitely sized protein (e.g., $20^{100} = 1.27x10^{107}$ different sequences of proteins with 100 amino acid residues), but there are only several thousand known protein folds. The single-molecule enzymological data provided by Lu, Xun and Xie (1998) and analyzed in Section 11.3.3 indicate that many ground-state conformations of cholesterol oxidase are thermally excited to a common transition state designated as $C^{\ddagger}$ in Figure 11-28.

The mapping between thermally excited states of enzymes (node C) and exergonic chemical reactions (node D) may be one-to-one due to the fact that these two nodes are *coupled* through the mechanism constrained by the generalized Franck-Condon principle (Section 2.2.3).

It is here suggested that the mapping between exergonic chemical reactions (node D) and IDSs (node E) (see Step 4 in Figure 14-7) is similar to the mapping between ground-state conformations of proteins (node B) and their excited states (node C), since both these mappings involve thermal excitations as discussed in Section 12.12 (see Figure 12-25). In other words, it is here postulated i) that there are more exergonic chemical reactions (each catalyzed by an enzyme) than there are cell functions and ii) that two or more different sets of exergonic chemical reactions can support an identical *intracellular function* or an *intracellular dissipaton*.

17.7 The Quality-Quantity Duality and Biocomplexity

The duality of *quality vs. quantity* is a well-established topic in philosophy. Spirkin (1983) states that the quality of an object is "the sum-total of its properties" and that the quantity of an object "is expressed by numbers". Table 17-5 lists some examples of the quantity-quality dualities that occur in molecular and cell biology.

Table 17-5 The quality-quantity dualities found in biology

	Quality	**Quantity**
Proteins	Amino acid sequences	Concentrations or copy number
RNA	Ribonucleotide sequences	Copy numbers
Genes	Deoxyribonucleotide sequences	Copy numbers
Ribonoscopy	RNA sequences	RNA Trajectories (or *waves*); i.e., n(t), where n is the copy number and t is time

When biologists think about proteins, RNAs or genes in the living cell, they tend to think more about the qualitative aspects of these objects, i.e., their sequences and 3-dimensional shapes than their quantitative aspects such as the changes in their concentrations (or copy numbers) inside the cell as a function of time. Qualitative aspects appear to be more closely related to *equilibrium structures* or *equilibrons*, while quantitative aspects are related to *dissipative structures* or *dissipatons* (Section 3.1.5). We may refer to this phenomenon as the "quality over quantity bias" in biology. This bias is prevalent in the field of microarray experiments where practically every measurement is interpreted in terms of *genes* (quality) underestimating the importance of their *concentration changes* in time or trajectories (quantity), leading to false positive (Type I) or false negative (Type II) errors (Section 12.6) (Ji et al. 2009a).

CHAPTER 20

The Knowledge Uncertainty Principle in Biomedical Sciences

According to the Knowledge Uncertainty Principle described in Section 5.2.7, all knowledge is uncertain (including physical, chemical, biological, mathematical, pharmacological, toxicological, medical, and philosophical knowledge), which agrees with the views expressed by many thinkers throughout the ages (Section 5.2.5). What is new in this book is the idea of quantitating the degree of uncertainty of a knowledge using what is referred to as *the Kosko entropy* or S_K in Section 5.2.7. A knowledge with $S_K = 1$ is least certain and that with $S_K = 0$ is 100% certain, which is thought to be beyond human capacity as indicated by Inequality 5-26. A knowledge has been defined as *the ability to answer a question or solve a problem* (Section 5.2.7). These ideas will be illustrated using the Nrf2 signaling pathway in toxicology as an example.

20.1 The Toxicological Uncertainty Principle (TUP)

Many drugs (e.g., acetaminophen or Tylenol®), dietary components (e.g., 6-(methylsulfinyl)-hexyl isothiocyanate or 6-HITC from Japanese horseradish *wasabi*), and environmental chemicals and radiations (e.g., ozone, UV light) can generate reactive oxygen and nitrogen species inside the cell. When cells are exposed to such pro-oxidants, they respond to counteract the effects of the resulting oxidative stress by activating *self-defense mechanisms*, including the Nrf2 signaling pathway shown n Figure 20-1. The mechanism of the Nrf2-mediated self-defense has been well worked out in recent years (Suhr 2003, Nguyen, Nioi and Pickett 2009, Kundu and Suhr 2010).

The Nrf2 (nuclear factor erythroid-2-related factor-2) (see nodes 8 and 10 in Figure 20-1) is a transcription factor that plays a major role in regulating the expression of the genes encoding many cytoprotective enzymes (see nodes 20-24) in response to oxidative stress. It is normally bound to the Kelch-like-ECH-associated protein 1(Keap1) (see nodes 7 and 9) which confines Nrf2 to the cytosol and prevents it from being translocated to the nucleus. Keap1 contains many cysteine residues (see SH on node 9) that can be oxidized or covalently modified (see SR on node 7) in other ways by prooxidants, resulting in the dissociation of Nrf2 from its grip (see the separation of the 9-10 complex into nodes 7 and 8). The dissociation of Nrf2 and Keap 1 is also facilitated by the phosphorylation of Nrf2 at serine (S) and threonine (T) residues by phosphotidylinositol-3-kinase (PI_3K) (Node 1), by protein kinase C (PKC) (Node 2), c-Jun NH2-terminal kinase (JNK) (Node 3) and extracellular-signal-regulated kinase (ERK) (see Node 2). Once translocated into the nucleus, Nrf2 heterodimerizes with MAF and binds to *antioxidant response element* (ARE) (see nodes 15, 16 and 19), thereby activating the transcription of genes encoding many Phase II enzymes (see nodes 20-24) that detoxify foreign chemicals or xenobiotics and reactive oxygen species (ROS) and reactive nitrogen species (RNS). In short, chemical stress activates the Nrf2 signaling pathway to induce enzymes that can remove the stressful compounds, which may be regarded as an analog of *the Le Chatelier Principle* on the intracellular metabolic level. As is well-known in chemistry, the Le Chatelier Principle states that, if a system in chemical equilibrium is disturbed, it tends to change in such a way as to counter this disturbance. In another sense, the Nrf2 signaling pathway may be viewed as an intracellular version of *self-defense mechanisms* that have been postulated to operate in the human body as a whole and local tissue levels (Ji 1991, pp. 186-199). Frustrating any of the many processes constituting self-defense mechanisms has been postulated to underlie all diseases, including cancer. According to this so-called "frustrated self-defense mechanisms (FSDM)" hypothesis of chemical carcinogenesis (Ji 1991, pp. 195-199), many cancers may originate by frustrating some of the biochemical and cellular processes underlying inflammation (including the cellular proliferation step in wound healing). The FSDM hypothesis appears to have been amply supported by recent findings (e.g., see Figure 1 in Kundu and Suhr 2010).

