"Type IV" = the IDS-induced conformons (e.g., DNA conformational transitions driven by changes in pH or ionic strength or membrane receptor activation-induced DNA covalent modifications (Holliday, 1989)).

Because of these multiple mechanisms, it is possible for the symmetry breaking influences to propagate from the interior of enzymes to the limits of cell boundaries and beyond (Type III), or from extracellular space to DNA or enzymes in the cytosol (Type IV). In other words, the distance scale over which various symmetry-breaking influences can be exerted can extend from the molecular dimensions (i.e., 1Å or 10^-10 m) to the cellular dimensions (i.e., 10 microns or 10^-5 m) (or vice versa), representing an amplification (or contraction) of distance by a factor of about 10^5. The net consequence is that the cell can convert the genetic information stored in DNA into its dynamic functions, and vice versa (see Section 1.12.5).

1.8.4. The Bhopalator: A Theoretical Model of the Cell

Two related ideas are essential in formulating the coherent and comprehensive theoretical model of the living cell that I named the Bhopalator: (1) It is possible to encode rate constants in the primary amino acid sequence of enzymes (and hence in the genome), and the sequence information of enzymes can be transduced into specific rate processes in the cell through the conformon mechanism of enzymic catalysis (Ji, 1974b), and (2) Prigogine’s dissipative structures can act as the link between the sequence information of biopolymers and cellular functions (Ji, 1985a,c; 1988).

Using the terminologies and concepts introduced earlier in this chapter, we may summarize the essential features of the Bhopalator as follows:

1) The cell consists of two major classes of machines—biopolymeric (i.e., DNA, RNA, proteins), and metabolic machines (i.e., basic metabolic and suprametabolic pathways (see Equation 1.12 and Table 1.11)).

2) Both biopolymers and metabolic pathways can exist in either the "resting" or the "activated" states, the latter requiring an input of Gibbs free energy. The resting states are examples of 3-structures and the activated states represent 4-structures, or events.

3) The activated state of a biopolymeric machine can be characterized in

...
terms of its unique set of conformons whose movement in space and time determines the spatiotemporal structures (or 4-structures) of biopolymers and hence their biological functions, just as the spatiotemporal distribution of the voltage values over the transistors in a computer chip determines its computing functions.

(4) The activated state of a metabolic machine is associated with a unique distribution of a set of diffusible chemicals around it, like a field around electrically charged bodies. A set of activated metabolic machines in the cell generates the intracellular gradients of molecular species called IDS; and IDS serve as the immediate (i.e., proximate) causes for all cellular functions, just as conformons are the immediate causes for all biopolymeric functions.

(5) Conformons and IDS can be interpreted as representing the internal states of biopolymeric machines (i.e., $S^{bp}$ in Equation (1.9)) and metabolic machines (i.e., $S^{mp}$ in Equation (1.12)), respectively.

(6) Conformons and IDS contain both Gibbs free energy and genetic information and hence are two different forms of gnergons, hybrid entities derived from the fusion of ergons (carrying free energy) and gnons (carrying information). Biopolymers and metabolic pathways in the resting states are examples of gnons while their activated states represent gnergons.

(7) Gibbs free energy and Shannon information can be exchanged between conformons and IDS's. The spatial amplification (or dilation), namely spreading of the spatiotemporal symmetry-breaking influences from the enzyme interior to the cytosol requires the conversion of conformons to IDS (i.e., Type III spatiotemporal symmetry-breakings), while the spatial contraction, namely the "focusing" of the spatiotemporal symmetry-breaking influences originating from the bulk cytosolic phase onto biopolymers, requires the conversion of IDS into conformons (i.e., Type IV spatiotemporal symmetry breakings).

(8) Through the interconversions and couplings possible between conformons and IDS, the living cell can transmit, receive, or transduce information both within the cell (e.g., from DNA to enzymes) and between the cell and its environment (e.g., hormone-induced activation of gene expression), a prerequisite for ontogeny (development of individual organisms) and phylogeny (evolutionary development of species) of living systems.

1.8.5. The Bhopalator in the Molecular and Algebraic Representations

The cell model incorporating all of the features listed in Section 1.8.4. is schematically shown in Figure 1.7.

The Bhopalator divides the overall cellular processes into 20 major steps:
DNA replication necessary for cell division, differentiation and evolution (step 1); DNA transcription and RNA splicing whereby genetic information is transferred from DNA to mRNA (step 2); translation in which the genetic information of mRNA is further transferred to the linear sequence of amino acids in polypeptides (step 3); expression (Monod, 1971) whereby polypeptide chains synthesized on ribosomes fold into catalytically active 3-dimensional proteins influenced by intracellular microenvironment (step 4); substrate binding in which specific amino acid side chains (labeled w, x, and y) and substrates interact to form an enzyme-substrate complex (step 5); activation where the thermal fluctuations of the enzyme-substrate complex create a transient conformational strain at the active site called the Franck-Condor conformon represented by an alignment of catalytic side chains w, x, y and z which is intermediate between the substrate-binding (w, x and y) and the product-binding (x, y and z) conformational strains, the Franck-Condor conformon facilitating the conversion of the substrate to an intermediate, I, by quantum mechanical tunneling (step 6); deactivation whereby the highly strained conformation of the active site in the transition state relaxes into the product-binding conformation, forcing the conversion of I into the product, P (step 7); product release (step 8) by which the newly formed P dissociates from the enzyme active site and contributes to the creation of intracellular dissipative structures (IDS), with the enzyme returning to its initial conformation ready for the next cycle of catalysis (step 9); and mutation and recombinations (step 10), leading to the production of new genes under the influence of local environment determined by IDS (e.g., local electrical field gradients, pH gradient, mechanical stress gradients in DNA, etc.). Steps 11 through 18 (represented by dotted lines) indicate feedback control interactions between IDS's and conformons of biopolymers, thus forming negative or positive feedback control loops. Finally, steps 19 and 20 depict the reception by the cell of information originating from its environment (including neighboring cells) and the output of information by the cell to its environment, respectively. Although not explicitly indicated, various receptors located in the plasma membrane, the cytosol, or the nucleus can be treated as pseudo-enzymes and members of biopolymer machines (see Table 1.10, footnote 4).

