VOLUME TWO

MEMBRANE STRUCTURE AND FUNCTION

Edited by

E. EDWARD BITTAR

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Preface

Ten years have now elapsed since the publication of the three-volume work Membranes and Ion Transport. During those years considerable advances have been made in our knowledge of membranes and ion movements. This particular volume is about ion transport. Though it is anything but a synthesis, its aim is to bring the essentials of ion transport into relief. Several topics frequently discussed in symposium books and reviews have been purposely avoided. This has kept the size of the volume rather reasonable. My hope therefore is that it will, like Volume 1, reach a wider circle of middle-of-the-road students and research workers.

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Madison, Wisconsin
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CHAPTER ONE

Network Thermodynamics

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1 INTRODUCTION

The history of the elucidation of biological structure and function has been essentially reductionist. It has been necessary to determine the function of each part of the cell and then, on isolation of these parts, to subdivide and analyze down to molecular level, isolating substrates, products, enzymes, proteins, and all the functional and structural units of the cell. In that analysis the complexity, basic economy, and elegance of cell chemistry has become increasingly apparent. Once the sequence of the individual steps of a process is clearly defined and made quantitative, both the energetics and dynamics of the whole process must be considered. The task is formidable: even if the mechanism and kinetics of each step were known, their synthesis to give the dynamical behavior of the process is a mathematical problem of the highest order. We must bear in mind the spatial dispersion of events that demand consideration of diffusional links between them and which will involve all the concepts of solution and membrane transport as well as the essential processes of energy transduction.

If dynamic processes must be accounted for in terms of local and global energy, then the discipline of thermodynamics is required. Moreover, since any cellular process, by definition, occurs at a finite rate, only irreversible thermodynamics will suffice. Onsager nonequilibrium thermodynamics has been of considerable use for numerous applications in biology, but it is restricted to what are, in essence, linear processes close to equilibrium. Biological processes are characteristically complex, involving both parallel and sequential steps which may not be confined to one location or one phase. The individual steps frequently are nonlinear, and indeed nonlinearity is an essential feature of structural organization (1), oscillatory phenomena (2), and most chemical reactions.

In their search for a viable calculus, biophysicists have stayed loyal to thermodynamic principles as the only rigorous basis for energy discussion, but in dealing with the topological problems of biological reaction/diffusion schemes, they look to circuit theory, linear graph theory, and various schemes of system dynamics currently used in physics and engineering. Such applications are not new to thermodynamics. Meixner, who did so much to develop Onsager's theory, also proposed a nonequilibrium thermodynamic treatment based on the theory of linear passive systems (3-7).

Oster, Perelson, Katchalsky, and Auslander (8-12), in a series of papers beginning in 1971, developed a much more widely based "network thermodynamics" capable of dealing with both linear and nonlinear and with highly reticulated biological schemes involving chemical reactions, diffusion, coupling, membrane phenomena, and energy transduction while incorporating cybernetic flows (at essentially zero energy levels) essential to all self-regulatory processes. The basis of their treatment is not new to engineering science or to physics, but their application of system dynamics and the "bond graph" formalism to problems in membranology and reaction diffusion kinetics has created new possibilities for greater understanding of complex biological processes.

Network theories of continuous systems have had a long and successful history in physics, engineering, and neurophysiology. It was shown by Sudarshan (13) and Hermann (14) that there is an underlying mathematical unity for most dynamical theories in physics. General dynamical theories can encompass, as special cases, classical and quantum mechanics, hydrodynamics, electrical circuit theory, and a number of other fields (see ref. 15). The methods of system dynamics—particularly the bond graph formalism of Paynter (16), Karnopp and Rosenberg (17), and Takakashi, Auslander, and Rabins (18)—are now an essential part of the curricula in engineering schools and are treated in several textbooks (e.g., see ref. 19). Oster, Auslander, Perelson, and Katchalsky have presented irreversible thermodynamics in bond graph terms.

The success of network methods in simulating the dynamics of continuum systems has been shown to be a natural consequence of the underlying unity of the mathematical structures of network and field theory. The ultimate criterion for the validity of the network approach and its ability to recreate field theory is the postulate of local equilibrium familiar to students of irreversible thermodynamics. This postulate requires that on conceptual and mathematical subdivision or reticulation of a continuum in which there are gradients of state variables, local regions may be considered to have thermodynamic state variables which have their normal meanings and in which the laws of thermodynamics still apply. The degree to which a system is subdivided in the reticulation process determines the ultimate precision of the model. In the limit, as the system is increasingly finely grained, the predictions of network theory and the field equations become identical.

