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Bioenergetics and the cellular microenvironment

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ABSTRACT. Elucidation of the nature of cellular *microenvironments* in recent years yields some far-reaching implications for the science of biothermodynamics and, by implication, for the discernment of where/when *heat* is produced in the organism. Modern-day physical principles from *information theory* and from *geometrodynamics* may be used to understand the microscale nature of heat-production in biological systems.

I call as witnesses the spacious sky
and earth and waves of Styx that flow below —
the most exacting, the most awesome oath
the blessed gods can swear.....

— Homer (THE ODYSSEY, Book V)

HEAT: WHENCE IT CAME, WHERE IT WENT

Thermodynamics, historically (and etymologically) the branch of physics dealing with the motive "power of heat," has manifested itself as a Stygian voucher in the biological world, binding the processes of life to the status of physical epiphenomena of an emerging, evolving, and, ultimately, decaying Cosmos. Dating notably to the early work of Lavoisier (and the French Academy), the generation of heat was instituted not only as a correlate, but, erroneously, as the motive property of physiological phenomena (*ref. 1*). Lavoisier reasoned that life and fire behave analogously and that the respiratory functions of living systems entail a simple burning of carbonaceous foodstuffs. The development of thermodynamic principles in the mid-1800's, in parallel with the advancements in the area of respiratory physiology, seemed to solidify this link between physics and life.

The modern science of thermodynamics emerged from the cauldrons and steam engines of the Industrial Revolution, with utilitarian interest in the mechanical equivalence of work and heat (*ref. 2*). The First Law of Thermodynamics, dealing with the conservation of energy, was formulated (for closed systems) as follows: $dU = dQ - dW$, where dU is the internal energy change, dQ the heat-exchange with the surroundings, and dW the work-exchange. For simple mechanical work, one has $dW = P \cdot dV$, where dV is the volume change and P the pressure. Concern over such issues as "efficiency," as regards the classical relationship between external work and heat-flow, led to the Second Law: $dS > dQ/T$, where dS is the entropy change of the system and T the absolute temperature. The Second Law inequality says that the heat flowing to the outside world does not tell the whole story of processes occurring inside the system. Clausius rectified this imprecision, by expressing the Second Law as an equality: $dS = dQ/T + dQ'/T$, with the condition $dQ' \geq 0$; the quantity dQ' he called the "uncompensated heat" (*ref. 3*). The inclusion of such internal work processes as chemical reactions led, historically, to the formulation of the famous Gibbs equation:

$$T \cdot dS = dU + P \cdot dV - \sum_i \mu_i \cdot dn_i \qquad (1)$$

where μ_i is the chemical potential and n_i the number of moles of the *i*-th reacting chemical species. (The First and Second Laws are extended to open systems by augmenting such terms as dn_i and dQ to include transport across the system boundary and the thermic effect thereof [see *ref 3*].) The Gibbs energy, $G = U + P \cdot V - T \cdot S = H - T \cdot S$ (where H is the enthalpy), is the thermodynamic state function most often employed in biochemistry to assess the available *useful energy*. Accordingly, the Second Law for a biochemical system (with appropriate modification for various energetic contributions) can be written as follows:

$$(-)dQ' = (dG)_{T,P} = \sum_i \mu_i \cdot dn_i \leq 0 \qquad (2)$$

The "uncompensated heat" (dQ') obviously does not correspond empirically to the heat measured by conventional calorimetry. We use the antiquated Clausius designation dQ' here purely to symbolize the mathematical entity (in actuality, the quantity, $T \cdot d_iS$, with d_iS being the internal entropy production) which must be added to the classical term dQ for a complete assessment of internal thermodynamic relations.

