A field and circuit thermodynamics for integrative physiology. III. Keeping the books--a general experimental method

A. S. Iberall

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A field and circuit thermodynamics for integrative physiology. III. Keeping the books – a general experimental method

IBERALL, A. S. *A field and circuit thermodynamics for integrative physiology. III. Keeping the books – a general experimental method.* Am. J. Physiol. 234(3): R85–R97, 1978 or Am. J. Physiol.: Regulatory Integrative Comp. Physiol. 3(2): R85–R97, 1978. – The ideas of Parts I and II of this series are continued to complete the account of field thermodynamics. Two space and time scales are discussed: that of single process fluctuations, and the larger scale at which near-equilibrium conditions prevail. Beyond that second larger scale, irreversible thermodynamic field processes can be seen. The basis for these two scales of thermodynamic phenomena is explained through a novel, nonanalytic formulation (in action space) that avoids the necessity to account for the detailed continuum mechanics in geometric space. Instead, the scheme permits accounting for the field processes directly from statistical moments of the fluctuations. The relations between mechanics and the statistical moments of fluctuations are introduced from the Einstein theory of Brownian motion. Action is shown to be quantized at every hierarchical level. Since there is an action-related time series succession of states at every observational level, all the required thermostatic and irreversible thermodynamic transport relations can be obtained from such time series. This new approach offers an experimental strategy that in principle renders the thermodynamic relations computable from experimental preparations. The strategy is then applied to biological systems, which are noted to have communal organization, transport phenomena, conservations, and spectra that are thermodynamic and functionally significant. A six-step experimental approach is outlined. For illustration, eight examples are given of fresh insights or solved problems arising from the approach to living systems through field thermodynamics.

homeokinesis; fluctuations; network analysis; transport

SECTION 1. THE NETWORK THERMODYNAMIC VIEW

Space-Time Motion and Change in Systems

Aristotle defined physics as the science of motion and change in systems. In Part I of this series (31), we remarked that physicists and biologists use different frames of references in contemplating movement and change. But it is our contention that both animate and inanimate nature can be viewed as "physics" from a single frame of reference that will even include motion and change in man, mind, and society. To achieve this claim we have to emphasize that the interiors of the living organism, as well as other entities, are made up of fields of atomisms, and in these fields only three movement-producing physical processes can be found. These processes are wave propagation, diffusive transport, and convection. All three lend themselves very directly to the point of view of a field thermodynamics and they are fundamental aspects of all natural phenomena. But we will place our stress on diffusive transport (e.g., of heat, mass, and momentum). That process is the *only* source of irreversibility in thermodynamics. In complex systems (whose internal physics we have referred to as homeokinetic), in which the internal field constitutes a complex factory system whose processes show long time constants and lags, the need to understand the internalized diffusive transport is as critical as understanding diffusion in the more rapidly changing externalized variables of simple point-like atomisms. We have already tried to show how diffusive transports, which lie behind understanding of phenomena occurring in gases and liquids (38), even apply to societies of cells, as well as societies of people (34, 40). In the present article we wish to indicate what the experimentalist, seeking a reduction to physics of the dynamical aspects of a biological system, must

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consider in the local field of a particular preparation. Those considerations will be strongly focussed on diffusive transports.

Morphologists and biochemists often take a static view of living systems (e.g., seeing a bud of a vescicle on a membrane in an electron micrograph; finding a spot by the immunoperoxidase method). But, biochemistry is surely more than chemical anatomy, and morphology without reflections on function is a pallid endeavor. On the other hand, whether or not they are comfortable with dynamics, most biologists are never far from thinking about processes—about motion and change—about physics! But there is a paradox here: the biologists seeking to describe functions may overlook their obligations to identify physical process when it comes to the specification for motion and change. The abstract language and concepts used in physics to describe function may seem both literally and figuratively "lifeless" to the biologist. The reason for the paradox is easily found: physics and biology seem to be considering wholly different aspects of nature. Consideration of motion and change in physical fields seems to involve a few abstract space-time processes, and a stingy enumeration of players. In contrast, the biologist may want to consider an apparently enormous chain of specific relationships among glucose levels, catecholamine levels, proinsulin, insulin, Golgi apparatus, rough and smooth endoplasmic reticulum, polyribosomes, secretory granules, exocytotic vescicles, and insulin secretion rates—all as part of the process of converting a blood sugar level into an insulin response by the beta cell of the islets of Langerhans in a mammalian endocrine pancreas.

Do these two views need each other, or have any basis for merging? We believe that the answer is yes, if we are ever to understand life more than in an empirical fashion. Empirical description has had, and probably always will have, great importance in biology—as it does in other branches of science. The problem is to explain what is described in a reductionistic fashion that is parsimonious of principles and concepts. Empirical description is not itself explanation, but only the material that is to be comprehended by concepts. Readers of the previous two parts of this series will know that we believe that field thermodynamics provides the basis for at least the first stage of the formation of scientific concepts about function in any system, from atoms to a universe of galaxies. (Even the subatomic microcosm has thermodynamic characteristics, but these have not yet been fully treated within physics itself.)

Some Background Literature—Whose Themes Do We Orchestrate?

The reader may find it of some interest to pursue a line of reading that would highlight earlier attempts to link a thermodynamic construct with both individual organismic life and societal life. The selection is not exhaustive; it is based on our tastes and experience. Our thinking was significantly influenced by Sechenov's lectures on the role of "vegetative" acts in animal life (53), Bernard's classic study on experimental biology (4), and Oparin's study of the basis for life (48). We have found Smuts' holistic point of view reasonable and provocative (55). Morowitz' book (45), completed in 1968 under the same biophysical program (NASA) that supported our work (33), is based on a thesis with which this series of articles is completely in accord, namely that the flow of energy through a system, in a nonequilibrium thermodynamic sense, acts to organize that system. At the end of chapter 1, he offers a list of references that is substantially similar to any selection we could make to illustrate the *physical* literature that encouraged and prepared us to tackle the connection between life and thermodynamics. It includes writings of Meyerhof (1924), Schrödinger (1945), Bridgman (1941), Prigogine (1955), Katchalsky (1965), Elsasser (1966), and Eyring (1941).

Most influential on the author in suggesting that physics could stretch to biology was Gamow's insatiable quest for understanding nature by way of science, and explaining it in ways that all might understand. Gamow's interests reached the subject of life (13, 14).

The dialogue that McCulloch carried out with physical scientists all over the world had one concern: "How could science explain the functioning of the brain, and the behavior of the organism?" That dialogue reached out to touch the author. We have offered preliminary forms of our answer (24, 37, 43).

A very specific thread of encouragement for a thermodynamic view came from the parallelism of thought and informal collaboration between the author and B. Goodwin. (For the parallelism, see (15, 24).)

A few more references might include Lotka (44) who introduced a "program of physical biology" that addressed irreversibility in an evolutionary context. A much lesser known work is the interesting but incomplete attempt by Seidenberg (54) to suggest the need to define a determinism of historical processes, under human culture, in thermodynamic terms. His work reaches out to a classic call by the historian, Henry Adams (1). More recently, of course, the work of Prigogine and his colleagues on dissipative structures, applied both to biological organism and society, has attracted great attention. (See for example (51).) Thus in the work of Morowitz (45, 46), Goodwin and colleagues (15), Prigogine and colleagues (51, 52), Katchalsky and colleagues (42, 49), Onsager's (see a memorial issue (12)), and ours (25, 40), to name a few investigators and illustrate their work, there are concentrated efforts to apply irreversible thermodynamics to the living system.

We have tried to accomplish some reduction to physics generally guided by a thermodynamics not only for process, but even for form, in the following areas of life sciences: metabolism (23), vascular organization (32, 35), osmosis (41), arterial pressures pulses (35, 57), behavior (37, 43), overall physiological rhythm analysis (8, 33), and social phenomena (30, 34). Although the accomplishments are uneven, the approach is unified, and the examples cited should indicate the potential wide range of applicability of the method. We acknowledge, but do not agree with, the views of Eccles and Popper (see (3, 50)) that a description of the internal

world ("World 2") of an organism cannot be reduced to a physical description. Our own tentative views, to date, have been expressed elsewhere (6, 37, 43).

