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A field and circuit thermodynamics for integrative physiology. I. Introduction to the general notions

IBERALL, A. S. *A field and circuit thermodynamics for integrative physiology. I. Introduction to the general notions.* Am. J. Physiol. 233(5): R171–R180, 1977 or Am. J. Physiol.: Regulatory Integrative Comp. Physiol. 2(3): R171–R180, 1977.—In this first of three articles on a physical basis for integrative physiology, statistical mechanical concepts are developed into a field thermodynamics. The development begins by comparing the different ways change is viewed in biology compared to physics. The Hamiltonian field concept unites the two. The requirements of a thermostatic description are introduced; then those of nonequilibrium thermodynamics are added. Conditions suitable for continuum, near-equilibrium analysis of systems are given; then the role of physical forces in organization is discussed. The development returns to statistical mechanics, and introduces conservation principles and equations of change for ensembles of interacting units. A general notion of systems and thermodynamic engines is discussed next, and a narrative account of the explanatory scope of field thermodynamics is given. Its applications to living systems are the subject of the subsequent two articles of this series.

biophysics; general systems; homeokinesis; irreversible thermodynamics; reductionism

THE DEVELOPMENT of integrative, quantitative physiology can be encouraged by strengthening its ties to physics. In this paper a general physical formalism is offered to the physiologist who seeks a basis for experimental strategies that can be developed into an integrative systems outlook. Subsequent papers (Parts II and III) will build from the physical notions introduced here toward a spectroscopic approach to physiological systems, and toward methods for describing cell, organ, or organismic process dynamics. The purpose of all three discussions is to show that integrative physiology can find a basis in physics that will guide experimentation. The physical basis will support a reductionistic attitude that does not lose sight of those emergent features of living systems, which are the interest of integrative physiology.

Some central themes of biology are that cells are reproduced by cells, the program for reproduction is encoded genetically, and the internal environment of the cell or complex organization of cells is regulated, even though constituents turn over (17). In addition to reliable reproduction, the living organism exhibits four other essential processes: *1*) sensory transduction, *2*) motor actuation, *3*) ingestion and energy transformation, and *4*) process governance in accordance with command-control algorithms. Finally, as an overall process, the cell or complex organism responds to external stimuli with a characteristic repertoire of behavior. A minimal, scientific reductionism that might be suitable for biology would claim merely that processes in living systems are compatible with the laws of physics and the transformations of chemistry (see (1) for examples). I propose to explore physical constructs much more deeply, and to suggest how the laws of irreversible thermodynamics might be used to describe hierarchies in physiological systems. The result of this analysis, if successful, could lead the biologist toward fresh experimental strategies that might help him realize a greater unity of understanding of living systems. A preliminary account of such an effort has been published (2).

Two Views of Change

There seems to be a great difference between the biologist's view of a stimulus-response chain for organismic behavior, and the physicist's view of motion and change.

As we surmise it, the biologist has an input-output view of motion and change

$$\text{S (stimulus)} \rightarrow \text{R (response)}$$

In simple (genetically limited) animals, the biologist considers behavior to be "stimulus bound," or stereotypic. In more complex animals, he views the response to be related less directly to the stimulus, viz.

$$\text{S} \rightarrow \text{O (organism)} \rightarrow \text{R}$$

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where the organism has an internal command-control system (including an extensive memory) that makes it seem "free" to interpose its "will" (or "won't"), rather than merely to react stereotypically to the stimulus.

In contrast, the physicist uses a causal view of change, of the form

$$\text{F (force)} \rightarrow \text{A (acceleration)}$$

Some connection between these two different outlooks is needed.

The Field Concept; the Idea of a Challenge

To introduce the biologist to the outlook of the physicist, it is appropriate to begin with Hamilton's field description of force, rather than with the more primitive description of force balance at a point.

The causal process of physics, apparently contrasting with stimulus-response, is force-acceleration of the test body, or loosely put, force-motion (implying change in the existing state of motion). Hamilton proposed to transform this notion about causality into a field form. Suppose a field can be characterized by potentials which are storage depots for internal energy, and which can create force upon interaction with a body. Now imagine that a challenging body is introduced into the field: the field can then be mapped by the trajectories undergone by the body, in the form of flux intensities, as the body interacts with the local potentials.

Hamilton's image of a field can be likened to ray optics. If you introduce a ray of light into a field, its trajectory is determined by the local property of the index of refraction. Hamilton developed a "ray mechanics," where the local potential provides a substitute for the index of refraction of ray optics. The general notion I propose here is that the character of any field, however complex, can be discovered by observing the trajectories of (or responses to) challenging or stimulating particles.

The term challenge is used to denote the characteristic destiny of a system (e.g., a living organism) which is confronted again and again by physical agencies. The organism manifests a recognition process, an algorithmic strategy to confront or guide the challenging agent, and some output response to the challenge. The result of the confrontation may be benign, beneficial, malevolent, decorative, or meaningless and irrelevant.