The living cell depicted in Figure 1.7 can be viewed as a complex machine and thus is amenable to description by the algebraic formalism used in cybernetics (see M. Holcombe, Chapter 4). The following equation encapsulates the essential properties of the living cell;

$$M^c = (I^c, S^c, O^c, d^c, l^c)$$  \hspace{1cm} (1.19)
where $M^c$ indicates the cell (c) machine; $I^c$ is the set of inputs into the cell, including Gibbs free energy in the form of exergonic (i.e., free energy-releasing) chemical reactants and photons from the sun, and chemical messengers; $S^c$ is the set of the internal states of the cell (called the "cell states" in analogy to the electronic, vibrational and rotational states of atoms and molecules (Ji et al., 1986)) characterized by the spatiotemporal distributions of conformons and IDS; $O^c$ is the set of outputs by the cell, including heat, chemical products, and mechanical work on its environment such as cell division (leading to the control of the Euclidean space), chemotaxis, and phagocytosis; $d^c$ is the relationship (or mechanisms of interactions) between the inputs and the internal states of the cell (to be called the "input program of the cell"); and finally $I^c$ is the relation (or mechanisms of interactions) between the internal states of the cell to its outputs (to be called the "output program of the cell"). Clearly, this algebraic representation of the cell fits the universal scheme representing machines in general depicted in Figure 1.1.

Figure 1.7. A molecular model of the living cell. It was first proposed at the Second International Seminar on the Living State -II, held in Bhopal, India on November 13-20, 1983.
1.8.6. The Cell as a Molecular Computer

The cell as modeled by the Bhopalator reveals striking similarities to the digital computer (see Table 1.14). Just as a computer is designed to transform inputs to outputs according to computer programs, so the cell can be viewed as a physical system of a microscopic dimension that has evolved to transduce (via $S$ in Equation (1.19)) inputs ($I^o$) to outputs ($O^o$), according to the "cell programs" ($d^o$ and $l^o$) stored in it.

The concept of the "cell program" emerges naturally from the Bhopalator. This concept is related to, but not identical with, the genetic programs stored in DNA. The cell programs presuppose the existence of genetic information in the cell in two forms—(1) the traditional, static sequence information stored in biopolymers, and (2) the new form of information stored in dynamic, spatiotemporally organized distributions of diffusible molecular species, namely IDS. The former is called the "Watson-Crick form" of genetic information, and the latter the "Prigoginian form," and biopolymers are postulated to interconvert these two forms utilizing conformmons (Ji, 1988) (also see Section 1.8.3).

Table 1.14. A Comparison between the Cell and the Computer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cell</th>
<th>Computer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current carrier$^1$</td>
<td>Electrons</td>
<td>Electrons</td>
</tr>
<tr>
<td>Current conductors$^2$</td>
<td>Chemicals</td>
<td>Wires</td>
</tr>
<tr>
<td>Current controller$^3$</td>
<td>Enzymes</td>
<td>Transistors</td>
</tr>
<tr>
<td>Mechanisms of control$^4$</td>
<td>Conformons</td>
<td>Photons</td>
</tr>
</tbody>
</table>
(Table 1.14 continued)

<table>
<thead>
<tr>
<th>Electron source</th>
<th>High-energy chemical</th>
<th>External voltage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electron sink</td>
<td>Low-energy chemicals</td>
<td>Ground</td>
</tr>
<tr>
<td>Memory</td>
<td>Biopolymers, IDS</td>
<td>Flip-flops, Capacitors</td>
</tr>
<tr>
<td>Structural rigidity&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Thermally fluctuating</td>
<td>Thermally robust</td>
</tr>
<tr>
<td>Size</td>
<td>Microscopic (ca. 10&lt;sup&gt;-3&lt;/sup&gt; cm)</td>
<td>Macroscopic (ca. 10&lt;sup&gt;2&lt;/sup&gt; cm)</td>
</tr>
<tr>
<td>Program location</td>
<td>Biopolymers</td>
<td>Softwares</td>
</tr>
<tr>
<td>Self-reproductibility&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Model&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Bhopalator</td>
<td>Turing machine</td>
</tr>
</tbody>
</table>

<sup>1</sup> Chemical reactions are not usually discussed in terms of electron flows, but I believe it is legitimate to view all chemical reactions (and not just redox reactions) as resulting from shifts in electron densities within the molecules participating in electronic rearrangements, leading to the conclusion that the only difference between electric currents through conductors and chemical reactions is that the former involves "continuous" electron flows in the macroscopic scale (≥ 50-100 nm) and the latter involves discrete electronic jumps in the microscopic scale (probably ≤ 0.1 nm), a scale difference of at least 10<sup>5</sup>-10<sup>3</sup> fold.

<sup>2</sup> Electron movements in chemical reactions can be divided into two parts—(1) the electronic density shifts associated with the electronic rearrangements occurring at the transition state of chemical reactions, and (2) the diffusion of chemicals that precedes or follows the electronic rearrangements. Therefore, the current flow associated with chemical reactions is spatially random due to the thermal fluctuations essential for diffusion, while the current flow in computers is deterministic due to the constraints imposed upon it by the macroscopic wires of the computer circuitry.

<sup>3</sup> Enzymes regulate the time evolution of enzyme-catalyzed chemical reactions through spatiotemporal symmetry-breakings driven by conformons as discussed in connection with Equation (1.18). Since the progress of chemical reactions is analogous to current flow in electronic circuitry, enzymes can be compared
The concept of the Prigoginian form of genetic information requires that there exist mechanisms for transmitting the information stored in IDS from the mother cell to daughter cells. Since IDS can control enzymic activities (e.g., intracellular pH and Ca$^{++}$ affecting metabolism) and since "maintenance methylase" can methylate DNA, it is possible that the cytosolic IDS information can be transduced into the information encoded in the pattern of DNA methylation, which can then be transmitted to daughter cells (Holliday, 1989).