The Objectives for Explanation and Analysis

In this present article we shall use notions introduced in this series to suggest to the experimental biologist what he would have to do to provide a generalizable physical description of the preparation of interest to him, should he be inclined to do so. Of course, a biologist is free not to attempt a physical description, or a reduction to physics; but then he can hardly claim that such reduction is impossible, a claim that we suggest is more often made than tested.

A physical (thermodynamic) reduction of a living system has three objectives.

1) To describe and account for (near) periodic processes that sustain the living organism in its various operating modes. These can be characterized by a spectrum for each physiological state of interest.

2) To describe and account for aperiodic processes by which a living system changes its mode of operation, or accomplishes successive stages of self-construction.

3) To analyze unit processes.

The works of Morowitz (45) and of Prigogine and Nicolis (52) and ours (40) serve as excellent background to approach these objectives, in which the thermodynamic description has been generalized to include both internally complex (homeokinetic), self-serving, autonomous systems more explicitly. These self-serving systems have internal process times and delays characteristic of complex atomistic systems with high bulk-to-shear viscosity ratios, and they transform energy by means of an internal flow field with many localized factory operations that are fluid processes, as described earlier (31).

These authors are concerned with defensible physical propositions of great generality. But an excellent beginning thought may be found in a theorem of Morowitz (45). The theorem is: "In steady-state systems, the flow of energy through the system from a source to a sink will lead to at least one cycle in the system." Developing his theme further, Morowitz demonstrates how molecular order arises in systems undergoing such energy flow.

Intrinsically that theorem permits us to begin to look at organized systems. As the area of his interest, Morowitz has very validly chosen the particular path of outlining and organizing the primitive chemistry of the life process (46). Ours persists on the path of a generalized kinetics and statistical mechanics.

Kinetic Space-Time Considerations in the Local Field

To set the scene for presentation of a method or strategy of applying a specific form of the thermodynamic approach to experimental biology, we shall proceed as follows. We summarize some of the general thermodynamic notions introduced in Part I of this series (31) and then, in SECTION 2, we show a new formulation, first as it is applied to a simple system. Though this new formulation contributes little novelty or convenience for simple systems, the novel approach lends itself better to experimental applications in biology than would a heavily analytic treatment. In SECTION 3 we shall discuss applying the new approach in a fashion that appeals more directly to the geometry or morphology of biological fields, and shall indicate that the formulation can be used to arrive at a computable form for experimental thermodynamics.

The difficulty in providing a general thermodynamics for internally complex atomisms (e.g., the organism, or a single cell) is that they are not made up of homogeneous isotropic spatial extensions. They contain both lumped and discrete subelements as well as field processes; they have many levels of coupling. They are factories. Therefore a unitary set of continuous field equations won't do as a description. The equations would have to be broken up into too many segments. Yet the equations do contain an accounting of the essential physical processes that might be represented. So, instead, we attempt to work our way from inside to outside, from below to above. We start from the identifiable repetitive elements in our field. In a physics for biology, say for the cell, this might be the collection of dissimilar organelles. We ascend to that level of suborganization because we now know that the cell, as a factory, operates through unit processes at the organelle level. Similarly for the complex organism, its physics might start from the recognition of organ systems rather than cells, and within those the functional unit of the organ is the elementary atomism. Professor E. H. Bloch, using a wealth of anatomic background and experimental material, has undertaken anew the pursuit of this atomism, still poorly defined in the complex biological organism. He has explored the issue in the liver (5). We have collaborated with Bloch on the functional unit in muscle. (For a preliminary report, see chapter 5 in (30).)

But we want to richly present the fundamental ideas of the tactics and methods, rather than present a detailed biological study. So we frame our discussion as if we were dealing with a simple physical example. The methodology, however, remains general.

To make the discussion concrete, let us begin with consideration of a simple system—that of a near-ideal gas in a container. In a simple system, its atomisms either have no internal structure, or their internal degrees-of-freedom quickly equipartition energy during each translational collision. We start with a single substance in a single phase. The atomisms are atoms (or molecules) of a gas, and these atomisms are in motion. They collide, and they may also exhibit longer range interactions when they are not in contact. Such interactions will be of the van der Waal type and they account for deviations of the behavior from that of an ideal gas. The confined gas has internal energy, manifested as kinetic energy, that is derived from the radiation field and from other sources (if any) available at the boundary. (In strictness we should also include quantum mechanical zero-point energy which can be viewed as arising as a nonthermal source from the universe outside (7).)

In the development to follow, we shall refer to processes in two or more different domains of time and space, basically in two. In a simple gas system, only a simple specification is needed of these two domains. In a gas we have an ensemble in which we can identify the fluctuating, atomistic units that persist in their fluctuations for a large, indefinite number of collisions. We can characterize the average fluctuations by two parameters: the space parameter δ_1, which is the average displacement between collisions, and the time parameter τ_1, which is the mean relaxation time between collisions. Both parameters are computed as moments of statistical sets. The domain of (δ_1, τ_1) is the smallest space-time scale to be considered. The ergodic hypothesis supposes that over any extended epoch of observation of the fluctuations, we shall obtain the same values of δ_1 and τ_1. An important aspect of fluctuations in the (δ_1, τ_1) domain is that they provide a significant measure of the full dynamic range open to the atomisms in the field system. For example, the ratio δ_1/τ_1 is the velocity of sound in the gaseous medium. In spite of the fact that the actual macroscopic (stream) velocity of the molecules is practically zero, the fluctuational velocity has an enormous range; it ranges from 0 to a number of times the velocity of sound.

Then there is a second domain, of greater extent in space and time than (δ_1, τ_1). It is a minimum macroscopic scale, with parameters δ_0 and τ_0, larger than δ_1 and τ_1 respectively, at which the system is nearly at thermodynamic equilibrium. In simple gases, the larger scale is about 10 times the smaller (38).

The Local Source of Diffusion and Wave Propagation

We wish to examine the fluctuating atomistic entities nested in (δ_0, τ_0) space. The atomistic entities in (δ_0, τ_0) space may be viewed as occupying their near-mean state, on the average, in some regular array. Now let the observer blink for τ_1 and examine the ensemble again. It will not look much different from before. The reason is that both the initial and final states are not very far from equilibrium. What one will see is a change in only a few entities, that will have exchanged location or state with others. As we blink repeatedly, the exchange motions may have the character of the incoherent motion of a random walk (prototypic diffusion) as a few states are exchanged between entities outside and inside some δ_1 spaces, or the exchanges may appear to have threads of coherent motion (wave propagation) within a line of δ_1 spaces. These are the only two modes possible at the scales of (δ_1, τ_1). As the space is extended to (δ_0, τ_0), these exchanges are describable by transport coefficients, whose measures are now constants independent of the fluctuation time scale.

In a simple atomistic system, the quantized (δ_1, τ_1) space will be developed by the interaction through collisions in the translational motion of the atomisms. There will be no significant graininess within that collisional process. On the other hand, in a complex atomistic system, in which there is an entire complex ring of factory processes within the atomism, the "day" of the interaction will be the entire cycle of discrete but organized factory modes that go on internally. That day and its scale will furnish the grainy (δ_1, τ_1) scale for such complex atomisms. For example, in a cell, the generation time is a most plausible time scale for τ_1. In a complex organism, quite often the physical day-night scale or the seasons of the year literally quantize the "day" of the organism, as long as we only concern ourselves with the life process, not the species reproductive cycle. Essentially all modal processes of the individual organism have been achieved on the average in a day. The distinctions among systems closures will have to be kept in mind. There is a thermodynamics of the individual that need not be concerned with the more extended social thermodynamics of the species. Nevertheless, we will address the problem of description as if we were dealing with a simple system, but the time and space scale has to cover the true fluctuating "day" of the organism.

Global Convection

Competence for transport arises among the atomistic entities from their collisional and dissipative interactions. Although only the two modes of local processes described above emerge from the local interactions—diffusion as an incoherent process and wave propagation as a coherent process at the (δ_1, τ_1) scale, both essentially at equilibrium at the (δ_0, τ_0) scale—nonlinear convective processes may be seen to begin as convective transports in the macroscopic field.

