Homeokinetics/Homeodynamics: A Physical Heuristic for Life and Complexity

F. Eugene Yates

University of California, Los Angeles
Department of Medicine
The John Douglas French Alzheimer's Foundation

This essay addresses the puzzlement, the missing piece, sensed when attempts are made to build a bridge from the synchronic, informational genotype to the diachronic, dynamic phenotype—a regular mapping that seems to be extraphysical. There is no formal, dynamic foundation for the bridge. Albert Einstein, Max Delbrück, and Erwin Schrödinger all expressed acute awareness of limitations of contemporary physics when considering biology because physics addresses much simpler sysems. As a proposed remedy, a new physical heuristic, *homeokinetics*, developed by Arthur Iberall and Harry Soodak (and later recast for biology by me as *homeodynamics*) is introduced here as a foundation for comprehending energy flows and transformations in complex systems, including those in metabolic networks of living systems. Their individual dynamic stability is flexible and marginal—it must allow for adaptations and changes in physiological and behavioral states to occur in an orderly fashion as external circumstances change. At the population level, stability must allow for evolvability of chemical networks that have energized terrestrial living systems for about 3.9 billion years. Homeokinetics/homeodynamics emphasizes that *persistent*, marginally stable metabolic networks, as open thermodynamic systems, *necessarily* organize energy processing as cyclic, physical action modes. Conceptually, that organization is under 2 kinds

---

of biological time pressure—time as a *cycle* that daily closes the thermodynamic books and time as an *arrow* orthogonally pressing the cyles into the future, creating joint time as a *helix*. In most animals, after maturity, the helix is additionally shaped into a tapered ellipsoid by a *senesence process* that gains influence as dynamic degrees of freedom are frozen out by the constructions of *development*.

INTRODUCTION AND BACKGROUND

As the first lecturer in the endowed series honoring the life and works of Arthur S. Iberall ("Ibby" to his friends), I begin with an autobiographical fragment to set the scene for the epiphany I experienced on meeting him—an encounter that changed forever my scientific outlook. It happened in 1965, on the Boardwalk in Atlantic City at the annual meeting of The Federation of Societies for Experimental Biology. A mutual friend introduced us, and Ibby immediately afterward grabbed my arm, pulled me to an exit from the conference hall onto the Boardwalk, and said, "We must talk!"

Several years earlier, my colleague John Urquhart and I had published an extensive review in *Physiological Reviews* (over 700 references, all got by hand—long before efficient computer searching of the literature was available) entitled, *Control of the Plasma Concentrations of Adrenocortical Hormones*. We hoped that it would become a classic because it approached control in biological systems from the perspective of elementary control theory in engineering. At the time this was a novel enterprise, so we saw ourselves being among the pioneers opening a new field (since known as *Biomedical Engineering*). When I met Iberall I was still full of the satisfactions and favorable notices that attended my publications with Urquhart. Iberall had read them and became very animated, but not in the way I expected. As we took the evening air on the Boardwalk, I was told, "You and John have good intentions, *but your science is wrong for your problem!*" That got my attention, and Iberall's remark initiated a friendship and collaboration that lasted from then until his death 37 years later (at which I was present with his family).

Most of the scientists I had known before Iberall seemed to have a defined, singular personal style for finding and solving their chosen scientific problems. In contrast, I found that Ibby had two different creative styles: Apollonian and Dionysian. Both were unsettling, for two reasons. First, they introduced foreign (to me) ideas from geometry and physics and even from classics in biology (that I was ashamed not to have already read, e.g., D'Arcy Thompson's "On Growth and Form"). I was alerted to Navier-Stokes's equations of fluid dynamics and the importance of bulk (associational) viscosity as a major (and neglected) participant in explaining hierarchies in complex systems. From there Ibby went into "wall effects in bounded flows" and a "hopping" character to Brownian motion and diffusional transports. His intense and synoptic lecture concluded

late at night, with a final assertion that biological forms during development could be understood best through the physical concept of an "intrinsic geometry." My head was spinning as I tried to sleep that night.

Second, Iberall's language, urgently pressed upon a listener or reader, though rich in vocabulary and proper nouns and technical details, had an exotic syntax and grammar (that some of his friends humorously called "Ibbanese"). During my early education I had been drilled in old-fashioned matters of grammar and rhetoric by a teacher very strict about diagramming sentences, so hearing or reading Ibbanese was a strain. However, after 37 years of exposure to Ibby's language (sometimes, literally, as a "translator" and editor for some of his publications), I confess that Ibby gave me my soundest introduction to multidisciplinary science.

Though Iberall's long career had many, varied achievements, the most important, to him and his close associates, surely was his invention (assisted by his colleague and mentor Harry Soodak) of a heuristic that extended standard physics in a manner that better suited it to deal with complexity. In creating homeokinetics, Iberall was like a honeybee sipping nectar from many flowers in the gardens of physics and transforming it into a new, flavorful honey—that is the subject of this essay.

FROM BIOPHYSICS TO PHYSICAL BIOLOGY

Fundamental physical theories deal most effectively with simple, conservative systems. The current pursuit of String (and/or M) theories and of loop quantum gravity by particle physicists does not conceal our embarrassment that even the most advanced physics of today can't properly account for the common properties of cake mixes and concrete (Weiss, 2003) or the flow of grain through a funnel feeding into a silo.

The diversity of the physical universe is impressive (there are classes of stars and galaxies), but it is not comparable to the overwhelming diversity of living systems. All electrons in the universe are alike (though their behaviors may vary in different settings), whereas no two living organisms are exactly alike. Some extension of physics is needed to account for such complexity. *Biophysics* involves applications of standard, terrestrially scaled, physical principles, expressed in conventional ways, to the description or modeling of biological structures and functions. It has been essential for our basic, *tactical* explorations of transport processes, biomaterials, kinetics, membranes, muscle contraction, thermoregulation, action potentials and their propagations, and network thermo-dynamics. No new physical laws have been discovered or required. Schrödinger and Delbrück separately speculated that something seemed to be missing. I believed that, if found, the missing piece would comprise a new *strategic physical biology*.

In the last 40 years there has been rapid development of so-called sciences of complexity in physics, mathematics, computation, and engineering, with emphasis on nonlinear, nonconservative processes, self-organization, broken symmetries, autopoiesis, and emergence. Examples of serious attempts to extend physical science to accommodate discovered complexities in nature can be found (for example) in dissipative structure theory (Prigogine), bifurcation theories (many fathers, from Euler to Abraham), synergetics (Haken), chaotic dynamics (many fathers), catastrophe theory (Thom), fractals (Mandelbrot), homeokinetics (Iberall and Soodak), the physics of symbols (Pattee), the mesoscopic "middle way" (Laughlin and Pines), relational biology (Rosen), complex adaptive systems (Santa Fe Institute), and even in attempts to apply quantum field theory to brain science (Vitiello). But there is no convergence among these differing perspectives, even though they are not mutually exclusive, and most are concerned with dynamics.

To clear the way for a general dynamical approach to complex systems, I note that four key aspects of the living state of matter must be taken into account by any theory of regulation or control of biological networks. They are listed here as negatives, as contrary to conventional wisdom:

- *Living systems are not highly ordered structurally;* instead their high order is functional, and very special.
- *Living systems do not operate far from equilibria dynamically.* (Equilibrium applies to the condition of a process, not a system, so we have mechanical, electrical, chemical ... equilibria separately. A system can be at mechanical equilibrium but be far from equilibrium chemically, for example.) This near-equilibrium claim is based on a detailed thermodynamic argument, not shown here where I merely note that the free energy changes in chemical, mechanical, and electrical features of metabolic networks are not great, and the various processes do not "knock" or leave the domain of time-independent thermodynamic potentials (i.e., there are no truly far-from-equilibrium shock waves). Even when biological systems may be far from chemical equilibrium, as in some microscopic regions such as ionophores or channels, overall they operate dynamically with low duty cycles. Informationally, in the very particular nonrandom sequences of bases in nucleic acid polymers and of amino acids in proteins, they may indeed be thought of as far from equilibrium, but the distributions of the monomers in the polymers often approaches $1/f$ noise!
- *Living systems do not change in a classically state-determined manner,* according to the common definitions of state in physics and engineering.
- *Living systems are not primarily program driven;* they are largely execution driven.

Execution-Driven Processes

Although living systems are often thought of as being program driven, especially during development, this view is inadequate to explain self-organization or the subsequent operation of a mature organism. A *program-driven process* requires that some rate-independent physical entity (the informational program) be present in advance, be capable of prescribing actions for all contingencies, be persistent, and be consulted frequently to stage the dynamics (Stent, 1987). In contrast, an *execution-driven process,* even when it has a quite regular outcome, does not have all the necessary hardware or software available in advance. The information and dynamics both emerge because new structures made during a preceding stage now constrain the behaviors that both create and are associated with the next stage. Broken symmetries and emergent properties govern the paths to a final construct. Living systems develop mainly through such execution-driven processes (such as protein folding or misfolding). A fresh and novel example of an execution-driven process is the clever laboratory synthesis of an octahedron molecule achieved by spontaneous organization from a synthetic, 1669 nucleotide, single strand of nonbiologic DNA (Shih, Quispe, & Joyce, 2004). In the presence of five 40-mer synthetic oligodeoxynucleotides, the strand folds into the octahedron by a simple denaturation-renaturation procedure.