An epistemological schism often exists between the focus of the cellular bioenergeticist and that of the physiological calorimetrist: the former is concerned macroscopically with Q' and the latter with Q. Of course, internal metabolic processes will contribute to the heat measured calorimetrically for a living system. Heat production is a natural concomitant of the irreversibility of the chemical reactions occurring within the organism. External temperature and mass-transport gradients aside, there arises the metabolic heat-generation, $Q_m = (\partial H / \partial \xi)_{T,P} \cdot \Delta\xi$, where ξ is the "extent of reaction"; the partial-derivative term is the familiar "heat of reaction" (at constant temperature and pressure) (*ref. 3*). Notwithstanding, living systems are not the mechanical heat engines as conceived by Lavoisier and others in the early days; they are, in essence, *chemodynamical* systems. Thus, metabolic heat represents (with the exception of specific homeothermic mechanisms) the "unused" part of the available energy and gives a nondescript picture of the internal bioenergetic design. As regards such utilitarian considerations as "cost," "yield," "efficiency," *etc.*, the really important quantity is Q' ($= \Delta G = \Delta H - T \cdot \Delta S$), with integration of *Eqn. 2* over a defined "extent of reaction" (or, in terms of reaction-velocity, over time). Global calorimetric data *prima facie* do not provide a quantitative understanding of ΔG, especially pertaining to the internal work-coupling (or energy-transduction) between metabolic subsystems.

The entity dQ' ($= dG$) represents the "motive property" of the living state, while dQ is the "price" that the Universe exacts for the organism's existence (the Stygian voucher, alas!). Of course, in the steady state the two are numerically equal (but of opposite algebraic sign, since, for the system itself, $dS = 0$ in the steady state); yet, their respective biophysical meanings are very different. The common analytical practice of "biological calorimetry" entails a *scalar* measurement of heat emanating from the life-form. Such analysis bespeaks nothing of the internal mechanistic, microscale, and *tensorial* nature of the processes relating to dQ'; nor does it tell us where/when heat is generated by the system.

For a machine-operation, the roles of "heat," "efficiency," *etc.*, stem ultimately from the import of the Second Law of Thermodynamics. There are at least 13 ways of stating the Second Law (*ref. 4*). Semantic differences therewithin (as well as the distinction between dQ and dQ') have led to confusion and disagreement in the application of thermodynamic principles to particular situations. The problem is compounded for biological systems, whose intricate infrastructure often makes it difficult to discern the "system" and the "surroundings" — the separation of which is crucial to a proper thermodynamic analysis. One must bear in mind, that the Second Law is not a "local" maxim, like most physical principles; rather, it is a book-keeping device operative at the system-boundary.

The various biothermodynamic disciplinary approaches must be integrated, if we are to gain a true understanding of such notions as "energy transduction" and "efficiency" for living systems. Toward this end, we offer some thoughts apropos of bioenergetic processes at the subcellular level, where the "system-boundary" delineation often can be focused on the molecular scale. We rely on analogical constructs from the physical areas of *information theory* and *geometrodynamics*. At the subcellular level, we attain a fuller grasp of the fact that the living organism is not an inchoate, scalar "heat engine," but rather a coherent montage of *chemodynamical molecular machines*.

MISE EN SCÈNE

Let us first consider the stage on which occur the intermediary metabolic processes of the cell. 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" (*ref. 5*). Calculations of protein concentrations associated with cytomatrix structures indicate high, crystal-like local density of protein molecules (*ref. 6*). It appears that cytomembranous and cytoskeletal elements have evolved to function as effective "protein collectors" in the operation of the cellular machinery (*refs. 6, 7*).

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 *refs. 8-11*). 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 (*ref. 12*). 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 microenvironments differ drastically from the kind of bulk-phase solution defined *in vitro* (*refs. 13, 14*). Theoretical models have provided some insight into the essence of energy-transduction modalities potentially extant in the organized regimes *in vivo* (reviewed in *refs. 15, 16*). The local transduction processes therein may be much more efficient than *in vitro* methodologies imply.

INFORMATION THEORY

Of the many ways of representing the Second Law of Thermodynamics, one form relates to loss/gain of information. From the standpoint of information theory, a "molecular machine" (*e.g.*, performing some unitary biochemical function) can be viewed as a device that executes the following process: INPUT → COMPUTATION → OUTPUT device (*ref. 17*). Then comes the *Question*: Where/When is heat generated? *Answer*: 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 ambient thermal noise, must dissipate some energy as heat. The term "dissipation" has a specific meaning here. The system loses control (and, therefore, *use*) of this energy; it becomes "lost" amongst the myriad degrees-of-freedom of the surrounding thermal reservoir and is not identifiable by a macroscopic observer. For example, as seen in biochemistry textbooks, a part of the large (negative) ΔG for *ATP* hydrolysis is due to the randomized electronic-resonance states accessible to the free orthophosphate, compared to the electronically-restricted configuration of the bound phosphates within the *ATP* molecule.