One notes that the equations of change describe field processes that determine DF/Dt, where F is a summational invariant (31). Since the total change in time depends both on space and time, in addition to $\partial F/\partial t$ the time-dependent component, there is a spatial-dependent component $V_i\ \partial F/\partial x_i$. It is that spatial-dependent component which represents convection, the sweeping of a velocity V_i stream into a field against a gradient. The process is macroscopic. It assumes the existence of a gradient and of a cooperative ensemble. Neither of these can be developed in less than (δ_0, τ_0) space. (However, it is not seriously possible to produce much convection at this scale. The power required is too great.)

Comments on Time and Space Domains, and Equilibrium

Part I of this series indicated that field thermodynamics applies to systems globally removed from, but locally near to, equilibrium (31). In the (δ_1, τ_1) domain, fluctuations cover the whole dynamic range open to the system, whether or not the system in the large is at equilibrium. In the larger (δ_0, τ_0) domain the system will always appear to be near equilibrium, whether or not it is at equilibrium on any larger scale. At a scale beyond (δ_0, τ_0) the global characteristics of a system, including its convective transport have to be considered. Globally a system will approach a uniform equilibrium unless some inhomogeneity of a thermodynamic potential is present or it is driven by some external force. Then at any domain larger than (δ_0, τ_0), macroscopic transport phenomena will be observed and will proceed

according to the principles of nonequilibrium thermodynamics.

Some discussions emphasize the far-from-equilibrium global aspects of biological systems. We think this is a misplaced emphasis in living systems if it neglects the converse statement that near-equilibrium considerations apply locally. Living systems are not explosive systems, and they transform energy at modest rates. They maintain local inhomogeneities by running engine processes.

Elements of Thermodynamic Description – Bookkeeping

In Tables 2 and 3 of Part I of this series the chief elements of description from the point of view of field thermodynamics were listed (31). Below we shall recapitulate these points briefly, in the form of six steps that would be required to obtain a complete bookkeeping of the thermodynamic accounts for a system manifesting motion and change. Then, in SECTION 2, we show how an experimental approach to that bookkeeping can be conceptualized.

We can now turn to the bookkeeping necessary to describe a simple system such as the gas under discussion.

Step 1. Identify the persistent atomistic units of interest (in this case atoms (or molecules) of the gas).

The experimentalist must always invest effort to identify the atomisms. His identification may not be perfect in his first modeling of the complex factory (e.g., of functional units) but will improve with increasing study.

Step 2. Quantify the thermostatic potentials, including those potentials that make up the equation of state.

Interaction in the ensemble is made up of supply processes (e.g., distant radiation or stores) and dissipative processes. As a result an equilibrium state is reached, locally, which is characterized by a time series of fluctuations with a well-defined average space and time scale. The ensemble will have a statistical distribution function. That distribution function will be made up of the statistically independent measures of summational or collisional invariants. For example, if there are only three invariants, mass, linear momentum, and energy, then the distribution function will relate to these three invariants. That distribution function will provide the measures for the three corresponding potentials: density (mean number per unit volume), pressure (mean momentum per unit surface area, independent of orientation), and temperature (mean translational kinetic energy).

An equation of state follows from the following elementary consideration. The independence and inclusiveness of the measures of summational invariance, associated with the atomistic fluctuations, means that they are linearly associative (as a linear relation among the mean fluctuations of mass, energy, and momentum). But in addition the fluctuation of each summational invariant, conserved during collisions, samples the entire dynamic range of the associated variable (e.g., the mean square of the velocity fluctuation samples the entire range). Therefore the difference equation expressing the linear association can be replaced by a continuous differential relation as long as the fluctuation space and time scale are not invoked. That differential relation should then be integrable if the form of the weighting coefficients is determined either theoretically or experimentally. That integration provides the equation of state as obtained for the local near-equilibrium region. It is extendable to all of the connected region which is free of phase change.

The equation of state is the summation, over fluctuations, of the linear associative relation among summational invariants.

Then other potentials may be defined in terms of these basic potentials (e.g., enthalpy, free energy). That all of these process definitions cannot be done solely in terms of mechanical variables is well known as the basis for the thermodynamic description. A constructive "explanation" has recently been provided (40). The net effect is that translational energy is partitioned among all atomisms in contact with the system by the measure of temperature. A second ensemble measure, the potential of entropy, indicates the direction that such translational energy exchanges will take between atomisms in contact. In both simple and complex systems, there will be characteristic processes by which translational energy appears to empower internal modes (21). Among all the potentials that can be formed, only a limited number from this set of potentials are independent. In the case of the simple gaseous system under discussion only two, say temperature and pressure, are independent (for a system with a fixed number of atomisms).

Step 3. Identify as deviations from the mean state the slow, dynamic changes that may be occurring.

Such dynamic changes are described by deviator equations of change, one for each summational invariant. They deal with how the diffusive transport processes that result from the presence of spatial gradients, or time-dependent inputs globally change the local summational invariants. Transport is a small or slow stream response to a stress. It is a strain rate or a deformation rate on a scale that is large compared to the atomistic mean free path, and long compared to the time period of the individual fluctuations in the microdomains. A system of nonlinear partial differential equations then describes both the (thermostatic) state and change in the field. A complete derivation is given in (22) for hydrodynamic systems. It includes chemical reaction among its processes. The set can be extended to include gravity, electromagnetic interaction, and elemental nucleosyntheses.

Step 4. Solve boundary value problems of interest, i.e., for whatever theoretical or experimental field is of interest.

The mathematical physics of such equation sets is richer than one might casually surmise. The issue of the relative stability of more than one type of mathematical solution reaches the current state of the art of this mathematical-physical subject (see for example (20)). Loosely speaking, three types of solutions seem to exist: the dissipative decay to a steady state, including the rest state (29), the emergence of inhomogeneities of

pure form (examples, Bénard cells, von Kármán vortex streets, Taylor cells), or the emergence of a complex spectrum of periodic processes that more or less tends to resemble chaos. There may be an intermediate region between the latter two. It is this richness of a possibility of nondecay states that is of merit for biology.

Step 5. Put together a systems' model.

After solving various boundary value problems, spatially lumped engineering "network" approximations can be derived. Thus, for example, for processes that are temporally very slow, a container of fluid acts as a simple mass-spring network with damping. (Part I gave the criterion that permits a lumped-parameter view of a system (31)). Large spatial gradients can lead to maintained conductive paths that would be regarded as "facilitated" systems processes rather than molecular processes. Out of the local near-equilibrium regions, a field or network of such conductive elements and processes can be pieced out. (There is no difference in final results between (δ_0, τ_0) computation and continuous computation.)

Most current attempts at biological modeling of interorgan processes (examine most of the papers in (36)) are based on such engineering network approximations. When viewed as scientific models, they fail to validate the underlying atomistic processes that give rise to their lumped compartment ad hoc assumptions. We have in general avoided that path of description, because it overlooks or glosses over the fundamental physiology of the processes. That fundamental physiology was contained in how the essential elements in the functional unit cooperated so as to produce the local summational invariants, by internal diffusion, wave propagation, and convection.

Neither the engineering network view, nor the thermodynamic view presented here succeed in reaching the problem of organismic evolution and development. But this thermodynamic view is open to such extension (witness stellar and cosmological evolution), whereas the hard-wired engineering view is not.

Step 6. Now identify the ring of modes of the system (e.g., the cooperative behavior among the functional units in an organ, or the cooperative organs in an organism).

The abstract character of modes possible are still diffusion, wave propagation, and convection, as mentioned above and in Part I (31), but now at a systems' level. The modal behavior should be obtainable from the engineering systems' model, or intuitively by comprehending the interactions between local components and the global system. Obviously the formalism can often help the intuition, but is no substitute for the intuition.

In applying the above six steps, there is surprisingly little need to deal with a description by temperature and entropy variables. They do not provide insight into the salient role which local dissipative processes play in the creation of structure and function. The equations of change that describe interesting transport phenomena do not require an explicit entropy-production equation, though entropy production is implicit in them.