In seeking a description by way of the notion of a stimulus or challenge, I confront an old conflict in physiology that existed at the time of Bernard and Pasteur. The physiologist, Bernard, believed that the primary question for a physiological science was the maintenance of relatively constant conditions of the internal milieu, independent of challenging vicissitudes. (His view implied a self-regulatory scheme that would have to be achieved by thermodynamic means.) The chemist, Pasteur, believed that the primary question with regard to challenges was the nature of the challenge itself and the level at which response is made. The general notion to be developed in this article is that both of the above views can be subsumed by the realization that regardless of the type of challenge, or the regulatory machinery to deal with it, all the interactions involved are thermodynamic in character. At this point I must caution the reader against the superficial opinion that thermodynamics provides only the limited, idealized, equilibrium-bound descriptions he probably encountered in chemical thermodynamics, or in courses on physical chemistry. I hope that as he examines the three papers of this series, the reader senses the more impressive descriptive power available from the thermodynamics of irreversible processes (nonequilibrium thermodynamics) which the author regards as the fundamental basis of all systems analysis. From the thermodynamic point of view, it is not necessary to make any important distinctions among the various types of challenges that may confront an organism.

As it is of concern in biology, a challenging moiety may be a food particle, a drug, microbe, a light ray, sound wave, or anything that impinges on the living space; the input stimuli or challenges may be physical or chemical complexes or even "informational." A general scheme of response to challenges will be developed in the form of a field or network, nonequilibrium, irreversible thermodynamics.

Nonequilibrium (irreversible), field thermodynamics deals with conditions that are *near equilibrium* (or at equilibrium, as a special case). It also can deal with repetitive phenomena, as will be explained later. Even though any particular challenge might seem to be an aperiodic, or unique event, it may always be considered as one of a repeated number of such challenges that have some kind of significant interaction with and within the organism, providing it is not immediately lethal. Then such challenges are taken to be part of the ongoing experience of the organism, and they are properly the subject of an irreversible thermodynamics for field processes.

A simple image of a field process is that of a giant pinball machine. A ball with high gravitational potential is injected into a field, in which it has many dissipative ("lossy") encounters (interactions) with many mechanisms on its path to an exit. An analogous biological image would be a handful of water molecules that have been imbibed by an animal: the problem is to describe their courses through the organism. The physical requirement is that the thermodynamic machinery has to take care of all processes (encounters, interactions, transformations, transports, exchanges, etc.). In the model of ingested water, as the water molecules pass through various conduits, some pass quickly; others are caught up into long-lasting metabolic chains, or are chemically or physically bound at various stations.

There are two points of view about how to approach field thermodynamics. From one engineering point of view, the electrical engineer would tend to think of fluxes and potentials which drive fluxes (e.g., the mechanical pressures or osmotic differentials that drive a flow of water; or the flow of water itself). This view leads to the electrical engineer's standard network analysis. On the other hand, a regulation and automatic control engineer, particularly if of a mechanical or industrial engineering bent, could very well think of transfer operations and station processes, of the sort of

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mechanistic interaction that one would find in a giant pinball machine, or coin changer, or production factory. In these latter examples, an entering particle is processed by a series of complex operations along a fairly well-defined trajectory or stationary family of trajectories. The operations are powered by an overall system of field and station potentials. Thus both aperiodic and continuous field processes of a physical nature have been used for a thermodynamically consistent practice of engineering "network" analysis. These networks all have a latent, dynamic spectrum, that can be revealed if they are tested by time-dependent, driving inputs. But my concern will be with a special class of systems, that manifest a spectrum spontaneously during their ongoing operation.

BACKGROUND DISCUSSION: THERMOSTATICS AND THERMODYNAMICS

It would not be proper to offer physiologists a physical basis for explaining phenomena of interest to them without including some technical comment about the physics being used. In this section I shall discuss in narrative form, without mathematics, the topics that provide the necessary background for a field thermodynamics. The physicist should be able to tell from the prose what laws and relations are being invoked, and the biologist should be able to detect the conceptual issues. In the subsequent parts of this series I shall assume the background given here.

Thermostatic Description

Classical thermodynamics is a science of equilibrium, reversible, ideal, nondissipative, and quasi-static processes. It would better have been named thermostatics. It provides some very profound relations and descriptions (e.g., equations of state, thermodynamic potentials). I shall not present these here—they are available in standard texts; however I would like to consider the question: how quiet, how near rest or equilibrium must a system be for these classical descriptions and relations to hold? The answer is encouraging. As long as spatial gradients and temporal process rates are not extreme, thermostatic relations hold for local regions. Even in the case of shock waves, where thermodynamics does not apply locally, there are "jump" conditions applying across the shock front so that thermostatic potentials are again applicable.

Nonequilibrium (Irreversible) Thermodynamic Description

Irreversible thermodynamics applies to near-equilibrium conditions in which thermostatic description holds locally. What the irreversible thermodynamics adds to the description is an explanation of how thermostatic variables change from region to region, because of differential gradients or rates of change. Gradients or flows will be characterized in this description by transport coefficients that provide measures of the "irreversible" component of entropy (S) change. The total change of S is given by the classical differential equation

$$TdS = dQ \tag{1}$$

(T is absolute temperature and dQ is heat flow) which specifies heat flow within the system, from region to region.

The idea of a continuum of underlying matter-energy particles is essential in thermodynamic description, and I shall try to impart it in considering further the applicable domain of irreversible thermodynamics.