It was postulated that the reason for the existence of these two forms of genetic information is that the Watson-Crick form is necessary for transmitting genetic information in the time dimension, while the Prigoginian form is required for transmitting genetic information in the spatial dimension, just as musical notes and sound waves are needed for transmitting musical information in time and in space, respectively (Ji, 1988). Such a clean separation of the two forms of genetic information may be possible only over the time and length scales that are greater than those accessible to molecular species through their thermal fluctuations, because in biopolymers information transmission in space and time appears to be coupled in the form of conformons.

1.8.7. The Bhopalator in a Field Theoretic Representation

A. What is a Field? In physics, the concept of a field began with the discovery of the electric and magnetic fields (Adair, 1987). A field in general refers

(Notes to Table 1.14 continued)

to transistors which control electron flow in computer circuitry.

4Just as the actions of transistors can be described in terms of the spatiotemporal distributions of photons, energy packets mediating all electromagnetic interactions, enzymic actions may be described in terms of the spatiotemporal distributions of conformons, the ultimate physical objects responsible for the biological actions of biopolymeric machines (see Section 1.5).

5Thermal fluctuations are essential for all enzymic catalyses, whereas thermal fluctuations of the circuit components of silicon chips are generally detrimental to computer functions (see 5.1.). This may be one of the most fundamental differences between computers and biological machines and serve as the ultimate barrier to the miniaturization of computers.

6Including not only the central processing unit but also input and output devices.

7The mathematical model of the universal computer was formulated by Turing in the 1940’s (Hopcroft, 1984). The Bhopalator, although expressible in an algebraic form, has not yet led to a rigorous mathematical model.
to a quantity defined at each point throughout some region of space and time ('t Hooft, 1980). There are two kinds of fields. A "scalar field" has only a magnitude associated with each point (e.g., the distribution of temperature values of each point on a frying pan). A "vector field" associates each point with a magnitude and direction (e.g., the distribution of the velocity of each molecule in a fluid).

B. The Intracellular Metabolic Velocity Field (IMVF): The concept of vector field is useful in visualizing the instantaneous metabolic state of the cell. This can be represented schematically as a collection of arrows distributed inside the cell as shown in Figure 1.8. Each arrow conveys three kinds of information—(1) the origin of each arrow coincides with the center of mass of an enzyme or an enzymic system located in the cell at a given time point, (2) the magnitude of an arrow indicates the instantaneous rate of the chemical reaction catalyzed by the enzyme, and (3) the orientation (not in the Euclidean space as shown but in an abstract "internal coordinate" space; see Section 1.8.1. and Equation 1.17) reflects the nature of the chemical reaction involved. All these three quantities of the vectors can vary with the location of enzymes within the cell and with time; i.e., each vector is a function of space and time. For convenience, we will call such a vector field the "intracellular metabolic velocity field (IMVF)."

The IMVF depicted in Figure 1.8 conjures up an image of a living cell in which all the arrows undergo constant fluctuations and motions, showing changes in their positions, directions, and sizes. As some enzymes get degraded and others newly synthesized, certain arrows may disappear altogether (annihilation of an IMV vector) from the scene and some others may appear suddenly out of nowhere (creation of an IMVF vector). Still other arrows may collide and thereby undergo changes. Collisions are not the only mechanisms by which arrows can interact; they can exchange diffusible chemicals as a means of interactions. All these mental images are reminiscent of particle physics, wherein the interactions among numerous high-energy particles have been successfully characterized using field theories (Adair, 1987).

C. The Biopolymeric Force Field (BFF): The mechanism underlying each arrow in Figure 1.8 can be analyzed in terms of the interaction between the catalytic properties of an enzyme and the local concentration of chemical substrates and cofactors for that enzyme. For this purpose, it is necessary to introduce two more fields—the biopolymeric force field (BFF), and the intracellular chemical concentration field (ICCF).
Figure 1.8. The Intracellular Metabolic Velocity Field (IMVF). The lines represent the cytoskeletal network, highly stylized, the little wiggly "particles" or "globules" positioned at the intersections are enzymes, and the small dots signify diffusible chemical species. Each enzyme possesses a vector, whose magnitude is proportional to the rate of the chemical reaction catalyzed by the enzyme at any given time and whose direction indicates the kind of the chemical reactions being catalyzed.

The arrows in Figure 1.9 schematically depict an instantaneous distribution of the force vectors of the catalytic sidechains of the enzymic active site. Of course these force vectors are determined by the vector sum of all of the other force vectors generated all along the polypeptide chain, but these are not shown for simplicity. Again, it is not difficult to imagine how the time evolution of these active site vectors would look like as the enzyme involved carries out its catalytic function. The spatiotemporal distribution and the changes in size and direction of the force vectors would look similar to the dynamics of the arrows in IMVF but much more constrained due to the linear linkage of the arrows in the polypeptide chain. We will call this vector field the "biopolymeric force field" to be designated with the symbol $\mathbf{F}$. Note that the collection of the force vectors is identical with a conformon located at the active site at the same time point; i.e., conformons can be viewed as the quanta of the biopolymeric force field, just as photons are the quanta of the electromagnetic force field.

D. The Intracellular Chemical Concentration Field (ICCF): The living cell
can be viewed as a collection of a finite number of material particles whose concentration inside the cell varies in both space and time. The intracellular material particles can be conveniently divided into two broad categories—(i) l-particles (l from "light") composed of small-molecular-weight chemical species such as protons, metal ions, inorganic phosphate, ATP, etc., and (ii) h-particles (h from "heavy") composed of biological macromolecules such as nucleic acids, proteins and carbohydrates. The most important property that differentiates l-particles and h-particles is probably their diffusibilities under physiological conditions of temperature and pressure. The diffusion coefficient (D) is defined as the number of particles per second crossing unit

**Figure 1.9. Biopolymeric Force Field (BFF).** The thick curves indicate the 3-dimensional arrangement of the protein backbone, side chains having been excluded for clarity. The arrows represent the instantaneous forces acting along the representative points of the backbone. The substrate (S) is being acted upon by a set of 6 force vectors at time t. Unlike the arrows in Figure 1.8, those in Figure 1.9 represents the direction of the force vectors in the Euclidean space.
area under unit concentration gradient and is inversely proportional to the square root of the molecular weight \( (M) \) of the particle; i.e., \( D \propto (M)^{1/2} \). Assuming that the average molecular weight of \( I \)-particles is \( 10^2 \) daltons and that of \( H \)-particles \( 10^6 \) daltons, we can conclude that the diffusion coefficient of \( I \)-particles is greater than that of \( H \)-particles by a factor of about \( 10^2 \).