SECTION 2. A NEW FORMULATION FOR A SIMPLE SYSTEM

The bookkeeping requirements listed above might seem to tax the experimentalist. To make thermodynamic descriptions more susceptible to quantification in the experimental laboratory, we offer here a novel approach that will be illustrated by considering diffusive transports and sustained fluctuations, the basic phenomena of field thermodynamics, at the local level in the case of a near-ideal gas. In SECTION 3 we shall consider its application to biology.

In a near-ideal gas the sustained fluctuations are dissipative because the interactions of the particles are not perfectly elastic. These dissipative interactions lead to a cooperative sharing, or "equipartition," of energy among and within neighbors in the ensemble. The fluctuations can be sustained because they meet their energy requirements by drawing from a common store of potential energy at the boundaries. Such fluctuations are exhibited as mean free path-relaxation time phenomena at every level – one may presume even down to quantum mechanical levels (7). It is important to realize that dissipative interactions, as fluctuations, constitute thermodynamic engines (25), and they can be regarded as approximate limit cycles in a phase space (with momentum-displacement coordinates). In such a plot the areas enclosed by the limit cycle trajectories represent the action of the fluctuations (see below). The trajectories are parameterized by δ_1 and τ_1 and the *limit cycle quantizes the action*. The above description applies whether or not an equilibrium is present globally, and is true whether the limit cycle is quantized by quantum mechanics or as some macroscopic engine process.

Mapping Geometric Space and Action Space

Action (A) is the product of energy × time. At the fluctuation level (single mode gas, or more complex ring of internal modes) action is given by

$$A = \frac{m(\delta_1^2)}{\tau_1} \qquad (1)$$

That energy-time product itself (the metabolic power passing through the atomism) can be used to define the limit cycle trajectory in a conceptual action space. The phase space in which the single mode or ring of modes is to be presented may be momentum versus displacement in the case of the simple system, or the ordered sequence of fractional daily power per mode versus time in the case of complex systems.

Our task is to indicate, now, following a simple system, how one keeps track of the local results.

So let us assign each atomism to a cubic lattice within which its motional fluctuations can be confined. This is a geometric space. If the sustained motions were conservative, one could imagine each atomism remaining in its box by making elastic collisions with its neighbors in a fluctuational cyclic fashion. (For gas molecules, whose mean free path is larger than one such box, one might have to picture three or more atomisms per box so as to satisfy momentum constraints in the x, y, and z directions, or one can imagine a larger domain made up

of mean free path size. But if we move on to the more complex case of liquid densities, then a more complex motion of a liquid molecule in its cell can be imagined by which its motional fluctuations can be confined. And finally if we move on to complex "homeokinetic" atomisms in which most of the action is internal we can similarly imagine motion and change within the confined space.)

We want to keep track of these fluctuational motions in action space. That abstract space, one cubicle per geometric cubicle, presents the action taking place in the geometric cubicle. For a simple gas molecule, occupied only in translational motion, a suitable space is the phase space of momentum versus displacement. The total in-phase action is the area within the closed cycle. For a more complex homeokinetic atomism, the phase space of fractional daily power versus external clock time can be used. In that space, the daily modes will be tracked. The system exhibits a characteristic scanning of its action modes, e.g., in a cell the cycle starting from simple cell division (or reproduction) back to division; in a mammal, the cycle from waking to waking; in a species, the cycle from birth to birth. Again, the total-in-phase action is the area within the closed cycle.

Insofar as the fluctuational motion persists, the distribution characteristics of the motion can be obtained by averaging over the cubicle per "daily" relaxation time through the various modes. This, for example, will provide information about the local density of each mass-species (e.g., as species composition of individual mass atomisms), local "pressure" (i.e., momentum delivered on adjacent cubicles), their average free energy, their average charge, and the average number of atomisms per unit volume (which is not precisely the same as mass for species that live and die. Note that one keeps track at the highest level of organization that makes up atomisms in the system. Although we specified "one molecule," "one cell," "one individual," it may be a collection of such no longer identical elements, a "heterarchy" of atomisms that make up the field system. In a cell this could be the total of all subelement organelles.).

The summational invariant character of the variables being used shows itself in two ways. *1*) We can see how they make up the distribution function of the ensemble, as we determine it from the individual action box. *2*) We can see how they make up the equation of state and other thermodynamic potentials of the ensemble.

Since the fluctuations are large, they each sample their dynamic space (e.g., the density in a fixed geometric box could fluctuate from no particles in it to being quite crowded, even though the box averages one particle; the velocity can fluctuate from plus to minus a few times the velocity of sound, even without making any particular movement away from the geometric box). We can characterize each fluctuation, not only by its mean value, which gave the distribution function, but by its next higher moment, the dispersion, e.g., the square root of the variance. The characteristics of these measures are that they are statistically independent. Since they are the *only* summational invariants, they are thus linearly dependent.

Since these fluctuations sample the entire dynamic space, that linearly dependent relation, representing a difference equation, can be integrated and it represents the equation of state, *as long as no shorter time than the fluctuating cycle time is invoked*. The cycle time bears a definite finite relation to the total summed time of all the relaxation modes (the "day" of the atomism). Other potentials then follow from definition (e.g., given U or T, and p, then ρ, S, H, F, and G can be defined).

However, the sustained motions in the geometric boxes are not conservative. The box walls are not perfectly elastic, perfectly reflecting. After a characteristic number of bounces the atomisms escape from their boxes. The walls act as if they were "translucent." Thus one does not find a true closed conservative cycle. That motion out of the geometric box is the prototype of a diffusion, a lossy or dissipative process.

But the atomisms in the field are engaged in a sustained collisional motion. They derive their lost energy per cycle from the radiation field equilibrium (or other sources, if made available through the boundaries) maintained at the wall boundary (e.g., as enclosure or supply temperature). Although there is a thermodynamic loss associated with that service, at this time we are not concerned with balancing the entire universal account, only in describing the internally sustained motion.

It is because that dissipative loss is made up, each cycle, that the atomisms can be thought of as operating in a limit cycle. Though on one hand, the individual atomism may drift out of our geometric box (or one may die, or interchange function with another), it is replaced. Thus in the action space, one actually sees essentially sustained closed cycles of performance, even though the actual geometric space is not closed.

The true action of concern to us, associated with the "free" energy available above the mean, or in the homeokinetic case, the mean daily power (e.g., 2,000 kcal/day for a human atomism, or some related specific figure for a cell) times the day represents the *net* action, or power-action available to overcome the dissipative losses. It is that power which quantizes the atomism in its action space. Note that the elementary kinetic theory of a gaseous mean free path provides it with the value ν/C, the ratio of kinematic viscosity to propagation velocity. The kinematic viscosity represents the lossy process of momentum diffusivity. Thus the sustained mean free path literally emerges from a lossy process.

So we observe how the statistical "mechanical" characteristics are derived within the atomistic geometric space which is mapped in a total or net action space.

Note that the basic step we have taken is to go from the conceptual framework of the analytic formulation of a force description—whether we precisely knew the form of the force law or not—and transform it by mapping into an action space in which we only have to keep track, equivalently, of statistical moments of the displacements, which were the effects of the forces. The primitive form of that process was demonstrated by

Einstein in his theory of Brownian motion, as Stokes-Einstein diffusion. It was represented by the mean square motional displacement as a function of time.

As Newton surmised, and Einstein underscored, we are dynamically constrained, mechanically via forces, only to the second derivative of displacement, and thus mathematically to the concordant three moments. These strictures apply equally to the thermostatics (average time-independent processes) *and* the irreversible thermodynamics (time-dependent processes that will depend on external forces or potentials).

Thus our thermostatics did not concern itself with the loss processes by which the steady-state equilibrium was maintained in the box. We said that if one imagined a sustained motion *in the geometric box* (a closed cycle in the action space), by which an invariant atomistic player would continue to perform its cycle (e.g., mean free path-relaxation time cycle, (δ_1, τ_1), or τ_1 and $\delta_1 = C/\tau_1$, or related mean free path definitions from net lossy "daily" power action), then one could obtain the thermostatic potentials, e.g., its "daily" power, the external time of its "day," the materials and charges that it processed (e.g., took in and put out), the matrix of its action modes, its morphological life time.