Relaxation Time, Mean Free Path, and the Continuum View

The domain of irreversible thermodynamics is limited quite specifically to the range in which its transport coefficients for diffusions and its wave propagative parameters are functions of thermostatic variables only, and not of time. However they may vary within the field space. For higher frequency processes, at which propagation in a medium is dispersive (i.e., velocity of propagation changes abruptly with frequency), the appropriate specialty is nonlinear acoustics. For fields that are spatially extremely grainy because of their particular atomistic ingredients, the appropriate specialty is far-from-continuum mechanics.

It is not difficult to specify the limits of continuum, irreversible thermodynamics. They stem from the notion that atomistic fluctuations always underly processes in a field. First there is an external relaxation time between interactions (10^{-10} s for gases; 10^{-12} s for liquids). Then, imagine fields in which some processes show considerable internal time delays (for gases, the internal relaxation time is negligible for monatomic molecules, it is of the order of 1×10^{-10} s for diatomic gases, and somewhat longer for polyatomic molecules; for liquids, it is 3×10^{-12} s for associated liquids, tending toward 10^{-10} s or longer for Kneser liquids; it is longer still for complex organic liquids and much, much longer for supercooled glasses). Now, the condition for the thermodynamic, near-equilibrium, continuum view is that we deal with disturbance effects averaged over more than 10 combined units of external and internal relaxation times. For gases, this means that we can have an irreversible thermodynamic description, locally sufficiently near equilibrium, at time scales down to perhaps $2\text{–}4 \times 10^{-9}$ s, or at frequencies up to 100 MHz.

Corresponding to relaxation time is the notion of a mean free path between atomistic units. The mean free path is given by the product of relaxation time and velocity of propagation. Representative values are: gases, $(2 \times 10^{-10}\ \text{s}) \times (3 \times 10^{4}\ \text{cm/s}) = 6 \times 10^{-6}$ cm; and water, $(4 \times 10^{-12}\ \text{s}) \times (1 \times 10^{5}\ \text{cm/s}) = 4 \times 10^{-7}$ cm = 40 Å. The condition for a near-equilibrium, continuum view is that we deal with dimensions 10 times greater than the mean free path. For water, the continuum appears at 400 Å. These statements about scales of time and space mean that with averaging over the proper space-time domains as specified, we can use thermostatic relations to describe fields locally to get the constitutive relations, and we can use near-equilibrium thermodynamics to describe motional changes.

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For flow processes, we must provide boundary conditions that are compatible with and also characterized by these fluctuation averages. If there is to be a near-continuum field description, wall conditions must be specified to the order of magnitude of one mean free path. For gaseous/solid systems, the boundary condition is defined by Knudsen slip, which is approximately the boundary velocity one would find if the velocity gradient were extended to zero at one mean free path into the solid wall. Between liquids and solid walls there is a rolling-boundary condition equivalent to one layer of rolling molecules (9, 10). These points are elaborated later.

Does the Thermodynamic Description Apply to the Living State?

The important reason for providing the above comments on the limits of applicability of thermodynamic description is to consider whether the spatial or temporal boundary conditions required for near-equilibrium description are met in living systems. Regions of concern are flow fields (transports) in the channels between capillary endothelial cells (e.g., 40-Å size), or through ionophores into cells, (e.g., 3-Å size). We have shown elsewhere that near-continuum flow fields in liquids can be described down to perhaps 15 Å for small molecules in a liquid state (9, 10). A molecular "cell" of $3 \times 3 \times 3$ molecules forms a field sufficiently near thermodynamic equilibrium, but in addition, a layer of bordering molecules is required that allows a rolling boundary to satisfy conditions for near-equilibrium flow fields.

It appears that the spatial conditions for a thermodynamic near-equilibrium, continuum description are met by processes involving solubility transport through membranes, and for transport in large vesicles (endocytosis, exocytosis). However, transports involving ionophores seem not to meet the conditions. Parsegian has described such processes (16), and it may be that they involve a distortion of the rolling-boundary condition for liquid/solid interactions. A kinetic description is required for these transports, but the same conservations that appear in thermodynamic descriptions will still be involved: energy, momentum, mass-species, charge.

For biology, temporal limitations are of significance in dealing with sequential steps in organic synthesis. For example, does protein synthesis in some small local region take place fast enough so that it can be treated as part of a continuum flow process? If not, then the production region (e.g., Golgi apparatus or endoplasmic reticulum) has to be characterized as a discrete factory, a region described by step-to-step kinetics, rather than by continuum thermodynamics.

Process Definition and Morphological Levels

A striking property of living systems is that they are doing something most of the time. With some notable exceptions (sperm frozen in a sperm bank, and spores), it is usually easy to demonstrate that mass, energy, or informational exchanges are taking place briskly between a living system and its surround, and that within the system, syntheses, transports, and other processes are occurring. Thus the term "homeokinesis" serves better than the traditional "homeostasis" to capture the essence of the dynamic regulations and interactions that constitute and preserve life (8).

Homeokinetic processes can be analyzed according to the space-time domains in which they occur, this analysis being process definition. Process definition can be carried out at any of the familiar organizational levels shown in Table 1 that are appropriate to the problem under study.