To completely describe the dynamic (i.e., quantum statistical mechanical) states of all these intracellular particles, it is necessary to have a mathematical or logical space composed of the 4-dimensional physical space of \( x, y, z, \) and \( t \) (to describe the time-dependent positions of all the particles inside the cell) and an \( N \)-dimensional "internal space" (to specify the chemical transformations of the particles, where \( N \) may be identified with the variety of the chemical species participating in the intracellular metabolism). Such a \((N + 4)\)-dimensional space will be referred to as the *intracellular chemical concentration field* (ICCF) (see the dots \( I \)-particles) and wiggly globules \( H \)-particles in Figure 1.8). So defined, any objects describable in ICCF can be identified with intracellular dissipative structures (IDS), discussed in Section 1.8.2. and Figure 1.4. In other words, IDS can be viewed as subsets of the elements of (or topological objects in) ICCF that have been selected by biological evolution owing to their essential roles in the survival of the cell. ICCF is to IDS what the ocean is to oceanic waves, what the field of mass densities in air is to sound waves, what the electromagnetic field is to radio signals in electrical communication systems (see Section 1.8.11. for related discussions), and finally what marble (i.e., the material cause of Aristotle) is to marble statues (i.e., the formal cause). In the parlance of electrical communications theory, ICCF may be equated with the communication channel and IDS with the signals carrying messages through that channel (Pierce, 1980). It was for these reasons that I pointed out several years ago that IDS might represent a new form of genetic information, alternative to the DNA sequence information, and suggested that we recognize two distinct forms of genetic information—the Watson-Crick form (analogous to musical notes) and the Prigoginian form (analogous to sound waves) (Ji, 1988).

**E. A Field Representation of the Living Cell:** Since the intracellular concentration of any chemical species would be determined by the balance of the rates of its formation and removal at any given time and location inside the cell, ICCF is a function of IMVF. At the same time, the rates of chemical transformations of any given chemical species are influenced by both its intracellular concentrations and the activities of the enzymes catalyzing the reactions involved; therefore, IMVF is clearly a function of ICCF and BFF. However, ICCF in general cannot directly affect IMVF, because most if not all of intracellular chemical reactions do not proceed until and unless catalyzed by appropriate enzymes. This contrasts with nonenzymic
chemical reactions where chemical concentrations directly influence the rates of their chemical transformations according to the laws of chemical kinetics, a hybrid discipline of quantum mechanics and statistical mechanics (Frost and Pearson, 1961). It appears as though biological evolution has selected for cellular metabolism only those chemical reactions that do not proceed in the absence of enzymes, a condition without which evolution cannot control or regulate cellular metabolism and cell functions through the modulation of enzyme structures. Therefore, enzymes must carry genetic information—i.e., proteins must act as a communication channel to transmit genetic information (see Appendix 1.B for related discussions). All of these complex interactions among IMVF, ICCF and BFF and their relations to cell functions may be schematically represented as shown in Equation (1.20), where the arrows indicate the exertion of unidirectional influences or controls.

Step 4 in Equation (1.20) represents those metabolic processes in which the mechanical state of biopolymers directly influences the cytoplasmic concentrations of chemical species. Examples of such processes include the set of metabolic reactions generally known as "energy-coupled" processes (Ji, 1974a, 1979) such as oxidative phosphorylation, active transport, and muscle contraction, where the free energy stored in the form of the conformational strains of proteins (i.e., conformons) are thought to drive the endergonic (i.e., free-energy-consuming) partial processes (e.g., ADP phosphorylation, transmembrane transport of ions, sliding of the thin filament relative to the thick filament, etc.). In addition, such conformon-driven processes may be implicated in the structural transformations of DNA underlying, for example, (i) recombinations that may involve long-range protein-protein interactions through DNA looping (Heichman and Johnson, 1990) and (ii) the enhanced binding by a repressor at a low-affinity site in the presence of a high affinity site.
Just as IDS can be viewed as the signals transmitting genetic information through the communication channel composed of ICCF, so conformons can be considered as the signals transmitting genetic information through the communication channels composed of biopolymers, namely nucleic acids and proteins. Again just as IDS represent a new form of genetic information as indicated above, so conformons can be treated as still another form of genetic information, which may be called the "conformon form" of genetic information (see Table 1 in Ji, 1988). It is interesting to note that the Prigoginian form of genetic information is effectuated (i.e., converted into cellular actions) through step 5 and the conformon form through step 6 in Equation (1.20).

Two features about Equation (1.20) seem to stand out—(i) The unidirectionality of the interactions between BFF and IMVF on the one hand (step 2) and IMVF and ICCF on the other (step 3). (ii) The duality of the mechanisms of cell functions, namely through ICCF and BFF (steps 5 and 6). The unidirectional interaction between IMVF and ICCF has been already explained above as the result of the fact that biological evolution has selected for cellular metabolism only those chemical reactions that absolutely depend on enzymes for their progression. The unidirectionality of step 2 may be considered as the inevitable consequence of the same fact. The cell functions that depend on ICCF (step 5) include all the secretory or excretory functions of cells such as endocrine cells secreting hormones and metabolic cells releasing nutrients and structural and transport molecules into circulation. The cell functions mediated by BFF (step 6) should include cellular motility underlying cell shape changes, cell division, and chemotaxis. In general, the ICCF-mediated cell functions have a larger domain of influences than the BFF-mediated cell functions; i.e., the ICCF-mediated cell functions are long-ranged, while the BFF-mediated cell functions short-ranged, just as the electrical communications are effective over much greater range of distances than the communications utilizing sound waves. The evolution of these two kinds of cellular effector mechanisms must have provided the cell with a greater degree of control over its space and time, leading to a greater adaptability to its changing environment.