On the other hand, the Stokes-Einstein diffusion shows a random-walk variance in the motion of a particle, that grows uniformly (e.g., spherically) with time. The microscopic effect of such individual random walks is exhibited as a relative directional diffusion between particles 1 and 2 in a medium in which a density gradient exists (whether of mass concentration, temperature, or velocity). The diffusion appears now, not as a random process but as vectored diffusion according to a constant gradient. (Such connection is shown by Eq. A1.60 in (41).)

Thus motional change out of the box can be assessed by watching the time-dependent change, e.g., linear change with time, among contiguous boxes. In (δ_0, τ_0) space, the collection of boxes near equilibrium, one will only find diffusions, wave propagations, and convections, although the processes may not be isotropic.

Summary

By abstracting real motion and change in geometric space, through transforming them into motions in action space, we can achieve a fresh view of thermostatics and of diffusive transports. This approach relieves us of the burden of dealing with the continuous differential equations of Newtonian mechanistic analysis, with its emphasis on idealizing detailed geometric paths of the fluctuations. Instead we emphasize the statistical moments of the fluctuation process, derivable from observational time series.

It is not necessary to deal with a continuous set of displacements, velocities, and accelerations in completing a description of local motion as diffusion, wave propagation, or proper ensemble (stream) motion. As Einstein's development of Brownian movement exhibits, the system is dynamically constrained in mechanical analysis by the forces acting on the local ensemble and their effects on the derivatives of displacement. When we are near equilibrium (no net external forces) the lowest moment of displacement approximates zero; the time series of the displacements sums to zero. (Its time series diverges like the number series 1, -1, $+1$, -1, $+1$, ... The atom doesn't seem to go any place.) The marvel of the Einstein derivation of Brownian motion was the decision to sum the second moment of displacement, i.e., the square of the displacement, its variance. By examining the equipartitioning of energy with the underlying field atomisms, Einstein showed that any isolated particle draws its sustenance (energy) from the apparent "noise" of the underlying atomisms, and so its mean square displacement increases linearly with time. That is the essence of the Stokes-Einstein diffusion process.

From its very nature, in which the fluctuating particle integrates the underlying motion, the Einstein fluctuation model cannot hold down to a fraction of the τ_1 time scale. By virtue of the integrating property, the description of motion becomes asymptotically valid at about the 2–3 τ_1 time scale. Below that scale, a different mapping with an appropriate kinetics must be used. This appropriate kinetics in some cases might be kinetic theory, or in some cases quantum mechanics.

The near-equilibrium physics, summarized above, emerged out of little more than a Newtonian mechanical outlook based on the physical forces of electromagnetism and gravitation, and a quantization of cyclic action. Through it, by taking the field view, we do not have to account for the instantaneous atomistic motions, but instead we transfer our attention away from the detailed continuous motions in geometrical space to the quantized action motions in action space. *In this transformation the underlying continuous motion generates a discrete time series of states.* That result is the key: it is from the time series of states that we extract the various statistical moments. The discrete elements of change are the fluctuations in τ_1 time. Any sustained accelerational bias via persistent forces in this Newtonian mechanics can be associated with a higher statistical moment in addition to the Einsteinian diffusion. But the lower statistical characteristics of all the quantized action cycles at the atomistic level provide us with a complete thermodynamic account consisting of the distribution function, the various thermodynamic potentials, and other constituitive relations for the ensemble in the (δ_0, τ_0) domain, without our ever having to attend to individual fluctuational paths. Then in the space-time scale beyond, only the remaining dynamic constraints are relevant. This fact represents an enormous simplification over the conventional analysis, and provides a basis for an experimental approach to thermodynamics of living systems that would otherwise be impractical (SECTION 3).

When a Stokes-Einstein fluctuation step is made, the process is near thermodynamic equilibrium locally, even though an individual fluctuation may be enormous. In a liquid, the process is at equilibrium. The underlying atomicities have been sampled for temperature, for density, for momentum. Each particle's state has been averaged through the ongoing actions of its neighbors. Thus, the Stokes-Einstein process, step by

step, can be used for descriptions *up to the limits of thermodynamic descriptions*. It is good to 2–3 τ_1. It can be used to account for Burnett-type transport (16–19, 21, 22) as well as for the near-continuum and continuum equilibrium of a Navier-Stokes description of fluid processes (41). We will make the point again that such processes may be far from equilibrium globally, over a large ensemble; yet locally, at time and displacement scales not too far removed from (δ_1, τ_1), they are near equilibrium. Why? Because individual fluctuations substantially sample the entire dynamic range and the system is integrated over a collection of sample data first up to and then beyond the (δ_0, τ_0) scale. The critical issue, as with all such time series, is the choice for an appropriate, finite scale to establish good statistical measures. For complex systems, we require bookkeeping only in terms of fluctuation numbers commensurate with the largest relaxation time that maps major segments of the modal action space. However, we must identify the modes. At this scale all of these fluctuations that constitute engine cycle processes with underlying subatomistic escapements appear "random," but *in summation* they make up the distribution function. Then, at system's scale beyond (δ_0, τ_0), we can develop the historical (time-dependent) process for the system by a network engineering description (29).

SECTION 3. APPLICATION TO BIOLOGY

Up to this point we have been mainly concentrating on a simple system, as if it were a near-ideal gas in which translational degrees-of-freedom dominate the expenditure of energy. But closely packed clusters of liquid or plastic cells, or living cells carry out dissipative processes within their many interior degrees-of-freedom, with translational motion being only a secondary consideration. Most of our concerns are the coherent ring of action modes among those essential actions required for the system to persist. In fact, examination of the caloric expenditure of an *Escherichia coli* organism shows that it spends about 85% of its energy just maintaining itself. Similarly, with human beings we find that the "basal" metabolic rate is likely to represent more than two-thirds of the daily caloric expenditure, even for active people. Therefore, we must now apply the nonanalytic, time-series approach to the statistical quantification of thermostatic and thermodynamic relations, to encompass systems much more complex than simple gases, especially homeokinetic systems. There is no inherent difficulty in extending the thermodynamic notions to a more general phase space of the modified degrees-of-freedom, which now include both the integrated fast external (e.g., translational) and slow internal (e.g., concentration, electric, or chemical potential) variables. There is no longer any need to assume equipartition of energy between external and internal degrees-of-freedom. The scale τ_1 can now refer to the cycle time of internal modes that is involved in the major average repeated cycles of action in the living systems, i.e., its "day." Action would still be the energy × time product (with an associated, virtual mean free path in action space).

A Metric for Complexity

By comparison to a human being, *E. coli* is simple. It has perhaps a thousand genes (and proteins), and a very limited repertoire of behavior. But there is no denying that it is a complete self-serving, autonomous, homeokinetic system, compared to which the nonideal gas, discussed above, is trivially simple. A metric of complexity would reflect the *number* of microstates (dynamic states in phase space complexions), or internal action modes available to a system. By that metric a monatomic gas would be the least complex of all (noncrystalline) systems, a diatomic gas would be simple, an *E. coli* organism would be complex, and a single human being would seem still more complex. A society of human beings, paradoxically, is not necessarily more complex than the individuals that comprise it and, indeed, superficially lends itself at least as readily to a field thermodynamic approach as does an individual organism. The reason is this: field thermodynamics is a statistical science; it deals with ensembles of individuals, but not with the uniqueness of individuals. In fact, it is only the common attributes required for survivorship by individuals that contribute to the statistical characteristics of an ensemble. Therefore, the artistic view of the uniqueness of each created unit is not encompassed in this statistical view. However, human individuals viewed as atoms operating near equilibrium in a statistical mechanical ensemble do generate the political, economic, and historical processes that define cultures (30, 34).

For those who wish to reflect upon a metric for order, or organization, Morowitz has offered an interesting approach (46), compatible with our Boltzmannian view (41).