EARLY DEVELOPMENT OF HOMEOKINETICS:
NEWTON AS STARTING POINT

Newton is still an essential starting point for dynamical analysis of macroscopic systems at terrestrial scales. He invented his scheme by imagining, first, a featureless three-dimensional, absolute space into which he placed a particle with no property other than inertial mass and invoked an absolute, flowing time. He recognized that the particle's state required independent specification of two values: position and momentum. Next, he permitted the environment of the particle to interact with it, and if the momentum changed (via velocity change, i.e., an acceleration occurred), he defined the influence of the environment as a force, in his second law of motion. (His inertial mass is passive, just responding to forces. In contrast, his gravitational masses are in a sense active—in multiples they generate force, i.e., by warping space-time. Even after Einstein's principle of equivalence and geometric description of gravity, there is a residual mystery.) Later mechanics was generalized by Hamiltonians and Lagrangians, but these still invoke conservative fields and reversible time even when frictional terms are involved, that is, only the first law of thermodynamics is operating. Furthermore, common mathematical models of the physical world in which differentials are exact, or at least meet the Lipschitz condition that guarantees the uniqueness

of solutions subject to prescribed sets of initial conditions, are very nongeneric (Rosen, 1991, 2000; Zak, Zbilut, & Meyers, 1997) and fail to help biologists who must face nonholonomic constraints and inexactness typically encountered in our models. Dynamical analysis of living systems may start with Newton and stay on the road with him until a branch point is reached at which he becomes a poor guide to the biological universe of autonomous morphogenesis, dissipative fields, hereditary descent, and context-dependent dynamics.

Modern science and engineering are still in the thrall of the state-determined causality of motion and change at the heart of the Newtonian dynamics. Its initial successes with regard to planetary motions were stunning, but living systems are not so classically state determined in their causalities. They may have no Hamiltonians. States do not imply their rates, so at every level of organization states and rates have to be newly and separately specified, partly because of emergent properties. Levels cannot be crossed by integrations or differentiations.

The revealed truths of "standard" physics, up to 1969, can be found in Landau and Lifshitz (1958–1969). Relying only on standard physics (Newtonian mechanics, relativity special or general, quantum field theory or QED), we are unable to achieve a comprehensive physical model of the regular dynamic trajectory of a human life from conception through development and maturation to senescent decline and death.

To go beyond Newton, a physical biology would have to accommodate the following points, among others:

- Particles in classical mechanics have very little internal structure or dynamics with any significance at mesoscopic or macroscopic scales. Some particles have both static and dynamic properties (e.g., rest mass and spin), and some particles are not fundamental but have internal structures (e.g., quarks). Some have no mass or associated time (e.g., photons) whereas others are unstable and reveal themselves to an observer through a characteristic time—a "half-life" of existence. However, usually, in our modeling of terrestrial- scale events (other than nuclear reactions), physical particles are treated as billiard balls having dead interiors, making all their mechanical exchanges with their environments in a Newtonian fashion, via external momentum exchanges after collisions (interactions). In contrast, living "particles" all have very active interiors, with delayed internal equipartitioning of energy or matter when either crosses their boundary with the environment.
- In biology, *information* is causal in a very special manner (Pattee, 1968, 1977, 1987, 2001; Rosen, 1991) not encountered in standard mechanics.
- Living systems carry their individual and tribal histories with them, even across generations, as a partially conserved genetic code, and in most multicellular, individual animals, also as a neural-based memory, estab-

lished dynamically and then stored structurally. In contrast, the simpler, semireversible "memories" of hysteretic loops, elastomeres, and some other inanimate objects, including computers, are not tribal or complex. Such physical systems are predominantly ahistorical—just responding to the fields in which they are embedded (though they can affect the fields locally). Strictly, in the fundamental theories of nonchaotic dynamical systems, a complete history of the world's dynamical conditions would imply one complete and unique history of its states, and even, in the vision of Laplace, a unique future. But that history isn't practically recoverable from any present state. Furthermore, initial conditions of chaotic systems cannot be retrodicted, and any physical process that passes through an equilibrium loses all its history. In contrast, biologists routinely retrodict biological origins from studies of DNA, RNA, or proteins, even looking back 3.9 billion years.

- Living systems are very obviously goal directed. (This feature is not merely an anthropomorphic projection on our part.) They exhibit teleonomic behaviors not found in inanimate objects.

If there is to be a strategic physical biology for complex systems, a new extension of standard physics will be required. (However, as Ernst Mayr [2004] insists, it may be that biology cannot ever be "physicalized," in which case we will forever have two separate universes within the range of our scientific theories.) I believe biologists need to find a new approach and a "fix" for physics if we are to hold to a unitarian conviction that biological entities are ultimately physical. The alternative is recidivism—a retreat to some naïve version of vitalism, entelechy, élan vital, or what have you. Physicists A. S. Iberall and H. Soodak, in founding their physical science *homeokinetics* (HK), have been showing the way for over 25 years (see Iberall, 2000, for an excellent summary of HK principles, with an Appendix B by Soodak explaining the essential physics). I have brought together some of their chief concepts and added some of my own, as *homeodynamics* (HD). In the following sections, I give some selected elements. The claims I make, necessarily in an ex cathedra style here, require more detailed support than can be provided in this essay. For additional justifications, see the references in the HK and HD reading lists.

HOMEOKINETICS/HOMEODYNAMICS (HK/HD) AS A GENERALIZED MECHANICS FOR BIOLOGY

The HK/HD proposal is that some of the familiar pieces of standard physics can be slightly modified to achieve approximations suitable for a new physical biology, out of which biological processes emerge. (For a general discussion

of phenomena of emergence, see Morowitz, 2002a.) The emergence starts with fluid mechanics and the thermodynamics of irreversible processes and open systems and invokes the concept of internal, bulk (associational) viscosity (λ) as seen in the Navier-Stokes (NS) equations of motion (see Glossary). External momentum exchanges are captured in the shear (or kinematic) viscosity term (η). Both viscosity terms, λ and η, provide dissipations and a nonconservative field. Just as spin glasses appeal to physicists looking for an epitome of complex self-organizing systems and critical phenomena, so HK/HD chooses the NS equations as its foundation for extending standard mechanics to embrace biology. Although these equations have been traditional in conventional physics for more than a century and a half, they are still rich in unexplored possibilities. Their nonlinear, partial differential character makes them, if not intractable, then at least extremely difficult to solve exactly. As a result, we still seek a satisfying account of turbulence, or of G. I. Taylor vortices, or Bénard cells (Koschmieder, 1993). In my opinion, the NS equations are among the richest equations of motion in all of physics (see Glossary). It is sobering that even with them, in spite of strenuous theoretical studies, we fail to come up with a model sufficiently comprehensive to capture all the major features of fluid behaviors, even in a simple apparatus with only one chemical component!

Competing Forces and Equipartitioning

A key concept of HK/HD is that physical models of complex systems require competing components in the equations of motion. The competing influences may be potential energy versus kinetic energy, or energy versus entropy, or symmetry versus broken symmetry, or incoherent diffusive transport versus coherent convection or coherent wave propagation. An internal or external fluctuation may tip the competition one way or the other, and then either of two possibilities will be realized: (a) the system may absorb or damp-out the fluctuation and so continue its current stability regimes or (b) the system structure may change. If the system structure changes, there are two further possibilities: it may change toward a new stability regime or it may change toward an instability, even leading to death of the system. This bifurcation is captured by the Reynolds number Re, which can be reinterpreted as expressing the ratio of convective to diffusive velocities in a perturbed complex system:

$$Re \approx V_{convective}/V_{diffusive}$$

As energy or matter enters the system from the outside, thermodynamics requires that there be a trend toward partitioning the energy or matter uniformly throughout the available regions of phase space. Diffusive processes will always start this equipartitioning, but these may be too slow to absorb the scale of the

intrusion. In that case convective processes start up. If they are fast enough to preserve system integrity, all is well; if not, the system encounters a bifurcation and must change form or break up.

Level Independence of HK/HD

The HK/HD principle of hierarchy asserts that for any complex, open thermodynamic collective with multiple scales of time and space, the dynamics of interest at any nominated scale for study will be "sandwiched" between constraints supplied by the next higher level in which they are embedded and also by structures and functions of the next lower level from which they emerge. This three-level sandwich can be experimentally or conceptually "moved" up and down the hierarchy to discover the new equations of change appropriate to each chosen point of current interest. The robust HK/HD principles renormalize at each such focus of attention. They are level independent. *Formal causal models* will rarely be able reach beyond the boundaries of each "sandwich"—because of inevitable emergent properties characteristic of complexity and its previously mentioned limitations imposed by inexact differentials and nonholonomic constraints. We resort to computed numerical approximations to cross levels.

Gateway to Form

The two viscosities of classical NS equations of fluid mechanics mentioned previously—shear (η, or its kinematic variant) and associational (λ, also called bulk)—are invoked by HK/HD through a formal derivation, to show that the dimensionless ratio λ/η scales the ratio of internal action/external action:

$$\lambda/\eta = (A_i/A_e) = (E_i \tau_i / E_e \tau_e),$$

where A is action, E is energy, τ is a cycle period processing energy, and the subscripts i and e refer to internal and external regions, respectively, all referring to a physically macroscopic system with a boundary.

It might be said that the ratio serves as a gateway to form, precisely because of its service as a measure of internal action (Fluctuational Energy × Internal Time Delay) relative to the external translational action (Fluctuational Energy × Translational Relaxation Time). In systems with intermediate values of λ/η, descriptions in terms of momentum transports or external motions fail to reveal the delayed character of energy equipartitioning, which is accomplished internally through the contributions of λ. (λ also subsumes effects of chemical reactivities, so it is very coarse and an improvement is needed!) The delay arises from the associational character of the bulk viscosity λ that passes energy up and down across levels rather than handling it only side-to-side, as does shear viscosity η.

