THE COMPUTATIONAL MACHINERY OF THE LIVING CELL

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The essence of science is to uncover patterns and regularities in nature by finding algorithmic compressions of observations.

-- Paul Davies (1992)

The search for a "physicalist" description of life would seem to be the culmination of the "linear" philosophical train instilled by the progression of Western (Greek) thought, via the *logical positivism* of the Vienna Circle. Throughout the history of science in the Greek (Western) tradition, many physical images, analogues, and metaphors have been invoked to rationalize the order of Nature. Since the mid-19th century, two powerful constructs have come to play encompassing descriptive roles: *field* and *computer*. Pursuing the "physicalist" bent, it is natural to ponder an intrinsic function thereof in the living world. Such a course of study is being forced on us, with increasing urgency, by the epistemology and ontology emerging from contemporary physics, as it attempts to unify scientific knowledge on the grand cosmic scale. The growing import of relativity and quantum physics suggests that the logical quest of science is "circular," rather than "linear." Humankind -- the sentient

observer of Nature -- has a biological essence, which imbues an active biotic (anthropic) character into the physical view of the Cosmos.

The annals of biology hold a rich and colorful history of discussion on the "field" metaphor (reviewed in Welch, 1992). The "circularity" in the advancement of science would appear to bring Western thought into direct confrontation with Eastern philosophy, *i.e.*, with the position that the living organism perceives (and orders) its external environment as a "field" because *life, itself, is a "field"*; we look into Nature and see our own reflection (Siler, 1990).

Perhaps it was the 19th-century English inventor, Charles Babbage, who brought into modern focus the metaphorical view of the physical world as a gigantic computer, with the notion that the laws of physics and computable mathematics form a closed circle of existence. There is, indeed, an increasing awareness in science of the link between physical processes and computation; whereby, the dynamical evolution of a physical system converts INPUT data into OUTPUT data via some kind of intermediary COMPUTATION. Here, we will discuss the possible isomorphism of this construct in the biological realm, specifically at the level of cellular metabolism.

2. THE ENIGMA OF BIOLOGICAL ORGANIZATION: THE METAPHOR REVEALED

One of the hallmarks of life is "organization." This feature is evident at all levels of the biological hierarchy, from the level of the cell to that of socio-ecosystems (Miller, 1978). Teleonomic questions of the *How?* and the *Why?* of the manifested "organization" have permeated biological thought since the writings of Aristotle. To many biologists, simple realization of the idea of "structure-function duality" seems to quench the inquisitive thirst here. However, such cognizance is myopic and arbitrary; it is based on case-specific physiological reasoning and, in the final analysis, begs the question. Moreover, attempts by biologists in modern times to objectify (and, alas, "quantify" by Cartesian alembic) the principle of "organization" have fractionalized and clouded the very issue.

True insight into the essence of "biological organization" can only be gained by a holistic approach to science, taking into account the circumstance that living systems are part-and-parcel (and, in fact, an epiphenomenon) of the physical evolution of the Cosmos (Davies, 1988). Taking such a view, for example, the "dissipative structure" paradigm elaborated by the Brussels school (Nicolis and Prigogine, 1989) provides penetrating analysis of the question of *How?* "organization" arises and perpetuates itself.

Access to the question of the *Why?* of "biological organization" demands a marriage of theoretical physics and physiology (or, perhaps, a reunion thereof -- see

Welch, 1987). Among the fruits of this union, we find the following lines of reasoning: First, one must appreciate the hierarchical symmetry and relational invariance spanning the living world, from the cellular to the socio-ecosystem level (Rashevsky, 1938; Welch, 1987). Despite the size-distinction and the varying component-jargon used at the different levels, the *processes* and the *relations among components* are isomorphic (Miller, 1978). Second, an epistemological metaphor is required for a "physicalist" characterization of the system-dynamics; herein lies the importance of such ideas as the "field" and the "computer." Third, a *superlative principle*, which serves to guide the dynamical behavior of the system, is required (fraught though this condition may be with metaphysical accoutrement, in physics as well as in biology -- see Welch, 1992). For a physical field, the formalism of Lagrangian dynamics, with its attendant "Principle of Least Action," comes to bear; while, for computer technology, the notions of dissipationless computation and maximal information-inclusion enter the scene.