Now let us examine what it takes to comprehend a system from a scientific (as opposed, for example, to a poetic, literary, or mystical) viewpoint. In Table 2, I show the components of scientific explanation, arranged in a hierarchy of increasing complexity. (I do not wish to define complexity here.) Each of the nine aspects listed are part of the comprehensive scientific examination of any system, but, of course, a particular inquiry can choose to emphasize one aspect more than the others. The reader will notice immediately that the

TABLE 1. *Morphological hierarchy of the living state*

Subatomic particles and processes
Atomic (single reactions)
Molecules (single reactions)
Viruslike particles
Molecular reaction chains (oxidative phosphorylation; photosynthesis; transports across membranes; replication; protein synthesis)
Organelles (especially membranes)
Cells (division)
Functional units (the minimum unit of organized, multicellular complexes that is capable of exhibiting and maintaining *all* the characteristic processes)
Organs
Multiorgan systems
Individual organism
Society (at all levels)
Biosphere
Planetary and stellar processes and structures

Reference 20 gives an even more extensive list.

TABLE 2. *Aspects of scientific comprehension of a system—the statistical mechanical basis*

1. Identification of atomistic or discrete entities present (atomisms)
2. Consideration of fluctuations in the sustained, collisional motions of the atomisms
3. Identification of the ensemble (all the atomisms in repetitive interactions and collisions)
4. Consideration of the dynamic states of the ensemble in phase space (complexions)
5. Specification of the distribution function (a statement about the probabilistic outcome of all the atomistic interactions)
6. Specification of the thermostatic state functions (the constitutive relations that emerge from the kinetics of the interactions and fluctuations that are described by the distribution function)
7. Specification of the field equations of change throughout the ensemble (this is the irreversible thermodynamic description)
8. Application of irreversible thermodynamics to the whole system (in the form of field hydrodynamics, or plastic-elastic, field mechanics)
9. Identification of the history of the system (including the normal course, pathological courses, lethal trajectories, evolution)

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language used in Table 2 is taken from physics, until the parenthetical addition to item 9, when the terminology suddenly becomes biological. The purpose of this paper and its companion parts is to show that the concepts and terms of Table 2 are in fact appropriate for *all* systems, physical or biological.

FORCES

The concept that a system is an ensemble of atomistic entities is so fundamental to physics that I define here three terms that support the concept: *1*) atomism, *2*) active, and *3*) ensemble.

Atomism (*generalized atom*). An atomism is a bounded, material object (of whatever size) that is active, and involved in processes that keep it active. (These are thermodynamic engine processes to be described later.)

Active atomism. Being active is to have the property of possessing, or drawing upon an energy supply to do work. Active entities can exchange energy over time, and the term *action* refers to the integrated product of energy and time.

Ensemble. An ensemble is a set of essentially similar atomisms, continually engaged in interactions (e.g., collisions).

The physical approach adds to the ideas of atomisms and ensembles the idea of force, in order to build systems. I shall discuss the various forces identified by laws of physics at present: there are not more than four forces (and perhaps only two): *1*) gravitational (a force that acts on mass; it is attractive between masses); *2*) electromagnetic (attractive or repulsive); *3*) strong nuclear; and *4*) weak nuclear. The latter two are involved in nuclear and subnuclear fundamental-particle interactions, and need not concern us at levels of organization above the atomic nucleus. Except for high-energy radiation effects, including radioactive decays, these nuclear forces are of little interest to modern biology. They may have been involved in prebiological organization, and are even now involved in mutation, but they can be excluded from a thermodynamic description of existing organization. Thus, in general a physical description in thermodynamic form would involve only gravitational and electromagnetic forces. The design characteristics of large animals involve gravitational force. Biochemistry, fluid mechanics, nerve processes, and osmosis involve electromagnetic force. Among the electromagnetic forces, it is principally the electrostatic forces that influence biological states. (These are the static ionic forces, or the quantum dynamic exchange forces. Static ionic force is due to the ± nature of electrical charge, found in homopolar, dipolar, or multipolar form. The quantum dynamic exchange force is due to the dynamic effects of rapidly penetrating electrical charge, e.g., electrons, that are shared by two more massive moieties such as nuclei, atoms, molecules, or ions.)

At the subatomic level (involving nuclei, electrons, and protons) the force systems are electrical. They create atoms, molecules, and ion systems.

At the atom-molecule-ion level (involving the atom, ion, molecule components, *and* electrons and photons), the forces are electrical. They involve ionic, polarization, orientation, and exchange forces, and are characterized by potential diagrams (Morse potentials). At all subsequent levels, more complex structures are found, and here the electrical forces may be high-order, multipolar forces relating to internal structure, and a weak gravitational force begins to make itself evident. The structures at this level in biology may be viruses, spores, cells, or multicellular systems or subsystems; in the nonliving world they may be geochemical, hydrological, or meteorological structures. At high levels of organization, force systems are identified either through potentials (by their ability to develop momentum), or through power-action modalities (programs of highly organized atomisms that allow them to switch on energy-expending modes, in the sense that a human operator switches on an automotive engine or a rocket engine without being altered himself).

The four primitive (or the two dominating) force systems may now be recognized in more specific forms, e.g., in mechanical forms – hydrostatic pressure, shear stress, dilitational stress; in electrical forms – chemical batteries, AC generators; and in electromechanical forms – electrophoretic, piezoelectric phenomena. There is also a more subtle form seen in homeokinetic, power-action systems where the dominant activity is internal expenditure of energy. This activity is then characterized by particular patterns or modes traversed by the system as it operates. The journeys through the modes are Markovian, branched processes, and they provide a rich, but finite, repertoire of behavior (8).