It is a striking feature of complex systems that their "stimulus-response" behaviors are highly varied, with emergent surprises arising from these internal delays in equipartitioning energy. A complex system has an intermediate value of λ/η between that of an ideal gas (very low value), and a rigid solid (high value). In fluid systems, intermediate values support highly nonlinear, complicated behaviors such as thixotropy, dilitancy, or plastic-elastic creep. Living systems are often referred to as showing an "orderly disorder," a term that expresses this kind of complexity.

Quantized Action and Limit Cycles

Physical action is given by the product of Energy × Time. It appears centrally in quantum mechanics: Planck's quantizing constant ($h = 6.626 \times 10^{-34} J \cdot s$) has the dimension of physical action. In complex systems, dynamics (motion and change) at all levels are most naturally expressed through physical action. Indeed, HK/HD asserts that *physical action is the fundamental, quantized variable at all levels of organization.*

At terrestrial scales, internal actions in open systems that are stable enough to persist for times that are long compared with the relaxation times of their interior interactions *must be temporally cyclic* so that initial conditions are recovered periodically while the books on both the first and second laws of thermodynamics are closed. The thermodynamic action cycles are deterministic in the sense that each cycle has a characteristic period τ_i for closure, but the period is not exactly the same for every cycle because each *cycle is independently initiated.* Thus, for any particular HK/HD cyclic process, there will be a *distribution of τs* (centered on τ_p). It takes an average over many cycles to reveal the period τ_p characteristic for that process, and as a result, in a power spectrum the peaks will be broad. The *dynamic signature of an HK/HD cycle, as seen in the power spectrum for many variables, is a set of multiple, broad peaks not harmonically related.* HK/HD cycles are wobbly (near-periodic) unless entrained by an external signal such as the geophysical day/night variation. For example, the cycle of light and dark, and in us, the associated activities of sleep and wake states, strongly entrain the endogenous circadian (nearly 24 hr) rhythm or "clock" found in almost all eukaryotic organisms. Each near-periodic cycle is a nonlinear, dissipative, limit-cycle-like, having the effect of quantizing actions at the macroscopic scale because at the completion of each cycle's period, a "lump" of energy has been processed. During the next period another, similar-sized lump has been engaged, and so on. *The asymptotic orbital stability of a limit cycle is not sensitive to initial conditions (except trivially for phase), so HK/HD systems do not exhibit chaotic dynamics as their chief signature for motion and change.*

Many nondissipative resonances in *ultramicroscopic* energy transfers among excited chemical bonds can be very fast and efficient. However, there are very

few *macroscopic*, linear, efficient, harmonically ringing "organ pipes" in living systems, where one initiating impulse produces an effect that lasts a long time (except for some special sound-producing organs or the resonating wings of some insects in flight; none of these is an HK/HD process).

Biospectroscopy

In human beings action cycles have periods ranging from milliseconds (electroencephalogram), seconds (heartbeat, breathing), minutes (pulsatile endocrine signals), hours (basic rest-activity cycle of 90–120 min), one day (the circadian rhythm), to months (the menstrual cycle). The spectrum is only sparsely filled, with broad peaks on a $1/f^m$ background "noise." Many of these action cycles continue in constant environments.

ACTION CYCLES: APPLICATIONS OF HD/HK TO THE PHYSIOLOGY OF METABOLIC NETWORKS

"Metabolomes" and Large-Scale Organization of Metabolic Networks

My focus is on the problem of regulating the distributed, nonlinear metabolic networks that currently support eukaryotic, multicellular living systems. These complex networks have been called the "metabolome" by Kathryn Brown (2003) in her comments on studies of plant metabolism being carried out by the German company Metanomics. Brown introduces the topic with words that are also apposite to metabolic analyses generally:

> The notion of metabolism was very well understood: like people, plants take in nutrients (sun, water and air) and then metabolize, or transform, those nutrients into lots of other things (metabolites), from vitamins to defense toxins. *But how does this choreography play out?* [Italics added.] That was largely a mystery. And although the emerging field of functional genomics had just begun to link genes to their protein products, most techniques stopped short of defining metabolic pathways....

The seemingly overwhelming scope of the problem of metabolic profiling can be grasped by looking at the published "proteome" of *Drosophila melanogaster* (Giot, 2003; see Figure 1). The journal *Complexity* devoted a special issue (White, 2002) to the large-scale organization of networks, and applications have been made to metabolic networks (Almaas, Kovács, Vicsek, Oltvai, & Barabási, 2004; Jeong, Tombor, Albert, Oltvai, & Barabási, 2000; Ravasz, Somera, Mongru,
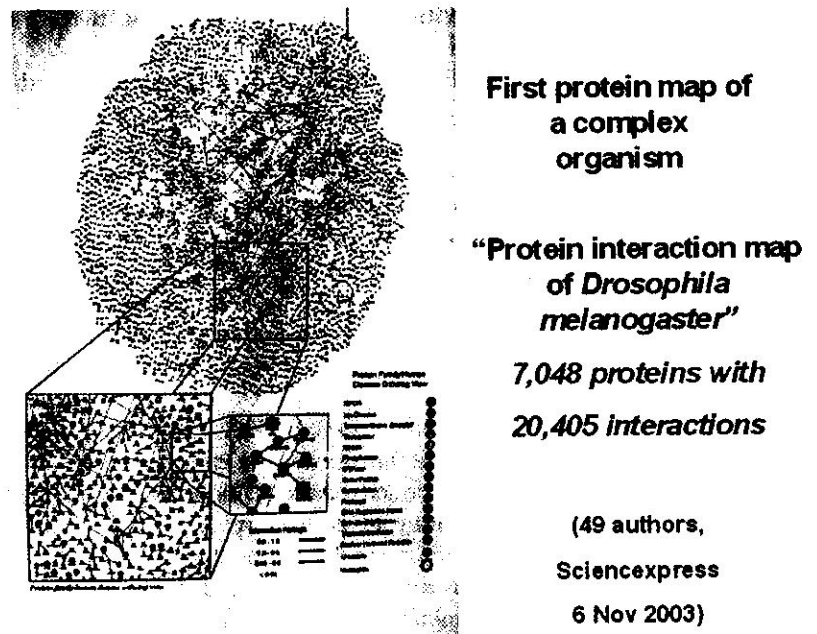
First protein map of
a complex
organism

"Protein interaction map
of *Drosophila
melanogaster*"

7,048 proteins with

20,405 interactions

(49 authors,

Sciencexpress

6 Nov 2003)

FIGURE 1   Example of a proteome. From Giot et al. (2003).

Oltvai, & Barabási, 2002; Wagner, 2002), in some cases using a graph theo-
retic approach to get around the daunting amount of molecular detail in these
"metabolomes." The products of a single gene may be many, and, as is well
known, each of the enzymatic protein products in a network may have its actions
conditioned by functions of substrates, cofactors, temperature, ionic strength,
pH, and small molecule effectors. Veech (2004) has published an outstanding
example of experimental methods and thermodynamic analyses that face up to
the difficulties and expose the biochemistry of energy fluxes to and through
mitochondria. To tackle the problem of metabolic regulations, we need more
of the kind of data Veech obtained, supplemented by a new, strategic, physical
biology.

Among members of Class Mammalia, after sexual maturity is reached and
before losses because of senescence have become prominent, the chief energy
expenditures flow through six behavioral modes: (1) routine maintenance, (2)
damage repair, (3) survival (get food and shelter), (4) defense or attack, (5) sexual
activity including reproduction, and (6) play or exploration. The distribution of
calories across these major modes shifts according to circumstances. If food
(potential energy) is scarce, most available energy is committed to Items 1–3,

and if necessary because of competition for resources, also to 4. If there is a surplus, Items 5 and 6 get attention.

The HK/HD approach to metabolic regulation/control analysis begins with the definition and description of distinct metabolic modes supporting these global behavioral modes as they might be engaged in sleeping, waking, feasting, fasting, exercise including migrations, recovery from injury, reproducing, growing, and combating the ravages of a wasting disease or those of senescence. These metabolic modes are emergent properties of multienzyme and cofactor networks that can operate individually but usually do so cooperatively (e.g., glycolysis, gluconeogensis, the TCA cycle, the Cori cycle, the electron transport chain, etc.). *Metabolic regulation and control resides not in any particular rate-limiting enzymatic reactions but chiefly in distributed actions of redox pairs such as NAD/NADH or in the ATP/ADP ratio, which act as indicators of the metabolic modes via DNA-binding proteins and other agencies* (Fell, 1997). The associated cellular phenotypes express coupled and functionally organized chemical interactions, having particular kinetic and thermodynamic features (Goldberg, Tewari, & Tung, 1995). The dynamic signature of each *marginally stable* metabolic mode lies in its quantized actions; these can be explored spectroscopically for their thermodynamic limit cycles, as noted previously, and this is the emergent metalevel at which physiology dominates the molecular details. (Note: If the metabolic modes were *stable in a strong sense,* the system would lock up and die.)

The *transition probabilities* among the set of major modes—those that process the most energy—define the overall dynamic "personality" of the organism. These probabilities are set both by structural, thermodynamic (regulatory) parameters and by informational (control) signals, physical and chemical. In toto the trajectory through the set of accessible dynamic modes generates helical time.