The theoretical principles of the *thermodynamics of irreversible processes* (using, for example, the Rayleigh-Onsager "dissipation function") provide an epistemological bridge between the "field" and the "computer" concepts, apropos of a description of the dynamical course of biological processes (Welch, 1992, 1993). Armed therewith, one may then approach the *Why?* of biological "organization" in a manner akin to that in pure physics. On this plane of reckoning, the ratiocination of substantific "organization" pales in significance. In physics, one does not ask *Why?* "organization" exists; one just *accepts* "organization" as a verity of Nature, attaches

a Cartesian-analytic metaphor (*viz.*, "field") thereto, and proceeds to ponder the mathematical essence of the process-behavior therein. In biology, as well as in physics, it is the teleonomic "function," in the end, that rationalizes the "structure."

Now, let us halt from any further slide into metaphysical abysm and attempt to reify the metaphorical issue of "biocomputation" at the level of the living cell.....

3. "BIOCOMPUTATION" IN THE LIVING CELL: THE ENZYME

The "computer" metaphor befits the function of the living cell at various levels, from that of the cell in its entirety through to the hierarchy of subprocesses operative therein. The fundamental "event-generator" in cellular metabolism is the *enzyme* -- a wondrous proteinaceous microcolloid, many of whose properties still elude the trenchant analysis of physical chemists. The textbook rationale for the existence of enzymes is to *speed-up* a chemical reaction, ostensibly by lowering the Arrhenius activation-energy barrier. Beneath the simplistic superfice of this most basic metabolic event lies a veneer of complexity.

First of all, most enzymes enhance the rate of their respective reactions, not by merely "lowering the activation barrier," but by providing an altered (albeit more energetically favorable) mechanistic path from substrate to product molecular states. Conformational substates within the macromolecular enzyme-substrate complex serve as the computational "logic-elements." An individual enzyme reaction, though, cannot perform macroscopic work on the surroundings. Constrained by the thermodynamic

character of the given chemical reaction, an enzyme speeds-up the process in the forward and reverse directions to the same degree. Thus, if left alone from the outside world (*i.e.*, not linked to other processes), the enzyme will, in time, just equilibrate the substrate-product concentration pools. Whereby, higher-order "computational" functions require the cell to couple whole enzyme reactions *per se* as the individual "logic-elements."

Consider the simple monomolecular reaction, $S \leftrightarrow P$, interconverting substrate (S) and product (P), catalyzed by an enzyme (E) in the following fashion: $E + S \leftrightarrow ES \leftrightarrow EP \leftrightarrow E + P$. Once the enzyme has bound the substrate (the "input" stage), the "computation" involves the generation of localized Gibbs free-energy events necessary to drive the enzyme-substrate (ES) complex through the $ES \rightarrow EP$ "transition state," followed by release of product (the "output").

The macroscopically-observed conformation of a protein dissolved in solution corresponds to a *mixture* of a large number of instantaneous (microscopic) conformational states in thermal equilibrium. Any measured property of the system (*e.g.*, the catalytic-turnover constant for the $ES \rightarrow EP$ transition) is a weighted average over all such states. Free-energy linkage ("computation") within this proteinaceous system is based ultimately on the equilibrium fluctuational character of the conformational microstates (Welch, 1986). The transduction of internal energy and heat exchange with the surroundings are interwoven, as part-and-parcel of the fluctuational interaction of the protein and the solvent.

Most enzymes are much larger in size (by a factor of 10 or so) than their respective substrates. As to the question, *Why are enzymes so big?*, the traditional rationale is that the remainder of the protein macromolecule serves as a mere "scaffolding" for the active-center geometry. It has now become apparent that the large-scale structure of the protein is designed to provide a local, specific *solvent-medium* for a given chemical reaction, wherein the combined chemical and protein subsystems engage in a fluid and variable exchange of free energy, facilitating the entrance of the bound chemical system into its transition state (McCammon and Harvey, 1987; Welch, 1986). Accordingly, the protein matrix serves as an intermediary, a "deterministic" mediator, between a localized chemical-reaction coordinate and the surrounding phase. One begins to appreciate, why such a large, "organized" macromolecular design is required for the selective and rapid action of enzymes. The dynamical $ES \rightarrow EP$ transition demands more than just an *energetic fluctuation*; it also requires a specific configuration in the *phase space* of the protein-conformational variables. The protein structure serves as a "filter," in selecting and focusing anisotropically a narrow band-width of the thermal noise relevant to the particular chemical reaction.