The theoretical foundation of this issue dates to the (in)famous "Maxwell's demon," as reasoned by Szilard and Brillouin. To be exact, an information-theoretic energy, Q_i (which, of course, constitutes part of Q'), defined by the following relation:

$$Q_i \geq k_B T \cdot ln(2) \tag{3}$$

(where k_B is the Boltzmann constant), must be dissipated per "bit" of information gained in a molecular computation (*viz.*, one which is coupled to an "output") (*refs. 17, 18*). The way, then, to improve the efficiency of operation (*i.e.*, to increase the performance of useful work per input of Gibbs energy) is to reduce the accessibility of the system to particle-states arising from the thermal bath in which the system is embedded. The lower bound on heat-generation (in the total absence of noise), per *Eqn. 3*, would be a pure Boolean-logic system.

Consider the following scheme: INPUT → COMPUTATION → OUTPUT. Loss of useful energy can arise at the boundaries (*i.e.*, the "arrows") and/or within the logic-elements of the "computation." This picture befits the enzyme-catalyzed reactions of cellular metabolism. The "input" is the binding of the substrate on the enzyme ($S + E \rightarrow ES$), and the "output" is the release of product from the enzyme ($EP \rightarrow P + E$); while, the "computation" relates to chemical catalysis within the enzyme-ligand complex ($ES \rightarrow EP$). The defined Gibbs-energy change for the overall reaction ($S \rightarrow P$) is usually a $\Delta G_{S \rightarrow P}$ value (*viz.*, a difference in chemical potential) measured between the "input" (*S*) and the "output" (*P*) states in bulk solution. In addition, the chemical-catalysis part, occurring within the macromolecular matrix of the enzyme, will, in general, entail numerous local Gibbs-energy changes (ΔG_E's) along a multi-step reaction path. In a nonequilibrium situation, heat-production can, in principle, ensue from any or all of these numerous subprocesses. It appears that some metabolic processes — in particular, the coupled energy-transduction motifs in the cytomatrix-associated (surface) regimes *in vivo* — are evolving toward the theoretical, minimal dissipation value specified in *Eqn. 3* (*refs. 15, 16*).

In some of the structured systems *in vivo*, metabolite molecules are effectively "channelled" 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 (*refs. 8, 15*). Moreover, in some such cases, the enzyme is "hooked-up" to a nonequilibrium energy source (*e.g.*, electric fields, proton gradients) in the cytomatrix, in effect designed to couple to (and modulate the $\Delta G_{S \rightarrow P}$ of) the chemical process, with the enzyme serving as an energy transducer (*refs. 14-16*).

Importantly, the "computation" portion of the device-operation can, in theory, be executed with virtual 100% efficiency; it is the linkage to the outside world (*viz.*, the "output") which, Szilard and Brillouin proved, demands at least *some* energy-dissipation (*refs. 17, 18*). To wit, one measure of the evolutionary "perfection" of enzymes has been shown to be the attainment of an equi-energy profile of all enzyme-bound intermediate states; and 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 (*ref. 19*). As the ΔG_E's for the enzyme-bound states are linked to conformational-mechanical modes in the protein molecule, the Gibbs-energy profile of these states can, potentially, be adjusted by the aforementioned nonequilibrium energy sources in the organized states *in vivo* (*refs. 14-16, 19*).

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 ΔG measurement (*ref. 20*). The macromolecular configurations in these microenvironments must have "machine-like" properties, in order to execute such a coherent energy transduction. The application of a kind of MOLECULAR-MACHINE design to the function of cellular work-processes has drawn considerable attention in recent years, dating especially to the work of McClare in the early 1970's (reviewed in *ref. 15*). A pure Boolean logic for such "bio-computation" is a distinct theoretical possibility (*ref. 18*).

There are interesting parallels with developments in computer technology, where there is also concern with dissipation-less computation (*ref. 17*). 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. It entails a billiard-ball scheme with baffles, which is quite analogous to the mechano-chemical features of molecular "channelling" in organized enzyme schemes. Metabolic "channelling," in effect, reduces the number of molecular "outputs" in the system, thereby expanding the configurational domain of the "computation" part (*refs. 14, 15*). This is an exciting area which is proving to be rich in metaphor and analogy (*ref. 21*).