Based on the above discussions, it can be concluded that Equation (1.20) is a field-theoretic representation of the living cell. In another sense, Equation (1.20) can be viewed as describing what may be called the "spacetime-elaborated" or "spacetime-modulated" chemical concentration field conducive to cell life. By "spacetime-modulated," I simply mean that the concentrations of the chemical species inside the cell vary, above and beyond the variations allowed for by enzymic reactions alone, as functions of space (x, y, and z), time (t), and genetic information (I) encoded in enzymes. This may be analogous to the general relativity theory,
wherein the gravitational force field can be equivalently represented by the set of numbers called "curvatures" that depend on space \((x, y, z)\), time \((t)\), and the distribution of matter \((m)\); i.e., the presence of matter curves spacetime, and matter moves along the shortest route (i.e., the geodesic) on the curved spacetime (for related discussions see Sections 1.8.9 and 1.12.1 of this chapter, and Smith and Welch in Chapter 6). Just as the gravitational force can be thought of as "elaborating" or "manifolding" (see Section 1.8.8) the curvature of spacetime from the uniform and flat one to a heterogeneous and "bumpy" one with peaks and valleys (Figure 6.1 in Chapter-6), so the cell force elaborates the structure of the intracellular chemical concentration field (ICCF) at every point in space and time to produce highly heterogenous and complex structures called IDS; i.e., IDS can be regarded as an indication of the existence of a new force in the cell called the cell force, just as the bending of light around the sun is an indication of the existence of the gravitational force around the sun. Furthermore, gravitational force is "caused" by the presence of matter; similarly, the cell force can be thought of as being "caused" by the presence of the genetic information encoded in biopolymers.


As evident in the previous section, the formulation of a physical theory of the living cell may be greatly facilitated by the availability of the concepts and terminologies developed in Einstein's general relativity theory. This may not be a happenstance, if our conjecture is correct that the domain of the validity of the general relativity theory is the spacetime on the cosmological scale, while the domain of the validity of cell biology is the spacetime on the microscopic scale, as already pointed out in Section 1.8.1. What I mean by this statement is simply this: To the extent that we can regard the "curving" of spacetime by matter as the "elaboration" and "complexification" of the structure of spacetime by matter on the cosmological scale, so we can view intracellular metabolism as the elaboration and complexification of spacetime by the cell on the microscopic scale. The physical motion implicated in the former is the accelerations of moving bodies relative to a frame of reference, while the physical motions underlying the elaboration of spacetime by the cell is chemical transformations of matter. The result of the macroscopic elaboration of spacetime by matter is the curved spacetime, or equivalently the genesis of the "gravitational force," and the consequence of the microscopic elaboration of spacetime by the cell is the "curved" intracellular chemical reactions (giving rise to IDS), or equivalently the birth of the "cell force."
The conclusion that the connection between general relativity and cell biology may be more than just an analogy but is a natural consequence of the underlying multifaceted properties of spacetime justifies our curiosity to know more about the connections between the general relativity theory and the other theories of the fundamental forces that have been established in physics during the past half a century. It is now an established fact that there indeed exist deep connections between the general relativity theory (which is in effect the theory of the gravitational force) and the other theories of the fundamental forces of nature, namely the electromagnetic, electroweak and strong forces (Davies, 1984, 1986; Kaku and Trainer, 1987; Lopes, 1981; Moriyasu, 1985; 't Hooft, 1980; Yang, 1977; Zee, 1986). It has taken theoretical physicists more than a half century to uncover the underlying unity among the fundamental forces, and this has been possible through the developments of gauge field theories (Moriyasu, 1985) and superstring theories (Green, 1985).

Since physicists have already demonstrated that gauge field theories provide the proper language to describe the connection between general relativity theory and other theories of fundamental forces, perhaps it is logical to ask the question whether or not gauge field theories would prove equally useful in analyzing the possible connections between the cell force and the gravitational force on the one hand and the cell force and strong force on the other. These and related topics are discussed below.

A. Manifolds: A manifold is a mathematical concept denoting a set of points or elements with characteristic properties such that they can be grouped into subsets. A plane is a two-dimensional manifold of points, because it is a set of all points, each of which being specified by two coordinates, \((x, y)\), and contains lines as its subsets. Euclidean space is a 3-dimensional manifold of points, each point requiring three coordinates, \((x, y, z)\), for its specification and contains subsets of lines and planes. In general, an \(n\)-dimensional manifold is a collection of \(n\) values assigned to any \(n\) variables \(x_1, x_2, \ldots, x_n\) (Levi-Civita, 1977). The study of the invariant properties of the structure of manifolds is called topology, a generalized geometry. The most important manifold in physics is the one involving the spatial and time coordinates, namely the set of 4 values assigned to \(x, y, z,\) and \(t\). This manifold is referred to as spacetime (Misner et al., 1973; Wald, 1977; Taylor and Wheeler, 1966).

One of the most useful and fundamental properties of a manifold is that each point in it can be replaced with another manifold; so you can have a manifold of manifolds of manifolds of \(\ldots\) etc. Such a mathematical tool is essential to represent complex physical systems or situations which cannot be analyzed at once but only in steps, due to the limited "focusing" power of the measuring instruments (e.g., light
microscope or electron microscope) or the observer (recall that the human eye cannot be focussed on the "forest" and the "tree" simultaneously).

The manifolds composed of a large number of smaller manifolds may be called "nested manifolds." The Russian doll that contains a half dozen smaller replicas of itself, each nesting within the next larger, can be regarded as a simple example of nested manifolds. In a sense, the human body can be viewed as a nested manifold, since the body is a 4-dimensional manifold of cells, each cell is a 4-dimensional manifold of molecules, and each molecule is a 4-dimensional manifold of atoms—4-dimensional, because the elements of each manifold are arranged not only in space but in time as well (e.g., the properties of the cells constituting our body vary depending on their locations in and the age of the body). Therefore, the mathematical concept of manifolds can be clearly related to the physical objects that we call "machines" in this chapter, in the sense that a large machine can be constructed by properly coupling a set of smaller machines, each one of which in turn can be constructed by coupling a set of even smaller machines, etc.