SUMMATIONAL INVARIANTS AND EQUATIONS OF CHANGE

We now have introduced active atomistic units and organizing forces with which to build complex hierarchical structures. These ideas can next be extended to include another concept of great importance in physics: conservation.

A profound property of ensembles in the physical universe is that they locally conserve mass-species, momentum, angular momentum, energy, and charge during interactions among their atomisms. Each physical attribute that is conserved is called a summational invariant for the obvious reason that conservation means the total value remains constant. The summational invariants are the fundamental elements in thermostatic and irreversible thermodynamic descriptions. They are the essence of statistical mechanics.

It is instructive to consider the possibility that living systems have an additional summational invariant, beyond the five listed above for electrical and mechanical systems. The additional summational invariant, not of exact invariance, but tending toward it, might be number of individuals. Out of the interactions of each generation is a tendency to preserve population number (the total mass of the organisms is no longer directly proportional to their population number). As living organisms die, they are replaced by a new generation and the species persists as a population of changing individuals of sufficient number.

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Equations of Change

As a result of summationally invariant interactions, a near-equilibrium distribution develops among atomistic entities that can be characterized by a mean free path and a (mean) relaxation time for the ensemble. This distribution represents the thermostatic equilibrium state of the ensemble. However, in slower time and larger space than the relaxation time and mean free path, the ensemble can react dynamically according to equations of change if it is subjected to external influences. A dynamical reaction means that field variables in local spatial regions of the ensemble must be able to change: that the average local values of the summational invariants will change in accordance with the equations of change. They do so as a consequence of transports of the different components of the summational invariants from region to region. Equations of change, if written in continuum form, are described by partial differential equations like the three that follow for mass, momentum, and heat.

mass: $$\frac{D\rho}{Dt} \neq 0 \quad (2)$$

ρ is density. Near equilibrium, the density of a region can change (e.g., in accordance with a transport of mass by diffusion). A similar relation for momentum is

momentum: $$\rho \frac{D\bar{V}}{Dt} \neq 0 \quad (3)$$

where momentum (per unit volume), $\rho\bar{V}$, can change, e.g., in accordance with a force derived from pressures that leads to accelerations, or with a dissipative (lossy) transport of momentum by diffusion through a viscous medium.

A similar relation for heat flow is

heat flow: $$\rho T \frac{DS}{Dt} \neq 0 \quad (4)$$

Disordered energy (per unit volume), as measured by an irreversible production of entropy (its heat flow), ρTdS, can change in accordance with viscous dissipation or the transport of heat by thermal diffusion.

An important question is how a homeokinetic description of a system can be obtained from the above description which is momentum and motion oriented. I suggest that the following approach might provide the desired connection. The stress tensor in a physical field is symmetrical. It can be developed in the most general, linear deviator form for a collection of mobile atomisms, as follows

$$S_{ij} = -\delta_{ij}\ p + a\ [V_{i,j} + V_{j,i}] + b\ \delta_{ij} V_{s,s} \quad (5)$$

+ other linear deviator terms (e.g., electric)

$\delta_{ij} = 1 \quad i = j$

$\delta_{ij} = 0 \quad i \neq j$

p = hydrostatic pressure; V_i = ith component of a stream velocity; $V_{i,j}$ = the covariant derivative; and a and b are transport coefficients. As transport coefficients, a and b can be identified as μ and $(\lambda - \frac{1}{3}\mu)$, respectively, where μ = shear viscosity and λ = bulk viscosity. The latter measures internal action delays (9). And so

$$S_{ij} = -\delta_{ij}\ p + \mu\,[V_{i,j} + V_{j,i}] + (\lambda - \frac{1}{3}\mu)\ \delta_{ij} V_{s,s} \quad (6)$$

Add the continuity equation

$$\frac{D\rho}{Dt} = -\rho V_{s,s} \quad (7)$$

We thus obtain

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

So for systems in which momentum counts for little we have

$$S_{ij} = -\ P\ \delta_{ij}\ V_{s,s} \quad (9)$$

There exists an internal "pressure" P, not solely the hydrostatic pressure, that does not arise from momentum collision or long range molecular force systems. It arises from action (energy × time) generated by internally complex electrohydrodynamic fields (11, 19).

Homeokinetic Operation as Fluid Process

The capability of internally complex systems to generate their own pressures for action, by processes with long delays, is the basic property of homeokinesis, and the pressures are "social" pressures, in both living and nonliving ensembles. The action appears to well up from the interior, but there is no mystery involved, because the atomistic interior is a flow field with factory processes, rather than a simple elastic field of the Hooke's law type. *The factory processes are fluid processes — this fact is the essence of homeokinetic operation.* They emerge from the great number of internal degrees of freedom of the system. The hierarchical character of the fluid processes can be found in nuclear fluids, macromolecular fluid interiors,[1] cellular fluids, human societal circulations, and in planetary and stellar atmospheres.