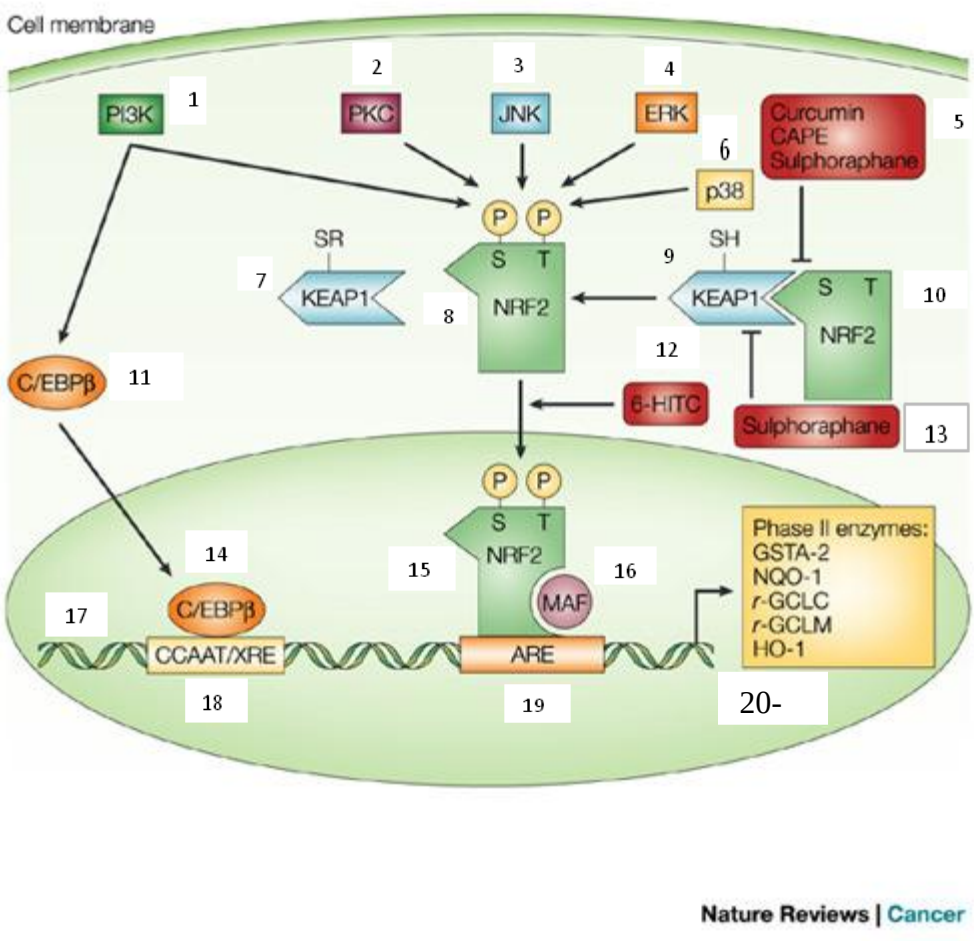


Figure 20-1 The Nrf2 signal transduction pathway as schematically represented by Surh (2003). The numbers are my additions. The figure was reproduced from
http://www.nature.com/nrc/journal/v3/n10/fig_tab/nrc1189_F4.html

The Nrf2 interaction network shown in Figure 20-1 can be represented as an interaction matrix (Table 20-1). Although there are some ambiguities in assigning node numbers (e.g., nodes 7 and 9 or nodes 8 and 10 may be combined into one entity each), the matrix representation is sufficiently accurate in capturing the key information embodied in the Nrf2 signaling network. The interaction matrix combined with the diagram of the original signaling network allows us to identify all the theoretically possible pathways that may be realized in the Nrf2 signaling network in the cell under a given condition.

Table 20-1 The *interaction matrix* of the Nrf2 signaling pathway constructed from Figure 20-1 (or Figure 4 Suhr 2003). The interaction between the i^{th} and j^{th} nodes is positive (+1, i.e., enhanced), negative (-1, i.e., inhibited), or non-existent (0, i.e., has no effect). Out of the 24x24 = 576 possible interactions, only 25 direc interactions have been found experimentally, thus the Nrf2 signaling pathway carries $\log_2(576/25) = 4.5$ bits Shannon/Hartely information (see Section 4.3 for the definition of the Shannon and Hartley informations). Please note that some of the assignments of +1, -1 or 0 (especially involving nodes 7, 8, 9 and 10) are ambiguous and admit other possibilities.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1	0	0	0	0	0	0	0	+1	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	-1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	+ 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	+1	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	0	+1	+1	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	0	+1	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+1	0	+1	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

For example, any agent (e.g., diacylglycerol or intracellular Ca^{2+}) that activates PKC (Node 2) can lead to the production of any one of the Phase II enzymes (Nodes 20 through 24) passing through nodes 8, 15, and 19, or may get stuck in the middle of any one of these pathways, thus generating a set of 8 possible pathways that can be engaged by the activation of node 2:

2-8-15-19-20, 2-8-15-19, 2-8-15, 2-8
2-8-15-19-21
2-8-15-19-22
2-8-15-19-23
2-8-15-19-24

Similar sets of signal transduction pathways can be engaged by the activation of nodes 1, 3, 4, 5, and possibly others, leading to the final set of Nrf2 signal transduction pathways numbering at least 40. For each one of these 40 possible pathways, one can raise a binary question. For example, "Is pathway 3 activated under the given experimental condition?" The answer to this question can be expressed in the unit of fits, i.e, any number between 0 (no) and 1 (yes), including decimals such as 0.3 (i.e., the degree of the yes answer being correct is 30%), or 0.9 (i.e., the degree of the yes answer being correct is 90%), etc., depending on the certainty of the relevant experimental data. Or these numbers may be viewed as the *probabilities* of the occurrence of the pathway being considered under the experimental condition. Table 20-2 lists all the possible answers to the binary questions elicited by experiments (i.e., the "apparatus-elicited answers" discussed in (6) of 13) in Section 5.2.7). These "apparatus-elicited answers" can also be viewed as the possible "mechanisms" of the actions of the agents that interact with the Nrf2 signaling pathway. For example, under experimental condition 1 (see the row labeled 1 in Table 20-2), the probabilities of the occurrence of the Nrf2 pathways 1, 2, 3,4, 5, 6, . . ., 39, and 40 are, respectively, 0.3, 0, 0.4, 0, 0.1 0.2, . . . , 0, 0, and 0. The corresponding probabilities under experimental condition 2 are 1, 0, 0, 0, 0, 0, . . . , 0, and 0, meaning that only pathway 1 is activated under this condition.
Once the *question-and-answer matrix* is determined, all the apparatus-elicited answers can be mapped onto the 2^{40}-dimensional hypercube discussed in Section 5.2.7. The uncertainty of each answer measured in term of the so-called *Kosko entropy* can be estimated using the coordinate values of each answer and Eq. (5-23). These entropies were calculated for the rows labeled 1, 2 and 3 in Table 20-2. As can be seen, Apparatus-elicited answer 1 is least certain, while apparatus-elicited answers 2 and 2^{40} are both much more certain than Answers 1 and 3.

Table 20-2 The question-and-answer matrix for the Nrf2 signaling pathway, each cell being filled with the fit (i.e., fuzzy bit) or the probability values (ranging from 0 to 1) derived from the experimental data on the Nrf2 signaling pathway depicted in Figure 20-1. Each question requires an answer consisting of 40 fits ranging from 0 (= No) to 1 (= Yes), inclusive. The elements of the matrix not explicitly shown and symbolized as dots can be assumed to be zero.

Aparatus-elicitied Answers	**Possible Binary Questions**											**Kosko Entropy, S_K**
	1	2	3	4	5	6	.	.	.	39	40	
1	0.3	0	0.4	0	0.1	0.2	.	.	.	0	0	0.872
2	0.9	0	0	0	0	0.1	.	.	.	0	0	0.00262
3	0.4	0	0.1	0.2	0	0.2	.	.	.	0	0.1	0.816
.												
.												
.												
$2^{40} = 1.10x10^{12}$	0	0	0	0	0.9	0				0.1	0	0.00262

The above method of calculating the Kosko entropy associated with any toxicological statement or knowledge can be summarized as shown in Table 20-3.