The mathematical objects that possess fundamentally similar (or self-similar) features at different levels of magnification (i.e., at different size scales) are called "fractals" (Barnsely et al., 1987; McNamee, 1990; Jürgens et al., 1990). Fractals are so called because of the fact that they have fractional dimensions unlike the integral dimensions of familiar figures of the Euclidean geometry. The self-similarity characteristic of fractals is inherent in nested manifolds and biological machines. Hence, we can assert that all biological machines, above the level of molecular machines, can be treated as fractal objects or fractals. Thus, we can anticipate that both the topology of manifolds and fractal mathematics will play important roles in the study of living systems and processes viewed as machines. It is encouraging that the utility of the fractal geometry has already been demonstrated in some branches of biology and medicine (Glass and Mackey, 1979; Jürgens et al., 1990; West, 1990).

B. Fiber Bundles: Fiber bundles are a special class of manifolds that have the following structures: (i) the basespace, (ii) the fiber space erected at each point of the basespace, and (iii) the connection which correlates the points of one fiber space to those of another (Moriyasu, 1985). The combination (or union) of the base space and the fiber space is called the "fiber bundle space" or "total space." These various components of the total space are depicted in Figure 1.10.

Although the fiber space in this figure is represented as a line, the dimensionality of the fiber space can be increased to 2 (circle), 3 (sphere), 4 (4-dimensional space), etc. The concept of the connection is a generalization of the concept of the curvature of a 2-dimensional surface such as the surface of the earth, and its formulation was due to H. Weyl who in 1917 attempted to develop a unified

The fiber bundle geometry provides us with a convenient method to visualize the concepts of the manifold and the internal space. To construct an \((m + n)\)-dimensional manifold from an \(m\)-dimensional manifold (where \(m\) and \(n\) are whole numbers), it is necessary and sufficient to carry out two operations: (i) Represent the \(m\)-dimensional manifold as a basespace, and (ii) Replace each point of the \(m\)-dimensional basespace with \(n\)-dimensional fiber space, which is equivalent to the "internal space" discussed in Section 1.8.1. Gauge theories discussed below can be also represented in terms of the fiber bundle geometry by associating gauge fields with the fiber space (or the internal space) erected at each point of spacetime which is treated as a basespace.

Figure 1.10. A schematic representation of the fiber bundle space (adapted from K. Moriyasu, 1985). The total space is divided into the fiber space (represented as the vertical plane on the left) and the basespace (represented as the horizontal plane). The basespace is identical with the spacetime in physics, and the fiber space refers to the internal space erected at each point of spacetime that specifies the nature of the events going on in spacetime. The total space (also called the fiber bundle space) is useful in depicting the function or the behavior of a machine; therefore the total space may be also called the "function space." The rules that allow one to compare the internal coordinates of one event with those of another are called "connections." (See footnote #2 in Table 1.15).
I believe that the fiber bundle geometry is valuable for biology, because it enables us to represent genetic information in terms of the fiber space, just as the curvature of spacetime can be so depicted. In this sense, the genetic information of cell biology may be equivalent to the curvature of spacetime in general relativity (see below). In view of the conjecture presented in Section 1.8.8 that cell biology elaborates spacetime on the microscopic scale while general relativity elaborates it on the cosmological scale, it may now be stated that the curvature of general relativity indicates the structure of spacetime on the cosmological scale, whereas genetic information of cell biology reflects the spacetime structure on the microscopic scale (Table 1.15).

Table 1.15. The unification of the fundamental forces of nature by gauge field theories

<table>
<thead>
<tr>
<th>Force</th>
<th>Interacting particles</th>
<th>Gauge bosons</th>
<th>Base space</th>
<th>Fiber space</th>
<th>Connection</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6)</td>
</tr>
<tr>
<td>1 Gravitational</td>
<td>Masses</td>
<td>Gravitons</td>
<td>Spacetime</td>
<td>Curvature$^3$</td>
<td>Gravitational potential field$^4$</td>
</tr>
<tr>
<td>2 Electromagnetic</td>
<td>Charged particles</td>
<td>Photons</td>
<td>Spacetime</td>
<td>Phase angle$^5$</td>
<td>Vector potential field$^6$</td>
</tr>
<tr>
<td>3 Weak Quarks &amp; leptons$^7$</td>
<td>$W^+$, $W^-$, $Z^{08}$</td>
<td>Spacetime</td>
<td>Isotopic spin$^{11}$</td>
<td>Weak vector field</td>
<td></td>
</tr>
<tr>
<td>4 Strong Quarks$^9$</td>
<td>Gluons$^{10}$</td>
<td>Spacetime</td>
<td>Isotopic spin$^{11}$</td>
<td>Isotopic spin potential field$^{12}$</td>
<td></td>
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</tr>
<tr>
<td>5 Cell$^{13}$ Biopolymers$^{14}$ Cytos$^{15}$ Spacetime Genetic information$^{16}$ Intracellular concentration field (ICCF)$^{17}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Also called "internal degrees of freedom," "internal coordinates," "internal space," "internal symmetry space," or "local variable" (Moriyasu, 1985; Adair, 1987). As particles move from one point in spacetime to another, their coordinates in this internal space will vary according to some rule, if spacetime and the fiber space are "coupled" through the presence of the gauge field or the connection.

2 The physical field that connects or couples the motions of particles in spacetime to the charges in their internal coordinates. Alternatively, it is called the gauge field and the associated field quanta are called gauge bosons.

3 Newton postulated that two masses separated in space attracted each other through the agency of the "gravitational force" that acted instantaneously. Such an "action at a distance" is disallowed by the special theory of relativity, according to which no interaction in vacuum can proceed faster than the speed of light; i.e., any instantaneous interactions violate the principle of the special theory of relativity. The correct theory of the gravitational force was successfully formulated by Einstein in 1925 in the form of the general theory of relativity, wherein the motions of material bodies driven by the "gravitational force" were replaced by the "geodesics" (i.e., the paths of the shortest distance between two points) on a "curved spacetime." In other words, Einstein replaced the gravitational force of Newton with the "curvature" of spacetime (Adair, 1987).