Protein structure contains a number of elements which suggest modes of energy transduction. Obvious possibilities are regions of local secondary structure, *viz.*, α-helix and β-structure. These have been implicated by many workers (reviewed in Welch, 1986), in generating local electric fields, protonation/ deprotonation events, proton semiconduction, vibrational excitation, *inter alia*. Also, *hydrogen-bond*

networks -- within single proteins and among conjoined proteins -- are of great interest as possible conduits for protochemical processes in enzyme action. Transient gaps ("faults") in the internal bonding arrangement can elevate locally the free energy of the system -- electrostatically and mechanically, as well as protonically. Catalytic functions would, then, depend on precise, anisotropic "fault" configurations (Lumry and Gregory, 1986). Such "faults" can arise thermally, in a protein dissolved in aqueous solution, in conjunction with binding/relaxation of bound water, fluctuating proton-transfer processes and charge-density fluctuations at the surface, *etc.* Inside the protein, these faults can migrate, for example, by proton-hopping (Nagle and Tristram-Nagle, 1983).

What, then, is the "driving force" on the "computational" process in enzyme catalysis? Because of its size, *the bulk-reservoir controls the situation* through its energy-level density (its entropy) and forces upon the system the *canonical distribution* of states -- within the anisotropic, internal constraints of the folded globular protein. Because of the great degeneracy of protein-conformational substates, the "computational" aspect of enzyme catalysis is essentially a *directed diffusion under a bias* (Kamp *et al.*, 1988). The enzyme-protein functions as a thermal *equilibrium chemodynamical machine* (Welch and Kell, 1986).

In a whole metabolic pathway, the component enzymes themselves become the individual "logic-elements" -- each behaving in the statistical-mechanical mode just described. If the pathway operates in a bulk-solution environment supplied with a

(steady-state) nonequilibrium substrate-source (and product-sink), the reaction-diffusion coupling of the sequentially-acting enzyme components engenders a *kinetic-irreversibility* for the pathway flux.

It is an empirical fact, that many enzymes of intermediary metabolism *in situ* are located in *organized, structured states* -- often associated with such nonequilibrium energy sources as *local electric fields* and *local proton gradients*. Within these cellular microenvironments, enzyme action may have rather bizarre qualities, compared to the familiar bulk-solution situation, and may be more akin to "molecular machines" driven in a cyclical manner by an external flow of energy.

4. ENZYME ORGANIZATION AND HIGHER-ORDER "BIOCOMPUTATION"

The simplistic view of the cell as a homogeneous, isotropic "bag" of metabolites and enzymes is now obsolete. Living cells, particularly the larger eukaryotic cells, are replete with infrastructure. This structure encompasses an extensive membranous reticulation, as well as a variform microstructure permeating the hyaloplasmic space (the so-called "ground substance") of the cell. The latter region is laced with a dense array of proteinaceous cytoskeletal elements and an interstitial "microtrabecular lattice" (Clegg, 1984). Calculations of protein concentrations associated with cytomatrix structures indicate high, crystal-like local density of protein molecules (Sitte, 1980). It appears that cytomembranous and cytoskeletal

elements have evolved to function as effective "protein collectors" in the operation of the cellular machinery (Sitte, 1980; Porter and Tucker, 1981).

Accumulating evidence shows that the majority of enzymes of intermediary metabolism function *in vivo* in organization with the particulate structures, and numerous thermodynamic and kinetic advantages have been attributed thereto (reviewed in Srere, 1987; Welch, 1985a; Welch and Clegg, 1986). Some metabolic processes (*e.g.*, electron-transport phosphorylation) are linked permanently to structure, while others exhibit defined variability and biphasic *modus operandi*. For example, with glycolysis in skeletal muscle, there is a bifurcation of enzyme locale (and of the kinetic properties of the respective enzymes, as well) between the cytosol and the cytomatrix (*viz.*, myofilaments) -- with the partitioning between bound and soluble forms being regulated *in vivo* according to the physiological state of the muscle (Masters, 1981). Increasingly, it appears that cytomatrix *surfaces* represent the "business" site of much (perhaps the majority) of cellular metabolism.