Table 20-3 The 5-step procedure for calculating the Kosko entropy as a measure of the *uncertainty* associated with a toxicological knowledge, statement, or mechanism.

Step	**Procedure**
1	*Summarize the pre-existing knowledge of interest in the form of a pathway such*

	as the Nrf2 signaling pathway (Figure 20-1).
2	*Construct the interaction matrix (e.g., Table 20-1) based on that pathway.*
3	*Construct the question-and-answer matrix (e.g., Table 20-2).*
4	*Fill in the appropriate boxes in the question-and-answer matrix based on the experimental observations (also called the apparatus-elicited answers) available.*
5	*Calculate the Kosko entropies for all apparatus-elicited answers (also called mechanisms) based on the numerical coordinates given in the question-and-answer matrix, using the Pythagorean equation, Eq. (5-23).*

This 5-step procedure for calculating the *Kosko entropy* associated with any toxicological statement represents or defines the content of the *Toxicological Uncertainty Principle*. As such, the same procedure can be applied to any toxicological statement, including those concerning the mechanisms underlying the liver toxicity of acetaminophen (also called paracetamol or Tylenol®), for example.

Over the past 4 decades, we have accumulated a massive amount of information about how *Tylenol*® in excessive doses can injure the liver (Ryder and Beckingham 2001, Larson et al. 2005) and how chronic and acute alcohol ingestions may aggravate or protect against, respectively, the drug toxicity (McClain et al. 1980, Prescott 2000). Acetaminophen is the most widely used over-the-counter analgesic and found in nearly 200 medications such as *Excedrin*, *Midol*, *NyQuil*, and *Sudafed*. Despite the long history of research, both basic and clinical, on the mechanisms responsible for acetaminophen hepatotoxicity, our knowledge about these mechanisms is still uncertain and may remain so even if much more detailed investigations are to be carried out in the future in this field. In parallel with further research along the traditional line, it may be helpful for the further progress in acetaminophen toxicology to introduce the Toxicological Uncertainty Principle as embodied in the Kosko entropy (see Table 20-2). That is, it may be necessary to calculate the Kosko entropies for all the *competing statements* about how acetaminophen injures the liver in order to evaluate the degree of certainty of their claims. To accomplish this task, it is necessary to summarize relevant existing knowledge in the form of various mechanistic schemes or pathways, two of which are discussed below.

In the early 1980's when I first entered the field of toxicology, one of the most intensely studied toxicant was acetaminopen. Although, when taken in pharmacological doses, acetaminophen is safe, it can injure the liver when taken in toxicological (or suicidal) doses (Black 1984). Many toxicologists believed in the hypothesis that the mechanism of the toxic action of this drug involved following key steps:

1) The metabolic activation of acetaminophen into its reactive intermediate catalyzed by cytochromes P-450 and other pro-oxidant enzymes (Kocsis et al. 1986), later found to be N-acetyl-p-benzoquinone imine (NAPQI) (Dahlin et al. (1984),

2) the depletion of the intracellular antioxidant, glutathione, GSH, and

3) the covalent-binding of NAPQI to essential nucleophiles including proteins and

DNA when the GSH store is depleted below a critical level (James, Mayeux and Hinson 2003).

Because of the highly reactive nature of NAPQI, it can bind non-discriminately to all electron-rich atoms, making it difficult to pin-point the critical macromolecule leading to cell injury. The experimental data available in the late 1980's indicated to me that the molecular mechanisms underlying acetaminophen hepatotoxicity may not be as simple (i.e., certain) as then widely believed, prompting me to propose what I called the "multiple metabolite-multiple target" (MMMT) hypothesis of chemical toxicity reproduced below:

The Toxicologist 9(1):161 (1989)

"MULTIPLE METABOLITE-MULTIPLE TARGET" HYPOTHESIS AS APPLIED TO BENZENE AND ACETAMINOPHEN TOXICITY.
S. Ji, Dept. of Pharmacol. and Toxicology, Rutgers University, Piscataway, N.J.

Existing experimental data on benzene (BZ) and acetaminophen (AA) toxicity support the general concept that the toxicological consequences of these compounds are derived not from one but many reactive or stable molecular species related to them and that these toxic species interact with not one but multiple molecular targets ("toxicological receptors"). In addition, the kinetics of the interactions between toxic metabolites and their respective targets is critical in the expression of the toxic potential of these xenobiotics. There are at least six possible toxic benzene metabolites (phenol, hyroquinone, p-benzoquinone, catechol, trihydroxybenzene and muconaldehyde), two target cell groups in bone marrow (stroma and stem cell), and two kinds of kinetics (one fast enough to effectuate toxic manifestations and the other too slow to do so), so that there are at least 6x2x2 = 24 possible mechanisms for benzene toxicity. Similarly, there are at least two toxic species for AA (AA itself, N-acetyl-p-benzoquinoneimine), three target sites (hepatocellular membrane, mitochondria, Kupffer cells), and two types of kinetics (effective and ineffective), thus giving rise to 2x3x2 = 12 possible mechanisms of AA toxicity. Such multiple mechanistic possibilities for AA and BZ toxicity are not surprising in view of the complex living systems with which they interact.

My students and I demonstrated in the isolated perfused rat live system that acetaminophen

and its metabolite, NAPQI, can inhibit mitochondrial respiration both reversibly and irreversibly (Cheng and Ji 1984, Esterline, Ray and Ji 1989), potentially weakening various intracellular self-defense mechanisms driven by ATP (Ji 1987) (see Steps 8, 9 and 10 in Figure 20-2).

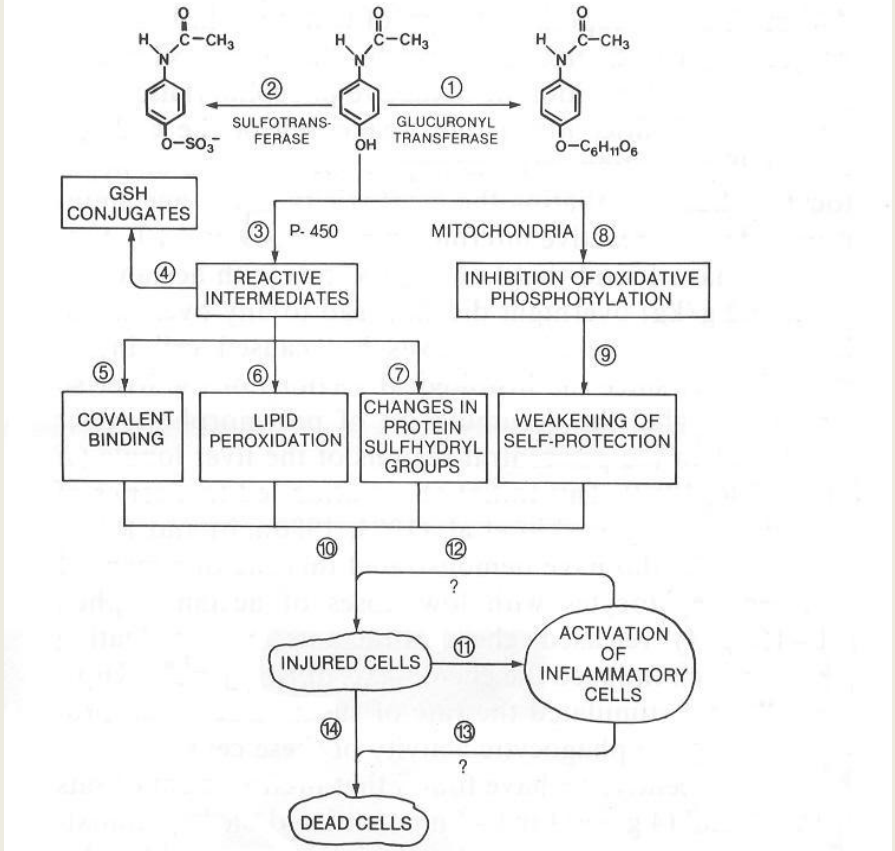


Fig. 4. A general model of the mechanism of acetaminophen hepatotoxicity. Detailed explanations are given in the text

Figure 20-2 A 14-step mechanism of acetaminophen hepatotoxicity proposed in (Ji 1987).