Communal Organization in Living Systems

The biological medium is more of a gel than possessed of a pure crystalline or fluid character. The implication of this fact is that when we view a morphological field we must expect to find evidence of fluidlike–both material and electric–communications among surrounding neighbors (e.g., cells in an organ). Iberall and Schindler (38) have concluded that communal organization in liquids, gels, or even in living cellular arrays, begins with a coordination number of about 20 near neighbors. An elegant article on amorphous solids (11) lends support to this conclusion. Its findings indicate an average packing ratio of 0.64 with peak occupation at $r = 1$ and $r = 1.75$. Modeling these numbers as spheres shows that 18 "spheres" cluster around a center. Quite often detailed crystallography obscures that simple fact that in mobile crowded media, all the close neighbors tend to be involved before a Stokes-Einstein diffusion step (a fluctuation) can take place.

Thus fluctuations tend to involve all the near neighbors, which can be imagined to be arrayed 3 × 3 × 3, if portrayed simply in a cubelike organization, or, in the case of a cellular tissue, perhaps as a more nearly spherical cell with six others in immediate contact, and two (circular) sheets of seven cells each, one above and one below the central cluster. The removal of one or two

cells from such a close pack then permits liquidlike diffusivity (38). More elaborate communal organization occurs in the form of the *functional units* of organs and tissues, the disparate cellular elements of organ unit, vascular unit, nerve units, lymphatic unit, and involving also nerve control of the vascular unit. (We are indebted to Professor E. Bloch for many useful discussions of functional units (5).)

A functional unit is that cluster of elements of various kinds that is just sufficiently organized to produce a complete element of persistent function, characteristic of the organ or tissue under examination. For example, in the case of muscle the functional unit appears to include the entire length of a bundle of muscle fibers, their capillary blood supply, their lymph supply, their afferent and efferent nerve supplies, and the autonomic nerve supply of the arterioles. (Notions developed in collaboration with Professor Bloch; see chapter 5 in (30).)

The islets of Langerhans of the endocrine pancreas are a clear example of a functional unit. The islets consist of an ordered cluster of α-, β-, and δ-cells capable of releasing glucagon, insulin, or somatostatin, respectively. (Other cells of unknown function are also present.) These cells talk to each other, and receive both sympathetic and parasympathetic innervation. They share a common blood and lymphatic supply. The islet is an atomistic factory station in the thermodynamic field of glucoregulation processes. Islets communicate with each other indirectly through their cooperative influences on blood glucose and amino acid levels that serve as inputs to all of them, and they are coordinated by the neural supply.

In every case of physiological analysis, at any field level, it is helpful to identify, at least approximately, the elements of function—the functional units—and to specify how they interact with each other as atomisms in a field. The advantage of this approach is that it forces structure and function to be considered simultaneously and according to the physical requirements of the system. It is not a trivial fact that *structure is function*, at all levels. Structure is always an expression of the functions of energetic particles at different levels, under conditions in which interactions are very strong. At each succeeding level, new functions emerge from the structures produced by lower level functions, generally involving weaker forces.

This outlook toward physiological analysis is based on the premise that the autonomous operation of the biological field under study is the concern of the investigator. Then the identification of the complete functional unit and the use of the apparatus of irreversible thermodynamics is necessary. On the other hand, many investigators have more limited concerns. Their interest may only be in identifying a particular unit process, e.g., the role of calcium in synaptic transmission. While identifying such unit processes creates most of the excitement in biological research, that interest must be distinguished from a different task, determining the integrative function in the system. That interest requires the thermodynamic view.

The complete thermodynamic view requires a knowledge of the unit processes (e.g., the functional units). Conversely the thermodynamic view can point to missing unit processes or functions at every organizational level in the organism (see for example (34) or (43)).

An important consequence of the communal organization of the atomisms of living systems is that we can expect to find for them a (δ_0, τ_0) domain in which near-continuum transport phenomena can be observed. The major difference between their complexity and that for simple systems is that the δ_0 space derives from the internal communal action. The three modes of transport identified for the simple gas system (diffusion, wave propagation, and convection) still characterize the transports, but a large amount of the diffusion will be internalized. Furthermore, these modes are easily found in various living systems, as exemplified below.

1) Diffusion: exchange of oxygen and other small molecules in capillary beds; thermal conduction of energy away from such heat-producing sources as muscle; or the spread of population, pottery, metallurgy, farming among people (see, for example, discussion in chapter 25, "How neolithic ideas spread" in (56) for illustrations of cultural diffusion, dealing with both the populations and their artifacts; or see in particular (10) which provides details on the spread of agriculture).

2) Convection: the circulation of the blood, internal heat transfer in the body.

3) Wave propagation: pacemaker rhythms in the heart, or uterus; wavelike coordination of locomotion spreading from cell to cell in multicellular organisms, or within a cell in single-cell organisms; population waves spreading from Europe or reverberating within the United States (as they are now doing from the West Coast back toward the East Coast, refracting toward the Sunbelt); the spread of revolution in France (vividly depicted and elegantly documented in Lefebvre, *The Great Fear of 1789*).

Wherever there are transport phenomena, field thermodynamics applies and tells us what we seek. After we have found the transport modes, we can look for the conservations underlying them. Below the atom, the many conservations exhibited by so-called fundamental particles are still in process of discovery. Above the atom we have the conservations of mechanical systems (energy, mass-species, momentum or action, charge). For a species of organisms, we have population number (not with the constancy of a physical conservation, but similar in character. As an extended version of a summational invariant, individual members of a species behave as if they mean to persist in numbers. For this they carry an elaborate genetic code and persistently exhibit processes that replicate individuals). For a modern human society we have value-in-exchange (a concept that clearly dominates economic behavior and is also of the character of a summational invariant). It takes some deep reflection to realize that value-in-exchange is in fact a thermodynamic variable that is conserved in transactions, and that a social physics can be built to include it (chapter 12 in (30); (34)).

Of all the transport phenomena, diffusion is the most profound because it plays the unique role of local dissipative exchange, the "arrow of time" for causality

(29), which is at the heart of all scientific systems analysis. But all three transport modes must be accounted for in a complete thermodynamic description. We recognize that biologists are usually focussed on particular cases of transport but we want to emphasize again the universality of transport phenomena. The very generality of physics cannot guarantee what strategies nature may have used in a particular case (unless a great deal of detail is available), but it does guarantee that transport will exist and will be of some general form (diffusion, wave propagation, or convection). Even the traces of ideas are subject to the laws of transport as surely as if they were material. One man's concept, spoken or written or otherwise manifested, is another man's percept, and a transport, commonly diffusive, has occurred between them.

If we seem to make an apotheosis of transports, perhaps irrelevantly but not irreverently, we offer the image on the ceiling of the tomb of Ramses VI, in the Valley of the Kings. There, in surviving, splendid color, is a vivid picture of the transport of the sun god Ra through the intestines of the goddess Nut, who swallows him at every dusk, and carries him in her bowels through the twelve stages of the night, to recycle him at each dawn, born again, and ready to being a new day (9).

The Experimental Approach

To achieve a rich thermodynamic description of the experimental field of observation the biologist will need to carry out the following steps.

1) Specification of the atomisms and ensemble of interest.

Table 1 suggests some examples of atomistic units and their ensembles, or clusters, that may seem appropriate for thermodynamic description. Each ensemble, or cluster, is part of a field at a given level in which many different station or factory processes are located. The image is that of a pinball machine (25). It can immediately be seen from Table 1 that the guidelines for identifying the true thermodynamic field and all the relevant players and factory departments for an ensemble of atomistic units are not obvious. In the case of the ideal gas the atomisms are all alike materially, though at any instant they vary energetically, and there is no difficulty in specifying the atomism or the ensemble field. What about the case in which atomisms in a field seem to be of different kinds? A thermodynamic field need not be homogeneous, isotropic, or of single substance and simple phase. In the biological case we have inhomogeneous, anisotropic fields of many different atomisms at many levels. The field of a eucaryotic cell has a great number of organelles that cooperate in producing its integrative function. A large number of alternative operating states of the kidney or liver have to be reviewed in determining what are their irreducible functional units. Depicting the circulations in a city or the conflict of polities in a civilizational web may complete the required images. The thermodynamic description must be arrived at with great care in all such cases, but, fortunately, the description may not be very complicated in its essentials even when the field is variegated. The fundamental notions of fluctuations, interactions, conservations, engine cycles, spectral properties, and transport modes still serve as the basis for the thermodynamic bookkeeping. If they are accounted for, the system will be described adequately in a physical sense. It is not trivial to define a thermodynamic field competent to support integrative function.