A grasp of the physicochemical nature of the microenvironments in these organized, surface states is of paramount importance to the understanding of the thermodynamic properties of cellular metabolism. Empirical evidence thereon is, at present, quite meager; it is clear, though, that these metabolic micro-environments differ drastically from the kind of "bulk-phase solution" defined *in vitro* (Siegbahn *et al.*, 1985; Westerhoff and Welch, 1992). In some of the structured systems *in vitro*, metabolite molecules are effectively "channelled" in a vectorial fashion from enzyme

to enzyme in a reaction sequence, thereby preventing the intermediates from equilibrating with the bulk phase and potentially maintaining some degree of control over the energy-states (chemical potentials) thereof. Theoretical models have provided some insight into the essence of energy-transduction modalities potentially extant in the organized regimes *in vivo* (reviewed in Welch, 1992; Welch and Kell, 1986). The local transduction processes therein may be highly efficient.

Long-range, mobile protonic states are finding increasing relevance to many organized cellular processes, stemming from Peter Mitchell's pioneering suggestion as to their role in electron-transfer phosphorylation (Mitchell, 1979). This kind of energy continuum is emerging as a unifying theme in cell metabolism. Consideration of the roles of mobile protons in enzyme structure, function, and evolution has led to suggestions that externally-derived high-energy protons may function in the modulation of enzymatic events in *organized states* intracellularly (reviewed in Welch and Kell, 1986).

Hydrogen-bond structures in proteins might also couple to other energy continua in organized states. A likely source would be the *electric fields* at the surfaces of cytological particulates. A mode of operation here was expounded by Fröhlich (1986), who conjectured that coherent dipole excitations of proteins (entailing phonon/soliton-like modalities) should play an important role in their biological activity. Over the years, theoretical calculations have supported this claim (Del Giudice *et al.*, 1986), although the direct experimental evidence is thus far limited.

Superimposed on these designs may be long-range electronic semi-conduction states, which might be important in some enzymes -- especially in organized states *in vivo*. Various modes of electronic coupling between enzyme and substrate have been offered as theoretical possibilities. Interaction of electronic and nuclear degrees of freedom is well known in solid-state physics. The potential roles of such modes in enzyme action have been widely discussed (reviewed in Welch and Kell, 1986).

In recent years, long-range electric-field effects on enzyme action have been discussed by a number of workers (reviewed in Fröhlich and Kremer, 1983; Welch and Berry, 1985; Pethig and Kell, 1987). Westerhoff *et al.* (1986) and Astumian *et al.* (1987) have developed realistic models for membrane-transport proteins driven by an electric field, involving direct coupling of the field to dipoles (*e.g.*, α-helices) in the protein structure. Noninvasive *dielectric analysis* of cellular membranous processes by Kell *et al.* (1988) and by Woodward and Kell (1991) has yielded exciting findings on the coupling of enzyme action to electric fields *in situ*.

There is still much to learn about the physicochemical properties of enzyme catalysts, especially regarding their operation in the living cell. Which of the aforementioned theoretical energy-transduction modalities will prove relevant remains to be seen. It has become apparent, though, that the enzyme serves as a local "field-transducer" in the events of chemical catalysis, and that many of the structured microenvironments *in vivo* are "energized" by nonequilibrium sources. Such a design is, of course, maintained at the expense of oxidative catabolic processes

in the cell. Interestingly, recent observations (Gregory and Berry, 1992) with hepatocytes (an oft-used cell-type in metabolic studies) show that a significant portion of the O_2-consumption has nothing to do with production/ utilization of *ATP* -- the central, diffusible "energy currency" of the cell. What is the role of this "residual" oxidative energy-generation?! The answer, perhaps, is to be found in the *surface* "metabolic field."

5. "BIOMOLECULAR ENERGY MACHINES" AND COMPUTER TECHNOLOGY

During the early 1970's, the late Colin W. F. McClare (1971, 1974) drew attention to the fact that far-from-equilibrium bioenergetic systems, owing to their molecular size, pose unique thermodynamic problems. For instance, how does the molecular transfer of energy in subcellular processes add-up to produce a macroscopic effect? Pursuing the issue, he coined the term "molecular energy machine," to describe a single enzyme molecule that, in a cyclical fashion, acts to couple the energy released by one form of reaction (*e.g.*, the chemical energy of ATP hydrolysis) to an otherwise unfavorable reaction without, during the lifetime of the cycle, being exposed to the macroscopic (and thermalizing) environment. The concept of a "molecular energy machine" entails the *storage (or "pumping") of energy* over a sufficient period of time such that useful work can be performed with it. As McClare realized (and as is obvious from **Section 3** above), such a *modus operandi* requires "organization" of the enzymic components, with an intrinsic modality for efficient coupling of molecular

energy sources with specific molecular work functions in order to minimize the heat-exchange during the energy-transduction processes. As reviewed elsewhere (Blumenfeld, 1981; Welch and Kell, 1986; Schneider, 1991), the biological relevance of "molecular energy machines" has drawn considerable attention in the 20 years or so since McClare's writings; and there are many biological examples where this construct is potentially applicable. More evidence thereof will emerge, as biologists get away from the prejudices ingrained by bulk-solution methods of analyzing enzyme action *in vitro*, in favor of holistic *in situ* approaches.