4 A unique set of numbers representing the curvature of a spacetime point determined by the presence of other masses in the neighborhood.

5 Quantum mechanics describes particles and fields in terms of wave functions. Any wave motion has three characteristics—frequency, amplitude, and phase angle. It is the phase angle of the waves of charged particles that provides the internal degrees of freedom which exhibits the property of "local gauge symmetry" or "local gauge invariance."

6 Also called the electromagnetic potential ($A_\mu$). This is distinct from the ordinary electromagnetic field, since it can exist in the absence of the magnetic field as demonstrated in the Bohm-Aharonov experiment (Moriyasu, 1985; Adair, 1987).

7 Leptons are spin 1/2 particles that do not respond to the strong force. Six different leptons are known—electron, mu particle, and tau particle, with massless neutrino for each.

8 The gauge bosons of the weak force predicted by the Weinberg-Salam-Glashow theory of electroweak interactions and experimentally observed in 1983 (Adair, 1987).
C. **Gauge Theories:** In recent years, physicists have made great strides in their attempt to develop a unified theory of the gravitational, electromagnetic, weak and strong forces (Davies, 1986). The gravitational force is important primarily for describing interactions between material bodies at large scales (e.g. macroscopic machines, planetary mechanics, cosmology), the weak and strong forces are effective only at very short distances (<10\(^{-15}\) m) and hence operate within the nuclei of atoms, and the electromagnetic forces are mainly responsible for the physical and chemical processes essential for life, ranging in scale from the microscopic (~10\(^{-10}\)m) to the macroscopic (~10 m). The physical theory that many believe will eventually

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(Notes to Table 1.15 continued)

10 The agents (i.e., field quanta) mediating strong interactions.

11 The internal degrees of freedom of nucleons that determine whether a nucleon is a proton or a neutron.

12 Also called the Yang-Mills potential.

13 It is postulated that there exists a new kind of force in nature called the cell force that "holds" together high-molecular-weight (i.e., biopolymers) and low-molecular-weight (i.e., small-molecular-weight chemicals) of the cell together in the living state against environmental perturbations, just as the strong force holds nucleons together in atomic nuclei against electrostatic repulsions.

14 The living state of the cell can be thought of as arising from the interactions among biopolymers (primarily between nucleic acids and proteins) mediated by the cell force, just as the structural stability of atomic nuclei can be viewed as originating from the interactions among nucleons mediated by the strong force. The interactions among biopolymers may be direct (if mediated by conformons) or indirect (if mediated by IDS). The conformon-mediated direct interactions may be regarded as the short-range actions of the cell force, and the IDS-mediated indirect interactions as the long-range actions.

15 The gauge bosons mediating the cell force will be called "cytons," a term constructed from "cyt-" meaning the cell and "-ons" meaning discrete entities. Cytons are composed of conformons and IDS (see Section 1.8.9 for more details).

16 The genetic information encoded in biopolymers is postulated to represent an abstract internal space of biopolymers that is analogous to the matter-induced curvature of spacetime, the phase angle of matter waves, and the isotopic spins of nucleons. This is the space whose structure is elaborated by biological evolution in contrast to the other internal spaces in Table 1.15 which are elaborated by the cosmological evolution that began with the Big Bang.

17 The identification of the component of the cell force corresponding to connection was least obvious. As evident in the text, ICCF has been assigned to this category more or less by default. Therefore, if future investigations produce more rigorous logical reasons to support this assignment, to that extent the concept of the cell force will be further strengthened.
lead to the unification of these forces is known variably as "local gauge field
theories," "gauge field theories," or simply "gauge theories" ('t Hooft, 1980;
Moriyasu, 1985; Adair, 1987). Some of the excitement of the physics community
generated by gauge theories is summarized by Moriyasu (1985):

The discovery of gauge theory rivals in importance the development of both
relativity and quantum mechanics. In contrast to the situation less than 10
years ago, gauge theory now dominates nearly all phases of elementary
particle physics today. Even the reasons for performing the new experiments
are now judged by their relevance for testing the predictions of gauge
theory. Spin 1/2 particles that respond to the strong force and the
fundamental constituents of the hadron (i.e., neutron, proton, and meson).
Six different quarks are known—up, down, strange, charmed, bottom, and
top quarks.

Essential to understanding gauge theories is the notion of gauge symmetries. I quote
P. Davies (1986):

... A simple example of a gauge symmetry concerns lifting a weight. The
work done in raising a weight from A to B depends only on the height
difference between A and B, not on their absolute height. It wouldn't matter
whether we measured height from ground level or sea level, for instance.
Thus, we may re-gauge the zero level of height (i.e., the gravitational
potential) without in any way altering the physics of the lifting process. In
other words, the system is symmetric under gauge transformations of height.

So, a "gauge symmetry" is associated with the existence of a measurable
property of a physical system whose magnitude remains invariant (symmetric) when
the measuring scale is changed (re-gauged).

Another important element in gauge theories is the idea of "local gauge
symmetry," in contrast to "global gauge symmetry" which the example cited by
Davies above is. A local gauge symmetry refers to the existence of a physical
property associated with every point in spacetime whose magnitude remains invariant
when the measuring scale is changed from place to place and from moment to
moment (Zee, 1986). The all-important physical quantity whose value is kept
invariant in local gauge transformations is called the "action," which has the
dimension of a product of energy and time (Lopes, 1983). The importance of action
in gauge theories can be traced to Hamilton's principle in classical mechanics (also
known as the principle of least action), which states that a system composed of many interacting particles undergo changes in the positions of the particles only in such a way as to keep the cumulative magnitude of the action of the system minimal (Goldstein, 1980).

We can now state the basic content of what is called the "gauge principle" (Zee, 1986) qualitatively as follows:

Whenever it is possible to perform local coordinate transformations in such a way as to maintain the action of the system invariant, there exists at least one new force field that counteracts the effects of changing the local coordinates.

The new field so identified is called the "gauge field" and its quanta (i.e., the agent that mediates interactions in gauge fields) are known as "gauge bosons" ('t Hooft, 1980).