Biological Time as a Helix: A Metaphor for Aging

Time as an arrow and time as a cycle (Gould, 1987) are familiar but incomplete metaphors. HK/HD common time is a helix generated by an orthogonal interaction between action temporal cycles (e.g., the approximately 24-hr, "circadian," daily metabolic and behavioral rhythms ubiquitous among living things) and the thermodynamic second law process arrow that is pressing the daily circadian cycles into the future via its "flowing," anisotropic time. (See Figure 2 for mention of modern views of nonflowing, physical time.) But the second law has another effect, according to the homeodynamic perspective on senescence described later, which surreptitiously decreases the Gibbs free energy that can be extracted from metabolic networks as time goes by. As a result, the lifetime energy budget for those of us in the best of health has the form of a truncated ellipsoid.
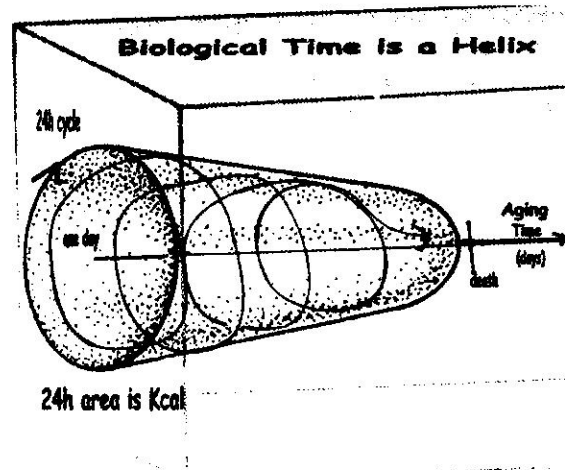
FIGURE 2 Homeodynamic time. This biological time appears as a daily cycle of metabolic action (cross-section area as circle at left end of object) being pressed into the future by the orthogonal flow of anisotropic, absolute physical time[1] so that each daily cycle fails to close exactly, creating a helix from the succession of cycles. A senescence process diminishes the action obtainable metabolically each successive day, so the circular areas get smaller, until too little daily action is left, the organism becomes fragile, and a previously tolerable fluctuation can now kill it.

Energetics and Scaling

Many open systems *self-scale* acquisition, transformation, and degradation of energy. A vivid example has been found from data covering over 2 millennia of the delivery of mail by equine express postal systems (Minetti, 2003). Some invariant features discovered from the historical analyses were the distance between horse-changing stations (20–25 km), the number of stations a single rider would reach (4–6), the average speed (16 km/hr), and the time for replacement of the horses (1.5 hr).

---

[1] I realize, of course, that since 1905 physics has abandoned the Newtonian concept of absolute time. According to some, modern physics is doing away with time entirely. For example, David Mermin (1990) has written, "Clocks do not measure some preexisting thing called 'time,' but our concept of time is simply a convenient way to abstract the common behavior of all those objects we call 'clocks.' While such a distinction may sound like splitting hairs, it is remarkably liberating to realize that time itself does not exist except as an abstraction to free us from having always to talk about this clock or that. The discovery that there is no time—only clocks—has deep and surprising consequences ... " (p. 111). However, the fact that we grow old and die provides a strong unidirectional arrow on time, in Newtonian style, not relativistic.

Modern studies have found that the metabolic cost for such riders is 1.9–2.4 L of oxygen per minute (which is 66.4% of the maximum human metabolic power that can be sustained during this activity for up to 276 min—equivalent to a distance of 92 km, or 4–5 stations). A young horse (4–7 years) with a mass of 390 kg, when galloping at 20 km/hr consumes 15–20 L of oxygen per minute (which is 69% of the equine maximum aerobic power of 40.5 L of oxygen per minute.) As the author comments, "It is surprising that the horses needed to be changed every 1.5 hours, whereas less athletic species, such as humans, can exercise at the same metabolic load for more than 4 hours." (The report goes on to explain the discrepancy.) The point worthy of note is this: "It is remarkable how several civilizations in the history of postal systems, without any knowledge of equine physiology, independently worked out the same optimal parameters (maximum distance traveled and related speed) for reducing the risk of life-threatening conditions . . . in their horses."

The dynamic range for aerobic metabolism in human beings, from rest to short-term work loads of several hours, is roughly tenfold (3.6–43 ml/kg/min oxygen consumption by lean body mass). The record for sustained metabolic output in humans may be that of Tour de France cyclists in their 3-week ordeal. Using instrumented bicycles, Asker Jeukendrup and colleagues found that world-class cyclists can sustain pedal power outputs of more than 300 W for as long as 6 hr (Jeukendrup, 2002). Lance Armstrong rode for 4 hr with a sustained power output of about 400 W and he has peaked at a rate equivalent to more than 466 W during a 200-km mountain stage of a race. At rest when their pedal power output is zero, cyclists would have a baseline metabolic power output as heat of about 100 W. No vertebrate has ever been found to *sustain* a metabolic output of more than about 5 times its resting level for long periods. (Armstrong's acute, maximum oxygen consumption in the standard laboratory exercise test is around 80 ml/kg/min-another astonishing figure!)

The metabolic demand of a hummingbird in daily flight (it would be greater in migratory flight) has been measured at 43 kJ/day (i.e., 5 W average power output; López-Calleja, Fernández, & Bosinovic, 2003), another colossal figure considering the small size of the bird studied (about 3 gm). At about 1–2 W/gm, the hummingbird's regular metabolism puts our basal state metabolism to shame (about 1 W per kilogram)!

The many consistent and reproducible scaling relations of energy throughputs for each species, and the concentration of metabolic power in the basic 24-hr rhythm of activity for all, justify treating action (Energy × Time) as a quasi-conserved physiological variable. (This conservation is, of course, not as strictly obeyed as are those of mass, charge, angular and linear momenta, total energy, and so on, nor does it have an associated symmetry and transport coefficient as do the others.) HK/HD energy scaling proposes a parabolic-like function for anabolism (usable fraction of total energy), optimized between "use it *or* lose it"

at low levels of energy throughput, and "use it *and* lose it" at very high levels—at which (to use a tachometer metaphor from performance of many automobile engines) mitochondria can be "redlined" (Figure 3).

Metabolic Networks and Emergent Graphs

The September/October 2002 issue of the journal *Complexity* (Vol. 8, No. 1) was devoted entirely to networks and graphs, with applications to biology. The cover story for the February 26, 2004, issue of *Nature* (Vol. 427, No. 6977) featured "Biochemical Networks: Mapping the Metabolic Super Highways," inspired by the paper by A-L. Barabási and colleagues (Almaas et al., 2004) with graphs of a flux-balance-optimized metabolic network for E. coli (strain MG1655). An important perspective on metabolic networks has been provided by Giuliani et al. (2004), who studied, with perfused rat livers, the effects of an enzymatic blockade at the rate-limiting, carnitine palmytoiltransferase 1 step in the β-oxidation of fatty acids, on the concentrations of different metabolites at different times, under approximately steady-state conditions. They found that "the same biochemical regulation network can assume different shapes in terms of constituting elements and intervening relations while remaining recognizable as a specific entity." The regulation pathways appeared as emergent properties at a different hierarchical level with respect to the intervening metabolites. As Morowitz (2002b) has remarked, "The metabolic chart is part of the phenotype of every organism. The phenotype ... has a robustness in spite of the constant buzz of noise in the underlying genomes. *The phenotype at the biochemical level is more stable than the genotype*" [italics added].
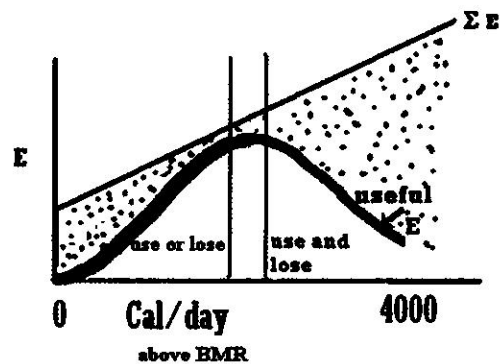

FIGURE 3 "Parabolic" effects of increasing energy throughputs in humans. "Use it *or* lose it"/"Use it *and* lose it." As energy throughput is increased above basal, the gap between the energy total and the usable energy (stippled area) narrows to a minimum (and optimum). Further energy expenditures become increasingly less efficient, and the gap widens again.

The metabolic phenotype can be appreciated through graphs, and it is these that expose what evolution has conserved. It is the graph that captures entailments (causalities), constraints, and the contexts (impressed forces) for function that arise in the environment in which the open system of interest is embedded. Metabolic graphs resist reductionistic fractionation into subsystems that can be superposed to recover the relational graph, and, expressing both syntactic and semantic aspects, they cannot be objectified by formal mathematics alone, restricted as it is to syntax only. Metabolic graphs are *patterns of relations* for an open system. HK/HD offers a quasi-physical basis for the invariances associated with these graphs.

SENESCENCE: WHY DO WE GROW OLD AND DIE?