Distinct parallels exist between the utilitarian advances of humankind in computer technology and the evolutionary development of the enzymatic machinery of cell metabolism. A design-concern in both worlds is the control of information-flow, "efficiency," and heat. Heat is produced where/when a particle in the system must *choose* among two or more available states. A molecular computation coupled to an output, in the presence of *thermal noise*, must dissipate *some* energy as "heat." The theoretical foundation of this issue dates to the (in)famous "Maxwell's demon," as rationalized by L. Szilard and L. Brillouin. To be exact, an energy, $E \geq k_B T \cdot ln(2)$ (where k_B is the Boltzmann constant and T is the absolute temperature), must be dissipated per "bit" of information gained in a molecular computation (*viz.*, one which is coupled to an "output") (Leff and Rex, 1990; Schneider, 1991). The way, then, to improve the "efficiency" of operation (*i.e.*, decrease the heat production) is to reduce the accessibility of the system to particle states arising from the surrounding *thermal bath*. The lower bound on heat generation (in the total absence of "noise") would be

a pure *Boolean logic*. Notably, the "computation" portion of a device-operation *can*, in theory, be executed with virtually 100% efficiency; it is the linkage to the outside world (*viz.*, the "output") which, Szilard and Brillouin proved, demands at least *some* energy-dissipation.

One measure of the evolutionary "perfection" of individual enzymes has been shown to be the attainment of an equi-energy profile of all enzyme-bound intermediate states on the $ES \leftrightarrow EP$ course, entailing an efficient dynamical matching of the fluid protein matrix and the localized chemical subsystem. There are numerous documented examples of this degree of "perfection," including the ATP synthase that couples ATP synthesis to the electron-motive proton gradient during oxidative phosphorylation (Kamp *et al.*, 1988).

Such evolutionary "perfection" applies to the level of supraenzyme organization as well. Within the structured multienzyme systems that "channel" intermediary metabolites, numerous potential modalities exist for modulating the Gibbs energy-profile of the intermeshed chemical and protein systems (Welch and Keleti, 1981). Moreover, as the changes for the enzyme-bound states are linked to conformational-mechanical modes in the protein molecule, the energy-profile of these states can be adjusted by the aforementioned nonequilibrium energy sources in the organized states *in vivo* (Welch and Kell, 1986).

Thus, there is the distinct probability that many of the intermediary metabolic processes in cellular microenvironments are much more "efficient" (and, therefore, generate less *heat*) than reckoned by the conventional, bulk-phase methods of Gibbs free-energy measurement of isolated metabolic processes (Welch, 1985b). The macromolecular configurations in these microenvironments must have "machine-like" computational properties, in order to execute such a coherent energy transduction. A pure *Boolean logic* for such "biocomputation" is a distinct theoretical possibility (Schneider, 1991).

In computer technology, of course, there is great concern with dissipation-less computation (*e.g.*, Bennett, 1988; Leff and Rex, 1990). In particular, we note a device, the "Fredkin gate," which is a *conservative-logic gate* that executes a Boolean function in a reversible, 100%-efficient manner (Fredkin and Toffoli, 1982). It entails a "billiard-ball" scheme with baffles, which is strikingly analogous to the mechanical

features of molecular "channelling" in organized enzyme schemes. Metabolic "channelling," in effect, reduces the number of "outputs" in the system, thereby expanding the configurational domain of the "computation" part of the metabolic machinery (Westerhoff and Welch, 1992).

The area of computer technology is rich in metaphor and analogy for biology. An amalgam of ideas is fitting, when we realize that the modern theoretical views of "field," "machine," "computer, "organism," and "physiology," as well as the conception of "work," "heat," and "efficiency," arose from a common crucible of Natural Philosophy in the mid-19th century. Thus, in one sense, today's quest for the "unity of science" is just a rediscovery of the past.

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