THE CONCEPT OF A SYSTEM

It is commonly held that a system differs from an aggregation or heap of parts in that the parts interact or have internal relations within a system, but not within a heap. The notion of internal relations as expounded in Hegelian philosophy has been a source of confusion and mischief in the growth of a philosophy of living systems. In what follows here the concept of a system, including interactions of parts, is given a statistical mechanical or thermodynamic treatment that not only avoids prior holistic confusions, but provides a reductionistic path from biology to physics that does

[1] After completion of this manuscript the author saw two papers that demonstrate the fluid character of the interior of biological macromolecules, thus lending interesting support to the theses developed herein. The references are: *1*) Robson, B. Biological macromolecules: outmoding the rigid view. *Nature* 267: 577–578, 1977; and *2*) McCammon, J., B. Gelin, and M. Karplus. Dynamics of folded proteins. *Nature* 267: 585–590, 1977.

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not lose the essence of life along the way. Rather, it emphasizes processes that, in their most immediate form, we think of as living (18).

In the statistical mechanical sense, a system is an ensemble of one or more species of atomisms that are bound by forces. The forces are attractive at long range (they assemble the system), and repulsive at short range (they prevent the atomisms from dissolving into each other). The ensemble has some boundary and does not leak away into nothingness. A very interesting class of systems is that of the autonomous systems.

Autonomous Systems

Imagine an ensemble in a surround such that it is exposed to time-independent potentials at its boundary, e.g., isothermal walls. We use the sun. The potentials may be space-dependent; forces may arise out of gradients or differences. If form and function persist within the ensemble in spite of this exposure, then the ensemble comprises an autonomous system. Somehow it is preserved. In general, autonomous systems are nearly closed with respect to preservation of the mass character of the ensemble, but are open with regard to energy and informational fluxes. The autonomous system is preserved by its interactions with potentials at its boundaries.

Next we must consider how a system comes to be in contact with potential gradients or differences. There are two possibilities: *1*) the time-independent potentials at the boundaries of the system are there by arrangement (from the point of view of the reference ensemble the arrangement is by a deus ex machina); *2*) the system can explore its surround to acquire the necessary potentials at its boundary that serve as sources of free energy for its own internal and externalized processes. In this case internal processes convert internal energy into a useful form of work that can change momentum and move the system to a favorable location. Possibility *1*, above, describes a *served system*; possibility *2* describes a *self-serving or homeokinetic system*. Both kinds of autonomous systems are thermodynamic engines, as defined below. It should be noted here that there is not a contradiction in the claim that at the same time some systems can be regarded as being both "served" and "autonomous." The requirement for autonomy is not continued function in isolation, but strictly, that there are no time-dependent inputs. Then a system will retain its full capability to transform energy by its own internal actions. Systems that are not autonomous will be driven toward an inoperable equilibrium state by exposure to time-dependent, potential gradients. Eventually, of course, all autonomous systems presumably decay to equilibrium, at least in our region of the universe; but they continue in form and function long enough to justify our regarding them as persistent.

Thermodynamic Engines and Cyclic Transformations of Energy

A thermodynamic engine is a system that draws energy from a high potential source, rejects some to a lower potential energy sink, and has the capability to do work. It can operate in an idling or degenerate mode in which it does no external work. "Work" in the sense of thermodynamic engines is a general notion, and it includes chemical syntheses involving endergonic reactions, transport of materials against their chemical potential gradients, or maintenance of postural tension in the muscles of a person standing very still. Of course it also includes mechanical work expressible as force × distance, or its electrical or other equivalents.

An important property of thermodynamic engines is that they transform energy and do work in a periodic, cyclic fashion. Clocks and internal combustion engines are obviously cyclic; the chemical battery is subtly cyclic, and the periodic nature of its operation can be discovered only through very detailed analysis. The chemical battery at first glance appears to be a potential source, and not itself an autonomous system operating as a thermodynamic engine. However, on careful reflection it will be found to meet all the requirements of a served, autonomous system. The boundaries of a dry cell, as you hold it in your hand, are not the chief boundaries of the ensemble that does the work. The electrode pair is a system embedded in an electrolyte surround. Connected to an external circuit the electrodes interact at the boundaries with the electrolytes, and work can be done through the external circuit.

Thermodynamics, in a limited sense, has no way to describe repetition of challenges. Causality for the repetition of a challenge usually seems to lie outside of the system. Within the context of thermodynamics, there are only a few basic responses that can be found. When a system is challenged by a disturbance, it may spread the energy of the challenging particle around until some uniformly shared state is restored throughout the system. That is the thermostatic state. As part of the thermostatic state, there is an underlying sustained atomistic motion, characterized by the distribution function of the system. Best known, in the case of a near-ideal-gas ensemble, is the Maxwellian distribution function for the velocity or kinetic energy. But there are other states that grossly exhibit a periodic, repetitive process disturbance. These may be regarded as the thermodynamic engine states. They may include lumped processes such as those found in an internal combustion engine (a working substance being carried through a cycle), or distributed processes such as a turbulent field exhibiting a broad range of fluctuating processes.