The problem I address here can be vividly seen in Figure 4 showing the quasi-linear declines in record performance with age (normalized to 100% at age 35), for women master athletes in a wide variety of track and field events (World Masters Athletics, 2004). Over a 50-year age range the loss rate is nearly constant at 1%/year, referenced to the initial value at age 35. These data come from

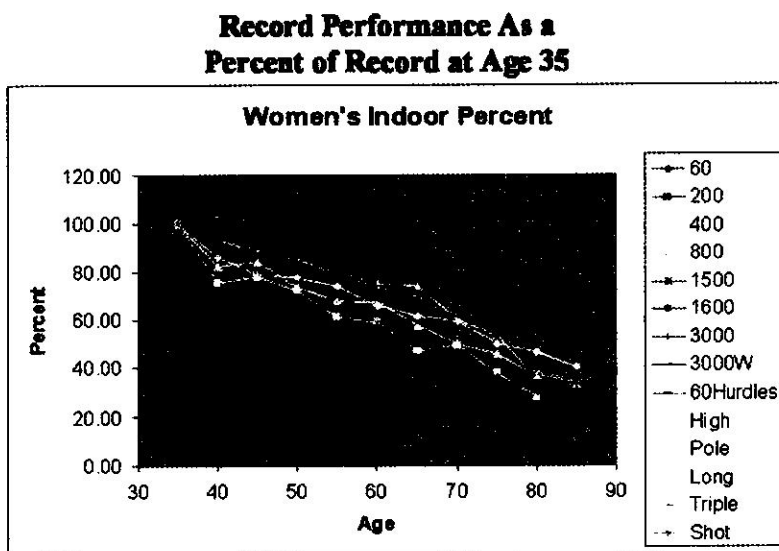**Record Performance As a Percent of Record at Age 35**

FIGURE 4   Effects of senescence. Quasi-linear losses of performance in various track and field events by women master athletes. Data are cross-sectional covering a period of 50 years (from age 35 to 85; World Masters Athletics, 2004). *Note.* Data collected but unpublished by Brian Peacock, NASA (retired).

women who are not only healthy—they are highly motivated and in the best of health for their ages. *What you see revealed is the progress of human senescence as it affects metabolic power output in the absence of major diseases.* I argue that senescence is not to be explained by a simplistic "gene for" claim, nor by sets of nonspecific images of localized blood flows or glucose uptakes in the brain, obtained under artificial conditions. To avoid the perils and pitfalls of obsessive reductionism, I suggest that we need a new, general, level-independent physical theory for inevitable declines in functional competence and stability of self-organized, complex systems of all kinds (Yates, 2007).

There is substantial intellectual tension, even hostility, between those who believe that the riddle of senescence (and much else in biology) lies buried in genes, singly or in clusters (Sharpless, 2003), and those who recognize that dynamics count for just as much, or even more, during all stages of life of a multicellular organism: growth, differentiation, development, mature stage stability, senescence, and death (a dynamic singularity). The "longevity assurance genes" du jour (in studies of yeasts), are the SIR genes, especially SIR2, whose protein product SIR2p seems to "sense" metabolic state. It is increased in caloric-restricted yeasts that have extended life spans. How it is increased (via an increased NAD/NADH ratio, or a decrease in nicotinamide or something else?) is a matter of intense debate (Couzin, 2004). In contrast, those who emphasize the importance of dynamics rightly insist on following energy supplies and transformations to understand the collective phenomena of senescence of individuals and the global characteristics of ecological niches (Odum, 1971). Furthermore, comparative energetics offers a dynamic perspective on hominid evolution (Leonard & Robertson, 1997). Evolution itself reflects the great importance of phenotypes (Weiss & Buchanan, 2003) and because senescence is progressive phenotypic instability, its study requires a dynamic analysis. Three essays by Richard Strohman (2000, 2002, 2003) present key themes from studies of the history of metabolic control, of thermodynamics/kinetics, and of redox pairs as symbols of regulated energetic states and call attention to the insufficiencies of genomics and proteomics in this construction. A "solved problem" in metabolic control is presented, and a new level of description and analysis is called for.

To help answer that call I direct attention to the HK/HD perspective on senescence. It notes that during their start-up, systems that are self-organizing create new forms and functions out of transformations of energy internally as long as there are degrees of freedom available for construction. During growth and development (stages with many "negentropic" features-see Glossary: Entropy), the energy budget is substantially increased by the costs of construction. Construction always requires that dynamical degrees of freedom be available for creation of new parts and initiation of new functions. While that condition is met, the net effect of energetic transactions can be negentropic internally. However, at maturity many of those degrees of freedom will have been frozen

out (i.e., constrained) by the differentiations that displayed new structures, so further energy transformations must then follow a maintenance scenario in which an accumulation of internal entropy is inevitable (Yates & Benton, 1995), taking many forms from many sources. Energy throughput will now slowly erode constraints and weaken couplings and connections. This is the central and most general physical cause of senescence. It shapes biological time as a helix and lifetime energy expenditure as an ellipsoid (Figure 2).

At the terminal stage of viability, the entropic accumulation begins to displace a living system from its normal, optimal operating point of "orderly disorder" (neither structurally crystalline nor amorphous; neither functionally regular nor random). Associated with the global increase in internal entropy, there may be some increases in spots of local order as insoluble aggregates precipitate out, and even some increased regularity of certain functions as processes become isolated from active inputs. However, the main effect overall is breakdown of regulations and controls, so behaviors lose coherence and complexity (Lipsitz & Goldberger, 1992), and the organism becomes fragile, unable to resist competently the inevitable assaults by stressors.

WHAT IS NEEDED NOW?

A provocative view of a prosperous future for biological science was stated by my friend Sir James Black (Nobel laureate, 1988), who saw in it "the progressive triumph of physiology over molecular biology!" (as quoted in Boyd & Noble, 1993, p. ix). I welcome that perspective and a similar call for physiology expressed by George Martin in the first issue of SAGE KE (Martin, 2002). The demonstrated strong control over gene expression *exerted by metabolites* now justifies a substantive change in focus of metabolic research. To accomplish advances in metabolic profiling, new training and new methods will be required because the intense reductionism of modern biology in the past 50 years has depopulated that cadre of physiologists and biochemists who can and will pursue such difficult, higher level studies emphasizing the emergent properties of complex networks. As evident from this essay, I believe that a particularly valuable physiological enterprise will come through analysis of metabolic regulation and control from an HK/HD perspective.

ENVOI

I have attempted to provide a glimpse of a general, physical "theory" (more correctly, a heuristic) for a fundamental understanding of the complex dynamic character of energetic metabolic networks and their regulations. The heuristic, HK/HD, is free of unjustified intentional or "smart" elements, of vitalisms,

or of Kiplingesque *Just So Stories* about causalities. It is synoptic and level-independent. It supports both reductionistic and holistic approaches to complex systems and avoids two dominant intellectual constraints of recent times, namely, genetic determinism from molecular biologists and the notion that contemporary particle physics has the wherewithal to come up with a "theory of everything."

With respect to medical science, HK/HD identifies "health" as stability, but the stability is marginal—of a special sort, expressing new principles of hierarchical organization, execution-driven processes, "sandwich" models of constrained dynamics renormalizable at each level, and of quantized actions with limit-cycle-like thermodynamic signatures. The HK/HD basis for comprehending health and disease requires, of course, that we continue to accumulate knowledge about genomes and proteomes as a start but adds the additional requirement that the constrained marginal stabilities of metabolic networks (metabolomes) be defined and recognized as the chief manifestation of physiological health. The robustness that emerges from healthy metabolic networks arises from a macroscopic *physical field*, in which "particles" (e.g., components, organs, cells, organelles, etc.) acquire and express their motion and change and play out their functions. To understand their dynamics, *biologists must identify both particle and field properties*, as physicists have understood for over 3 centuries. There is no shortcut.

As a start toward a physical-field biology, HK/HD updates and extends aspects of system science for complex systems by building on thermodynamics of irreversible processes and fluid mechanics but adding novel features so as to extend the scope of nonlinear mechanics of open systems. The extended scope aims at filling in the "missing piece" that has perplexed those who believe that biological systems are thoroughly natural, physical systems, constituting a distinct form of matter, along with gases, liquids, solids, glasses, plasmas, and so on. Some have said that physics envy is the curse of biology, and indeed, big problems in biology (e.g., the origin of life, evolution, development of a multicellular organism, human senescence, consciousness, etc.) have so far been resistant to illumination by physics. Perhaps it will always be so, but then there would be not one nature but at least two, in this, our universe (one of many?).

Finally, I emphasize again that the genius of Arthur Iberall sparked all the developments of HK (and its modest extension for biology, HD) outlined in this essay. But the scope of his achievements ranged more widely than I have indicated here. From 1973 to 2000 he published 22 papers, alone and with colleagues, in an area he called "social physics." More than that, over the same time period, he turned to problems of the mind and neurobiology with extraordinary originality that can be found in 11 publications. Because my focus here has been on complex metabolic networks, I have not included these 33 papers in the bibliographies, but I will provide a list of them on request, directed to my e-mail address (gyates@jdfaf.org).

GLOSSARY

Some technical terms (e.g., action) are already defined in the text and are not repeated here. The following definitions and explanations are a mix of formal and informal entries, and where a term has multiple possible meanings, only those of particular relevance to the present discussion are included.

Bifurcations: Bifurcation theory asks how the solution or value of interest for a dynamical system changes as some control parameter or variable is gradually changed. The solution (itself a dynamical behavior) can change in a subtle manner or very abruptly at critical parameter values. Changes in states (phases) such as the freezing of liquid water into ice represent a familiar bifurcation. Changes in flows from laminar to turbulent as the velocity is increased also represent a familiar bifurcation. Systems are sensitive to minor perturbations at bifurcation points.