Using the same experimental system as in Figure 20-2 and isolated granulocytes and hepatocytes from the rat, we also demonstrated that the irreversible inhibition of mitochondrial respiration was

(1) not blocked by 500 μM metyrapone, indicating that NAPI was not generated from cytochrome P-450,
(2) accompanied by lactate dehydrogenase release,
(3) blocked by 10 mM mannitol, a hydroxyl radical scavenger,
(4) required Ca^{++} in the perfusate,
(5) abolished in the liver isolated from hypophysectomized rats,
(6) abolished in the liver isolated from thyroidectomized rats, and
(7) enhanced in the liver isolated from arenalectomized rats.

In addition we found that

(8) isolated granulocytes (also called neutrophils) caused the covalent binding of tritiated acetaminophen (^{3}H-AA) to granulocyte proteins when stimulated with phobol myristate acetate,
(9) synthesized NAPQI irreversibly inhibited the respiration of isolated rat liver mitochondria, and
(10) the acute administration of alcohol to rat increased the liver content of granulocytes by 3 fold.

To account for these varied experimental observations, we were led to propose the 14-step mechanism for the alcohol-potentiated acetaminophen hepatotoxicity shown in Figure 20-3. In a separate series of experiments performed in collaboration with D. Laskin and her group at Rutgers, we discovered that acetaminophen hepatotoxicity is in part mediated by macrophages (Laskin, Pilaro and Ji 1986), which could be readily accommodated by including liver macrophages (also called Kupffer cells) in the same node where neutrophils appear in Figure 20-3. To accommodate the most recent finding that reactive nitrogen species (RNS) are also implicated in acetaminophen-induced mitochondrial damage (Burke et al. 2010), it is only necessary to include RNS in the same node where reactive oxygen species (ROS), i.e., superoxide anion, hydrogen peroxide and hydroxyl radicals, are located in Figure 20-3.

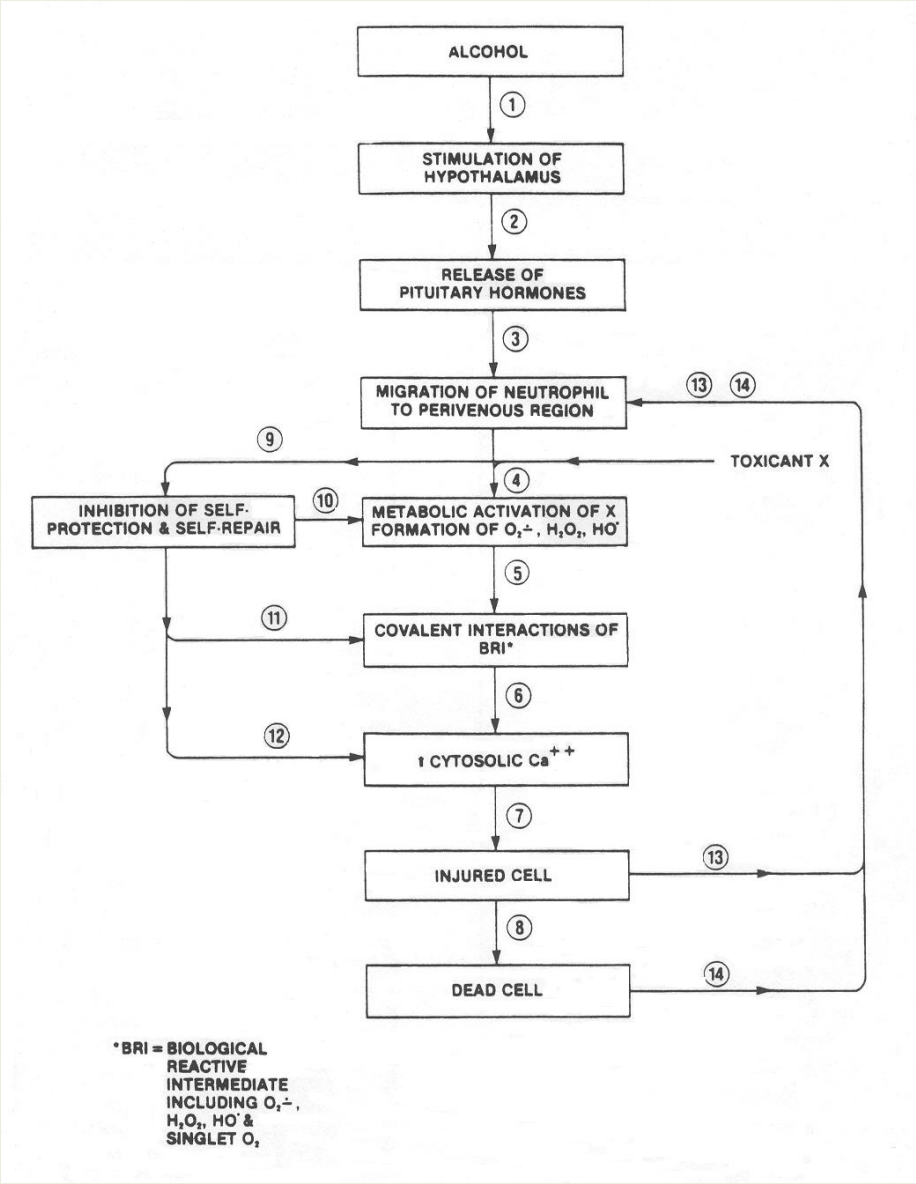


Figure 20-3 A 14-step mechanism of the alcohol-potentiated acetaminophen hepatotoxicity. This figure was constructed around 1987 on the basis of the experimental observations reported in (Ji, Ray, Esterline and Laskin 1988).

There are a considerable amount of overlap between the two mechanistic schemes or pathways shown in Figures 20-2 and 20-3. Therefore it should be possible to combine these two pathways into a new one with less than the sum of the steps involved in the two separate pathways, i.e., less than 28 steps. This new pathway can then serve as the starting point (i.e., Step 1 in Table 20-3) for applying the Toxicological Uncertainty Principle to estimate the uncertainties (i.e., Kosko entropies) associated with all of the

mechanistic statements published so far about the acetaminophen hepatotoxicity in humans based on animal experimental data and epidemiology.