Reduction to Physics—a Different View

The most elementary physical classification of systems identifies three states of matter: the gaseous, liquid, and solid. Somewhat more sophisticated considerations would distinguish greater specialization in such systems: vitreous, amorphous, and polycrystalline solids; plastic-elastic systems; the living state—viruses, spores, organelles, cells, multicellular complexes; surface-bound systems such as planetary atmospheres, planetary hydrospheres, planetary plate tectonics, and various sorbed states among earth-bound species—the living kingdoms, the biosphere as a whole, human

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beings bound into groups, groups bound in polities, and polities bound in civilizations (ecumenes). There is a specialized thermodynamic form associated with each such system, *but each form rests on a statistical mechanics that is essentially the same at each level* (6). This claim deserves close attention: it is the basis upon which it becomes possible to create a general systems theory that is both reductionistic, yet faithful to the desire we have to understand emergent properties and hierarchies. Past attempts to reduce biology to "physics" have tried to descend toward the lower morphological levels, such as macromolecules. Such reduction sometimes works as explanation, but ultimately it fails, and it is doubtful that economic systems involving societies can be explained in a nontrivial way by recourse to the language of molecular biology.

What is different in the present approach is that it analyzes all systems, at any morphological level, in terms of physical principles that are level-independent (5). Thus, the reduction is to physics, not to structures like molecules. Much of the traditional tension between reductionism and holism, or between physics and biology, disappears in the light of this approach.

DYNAMIC REGULATION (HOMEOKINESIS)

Form and function are maintained in both kinds of autonomous systems (served and self-serving) by dynamic regulation of their thermodynamic engines (7, 8, 19). Dynamic regulation involves switching among various, marginally stable operating modes (states). In each mode the periodic processes of the various thermodynamic engines each follow limit-cycle trajectories, and these engine processes are sufficiently coupled or mutually entrained to constitute a constellation of oscillators with a frequency spectrum that characterizes the overall, particular operating mode. (This concept will be developed further in Part II of this series.) For each oscillator, the limit cycle is the only trajectory (in the phase plane) that the theory of nonlinear mechanics allows as a stable regime for dissipative systems (12). All real systems of interest are dissipative: they lead to a net increase of entropy through all of their operations, even when these operations generate local "accumulation of negentropy," as through synthesis and repair of structure, or through feeding.

In a self-serving autonomous system, there is a command-control engine system which responds both to internally and to externally perceived states, and controls the modal switching. The switching program may also involve cycles (7). Nervous systems exemplify the most complex form of such command-control. Life developed on earth with self-serving characteristics, but rivers and local climatic systems also have such characteristics. The living, self-serving system is not describable as a hard-geared, clockwork system (the Cartesian notion); instead, it exhibits the four essential processes I mentioned earlier: sensing, a motor actuation, ingestion, and command-control. Elliott (3) has provided a most elegant introduction to command-control in living systems. A common opinion is that only living systems are capable of self-generated motions for maintenance of function (e.g., see (13)). This opinion is wrong: a candle flame moves under conditions that threaten to extinguish it, and can do so in a manner that maintains the flame. Many such examples of self-maintenance by inanimate systems can be found, but I shall not explore that idea further here.

Transport Phenomena

When a system is not at equilibrium, but is sufficiently near to it, with respect to the internal distributions of mass-species, temperature, pressure, etc., so that thermodynamic descriptions hold, then the equations of change give the basis for transport phenomena. They do not, however, give the modes of the transports. There are three possible modes: *1*) diffusion – an incoherent, local process at the scales of the mean free path and relaxation time; *2*) wave propagation – a coherent, local process at the same scales; and *3*) convection – a field-scale process. All the forms of transport have the same origin: they emerge from collisional, lossy interactions at the level of atomisms. I shall not develop here the details about the determination of which transport mode predominates. The interested reader may consult (6) for further discussion.

Lumped Versus Distributed Models of Propagation in Networks

An ensemble in which a transport phenomenon is occurring will have some characteristic velocity of propagation. Consequently, there is both a spatial and a temporal scale at which the parameters of the system can be considered lumped, and another, finer scale, at which they must be viewed as distributed. A general rule is that the lumped-parameter view may be taken if the phase of a disturbance being propagated is everywhere the same throughout the system. In practice that means that systems smaller than one-fourth the wavelength of the highest frequency of interest in the wave of excitation may be treated as lumped. For example, consider the transmission of the pressure pulse in the human systemic arterial vascular network. The characteristic velocity of propagation is about 1,000 cm/s. If 10 Hz were the highest frequency of interest, then the shortest wavelength of interest would be 100 cm, and vascular segments shorter than 25 cm may be treated as having lumped parameters (e.g., as if all the resistance were concentrated at a point).

The Importance of the Boundary Conditions

The simplest form of ensemble organization that physics treats is the ideal gas, but the ideal gas does not exhibit any transport properties. The descriptions of field thermodynamics begin with deviations from the ideal gas state, such as the cubic instability characteristic of a van der Waal gas, or the appearance of form through condensation. In the nonideal case very interesting attributes emerge; there is inhomogeneity of form, and of transports, and these inhomogeneities are very intimately related to extremely specific conditions

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at the boundary of the ensemble. The walls have a profound influence on small-scale processes within the systems.

In a simple approach to the theory of a gas, it is usually assumed that the boundary conditions are elementary and as idealized as is the ideal gas. Specifically, it is assumed that the velocity is zero at the boundary of the hydrodynamic field. In this case the boundary process is not coupled to mean free path or relaxation time phenomena within the fluid and the model is like that of an Eulerian flow field which has not been coupled to the transport phenomena discussed earlier. Clearly, this overidealized model, though useful, avoids the very real consequences of nonideal behavior that it is the purpose of the field thermodynamics described here to accommodate.