Chaos: Chaos is an irregular, aperiodic fluctuation of a variable—unpredictable in the long run—generated by a fully deterministic, nonlinear process without noise. The formal definitions of chaos require that a system show as typical motions toward and on its attractors (bounded regions of phase space that contain the final motions after the transients have ended) trajectories with a positive Lyapunov exponent—which is equivalent to saying that trajectories that start close together initially, eventually diverge exponentially. (The sign of the exponent is robust and indifferent to time coordinate transformations.) The attractor containing the ultimate motions usually has a fractal dimension. In order to produce chaos in nonlinear models based on ordinary differential equations, one needs at least three continuous independent variables. However, in the case of nonlinear models based on finite difference equations, the dynamics of a single variable can have chaotic regimes.

Competing influences: When two or more competing physical, chemical, or even psychological influences act simultaneously to influence or set the operating point of a system, a richness of possible behaviors can be exposed by seemingly minor fluctuations and bifurcations become likely. Weather is full of examples in which thermal convections, Coriolis forces, and gravity interact so that a slight change in the balance of the three can create a tornado. Behavioral science is also rich in examples: the attack of a grizzly bear can resolve in a bluff, or in death of the targeted party, depending on slight variations in the attitude or posture of the potential victim and on the election of fight, flight, or playing "possum."

Complexity: This is a large subject with no general agreement as to what constitutes a complex system. Complexity implies some kind of irreducibility: the behavior we are interested in evaporates when we try to reduce the system to a simpler, better-understood one. Complex systems have counterintuitive

behaviors and emergent properties. A complex system cannot be comprehensively described by one overarching model, and successful analysis does not imply a successful route to synthesis, in contrast to machines that are designed in just such fashion (Rosen, 1991, 2000).

Constraints: A constraint is an auxiliary condition (structural or functional) that sets limits on and particularizes the behavior of a dynamical system that otherwise has broad capabilities for motion and change. Holonomic constraints (also called integrable because when they are included in a mathematical differential model a solution for given initial conditions can be obtained by integration) restrict configurations. Rigidity of a structure, such as a cube of sugar made up of crystals of sucrose, is an example. The particles are frozen in position and have no independent motions, though the whole cube can be moved. Nonholonomic constraints (nonintegrable) restrict only motions. They lead to models that cannot be solved in advance, and the behavior is revealed only after motion starts. The mechanical model classically invoked is that of a rolling disk on a plane, but nonholonomic constraints in biology are best appreciated using the concept of mappings. When there is a constraint on chemical events such as provided by a gene, if only one protein can result from its activation (as in prokaryotes), the gene is a holonomic constraint set by its sequence of bases, which is relatively rigid and fixed. But in the case of eukaryotes, in which a gene can make more than one protein depending on various ways it is activated and addressed, nonholonomic constraints are present, and the outcome, however modeled, cannot be computed in advance. One-to-one mappings are under holonomic constraints. Many-to-one or one-to-many mappings involve nonholonomic constraints. Physical laws also act as constraints (e.g., Newton's first law, $x''(t) = 0$, mandates that a particle in a featureless environment cannot accelerate).

Control (see Regulations)

Cycles, clocks, and near-periodicity: A cycle is a repetitive motion that regularly returns to its starting point within a characteristic time. A *sinusoidal trajectory is the classical example*, and it has mean value, amplitude, period, and phase as its four parameters, all of which are fixed. It has only one initiating cause, given by its linear, dynamic equation of motion, and once started, all cycles are guaranteed to evolve without further causation and with exactly the same period. In contrast, *limit cycles* are generated by nonlinear processes and each cycle is independently initiated. The up (or on) phase of the cycle usually has a different cause than does the down (or off) phase. The heart beat is an example: the contraction of the ventricles in the first part of the cycle has a different basis from the relaxation phase, and each cycle is independently initiated. One beat doesn't guarantee the next. A common model for a limit cycle is "integrate and fire," namely, some variable accumulates until a threshold is reached, at which point the accumulation abruptly ends and a

decompression (relaxation) immediately follows by a different mechanism. In breathing at rest, inhalation is active until a threshold stretch of the lungs and chest is reached. Then the active muscles relax and a passive, elastic recoil accomplishes the exhalation. The next breath is not implied by that cycle but must be independently initiated.

A harmonic (sinusoidal) oscillator is linear and expresses the first law of thermodynamics as potential and kinetic energies slosh back and forth without loss of total free energy. A linear spring (i.e., one that obeys Hooke's law with a constant of proportionality between stress and strain, K) hung from the ceiling, with a mass (M) attached, follows the classical second-order linear differential equation dynamic when pulled down and then let go. A sinusoidal oscillation results that goes on forever (in the frictionless case without dissipations):

$$M(d^2x/dt^2) + Kx = 0,$$

where x is position (distance) down from the ceiling.

Physical systems that approximate pure harmonic oscillations of this kind are, in engineering jargon, called "high-Q" systems. Once excited, they keep on cycling. They approximate perfect clocks with invariant periods without dissipation of energy.

If the second law is having an influence, as it must in all real macroscopic situations, there will be dissipations. Frictional losses of free energy, which are a function of velocity of motion in mechanics, are specified by the coefficient D, and the equation of motion is then

$$M(d^2x/dt^2) + D(dx/dt) + Kx = 0.$$

A damped oscillation results, which has an invariant period, but the amplitude decays (exponentially) to zero. To make a real, sustainable clock out of such a system it is necessary to inject a pulse of energy $\varepsilon(\theta)$ (at a particular phase θ of the oscillation) exactly to compensate for the dissipations. The first and second laws are simultaneously satisfied, and the periodic motion continues, as long as each cycle gets its own injection of energy, as follows:

$$M(d^2x/dt^2) + Kx = \underline{\varepsilon(\theta) - D(dx/dt)} \cong 0,$$

where the underscoring indicates a cycle average.

The pulse of energy is injected via a nonlinear mechanism; in a classical "grandfather's clock" (for example) it is called an *escapement*. This is elementary clock theory, and a research problem in HK/HD is to identify the biochemical equivalent of the escapements during action cycles.

A further departure from the idealized harmonic oscillator arises if the pulses of energy (which are functions of phase and not time) are imperfectly timed. Then the periods of the cycles are not identical but statistically distributed about a mean value. The oscillator wobbles. That is a common feature of many biological rhythms, unless they are strongly entrained by a precise geophysical rhythm such as a light/dark cycle.

Finally, there are motions on chaotic attractors that can be near periodic, without escapements (Glass & Mackey, 1988).

Degrees of freedom (dynamic): A dynamic system has a degree of freedom (for action) for each independent variable it possesses. Mathematically each degree of freedom provides a dimension or axis (in phase space representations) in which motion and change can occur.

Dissipations: A dissipative process (away from equilibrium) is one in which the second law of thermodynamics causes a decrease in Gibbs free energy and an increase in entropy and therefore a loss of the ability to do "useful" work, such as syntheses or locomotion. Diffusion is a classical example of a dissipative process.

Dynamics: A system with n degrees of freedom (i.e., one with n different, independent variables) can be thought of as living in an n-space. If the motion of a point in n-space follows some rule acting on the positions (magnitudes) of the variables and their velocities, then that rule defines a dynamical system and the n variables are then more than a mere aggregate.

Entropy: In classical thermodynamics it is an extensive state function that expresses the inability to get work out of *isolated systems* at equilibrium. It is at a maximum for the conditions at an equilibrium state, while simultaneously, Gibbs free energy (the ability to do work) is at a minimum. However, in *open systems* the concept of entropy has many guises and is frequently misinterpreted and confounded with information. Corning (2005) has deplored the abuses of the term *entropy* and suggested appropriate corrections. I agree with his views, but to avoid the strenuous effort of clarifying the difficult concepts, as he does well, I use the term *entropy* only semiformally, to express deleterious effects of natural processes that degrade structure and function in open (living) systems.

Fractals: Fractal geometry is based on the idea that the natural world is not made up of the familiar objects of Euclidean geometry: circles, triangles, squares, and the like. The irregular natural world of clouds, coastlines, and mountains cannot be described by such geometry. They are fractals, structures that always look the same, either exactly or in a statistical sense, as you endlessly enlarge portions of them. They have three features: heterogeneity, self-similarity, and the absence of a well-defined, characteristic scale of length (Mandelbrot, 1983).

Irreversibility: Irreversibility can arise from kinetics (the process can reverse, but one direction is so slow compared with the other that for practical purposes it runs in only one direction) or from thermodynamics—as the process runs, the second law degrades usable free energy and there is no recovering the ability to get work out of the system at the initial level—unless some other agency does work on it or provides a potential the process can tap for a shot of new energy.

Homeostasis, Homeokinetics, Homeodynamics: Homeostasis is a general, physiological theory of organismic stability that asserts that state variables in living systems can recover their initial (normal) levels or motions after perturbations (limited in magnitude). It is data based but has no physical, theoretical foundation (Cannon, 1929). Contrary to a common misreading of Cannon, the normal operation need not be constancy, but motions must be bounded inside a regulation band. *Homeokinetics* (see HK reading list) is an expanded physical theory for many sciences. In biology it addresses (among other things) concepts of organismic stability and emphasizes modes of global behaviors and switchings among them. *Homeodynamics* is my interpretation of homeokinetics, with additional emphasis on order parameters, information/dynamic duals and regulations, and controls of metabolic networks (see HD reading list).

Limit cycle (see Cycles): Strictly, a limit cycle is a two-dimensional (2D) attractor. However, HK/HD proposes and requires that attractors for action cycles occurring in 3D, when projected onto 2D, have a nearly limit-cycle-like form.