Finally, in a qualitative sense, the *Toxicological Uncertainty Principle* may be formulated by extending *Einstein's Uncertainty Thesis* (see Statement (5-38) in Section 5.2.7) from physics to toxicology, leading to the following statement:

"As far as the laws of chemistry and molecular biology refer to chemical toxicity, they are not certain; and as far as they are certain, they do not refer to chemical toxicity." (20-1)

20.2 The Pharmacological Uncertainty Principle (PUP)

According to the Knowledge Uncertainty Principle (Section 5.2.7), all our knowledge about how drugs work in the human body are uncertain, which may be referred to as the Pharmacological Uncertainty Principle (PUP). PUP has two aspects – quantitative and qualitative. The quantitative aspect of PUP can be expressed in terms of the Kosko entropy, S_K, which can be estimated using the 5-step procedures presented in Table 20-3 in the previous section. One way to formulate the qualitative aspect of PUP using Einstein's Uncertainty Thesis (Section 5.2.7) would be as follows:

"As far as the laws of molecular mechanisms refer to drug actions, they are not certain; and as far as they are certain, they do not refer to drug actions." (20-2)

20.3 The Medical Uncertainty Principle (MUP)

Although not discussed explicitly among medical professionals, the fact that all our knowledge about human diseases, despite decades of intense research, are fraught with uncertainties is probably widely recognized. Similarly to the Toxicological and Pharmacological Uncertainty Principles described in Sections 20.1 and 20.2, the Medical Uncertainty Principle (MUP) can be formulated, both quantitatively following the 5-step procedures for estimating the associated Kosko entropies and qualitatively using Einsteins'Uncertainty Thesis as a template. One possible formulation of the qualitative aspect of MUP is given below:

"As far as the laws of molecular biology refer to diseases, they are not certain; and as far they are certain, they do not refer to diseases." (20-3)

If TUP, PUP, and MUP turn out to be true, they are predicted to have important practical consequences in the fields of risk assessment, drug development, and medicine, particularly in the emerging field of personalized medicine.

20.4 The U-Category: The Universal Uncertainty Principle as a Category

It is clear that the Einstein's Uncertainty Thesis (EUT) introduced in Section 5.2.7 (see Statement (5-38)) can serve as a convenient and veridical 'logical template' (or a category) to express the action of the Universal Uncertainty Principle (UUP) (Section 5.2.8) in many fields of inquiries. I therefore suggest here that the combination of EUT and UUP can logically lead to the following general statement which may be viewed as a category in the sense defined in Statements (15-51) and (15-52) and hence referred to as the *Uncertainty Category* (U-category or UC):

"As far as X refers to Y, X is not certain; and as far as X is certain, X does not refer to Y." (20-4)

The examples of X and Y that have appeared in this book are listed in Table 20-4.

Table 20-4 The Universal Uncertainty Principle (as a type) and its various manifestations (as tokens).

Fields	**X**	**Y**
1. Einstein's Uncertainty Thesis (Statement (5-38))	Laws of mathematics	Reality
2. Knowledge Uncertainty Principle (Statements (5-33) through (5-37))	Laws of crisp logic	Reality
3. Cellular Uncertainty Principle (Statement (5-51))	Laws of energy	Reality
	Laws of information	Reality
4. Toxicological Uncertainty Principle (Statement (20-1))	Laws of chemistry	Toxicology
5. Pharmacological Uncertainty Principle (Statement (20-2)	Laws of molecular biology	Pharmacology
6. Medical Uncertainty Principle (Statement (20-3))	Laws of molecular biology	Medicine

CHAPTER 21

Towards a Category Theory of Everything (cTOE)

In 1943, Schrödinger attempted to answer the question, *What Is Life?*, in his historic book with the same title which contained about 90 pages. Six decades later, in this book, I needed more than 700 pages to try to answer the same question. The 8-fold increase in the number of pages in this book relative to that of Schrödinger's probably does not do justice to the enormous increase in our experimental knowledge about living systems that has occurred since 1943 (e.g., see Table 11-1). In his book, Schrödinger proposed three main ideas:

(1) The gene is a molecule that encodes heritable traits and contains "the means of putting it into operation" (Schrödinger 1943, p. 68).
(2) The gene is "the aperiodic solid" (Schrödinger 1943, p. 60).
(3) "The living organism feeds on *negative entropy*." (Schrödinger 1943, p. 70)

It is not the purpose here to analyze in detail these well-known claims of Schrödinger, except to point out that the first of the ideas has largely been validated by experimental findings since Schrödinger's time, the second idea has been invalidated since genes (whether viewed as DNA segments as in the contemporary sense or chromosomes as Schrödinger thought) are not solids that *resist thermal fluctuations* but rather *deformable bodies* that actively utilize *thermal fluctuations* for their biological functions (see Section 12.12), and the last idea must also be judged as invalid, since it violates the Third Law of Thermodynamics (see Section 2.1.5).

If I had to summarize my own answer to the question, What Is Life?, in one sentence, I would suggest that the following is one possibility:

"Life is the property of self-reproducing systems composed of molecular machines driven by chemical reactions under the control of genetic information, obeying the generalized Franck-Condon principle ." (21-1)

There are 5 key concepts in Statement (21-1), i.e., *self-reproduction*, *molecular machines* (Alberts 1998), *chemical reactions* (Prigogine 1977, 1980, 1991), and *genetic information*, and one fundamental principle, the *generalized Franck-Condon principle*, which enables molecular machines to utilize the free energy supplied by chemical reactions (see Section 2.2). Not all of these 5 items appear in any of the contemporary theories of life to the best of my knowledge as summarized in Table 21-1.

The theory of life presented in this book contains all of the 5 items in Table 21-1 and

Table 21-1 A comparison among different theories of life. The meaning of the symbols: + = "is included at least implicitly", - = "is not included explicitly or implicitly"

	self-reproducing system	**molecular machine**	**genetic information**	**chemical reaction**	**Generalized Franck-Condon Principle**
1. *Schrödinger* (1943)	+	-	+	-	-
2. *Prigogine* (1977)	+	-	-	+	-
3. *Blumenfeld & Tikhonov* (1994)	+	+	+	+	-
4. *Alberts* (1998)	+	+	-	-	-
5. *This book* (2011)	+	+	+	+	+

the theory proposed by Blumenfeld and Tikhonov (1994) contains four of these. One difference between the theory of Blumenfeld and Tokhonov and that proposed in this book is the generalized Franck-Condon principle (GFCP) with the discussion of which this book began (see Section 2.2). Please recall that it is this principle that enables proteins to transduce chemical energy into mechanical energy called *conformons* (Section 8) which then drive all the functions of molecular machines including DNAs and RNAs (see Sections 11.3, 11.4, and 11.5).

In the following excerpt, Blumenfeld and Tikhonov (1994) point out that, to explain the functioning of molecular machines (Alberts 1998), it is necessary to apply principles other than those of classical statistical physics, although the authors did not indicate the nature of such new principles.

"*. . It has become fashionable today to speak of the machine-like behavior of enzymes, intracellular particles (e.g., ribosomes), etc., during their functioning. The phrases "a protein is a machine", "an enzyme is a machine" are now trivial clichés, and at the same time remain vague. The main reason for this is the very approach used by the majority of scientists in the treatment of the chemical properties of biopolymers. In spite of speculation regarding the "machineness" of proteins, they apply, as a rule, to the conventional approaches of chemical thermodynamics and chemical kinetics that have*

been developed for the reactions of low-molecular (weight; my addition) compounds in gaseous phases and dilute solutions. These approaches are based essentially on the classical statistical physics of ergodic systems, i.e., on the assumption that the systems under consideration have only statistical, thermal degrees of freedom fast enough to exchange energy for each other. However, if biological constructions (beginning at the level of macromolecules) are machines, in the course of their functioning there might be excited specific, mechanical degrees of freedom which exchange slowly with the thermal ones. This requires an essentially different approach to their description (different from the classical statistical physics; my addition)."