An improved step in modeling the gas behavior is to introduce the Knudson theory, through which a characteristic slip is allowed at the walls. The slip involves adsorption and subsequent random emission, to "correct" for the discrepancies that result when realistic, nonideal cases are treated as if they were ideal.

Similar problems arise in the treatment of flow in liquids, and we have provided a rolling boundary or saltation model to make appropriate corrections for nonideal conditions (9, 10). Maxwell's early work in kinetic theory contained implicitly the issues behind slip and rolling boundary phenomena (14).

Remarks about boundary phenomena are by no means addressed to a trivial mechanical detail. Interactions at boundaries represent the effects of nonholonomic constraints (22). Holonomic constraints are integrable displacement motions, such as that of two nonslipping wheels. Pattee has pointed out the importance of nonholonomic constraints, at the level of genes, to assure reliable reproduction (21). Parsegian (16) has raised related questions in the study of the interaction of ions and membranes. Boundary conditions become extremely important for processes occurring at the scale of the mean free path in gases, and at monomolecular dimensions in liquids. Monomolecular boundary conditions become dominant influences in catalysis, corrosion, wear-and-tear, sorption, and life processes. The presence of nonholonomic constraints at the boundaries between condensed phases, and the dynamic richness that can emerge from them, are one basis for explaining the essential roles of membranes and macromolecules in life processes.

I am not concerned here with a thermodynamic analysis of the problem of the origin of terrestrial life, but the interested reader may consult Oster et al. for such a discussion (15). Suffice it to say that a chemical code at a molecular level exists, that this is incorporated in cellular structures that can grow in size, express their functional performance, and divide or join to reproduce. My task is to provide a "physiological" thermodynamics for the very many classes of constituents that pass through the complex organismic systems that make up form and function in living species. The understanding of form follows from that of function, because form is function at a low morphological level, at the level of quantum mechanical constraints in molecular orbitals.

Nonholonomic Constraints—Kinetics

The branch of mechanics that is dynamics deals both with the motions of bodies per se apart from their causes (kinematics), and with the action of forces in changing those motions (kinetics). The motions that follow equations of change arise ultimately from the kinetics of atomistic interactions at a lower level. The nonholonomic constraints at the boundaries are not integrable in terms of the mechanical variables at the level of the equations of change, and therefore they must be accounted for by a kinetic treatment at the lower level. The kinetics of the interactions at the boundaries, through the nonholonomic constraints to which they give rise, assures that when a system is challenged by a particle, or a stream of particles, the energy degradations that follow will be consistent, when averaged in space and time.

Summary of Thermodynamic Explanations

Field or network (circuit) thermodynamics is constructed from the dual descriptions provided by irreversible thermodynamics and the underlying kinetics. To the dual description must be added the boundary conditions. Table 3 summarizes the components of field or network thermodynamics that assure consistency and completeness of description.

Field thermodynamics has an advantage over any other description in that it can prescribe those variables to which autonomous behavior can be ascribed without having to deal with every individual atomistic entity. Thermodynamics needs to deal only with summational invariants as primary variables, and with the consequences of interaction among the atomistic entities. Use is made of the ensemble averages that make up the bulk field. For a simple, single kind of atomism in a single phase, we need consider only the conservations related to mass, energy, momentum, and charge (if

TABLE 3. *Summary of components of field and network (circuit) thermodynamics*

1. Thermostatic descriptions (equilibrium, mean free path, relaxation time, equations of state, chemical potentials, distribution functions)

   These involve time-independent (mean) processes

2. Irreversible thermodynamic descriptions (transport phenomena, equations of change, summational invariants, losses of free energy)

   These involve dissipative, time-dependent (flux) processes

3. Field boundary conditions (nonholonomic constraints, kinetics of atomistic interactions)

   The boundary condition must be developed from a theory in the mean free path or relaxation time variable, and the theory must be compatible with thermostatic and transport descriptions in terms of the same variable

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there are current fluxes). If there is more than one phase, we need to deal with these same conservations in each phase, but then we must also provide phase boundary conditions. Typical boundary conditions at equilibrium are equality of temperature and pressure (but not density). If there is more than one kind of persistent, atomistic entity, the conservations are augmented by individual conservations for each mass-species. In addition to a conservation of the total mass compartment, there are $n - 1$ conservation laws for n possible mass-species involved. Then the phase and component relations that Gibbs proposed govern equilibrium and boundary conditions.

CONCLUSION

In this paper I have tried to acquaint the biologist with some important, selected concepts from various branches of physics: thermostatics, statistical mechanics, kinetics, nonlinear mechanics, and irreversible thermodynamics. These concepts have been assembled to provide a physical basis for a general theory of systems, including living systems. This general theory I referred to as field, network, or circuit thermodynamics.

Field thermodynamics can deal with complex systems because it can order space, time, and energy into one-dimensional arrays. It permits focus on selected forms and functions, and is itself level-independent (even though it is most easily comprehended through examples dealing with transport phenomena involving atoms or molecules of a nonideal gas). Above all, field thermodynamics indicates the accounting that must be done if an explanation is to have scientific validity. It is not too much to say that whatever else an explanation may do, it must be correct in the terms of field thermodynamics or it will ultimately fail.

In the subsequent two parts of this series of papers, I shall attempt to show how the general theory of systems provided by field thermodynamics can help to explain biological phenomena.

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