In closing, we call attention to an example, where lack of concern for internal "molecular computation" leads to gross error in the calculation of efficiency (see *ref. 22* for details). Consider the case of "regulatory" (information-handling) organs, such as kidney and brain, which do very little external work but which, paradoxically, exhibit very high energy cost (in terms of O_2 consumption). For the human kidney, a conventional calculation of renal work output, based simply on the "external" osmotic work, leads to a value of 2.0 $J \cdot min^{-1}$; while, the renal power input, as determined by O_2 consumption, is 400 $J \cdot min^{-1}$. Thus, the *apparent* efficiency is less than 1%! Now, the main work of the kidney is "regulatory," rather than osmotic. The renal tubules regulate the composition of the extracellular fluids, by making a Boolean selection on molecules and ions (especially sodium). Utilizing *Eqn. 3,* along with a reasonable signal-to-noise ratio, one arrives at an efficiency of about 30% — a much more sensible value, indeed (*ref. 22*). Why does this microenvironmental "regulatory" work escape detection by conventional, bulk-phase thermodynamic analysis?! The molecules and ions "selected" by the renal tubules are immediately returned to the extracellular fluid, so that the Gibbs energy resulting from the local sorting-computation is lost in the entropy-of-mixing in the surrounding thermal bath.

GEOMETRODYNAMICS

In present-day theoretical physics, the geometrical "field" concept has reduced the material world to an intertwined web of dynamical space-time symmetries and invariance relations. Geometry has played sundry roles in modern biology, as well. However, contemporary biologists, unlike physicists, are not accustomed to thinking of "geometry" as a deterministic *dynamical* element in the processes of the living state. The modern science of biology, we would aver, may benefit from a repossession of the spirit of "compleat Natural Philosophy" in the early 19th-century — when the physiologists of the day were keen to meld biological principles with ongoing developments in contemporary physics (*ref. 16*). Here, we note some lessons about the thermodynamics of microenvironmental biochemical processes to be learned from geometrical considerations.

LESSON 1. The age-old concept of "structure-function" duality, spanning the biological world — from the microscale of the cell to the macroscale of socio-ecosystems, displays a hierarchical symmetry (or relational invariance) (*ref. 23*), which is ascribable to the theoretical constructs of fractal geometry (*ref. 24*).

Fractal (or "self-similar") structures are disordered systems, whose disorder can be described in terms of *nonintegral dimension,* ***D***. Fractal geometry is drawing increased attention in the description of physiological phenomena (*e.g.*, *ref. 25*), including cellular metabolism (*e.g.*, *ref. 26*). The evolutionary character of cellular infrastructure (per the description above) befits a fractal pattern called the *Sierpiński sponge*, which manifests the evolutionary property, that its geometric volume shrinks to (the theoretical limit of) zero as its surface area increases to infinity (*ref. 24*).

LESSON 2. Nonequilibrium flow processes on fractal surfaces do not behave the same as in a Euclidean medium (with $\boldsymbol{D}$ = *1,2,3*).

In the linear thermodynamic regime (which is applicable to many surface phenomena in cell metabolism), the rate of energy dissipation for a nonequilibrium process is defined mathematically as the product of the flow (J) times the thermodynamic force (X), with the flow-force relation, $J \propto X$ (*refs. 3, 27*). For a (electro)chemical reaction, we have the familiar (stoichiometrically-unsigned) relation, $J \propto \Delta\mu$, where the force is just the (electro)chemical potential-difference across the reaction. However, for a fractal system, we are faced with the following "local" condition:

$$(\partial^{\alpha}/\partial t^{\alpha})\cdot [J(t)] \sim \Delta\mu^{*}(t) \tag{4}$$

where α is a noninteger related to the *fractal dimension, $\boldsymbol{D}$* (*i.e.*, the "metric" of the local medium), and the "asterisk" denotes a distinction between the *local* force and an asymptotic (*e.g.*, bulk-phase stationary-state) value thereof (*ref. 28*). (Note the appearance of *time, t,* in the local fractal domain.) Clearly, a formal understanding of the dynamics of energy dissipation in cellular microenvironments requires that we exceed the bounds of classical thermodynamics of irreversible processes! In a true Einsteinian sense, the local processes have a *geometrodynamical* character (see also *ref. 16*).