TABLE 1. *Some biological fields for thermodynamic description*

Atomistic Units	Relevant Ensemble, Cluster, Factory Stations – in the Field of the Same Level*
1. Polyribosome	1. Rough endoplasmic reticulum
2. Mitochondrion	2. Clusters of mitochondria at sites of transports or syntheses
3. *E. coli* organism	3. Colony of *E. coli*
4. DNA	4. DNA, and the constellation of RNA's, and enzymes that accomplish synthesis, repair, excision, readout, etc.
5. Hepatocytes	5. Functional unit of liver (with blood supply, neural supply, bile duct, Kupfer cells)
6. Quadriceps muscle	6. Extensors and flexors of thigh
7. Extensors and flexors of thigh	7. Whole musculoskeletal system and motor control system
8. Liver as organ	8. Cluster of digestive tract organs, exocrine and endocrine, with their informational connections through hormones and nerves
9. Admissions committee member (e.g., of a medical school)	9. The committee as a body
10. The Admissions committee	10. The faculty, student body, administration, and the applicant pool

* These are putative fields. Further consideration of particular cases would almost certainly lead to a redefinition of the field. The very act of deciding on the field highlights thermodynamic issues very effectively and stimulates a deeply meaningful consideration of what it means to relate structure and function.

2) The time series of fluctuations must be determined.

Because the fluctuations will usually be manifestations of engine cycles, a statistical spectral analysis represents a first approach (23, 33, 47). Zero frequency, low, middle high, and very high frequency domains can be described. For example, neurons of the locus ceruleus twinkle at several hundred times per second; parts of the thalamus respond, and the signals forwarded to the neocortex cause it to cycle in alertness, in oral behavior modes, in dreaming (REM) sleep, and NREM sleep, involving 90-min episodes, 24-h periods, and probably even still longer periods. Here the thermodynamic field is that of the brain structures involved in activity and alertness or their opposites.

3) Diffusive processes must be identified.

We refer here to a Stokes-Einstein type of process occurring on the (δ_1, τ_1) scale appropriate to the atomisms in the field. For instance, a major news event may diffuse and propagate through the various polities and communities of human beings before, during, and after the very high frequency wave propagation by radio and television. In the case of word-of-mouth interactions, mean free paths and mean times between contacts can be found, and they parameterize the process. We deliberately chose a communicational example in which human beings were the atoms to illustrate a diffusive phenomenon, to make certain that the reader understands that diffusive transport is not limited to molecules. It is a generalized phenomenon. However, it

is necessary to study whether the geometric field is involved in isotropic and homogeneous fashion or, as is more usual in living systems, inhomogeneously and anisotropically. One notes that the field of the living system is remarkably organized with potentials that do not particularly exceed 70 mV, 25 Torr, a few degrees Celsius.

4) Other transport modes must be identified.

These are wave propagation and convection. To illustrate: axoplasmic flows in neural nets should lend themselves well to thermodynamic description. What are the characteristic time and space parameters? What are the atomistic units in the dendrites, axons, and soma (microtubules?)? What is the transport mode (diffusion, convection, or wavelike propagation?)? What is the energy source? What is the spectrum?

By integrating over experimentally derived data, an empirical determination of coefficients for all of the exhibited transports, propagations, and convections can be obtained, according to the technique outlined in SECTION 2. Both wired nets (facilitated paths) and fields will be found.

5) A summarizing description for the field should be generated.

Having identified atomisms, fields, transport modes, and spectra, and the statistics of fluctuations, we can now concentrate on the quantities that are conserved in the interactions and their more global changes. (Note that structure itself and its persistent function is conserved, through maintenance!) Now we are prepared to close the books. From all these qualitative and quantitative specifications a summarizing field thermodynamic description must emerge, in three parts: *a*) the thermostatic description, *b*) the irreversible thermodynamic description, and *c*) the engineering network description. We ask that the fundamental physiology of state and rate be identified and developed before the common analytic processes, generally invoked by systems biologists and biomedical engineers, is applied (36).

At the present state of description, we do not believe that an understanding of biology in physical reductionist terms (Anderson (2)) is to be secured at the formidable analytic level of modern physics (*Physical Review, Reviews of Modern Physics*) but, rather, as looser, more philosophic constructs, that would have satisfied Maxwell, Jeans, Rayleigh, Eddington, Gamow, and perhaps even Einstein. We have concerned ourselves only with the basis for the principles of physical explanation. Therein, we expect no great surprises. As logical elements, the use of these principles on the complex interconnected morphology of living systems is difficult enough; after all, the living state is more complex than gas, liquids, or solids. While we have provided a syntheses of ideas, someone else may be capable of providing a better, more condensed abstract formulation.

The descriptions we have offered can provide fresh insights into the structure and function of biological systems, and solutions to specific problems. For example, we direct the reader to *1*) a similarity analysis of mammalian circulatory systems across the complete size range (26); *2*) a proposed neurophysiological basis for war (27); *3*) the prediction of periodicities in blood glucose levels (47); *4*) the definition of boundary phenomena in liquids (39); *5*) the explanation of the frequency of occurrence of lexical units in written language (APPENDIX II, Part II, this series (41)); *6*) flow regulation in mammals (28); *7*) identification of the basis for direct and cross-coupled phenomena in transports (APPENDIX I, Part II, this series (41)); and *8*) an analysis of transportation problems of cities (34), which is still a small sample of the diversity of problems to be solved. Your attention and help would be appreciated to provide the bricks and mortar for the real "constructionist" path of reductionism (2).

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REFERENCES

1. ADAMS, H. A letter to American teachers of history. In: *The Degradation of the Democratic Dogma*. New York: Macmillan, 1919.
2. ANDERSON, P. More is different. *Science* 177: 393–396, 1972.
3. AYALA, F., AND T. DOBZHANSKY (Editors). *Studies in the Philosophy of Biology*. Berkeley, Calif.: Univ. of Calif. Press, 1975.
4. BERNARD, C. *An Introduction to the Study of Experimental Medicine*. New York: Schuman, 1949.
5. BLOCH, E. The structure and operational characteristics of the community of cells that characterize an organ: the functional units of organs. In: *Regulation and Control in Physiological Systems*, edited by A. Iberall and A. Guyton. Pittsburgh, Pa.: Instr. Soc. Am., 1973.
6. BLOCH, E., S. CARDON, A. IBERALL, D. JACOBOWITZ, K. KORNACKER, L. LIPETZ, W. MCCULLOCH, J. URQUHART, M. WEINBERG, AND F. YATES. *Introduction to a Biological Systems Science*. NASA CR-1720, Feb. 1971. (Available from Natl. Tech. Info. Serv., Springfield, Va.)
7. Boyer, T. Random electrodynamics. *Phys. Rev. D.* 11: 790–809, 1975.
8. CARDON, S., AND A. IBERALL. Oscillations in biological systems. *Currents Modern Biol.* 3: 237–249, 1970.
9. CASSON, L. *Ancient Egypt*. New York: Time-Life, 1965, p. 90–91.
10. CAVALLI-SFORZA, L. The genetics of human population. *Sci. Am.* 231: 80–91, 1974.
11. FINNEY, J. Modelling the structures of amorphous metals and alloys. *Nature* 266: 309–314, 1977.
12. FOX, S. Lars Onsager (1903–1976). *Biosystems* 8: 161, 1977. (Other acknowledgments and citations are found in p. 163–288.)
13. GAMOW, G. *Biography of the Earth*. New York: Viking, 1941.
14. GAMOW, G. *One Two Three–Infinity*. New York: Viking, 1947.
15. GOODWIN, B. A statistical mechanics of temporal organization in cells. In: *Toward a Theoretical Biology. 2. Sketches*, edited by C. Waddington. Chicago, Ill.: Aldine, 1969.
16. GREENSPAN, M. Propagation of sound in rarified helium. *J. Accoust. Soc. Am.* 22: 568–571, 1950.
17. GREENSPAN, M. Combined translational and relaxational dispersion of sound in gases. *J. Accoust. Soc. Am.* 26: 70–73, 1954.
18. GREENSPAN, M. Propagation of sound in five monatomic gases. *J. Accoust. Soc. Am.* 28: 644–648, 1956.
19. GREENSPAN, M. Rotational relaxation in nitrogen, oxygen, and air. *J. Accoust. Soc. Am.* 31: 155–160, 1959.
20. GUREL, O., AND O. RÖSSLER (Editors). Bifurcation theory and applications in scientific disciplines. *Ann. N.Y. Acad. Sci.* In