I suggest that the approach described in this book, i.e., the *conformon* approach based on *GFCP* (see Sections 2.2 and 8 and Statement 21-1), provides one plausible mechanism by which molecular machines actually work, *the ultimate cause of life.*

Having provided a comprehensive molecular theory of cell biology in this book, it appears natural to ask the question -- How does the proposed biological theory relate to the fields of human knowledge beyond biology ? For example, how does the new biological theory relate to what Popper (1978) refers to as *world 1* (the physical world, both living and non-living), *world 2* (the mental world), and *world 3* (the world of the products of the human mind, including mathematics, philosophy, art, literature, and engineering) ? Or how is the proposed new theory of biology related to what Rosen (1991) calls the *natural* (N) and *formal* (F) systems ? Finally, how does the new theory of biology relate to the *mind-body problem* or the problem of *consciousness* recently reviewed by Pinker (2003, 2011) ? Possible answers to these questions appear to emerge when it is attempted to correlate and integrate the following four hybrid words, *mattergy*, *gnergy*, *liformation*, and *infoknowledge using category theory*. The first three of these terms have already appeared in this book (see Table 2-6 and Sections 2.3.1 through 2.3.5) and the last one was coined just recently (Ji 2011) based on the suggestion by Burgin (2004, 2011a, 2012) that the relation between *information* and *knowledge* is akin to the relation between *energy* and *matter*. For convenience, we may refer to this suggestion as the *Burgin's analogy*.

The principles of *complementarity* and *supplementarity* described in Section 2.3.1 will play key roles in integrating the four hybrid terms and their associated theories and philosophies. Supplementarity is an additive principle, i.e., A + B = C, and complementarity is non-additive, i.e., A^B = C, where the symbol ^ indicates that A and B are complemtary aspects of a third entity C. These priciples led to the coining of the terms, *gnergy* and *liformation*, respectively (see Table 2-6, Section 3.2.2). My initial attempt to integrate the four hybrid terms started with the diagram shown in Figure 21-1.

Burgin's suggestion that that the relation between *information* and *knowledge* is akin to that between *energy* and *matter* is depicted at the center of Figure 21-1 (see Arrows 1 and 4 in this figure and Table 21-2). Since *energy* and *matter* are related to each other through $E = mc^2$, which can be viewed as a *supplementary relation*, and, since the combination of *energy* and *matter* is conserved according to the First Law of thermodynamics, it is natural to combine these two terms into one word, *matter-energy* or *mattergy*, more briefly. Analogously, it may be convenient to coin a new word to represent the combination of *information* and *knowledge*, namely, 'information-

knowledge' or 'infoknowledge', more briefly (see Arrows 4/5 relative to Arrows 1/8 in Figure 21-1 and Table 21-2).

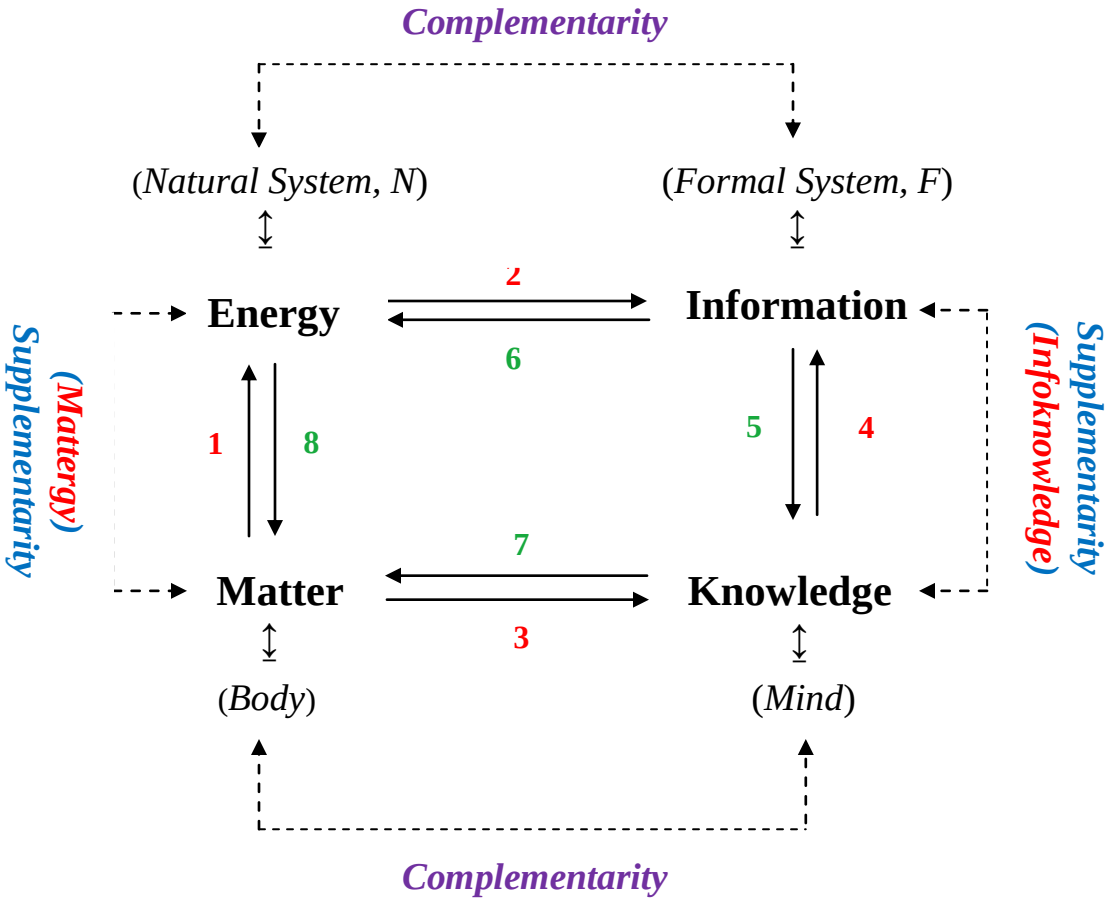


Figure 21-1 The suggested qualitative (or *complementary*) and quantitative (or *supplementary)* relations among *energy*, *matter*, *information*, and *knowledge*. The meanings of the numbered arrows are explained in Table 21-2. *Mattergy* = the combination of matter and energy that is conserved in the Universe, according to the First Law of thermodynamics. '*Infoknowledge*' = a new term coined by combining *information* and *knowledge* in analogy to mattergy. Unlike mattergy which is conserved, *infoknowledge* may increase with time.

Table 21-2 The integration of the ideas of Rosen (1991), Burgin (2004), Polanyi (1958/62) and Stenmark (2001) within the framework of the postulated "mattergy-infoknowledge complementarity" depicted in Figure 21-1. The various symbols appearing in this table are: E = energy; m = mass; c = speed of light; H = Shannon entropy; p(x) = the probability of the occurrence of event x; S = thermodynamic entropy; k = Boltzmann constant; W = the variety of molecular configurations compatible with thermodynamic constraints; C = channel capacity of a communication system; B = band width of the communication channel; P = power of the message source; N = noise of the communication channel.