Navier-Stokes equations: The mathematical description of a (macroscopic) moving fluid is effected by means of functions that give the distribution of the fluid velocity $v = v(x, y, z, t)$ and any two thermodynamic quantities pertaining to the fluid (e.g., the pressure $p(x, y, z, t)$ and the density $\rho(x, y, z, t)$). All the thermodynamic quantities are determined by any two of them, together with the equation of state. Therefore, p, ρ, and the three components of velocity completely determine the state of the moving fluid.

The NS equations are the fundamental partial differential equations that are used to describe the flow of fluids (Tritton, 1989). They take account of three forces: viscous, pressure (p), and the body force. The equations express conservations of mass, momentum, and energy.

A very general form of the NS equation (where ρ is density) is

$$\rho\{\partial v_i/\partial t + v_k(\partial v_i/\partial x_k)\} =$$

$$- \partial p/\partial x_i + \partial/\partial x_k\{\eta(\partial v_i/\partial x_k + \partial v_k/\partial x_i$$

$$- 2/3\delta_{ik}(\partial v_i/\partial x_i))\} + \partial/\partial x_i(\lambda(\partial v_i/\partial x_i)),$$

where η is the dynamic (shear) viscosity and λ is the second viscosity coefficient, that is, the bulk, associative viscosity (both positive). δ_{ik} is the viscous stress tensor.

Both λ and η are functions of p and temperature and are not necessarily constant throughout the fluid—so they cannot be taken outside a gradient operator. However, it is usually assumed that they are constant to achieve the following simplification:

$$\rho[\partial v/\partial t + (v \cdot grad)v] = -grad\ p + \eta\Delta v + (\lambda + 1/3\eta)grad\ \mathrm{div}\ v$$

At this point it is common to proceed by restricting further development to incompressible fluids in which the viscosity coefficients remain constant and the curl $\nabla \cdot u = 0$, (div $v = 0$) so the bulk viscosity is suppressed. However, as I have indicated, HK/HD *insists that it is not proper to eliminate the λ (bulk viscosity) term in dealing with complex systems! In fact, the gateway to complex form is λ/η.*

My reason for emphasizing the NS equations is that, in my opinion, they are the exemplar of the second law operating in mechanics, outside of the formal expressions of thermodynamics itself. They express more complexity than can be found in most other equations of motion in physics. If there is to be an extended physics capable of addressing complex systems, I believe it should start here.

Noise (1/f) (f is frequency): Noise is any signal unwanted by an observer or a contaminant of an underlying dynamic. It may be deterministic or stochastic. $1/f$ noise is a ubiquitous background variation in the natural world. It gets its name from its power spectrum, which is a plot of the logarithm of power (or variance or amplitude squared) against the logarithm of frequency (f). A spectral plot may show log-power as independent of frequency (i.e., as $1/f^0$ distribution, perfect "white" noise) or as "brown" fractal-like (Mandelbrot) noise ($1/f^1$ distribution) or as Brownian motion ($1/f^2$ distribution, as in diffusion). In the log-log spectral plots, these exponents are the negative slopes of lines. For each exponent on frequency (or equivalently on space or in a sequence) from 0, 1, 2 as indicated, a different physical basis is required. In some cases the exponent may not be an integer, so the general symbol is $1/f^m$. An interesting discussion of these matters can be found in Bak (1996).

Regulations (and control): Biologists often use the words *regulation* and *control* as synonyms, but technically they are different concepts. I explain that difference because I believe that regulations, being simpler and closer to the structure of systems to which they apply, surely appeared first in biological evolution and are still underlying the stability of metabolic networks whose performance was later fine-tuned by the addition of controls.

Elementary *regulations* stabilize open systems and protect their performance from perturbations. There may be self-regulation intrinsic to the system dynamics, or a separate dynamical object—a "regulator," "compensator," "governor"—may be attached. Regulation establishes a bounded amplitude band as constraint on the magnitudes of variables, within which band, as time progresses, some variability may be allowed. However, if a regulated variable is kicked out of the band, restorative mechanisms impel it back to its home within the band. Topologically the regulation band reflects the presence of a point attractor surrounded by a basin of attraction within which the system can recover from perturbations. The restorative mechanisms reside entirely in parameters associated with structures and kinetic rate constants. There are no separate codes or programs, no comparators, models, algorithms, or data banks. There may be memory, but if so it will be a direct property of materials.

Regulation arises immediately from dynamics (rules governing motion and change under constraints) without explicit information designating goals: it can either be imposed by a component or be distributed across the system. The classical, early example of a completely analyzed component regulator is the Watt flyball "governor" for steam engines. The mechanics of a regulator, if it is a separate object, become part of the overall system dynamics—there is no "smart" informational element operating outside of those dynamics, sensing the state and making decisions about corrective actions.

Elementary *control* also stabilizes system performance against perturbations but in addition causes outputs to be able to track time-varying, command inputs. It does so chiefly by negative feedbacks and is goal directed. In contrast to the case of regulation, "smart" elements are present with information, programs, goals, set points, sensors, comparators, optimizers, adaptors, evolvers, and so on, lumped in discrete and specialized components (i.e., in controllers) situated outside of and different from the dynamics of the system being controlled. The output of the controller, using information, manipulates system variables or parameters that actively affect the dynamics of the system being controlled.

Controls may be superimposed on a regulated system to further enhance performance. However, if the system being controlled does not have intrinsically well-regulated dynamics, it may be very difficult to manage by a controller. With respect to aircraft, as an example, an airplane that is inherently stable aerodynamically (e.g., some of the biplanes of WW I) can be flown "by stick," meaning that the only smart element needed on board is the pilot. Modern, advanced jet fighters, in contrast, are inherently unstable and must be flown "by wire," meaning that computerized controllers using models, sensors, and information must do most of the flying because the dynamic problems that arise continuously cannot be solved, either reliably or fast enough for stabilization, by a human pilot. A somewhat counter-

intuitive benefit of such managed instability is *maneuverability*, and even sea lions have discovered it (Fish, Hurley, & Costa, 2003)! Instabilities, if not overwhelming, also support change, evolution, progress, creativity, and intelligence (Zak, Zbilut, & Meyers, 1997).

State (state-determined systems): This is a very broad subject that requires an understanding of constraints (holonomic and nonholonomic as well as laws) and the difference between autonomous and nonautonomous systems. Newton established the starting point for all subsequent views of states in physics. In the Newtonian world of absolute space and time, a state is a set of data (in his simplest model, positions and velocities of single particles) that in the deterministic limit (of a state-defined system) give us all that we need to know to predict future behavior. The general equation of motion shows that states determine rates, namely,

$$dX/dt = F_i(X),$$

where F is the dynamic rule (law) governing motion or change, parameterized by $i = p_1, p_2 \ldots$, and beginning with specified initial conditions. X is the state configuration vector of as many dimensions as there are degrees of freedom (independent variables)—in Newton's simplest case, one.

Because every differentiable function entails its own derivative as another *function*, this view is physically trivial. Newton's genius was to see that there was in "reality" no entailment at all between values entered in position and those (measured) in velocity, that is, in the real world the *value* of a function at an instant entails nothing about the *value* of the derivative at that instant. Thus there are two state variables—position and velocity. The reaction of a particle to the environment will determine changes, and the effective aspect of the environment is a force F. What happens to a single particle through the environmental F will depend on x (position), x' (velocity), and maybe on time:

$$F(x(t), x'(t), t) = mx''(t).$$

If the environmental F does not depend on time, then the particle is autonomous; otherwise it is nonautonomous. (Autonomy is thus a condition on the environment.) In the autonomous case, Newton's (second) law famously says,

$$F(x(t), x'(t)) = mx''(t).$$

This law is a constraint expressing the equation of motion for the particle. We now recognize that state is recursive (Taylor's theorem) and so the two variables alone, position and velocity, determine subsequent state, but this is a very restricted, nongeneric condition.

As Rosen (1991) has remarked,

> Newton's Laws thus serve to transmute the initial dualism between system and environment into a new dualism, that between *phase (states) and forces*, or between *states and dynamical laws*. The states or phases constitute a description of the system. Environment, on the other hand, gets an entirely different kind of description; it is described in terms of the specific recursion rule it imposes on states or phases. It is this dualism between states and dynamical laws that, more than anything else, determined the character of contemporary science. (pp. 91–93)

However, there is a difficulty. Newton's mechanics as a formalism has only a very weak inferential structure. Almost everything of importance is left unentailed. This fact, and the preference for the special autonomous conditions, has assured that standard physics and engineering approaches to dynamics, still in the Newtonian mold, are certain to fail to describe motion and change in living systems, loaded with entailments and facing nonautonomous conditions (Rosen, 1991, 2000).

BACKGROUND READINGS IN HOMEOKINETICS AND HOMEODYNAMICS

Homeokinetic References (Chronological Order)

Iberall, A., & McCulloch, W. (1969). The organizing principle of complex living systems. *Journal of Basic Engineering, 91,* 290–294.

Yates, F. E., Marsh, D. J., & Iberall, A. S. (1972). Integration of the whole organism: A foundation for a theoretical biology. In J. A. Behnke (Ed.), *Challenging biological problems: Directions towards their solution:* AIBS 25-year celebration volume (pp. 110–132). New York: Oxford University Press.

Iberall, A. S. (1977). A field and circuit thermodynamics for integrative physiology. I. Introduction to the general notions. *American Journal of Physiology, 233,* R171–R180.