D. A Qualitative Comparison of the Cell Force with the Fundamental Forces of Nature: Utilizing the concepts and terminologies of the gauge field theories and the fiber bundle theory introduced in the previous subsections, we can now compare the cell force with other fundamental forces in nature, namely the gravitational, electromagnetic, weak, and strong forces (Table 1.15). If the cell force indeed exists, the cell force might reveal a set of common physical characteristics shared by the other fundamental forces.

The purpose of Table 1.15 is two fold: (i) To describe the qualitative characteristics of the four fundamental forces (rows 1, 2, 3 and 4) using the concepts and terms derived from gauge field theories (columns 2 and 3) and fiber bundle geometry (columns 4, 5 and 6), and (ii) To compare the cell force (below the dotted line) with the common characteristics of the four fundamental forces (above the dotted line) under five different categories (columns 2 through 6). The technical terms and concepts appearing in the table are explained in the extensive footnotes attached.

On the basis of the "table theory" introduced in Section 1.3, it is clear that Table 1.15 contains four F vectors (F from "familiar;" i.e., rows 1 through 4) and one U vector (U from "unfamiliar;" i.e., row 5). The four F vectors establish the common characteristics of the row vectors under five different categories—(i) interacting particles, (ii) gauge bosons, (iii) basespace, (iv) fiber space, and (v) connection. The validity of the U vector (i.e., row 5 and the concept of the cell force) will largely depend on the "goodness of fit" between the components of the U vector identified under these five categories and the corresponding components of the F vectors.
The first and the third components of the cell force (i.e., biopolymers, and spacetime) are self-explanatory and reasonable. The term "cyton" appearing as the second component of the U vector is a new word coined to indicate the "gauge boson" mediating the cell force (see footnote #15 for the derivation of the word). Unlike the gauge bosons of particle physics, which have no internal structures, the cyton is postulated to be composed of conformons and IDS, one of the most fundamental assumptions of the cell theory advanced in this chapter.

It is probably safe to say that what distinguishes life from nonlife is genetic information. Since the cell force is postulated to be also fundamental to life, the question naturally arises as to the nature of the theoretical relationship between the cell force and genetic information. Table 1.15 suggests two possible interrelationships, genetic information represents (i) the fiber space, or (ii) connection of the fiber bundle space describing the living cell (see the L-space in Figure 1.11). Primarily based on the assumed similarity between genetic information and the curvature of spacetime as already alluded to above (Sections 1.8.7 and 1.8.8), I have been led to assign genetic information to the category of fiber space (see row 5 and column 5 in Table 1.15); i.e., I am assuming that genetic information in cell biology is analogous to the curvature of spacetime in general relativity. This leaves only one component of the cell force undefined, namely the component belonging to the connection category (row 5 and column 6). The best candidate for this component, I think, is the intracellular chemical concentration field (ICCF) discussed in Section 1.8.7. According to this assignment, ICCF is analogous to the gravitational potential field in general relativity on the one hand and to the vector potential field of electromagnetism on the other. It is possible that the rise or fall of the concept of the cell force will depend critically on future theoretical investigations on the validity of the last two assignments, namely genetic information as the fiber space and ICCF as the connection (see Figure 1.11 for a related discussion).

It is interesting to point out in Table 1.15 that the coordinates to which local gauge transformations are applied are different for different forces (see Fiber space)—the spacetime coordinates themselves for the gravitational force, the phase angle of the electron wave function for the electromagnetic force, and the isotopic spin states of the nucleons (i.e., protons and neutrons) for the strong force ('t Hooft, 1980). The spacetime coordinates are external to material particles, while the phase angle of the electron wave function and the isotopic spin states of nucleons are internal to the particles involved. For this reason the latter two are examples of what is called the "internal coordinates" (see Section 1.8.1).

This idea of "internal coordinate" is interesting from two perspectives: (i) It is related to the fiber space of the fiber bundle theory, and (ii) The genetic
information encoded in biopolymers (DNA, RNA and enzymes) and the cell (i.e., "cell programs") may be viewed as the biological analogue of the internal coordinates of subatomic particles as already mentioned.

Just as the development of Einstein's theory of general relativity heavily depended on the Riemannian geometry, many believe that the ultimate unification of the fundamental forces through gauge theories will be facilitated by the theory of fiber bundles. If the theory of fiber bundles is useful in unifying the fundamental interactions in nature, it may also be useful in developing fundamental theories of living processes. By expressing biological theories in the same language as used in describing fundamental interactions in physics, albeit qualitatively, it may be possible to obtain useful hints and guidelines from gauge theories. The "fundamental particles" approach of physics may be applicable to biology in the sense that we may begin to view chemicals (l-particles), biopolymers (h-particles), cells (c-particles) and multicellular organisms (o-particles) as "fundamental" particles at different levels of biological organization, despite the fact that these are immensely more complex in their internal structures compared to elementary particles studied in physics. In defense of this conclusion, I present the following argument:

(i) In contrast to particle physicists whose direction of progress has been from the less detailed to the more detailed picture of elementary particles (e.g., from nucleons to quarks and leptons (Davies, 1986)), perhaps biologists may benefit from approaching biological interactions from quite the opposite direction—from the detailed to the less detailed; e.g., away from the detailed 3-dimensional and static X-ray crystallographic enzymes or even from the 4-dimensional "screaming and kicking" NMR-determined enzymes in solution to a much simpler view of enzymes as small, deformable particles with "internal degrees" of freedom, called genetic information.

(ii) The "direction of decreasing details" may not be as heretical as it may sound, if we take into account the fact that the "depth of focus" of the human mind may be intrinsically limited, so that the detailed picture of what may be called the "bio-particles" (namely, l-, h-, c-, and o-particles defined above) at one "focal plane" may obscure the picture on the adjacent planes of focus. In other words, it is possible that we can be confronted with too detailed pictures of bio-particles all at once, preventing us from "seeing the forest for the trees." We may formulate the following statement to be referred to metaphorically as the "forest-for-trees" principle of the human mind:

The depth of field of the human mind is much narrower than the thickness of the objects of nature, so that the full description of nature requires viewing