Authors	Arrows and nodes in Figure 21-1	Meaning or referent
M. Burgin (2004, 2011a)	1	"contains"
	4	"contains"
	2, 6	"similar"
	3, 7	"similar"
	1, 2, 3 & 4	The "fundamental unit of knowledge", with the following identification of the *nodes* in Scheme (3) in Burgin (2004, 2011a) and those in Figure 1 above
	Matter	"U" or objects of knowledge
	Energy	"W" or intrinsic properties of objects
	Knowledge	"C" or names of objects
	Information	"L" or ascribed properties of objects
M. Polanyi (1958/62)	Information	"explicit knowledge"
	Knowledge	"tacit knowledge"
Stenmark (2009)	4, 5	"information" = Information; "knowledge" = Knowledge
R. Rosen (1991)	1, 8	"causality" governing the processes occurring in the natural system, N
	4, 5	"inference", or "implication" governing the processes occurring in the formal system, F
	3	"encoding" of N in F
	2, 7	"decoding" of F to infer N
S. Ji (2011)	1	$E = mc^2$, and S = k lnW, chemical reactions, quantum mechanics. It is assumed that *Energy* in Figure 1 includes free energy which is a function of both matter-energy obeying the First Law and entropy obeying the Second Law of thermodynamics.
	2	Big Bang cosmology and biological evolution or measurements by Homo sapiens
	3	Biological evolution, phylogenesis, ontogenesis (speculative)
	4	$H(X) = -\sum p(x) \log p(x)$, where X is a set of messages or events, x is its members, and p(x) is the probability of the occurrence of event x (Shannon and Weaver 1949). Communication, languages. It is interesting to note that the Boltzmann equation, S = k lnW is postulated to be associated with Arrow 1, whereas Shannon equation is postulated to be associated with Arrow 4. In other words, S and H are thought to be complementary to each other.
	5	Cognitive sciences

	6	C = B log (1 + P/N) indicates that energy dissipation is absolutely necessary for any information transmission, i.e., for any communication (Shannon and Weaver 1949). "*Without energy, no communication*"
	7	Epistemology, learning, inquiry. Since i) knowledge is stored in the brain, ii) the brain is made out of cells, and iii) cells are made out of matter, it would follow that "*Without matter, no knowledge*."
	8	Big Bang cosmology and biological evolution.
	4, 5	"Infoknowledge"

As a theoretical cell biologist interested in discovering the molecular mechanisms underlying living processes, I was led to conclude in (Ji 1991) that *information* and *energy* are complementary aspects of a third entity called *gnergy*, the complementary union of information (gn-) and energy (-ergy) (Chapter 2.3.2). In addition, I postulated that *gnergy* is the necessary and sufficient condition for all organizations in the Universe, including life (Chapter 4.13). In Chapter 2.3.1, , I hypothesized that the relation between *information* and *life* is akin to that between *energy* and *matter* (see Schemes (21-2) and (21-4)), leading to coining the term 'liformation', in analogy to mattergy (Scheme (21-4)). Thus the *energy-matter relation* has given rise to two hybrid terms, *infoknowledge* (based on Burgin's analogy (2004) and *liformation*, both embodying the principle of supplemantarity of Bohr (1958):

f
Matter ----------> **Energy** (*Mattergy Category*(21-2)) .
g
Knowledge --------> **Information** (*Infoknowledge Category*) (21-3)

h
Life ----------> **Information** (*Liformation Category*) (21-4)

In Chapter 2.3.1, it was suggested that *life* and *information* are quantitatively related, i.e., *liformation* reflects the principle of supplementarity:

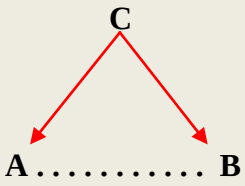
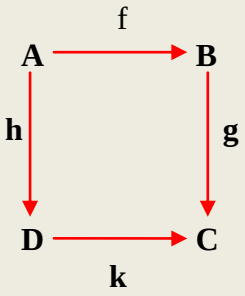
"*Just as matter is a highly condensed form of energy, so life may be a highly condensed form of information* (21-5)*nsed form of information*."

The set of the three hybrid terms, mattergy, infoknowledge and liformation, can be viewed as the names of the associated categories as shown in Schemes (21-2) through (21-4). A category is a mathematical entity consisting of *nodes* and *arrows* (Lawvere and Schanuel 2009, Hilman1997). A category is a mapping graphically represented as f: A ---> B, where A and B are, respectively, the *domain* and *codomain* and f is tcalled he *morphism*.

We can recognize at least three hierarchical levels of categories as shown in Table 21-3.

Examples of each class of categories are also provided. It is interesting to note that the categories in Schemes (21-3) through (21-4) are line segments, those in Figure 21-3 are triads, and that in Figure 21-4 is a quadrat.

Table 21-3. The category theory of everything (cTOE) integrating Peirce (1839-1914), Popper (1902-1994), Rosen (1934-1998), and Wheeler (1911-2008).

Category Class	Nodes	Arrows	Examples
Class I Category	objects	Morphisms[1]	**A** ⟶ **B** **A/B (**arrow**)** = Matter/Energy (Conservation of *mattergy*) Life or Knowledge/Information (Conservation of *liformation*[2] ?)
Class II Category	categories	Functor[3]	 **A** = Mattergy **B** = Liformation or Infoknowledge[4] **C** = Category of gnergons[5] Functor = the principle of complementarity (?)
Class III Category (or the functor category)	functors	natural transformation[6]	 **g**○**f** = **k**○h **A** = Gnergy[7] (or Natural Law of Rosen ?)

[1]Characcterize the structure of a category.
[2]The hybrid term indicating the combination of *life* and *information* in analogy to *mattergy*, the combination of *matter* and *energy; see* Scheme (21-4).
[3]A higher-level morphism characterizing the structural relationships between categories.
[4]The hybrid term indicating the combination of information and knowledge, in analogy to mattergy; see Scheme (21-3).
[5]The discrete units of gnergy such as conformons, the conformational energy packets localized at sequence-specific sites within biopolymers (see Chapter 8) and dissipatons (Chapter 3.1.5).
[6]"morphisms from functor to functor which preserves the full structure of morphism composition within the categories mapped by functors" (downloaded from Mark C. Chu-Carroll's post dated 6/19/2006).
[7]The hybrid term constructed from information (gn-) and energy (-ergy) that is postulated to represent the material source and the organizational force of our Universe (Ji, 1991, 2012).

Table 21-4 attempts to capture the common features of the philosophical systems advocated by the four scholars whose thoughts are being integrated in Table 21-3 in relation to the metaphysical and scientific theories described in this book.

Table 21-4. The three-component philosophical systems of Peirce, Popper, Rosen and Wheeler. The Arabic numerials in bold refer to those appearing in Rosen's modeling relation shown in Figure 21-5.

Authors	**Component I**	**Component II**	**Component III**
Rosen	Natural Law (**2** & **4**)	Natural System (**1**)	Formal System (**3**)
Peirce	Firstness[1]	Secondness[2]	Thirdness3
	Sign[4] Interpretant	Object[5] Object	Interpretant[6], or Sign (?)
Popper	World 1[7]	World 2[8]	World 3[9]
Wheeler	Participant/Observer[10]	It[11]	Bit[12]
Ji	Gnergy	Mattergy	Liformation
	Cosmolanguage[13]	Cell Language[14]	Human Language[15]

[1]Any entity or process that can exist without anything else, e.g., quality, feelings, possibilities (see Table 6-7).
[2]Any entity or process that exists because of another entity, e.g., facts, actuality, reaction.
[3]Any entity or process that exists as the mediator between two other entities or processes, e.g, representation, mediation, thought.
[4]Something which stands for something other than itself (see Section 6.2.1).
[5]The thing that is referred to by a sign (see Chapter 6.2.1).
[6]The effect that a sign has on the mind of the sign processor.
[7]The physical world including the living world.
[8]The mental world.
[9]the world of the products of the human mind, including poems, arts and scientific theories.
[10]The human as the observer and participant in defining the reality.
[11]The reality or the object of measurement
[12]The result of measurements
[13]The language that enables cell and human angauges (see Chapter 6.2.6).
[14]The molecular language used by living cells to communicate within and between themselves.
[15]The symbolic and iconic languages (see Chapter 6.2.5) used by Homo sapiens to communicate within and between themselves.