press.
21. HERZFELD, K., AND T. LITOVITZ. *Absorption and Dispersion of Ultrasonic Waves*. New York: Academic, 1959.
22. HIRSCHFELDER, J., C. CURTISS, AND R. BYRD. *Molecular Theory of Gases and Liquids*. New York: Wiley, 1964.
23. IBERALL, A. Human body as an inconstant heat source and its relation to clothes insulation. 1. Descriptive models of the heat source. 2. Experimental investigation into dynamics of the source. 3. Precise measurement of clothes insulation during controlled operation of the human. *Trans. ASME, Ser. D., J. Basic Eng.* 82: 95–102; 103–112; 513–527; 1960.
24. IBERALL, A. A personal overview, and new thoughts in biocontrol. In: *Toward a Theoretical Biology. 2. Sketches*, edited by C. Waddington. Chicago, Ill.: Aldine, 1969.
25. IBERALL, A. *Toward a General Science of Viable Systems*. New York: McGraw, 1972.
26. IBERALL, A. On growth, form, and function—a fantasia on the design of a mammal. *Trans. ASME, Ser. G, J. Dyn. Syst. Meas. Contr.* 95: 291–295, 1973.
27. IBERALL, A. A proposed neurophysiological basis for war. *Ann. Biomed. Eng.* 1: 446–454, 1973.
28. IBERALL, A. Flow and pressure regulation in the cardiovascular system. In: *Flow: Its Measurement and Control in Science and Industry*, edited by W. Vannah and H. Wayland. Pittsburgh, Pa.: Instr. Soc. Am., 1974, vol. 1, part 3.
29. IBERALL, A. On nature, man, and society: a basis for scientific modeling. *Ann. Biomed. Eng.* 3: 344–385, 1975.
30. IBERALL, A. *On Nature, Life, Mind and Society—Fragments of a Vigorous Systems' Science*. Upper Darby, Pa.: Gen. Tech. Serv., 1976.
31. IBERALL, A. A field and circuit thermodynamics for integrative physiology I. Introduction to the general notions. *Am. J. Physiol.* 233: R171–R180, 1977 or *Am. J. Physiol.: Regulatory Integrative Comp. Physiol.* 2: R171–R180, 1977.
32. IBERALL, A., E. BLOCH, AND N. SUWA. Table 144. In: *Respiration and Circulation*, edited by P. Altman and D. Dittmar. Bethesda, Md.: Fed. Am. Soc. Exptl. Biol., 1971.
33. IBERALL, A., AND S. CARDON. Control in biological systems—a physical review. *Ann. N.Y. Acad. Sci.* 117: 445–518, 1964.
34. IBERALL, A., AND S. CARDON. Systems models for transportation problems. I. Introducing a systems science for transportation planning. II. An introduction to urban center modeling. III. A computable command-control system for a social system. IV. The development of urban dynamics and its possible regulation. Dept. Transportation Rept. DOT-TSC-OST-76-12. 1976. (Available from Natl. Tech. Info. Serv., Springfield, Va.).
35. IBERALL, A., S. CARDON, AND E. YOUNG. *On Pulsatile and Steady Arterial Flow, the GTS Contribution*. Upper Darby, Pa.: Gen. Tech. Serv., 1973.
36. IBERALL, A., AND A. GUYTON (Editors). *Regulation and Control in Physiological Systems*. Pittsburgh, Pa.: Instr. Soc. Am., 1973.
37. IBERALL, A., AND W. MCCULLOCH. The organizing principle of living systems. *Trans. ASME, Ser. D, J. Basic Eng.* 19: 290–294, 1969.
38. IBERALL, A., AND A. SCHINDLER. *Physics of Membrane Transport*. Upper Darby, Pa.: Gen. Tech. Serv., 1973.
39. IBERALL, A., AND A. SCHINDLER. A kinetic theory, near continuum model for membrane transport. *Ann. Biomed. Eng.* 1: 489–497, 1973.
40. IBERALL, A., AND H. SOODAK. Physical basis for complex systems—some propositions relating levels of organization. *Collective Phenomena*. In press.
41. IBERALL, A., H. SOODAK, AND F. HASSLER. A field and circuit thermodynamics for integrative physiology. II. Power and communicational spectroscopy in biology. *Am. J. Physiol.* 234: R3–R19, 1978 or *Am. J. Physiol.: Regulatory Integrative Comp. Physiol.* 3: R3–R19, 1978.
42. KATCHALSKY, A., V. ROWLAND, AND R. BLUMENTHAL (Editors). *Dynamic patterns of brain cell assemblies*. Boston, Mass.: Neurosci. Res. Program Bull. 12, 1974.
43. LLINAS, R., AND A. IBERALL. A global model of neuronal command-control systems. *BioSystems* 8: 233–235, 1977.
44. LOTKA, A. *Elements of Mathematical Biology*. New York: Dover, 1956. (Original ed. 1924.)
45. MOROWITZ, H. *Energy Flow in Biology*. New York: Academic, 1968.
46. MOROWITZ, H. The biological time scale. In: *Temporal Aspects of Therapeutics*, edited by J. Urquhart and F. Yates. New York: Plenum, 1973.
47. OOKHTENS, M., D. MARSH, S. SMITH, AND F. YATES. Fluctuations of plasma glucose and insulin in conscious dogs receiving glucose infusions. *Am. J. Physiol.* 226: 910–919, 1974.
48. OPARIN, A. *Origin of Life*. New York: Macmillan, 1938.
49. OSTER, G., A. PERELSON, AND A. KATCHALSKY. Network thermodynamics; dynamic modeling of biophysical systems. *Quart. Rev. Biophys.* 6: 1–134, 1973.
50. POPPER, K., AND J. ECCLES. *The Self and Its Brain*. New York: Springer-Verlag, 1977.
51. PRIGOGINE, I. Order through fluctuation: self-organization and social systems. In: *Evolution and Consciousness—Human Systems in Transition*, edited by E. Jantsch and C. Waddington. Reading, Mass.: Addison-Wesley, 1976.
52. PRIGOGINE, I., AND G. NICOLIS. Biological order, structure, and instabilities. *Quart. Rev. Biophys.* 4: 107–148, 1971.
53. SECHENOV, I. *Selected Physiological and Psychological Works*. Moscow: Foreign Languages Publishing House, 1952–1956.
54. SEIDENBERG, R. *Post-historic Man: An Inquiry*. New York: Viking, 1974. (Original ed. 1950.)
55. SMUTS, J. *Holism and Evolution*. London: Macmillan, 1926.
56. VAN DOREN STERN, P. *Prehistoric Europe*. New York: Norton, 1969.
57. YOUNG, E. Transient behavior of arterial systems in response to flow pulses. *Bull. Math. Biophys.* 30: 359–385, 1968.

A. S. Iberall
General Technical Services, Inc.
Upper Darby, Pennsylvania 19082

Correction to Part I

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Page R171: A. S. Iberall. "A field and circuit thermodynamics for integrative physiology. I. Introduction to the general notions." Page R176: delete $V_{s,s}$ from *Eqs. 8* and *9*, which should now read

$$S_{ij} = -\left[p + \lambda \frac{D \ln \rho}{Dt} \right] \delta_{ij} \qquad (8)$$

$$S_{ij} = -P\delta_{ij} \qquad (9)$$

Page R180: reference 21 should read; Waddington, C. *Toward a Theoretical Biology. 2. Sketches*. Chicago, Ill.: Aldine, 1969. (Discussion by H. Pattee, p. 268–284.)