LESSON 3. Thermodynamic potentials in fractal systems are coupled to the *fractal dimension, $\boldsymbol{D}$*.

The concept of "extensity" (say, mass, or mole number n_i), normally, is determined by the existence of a mathematical ("local") volume-density, ρ_i, such that

$$n_i \sim \int_V \rho_i \cdot dV \tag{5}$$

The concept of "intensity" (say, μ_i) is related to n_i, through the connection, $\mu_i \sim (\partial S/\partial n_i)_{U,V}$ (see *Eqn. 1*) (*ref. 3*). There is no problem with this representation in Euclidean media, where it is tacitly assumed that dV can be measured *ad infinitum* on the microscale. Such is not the case in fractal systems, where the details of the microworld are fuzzy and discontinuous (*ref. 24*). In fractal media, the entropy (S) becomes a function of the *dimension* ($\boldsymbol{D}$) (*ref. 28*). Whence, we confront the relation, $\mu = h - T\cdot s(\boldsymbol{D})$, where h and s are the *molar* enthalpy and entropy, respectively. Provided, then, h is invariant with a change in the "metric" ($\boldsymbol{D}$), a correlation should exist between μ and $\boldsymbol{D}$. This relationship has, in fact, been observed in the behavior of fractal electrodes (*ref. 28*). Invariance of the enthalpy implies that the fractal structure must be able to gauge (*e.g.*, electrostatically) the *local* energetic microenvironment, as regards the standard-state (electro)chemical potential (*ref. 16*).

In summary, we see that, in a fractal medium like that extant *in vivo*, not only are the thermodynamic flow-force relations unconventional, but also the definition of the thermodynamic potentials themselves. Applying "geometrodynamical" thinking, along with a physical grasp of the nonequilibrium energy states (*e.g.*, electric field, proton gradient) extant in cellular microenvironments, we may hope to reach a deeper (albeit iconoclastic) understanding of the cause-and-effect nature of bioenergetic phenomena and to acquire a fuller appreciation of the "motive" power of thermodynamics in the biological world. The allure of the "field" metaphor seems inescapable (*ref. 16*).

IN SEARCH OF THE HEAT . . . .

Among the various subdisciplines of the science of biothermodynamics, there remain inconsistencies in the analytical and conceptual definitions of "heat," "efficiency," "work," "energy cost," *inter alia*. Perhaps a fitting tier in life's hierarchy to begin a unification is at the cellular — nay, protoplasmic — level, what the patriarchal physiologist Claude Bernard calls "life in the naked state." Here, we come to realize that the living system is not a heat engine, but rather a coherent array of "chemodynamical molecular machines." Logic suggests that much of the observed heat-production at this level is due to the "cost" of maintaining the infrastructural nonequilibrium energy-states (*e.g.*, mitochondrial "protonmotive force" and cytoplasmic redox potentials), which are required to execute the "work" of the local, potentially-conservative (electro)chemical events of intermediary metabolism. (In liver cells, for example, a significant part of the O_2 consumption appears to be unrelated to production/utilization of *ATP* — the soluble energy-currency [see M. N. Berry, *these proceedings*].) Moreover, as the envisaged MOLECULAR MACHINES are proteinaceous and employ protein-dynamics for functionality, a perfectly-noiseless "computation" will usually not be attainable, owing to the degeneracy of conformational-substates therein (*refs. 15, 19*). Also, the role of speed sometimes must take physiological precedence over that of "efficiency" (*ref. 27*). We must appreciate that biological evolution is not complete; it is an ongoing, perfecting process. In the end, we come to realize that the term "efficiency" is indistinct and harks back to mid-19th-century utilitarian thinking. In biology, the idea of "efficiency" must always be treated in a *relative* manner — physiologically, ecologically, and evolutionarily speaking; it is meaningless to approach the quantification of efficiency, in a Darwinian superlative sense, out of such context. The Einsteinian heritage of the 20th century teaches that there are no absolutes, neither in physics nor in biology — save for the subtellural flow of the Styx.

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