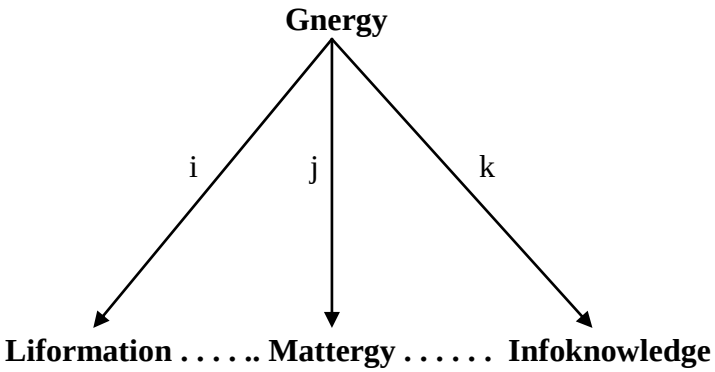


Figure 21-3 Liformation**,** mattergy and infoknolwedge as the reification of gnergy.

Figure 21-3 represents the postulate that liformation, mattergy, and infoknowledge are the complementary aspects of gnergy or that gnergy is ultimately responsible for (or reifies into) liformation, mattergy, or infoknowledge, through mechanisms (or laws, rules, etc.) denoted as i, j, or k, respectively. The functor i, j, or k signifies "*gives rise to*" or "*reifies into*" and are thought to be associated with the principle of *complementarity.*

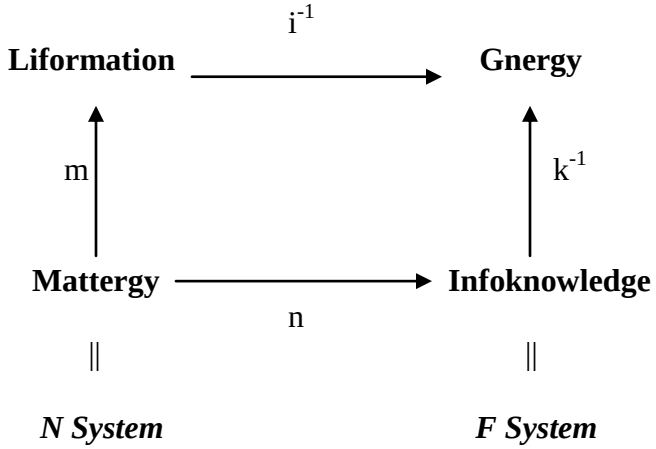


Figure 21-4 A class III category endowed with the commutativity relation shown in Equation (21-6).

Figure 21- 4 depicts the Class III category that integrates the four hybrid terms defined in Table 21-3. Most significantly, The diagram in Figure 21-4 is postulated to embody the commutativity realtin given in Eq. (21-6).

$$(i^{-1}) \text{ x } m = (k^{-1}) \text{ x } n \qquad (21\text{-}6)$$

The precise nature of the functors appearing in Eq. (21-6) are currently unknown. One possible set of the meanings/properties of the functors is suggested below:

m = the origin of life through self-organizing properties of matter and energy (see the Shillongator in Ji 1991, pp. 156-163, 230-237).
n = the registration or recording of the history of the Universe in the structures of the environment and genomes of organisms
i^{-1} = the inverse of morphism i in Figure 21-3; cell language (Chapter 6.1.2) (?), and
k^{-1} = the inverse of morphism k in Figure 21-3; cognition (?)

If Eq. (21-6) turns out to be correct, and if, the commutative diagram in Figure 21-4 can be divided into two halves, each denoted as the natural (N) system and the formal system (F) system, following Rosen (1991) (see Figure 21-5 below), the Class III category shown in Figure 21-4 may be represented as shown in Equation (21-7), where *natural transformation* p may be identified with *ontology* and *natural transformation* q with *epistemology*. If $p = q^{-1}$, or equivalently, $q = p^{-1}$, then N and F would be isomorphic (Lawvere and Schnauel 2009, p. 40) and our Universe would be a self-knowing universe, a conclusion reached in (Ji 1991, pp. 236) via a totally independent route without depending on any category-theoretical argument.

$$\mathbf{N} \underset{q}{\overset{p}{\rightleftharpoons}} \mathbf{F} \qquad (21\text{-}7)$$

If the conjectures formulated above prove to be true in the future, the Class III category presented in Figure 21- 4 for the first time may be justifiably called the category theory of everything (cTOE).

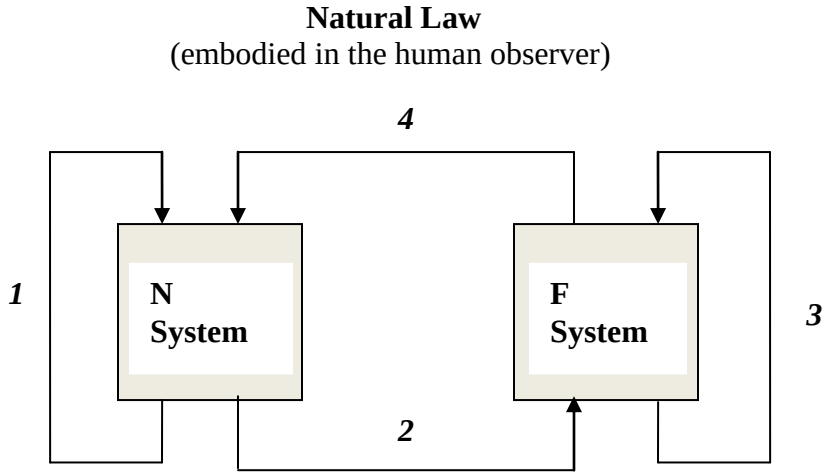


Figure 21-5. Rosen's modeling relation. N = the natural system, or the part of the Universe exhibiting regularities; F = the formal system; 1 = causal entailment; 2 = encoding; 3 = inferential entailment; 4 = decoding/actualization

Two applications of cTOE suggest themselves:

(1) Popper (1978) divides our universe into "three interacting sub-universes" which he calls world 1 (the physical world, both living and non-living), world 2 (the mental and psychological world), and world 3 (the world of the products of human mind, including "languages; tales and stories and religious myths; scientific conjectures or theories, and mathematical constructions; songs and symphonies; paintings and sculptures. But also aeroplanes and airports and other feats of engineering"). cTOE suggests the following internal structures of Popper's worlds:

World 1 = Gnergy-Mattergy
World 2 = Mattergy-Liformation, and
World 3 = Liformation-Infoknowledge.

(2) According to cTOE, the *mattergy category* (to which *energy* belongs) and the *liformation category* (to which *information* belongs) are mutually exclusive and complementary aspects of *gnergy* and hence it would be impossible to convert

information to *energy* in the same sense that *matter* can be converted into *energy*. The correct relation between *information* and *energy* may be derived from Shannon's channel capacity equation (Shannon and Weaver 1949), according to which no information can be transmitted nor any control exerted without requisite dissipation of free energy (Chapter 4.8). Therefore, the experiments recently performed by Toyabe et al. (2010) (and many similar experiments reported in the literature during the past couple of decades) may not demonstrate any *information-to-energy conversion* as claimed but rather the *energy requirement for controlling molecular events* as entailed by the channel capacity equation of Shannon (Shannon and Weaver 1949).

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