Iberall, A., & Soodak, H. (1987). A physics for complex systems. In F. E. Yates (Ed.), *Self-organizing systems: The emergence of order* (pp. 499–519). New York: Plenum.

Iberall, A. S., Soodak, H., & Hassler, F. (1978). A field and circuit thermodynamics for integrative physiology. II. Power and communicational spectroscopy in biology. *American Journal of Physiology, 234,* R3–R19.

Iberall, A., & Soodak, H. (1978). Physical basis for complex systems—some propositions relating levels of organization. *Collective Phenomena, 3,* 9–24.

Soodak, H., & Iberall, A. (1978). Homeokinetics: A physical science for complex systems. *Science, 201,* 579–582.

Yates, F. E. (1979). Physical biology: A basis for modeling living systems. *Journal of Cybernetics and Information Science, 2,* 57–70.

Yates, F. E. (1982). Outline of a physical theory of physiological systems. *Canadian Journal of Physiology and Pharmacology, 60,* 217–248.

Homeodynamic References (Chronological Order)

Yates, F. E. (1992). Fractal applications in biology: Scaling time in biochemical networks. In L. Brand & M. Johnson (Eds.), *Numerical computer methods: Vol. 210. Methods in enzymology* (pp. 636–675). New York: Academic.

Yates, F. E. (1993). Self-organizing systems. In C. A. R. Boyd and D. Noble (Eds.), *The logic of life* (pp. 189–218). New York: Oxford University Press.

Yates, F. E. (1994). Order and complexity in dynamical systems: Homeodynamics as a generalized mechanics for biology. *Math and Computer Modelling, 19,* 49–74.

Yates, F. E., & Benton, L. A. (1995). Biological senescence: Loss of integration and resilience. *Canadian Journal of Aging, 14,* 106–130.

Yates, F. E. (1996). Homeostasis. In J. Birren (Ed.), *Encyclopedia of gerontology* (Vol. 1, pp. 679–686). New York: Academic.

TEXT REFERENCES

Almaas, E., Kovács, B., Vicsek, T., Oltvai, Z. N., & Barabási, A-L. (2004). Global organization of metabolic fluxes in the bacterium *Escherichia coli. Nature, 427,* 839–843.

Bak, P. (1996). *How nature works: The science of self-organized criticality.* New York: Springer-Verlag.

Boyd, C. A. R., & Noble, D. (Eds.). (1993). *The logic of life.* New York: Oxford University Press.

Brown, K. (2003, April). Working weeds: A German company develops a way to peek into plant metabolism. *Scientific American,* pp. 34–36.

Cannon, W. B. (1929). Organization for physiological homeostasis. *Physiological Reviews, 9,* 399–431.

Corning, P. (2005). *Holistic Darwinism: Synergy, cybernetics, and the biomechanics of evolution.* Chicago: University of Chicago Press.

Couzin, J. (2004). Aging research's family feud. *Science, 303,* 1276–1279.

Fell, D. A. (1997). *Understanding the control of metabolism.* London: Portland Press.

Fish, F. E., Hurley, J., & Costa, D. P. (2003). Maneuverability by the sea lion *Zalophus califorianus*: Turning performance of an unstable body design. *Journal of Experimental Biology, 206,* 667–674.

Giot, L. (with 48 co-authors). (2003). A protein interaction map of *Drosophila melanogaster. Sciencexpress/www.sciencexpress.org/* 6 November (2003) 10.1126/science.1090289.

Giuliani, A., Zbilut, J. P., Conti, F., Manetti, C., & Miccheli, A. (2004). Invariant features of metabolic networks: A data analysis application on scaling properties of biochemical pathways. *Physica A, 337,* 157–170.

Glass, L., & Mackey, M. C. (1988). *From clocks to chaos: The rhythms of life.* Princeton, NJ: Princeton University Press.

Goldberg, R. N., Tewari, Y. B., & Tung, M. (1995). *Thermodynamics of enzyme-catalyzed reactions.* National Institute of Standards and Technology (NIST) Standard Reference Database 74. (http://wwwbiotech.nist.gov:8080/enzyme/enzyme.html)

Gould, S. J. (1987). *Time's arrow time's cycle.* Cambridge, MA: Harvard University Press.

Iberall, A. S. (2000). What makes Sammy-Samantha and other mammals run? *Ecological Psychology, 12,* 109–139.

Jeong, H., Tombor, B., Albert, R., Oltvai, Z. N., & Barabási, A-L. (2000). The large-scale organization of metabolic networks. *Nature, 407,* 651–654.

Jeukendrup, A. E. (Ed.).(2002). *High-performance cycling.* Champaign, IL: Human Kinetics Publishing, Inc.

Koschmieder, E. L. (1993). *Bénard cells and Taylor vortices*. New York: Cambridge University Press.

Landau, L., & Lifshitz, E. (1958–1969). *A course in theoretical physics* (9 volumes). Reading, MA: Addison-Wesley.

Leonard, W. R., & Robertson, M. L. (1997). Comparative primate energetics and hominid evolution. *American Journal of Physical Anthropology, 102,* 265–281.

Lipsitz, L. A. & Goldberger, A. L. (1992). Loss of complexity with aging: Potential applications of fractals and chaos theory to senescence. *Journal of the American Medical Association, 267,* 1806–1809.

López-Calleja, M. J., Fernández, F., & Bosinovic, F. (2003). The integration of energy and nitrogen balance in the hummingbird *Sephanoides sephanoides. Journal of Experimental Biology, 206,* 3349–3359.

Mandelbrot, B. (1983). *The fractal geometry of nature*. New York: Freeman.

Martin, G. M. (2002, March 6). Help wanted: Physiologists for research on aging. *Scienceonline,* SAGE KE.

Mayr, E. (2004). *What makes biology unique?* Cambridge, UK: Cambridge University Press.

Mermin, D. (1990). *Boojums all the way through*. Cambridge, UK: Cambridge University Press.

Minetti, A. E. (2003). Efficiency of equine postal systems. *Nature, 426,* 785–786.

Morowitz, H. (2002a). *The emergence of everything: How the world became complex*. New York: Oxford University Press.

Morowitz, H. (2002b). Phenetics, a born again science. *Complexity, 8,* 12–13.

Odum, E. P. (1971). *Fundamentals of ecology* (3rd ed.). Philadelphia: WB Saunders.

Pattee, H. H. (1968). The physical basis of coding and reliability in biological evolution. In C. H. Waddington (Ed.), *Towards a theoretical biology* (Vol. 1, pp. 69–93). Edinburgh, UK: Edinburgh University Press.

Pattee, H. H. (1977). Dynamic and linguistic modes of complex systems. *International Journal of General Systems, 3,* 259–266.

Pattee, H. H. (1987). Instabilities and information in biological self-organization. In F. E. Yates (Ed.), *Self-organizing systems: The emergence of order* (pp. 325–338). New York: Plenum.

Pattee, H. H. (2001). The physics of symbols: Bridging the epistemic cut. *BioSystems, 60,* 5–21.

Ravasz, E., Somera, A. L., Mongru, D. A., Oltvai, Z. N., & Barabási, A-L. (2002). Hierarchical organization of modularity in metabolic networks. *Science, 297,* 1551–1555.

Rosen, R. (1991). *Life itself.* New York: Columbia University Press.

Rosen, R. (2000). *Essays on life itself.* New York: Columbia University Press.

Sharpless, N. E. (2003). The persistence of senescence. *Science 2003, no. 33 SAGE KE, (August 20), p.pe24.*

Shih, W. M., Quispe, J. D., & Joyce, G. F. (2004). A 1.7-kilobase single-stranded DNA that folds into a nanoscale octahedron. *Nature, 427,* 619–621 (cover picture for the issue).

Stent, G. S. (1987). Programmatic phenomena, hermeneutics, and neurobiology. In F. E. Yates (Ed.), *Self-organizing systems: the emergence of order* (pp. 339–345). New York: Plenum.

Strohman, R. C. (2000). Organization becomes cause in the matter. *Nature and Biotechnology, 18,* 575–576.

Strohman, R. C. (2002). Maneuvering in the complex path from genotype to phenotype. *Science, 296,* 701–703.

Strohman, R. C. (2003). Thermodynamics—old laws in medicine and complex disease. *Nature and Biotechnology, 21,* 477–479.

Tritton, D. J. (1989). *Physical fluid dynamics* (2nd ed.). Oxford, UK: Clarendon.

Veech, R. L. (2004). The therapeutic implications of ketone bodies: The effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Leukotrienes and Essential Fatty Acids, 70,* 309–319.

Wagner, A. (2002). The large-scale structure of metabolic networks: A glimpse of life's origin? Mapping an organism's network structure. *Complexity, 8,* 15–19.

Weiss, P. (2003). Mastering the mixer: The frustrating physics of cake mix and concrete. *Science News, 164,* 56–58.

Weiss, K. M. & Buchanan, A. V. (2003). Evolution by phenotype. *Perspectives in Biology and Medicine, 46,* 159–182.

White, D. (Ed.). (2002). Small World Networks. [Special issue]. *Complexity, 8*(1).

World Masters Athletics (WMA). (2004, February 2). Available at http://www.world-masters-athletics. org/index.php?id=records

Yates, F. E. (2007). Theories of aging: Biological. In J. Birren (Ed.), *Encyclopedia of Gerontology* (2nd ed., pp. 601–610). New York: Elsevier.

Zak, Z. M., Zbilut, J. P., & Meyers, R. E. (1997). *From instability to intelligence: Complexity and predictability in nonlinear dynamics.* New York: Springer.