A single unit approximation to any process is termed a *lump*. The one-lump network, although crude, contains the minimum information required to reproduce the major features of the real system. To illustrate, many of the examples given in this chapter are one-lump models. The bond graph notation of network thermodynamics provides a generalization of electrical circuit theory and borrows some of its nomenclature from that discipline. The major appeal of network thermodynamics to the biologist is that it is specifically designed to follow energy rate (or, equivalently, power flow) through a system. In this way the dual requirements for information energy and rate, necessary for a complete bioenergetic analysis, are satisfied. As with other graphical methods, it also allows informational or zero power signal bonds to be incorporated. These progressively update the constitutive relationships of the graph components to take account of the changing physical response of the system as it evolves or decays in response to external conditions. These signal bonds are essentially feedback controls and are of primary importance in self-regulatory and oscillatory phenomena.

Experience in the application of system dynamics to physical and engineering problems has created a large literature of techniques in computer analysis of such systems, which may now be transferred directly to bioenergetic problems. The bond graph of a dynamic system is essentially a topographical map in which the relationships between the components are immediately obvious and in which the mathematical equations for system response are arrived at by using the bond graph algorithmically to facilitate computer analysis (20).

2 BOND GRAPH NOTATION

2.1 The Power Bond

The power $P(t)$ entering or leaving a subsystem at any time (t) may be obtained from the product of an effort $e(t)$ and a flow $f(t)$:

$$P(t) = e(t)f(t) \tag{1}$$

If S is a subsystem of a network, then the power "lost" in S is $e_1 f_1 - e_2 f_2$ (Figure 1). Power bonds are represented in the manner of chemical bonds, as a single line on which the half arrow indicates the assigned direction of power flow. For electrical circuits effort and flow are simply voltage and current, whereas for thermodynamic networks they are chemical potential, μ_i, and molar flow, J_i ($= dn_i/dt$). In all cases their product, $e(t)f(t)$, has the dimensions of joules per second (watts). Effort and flow thus are classified as power variables.

The definition of effort and flow is to some degree arbitrary, but for thermodynamic systems the Gibbs equation is used to define these quantities:

$$dU = T\,dS - P\,dV + \Sigma\mu_i\,dn_i + v\,dq \tag{2}$$

The thermodynamic terms have their usual significance and v and q are voltage and electrical charge in coulombs, respectively. Each term on the right-hand side of Eq. 2 represents a possible work interaction. These are, in sequence, thermal, mechanical, chemical, and electrical. Following Eq. 2, the corresponding efforts are temperature T, pressure P, chemical potential

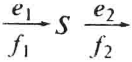

Figure 1 A two-port system, S, with power input e_1f_1 and output e_2f_2 indicated by the half-arrows on the power bonds. S may be a basic two-port such as a transformer or any more complex unit which has two points at which power may be exchanged with the environment.

μ_i, and voltage v; the conjugate flows are the time differentials of entropy, volume, moles, and charge. Since these differentials are flows, they are given the symbols J_S, Q, J_i, and i (the electrical current in amperes).

Table 1 summarizes commonly used power variables in a number of energy domains. Since network thermodynamics traces power flow it is particularly suited to analyses of energy transduction between any pair of the four energy domains: thermal, mechanical, chemical, and electrical.

2.2 Energy Variables

In a dynamic system, effort $e(t)$, flow $f(t)$, and power $P(t)$ all vary with time (except in the special case of the steady state). By the formal analogy with mechanical systems, the time integrals of effort and flow are defined as generalized momenta and displacements, respectively, in all energy domains.

The momentum $p(t)$ is defined by

$$p(t) = \int^{t} e(t)\, dt = p_0 + \int_{t_0}^{t} e(t)\, dt \tag{3}$$

In mechanical systems, where $e(t)$ is the Newtonian force $F\ (= m\dot{V})$, Eq. 3 defines kinetic momentum $p\ (= mV)$.

In a similar fashion the generalized displacement $q(t)$ is defined as the integral of flow, leading, as we shall see, to the concept of a generalized capacitance:

$$q(t) = \int^{t} f(t)\, dt = q_0 + \int_{t_0}^{t} f(t)\, dt \tag{4}$$

Again the term "displacement" is borrowed from mechanics, where flow $f(t)$ is simply velocity and so $q(t)$ is a linear displacement in the direction of the force. Efforts, flows, momenta, and displacements in the common energy domains are given in Table 1. Oster, Perelson, and Katchalsky (12) point out that notation is "a major difficulty in extending network techniques to thermodynamic systems." There is no better example than the preceding notation. The definitions of momentum and displacement, although seemingly logical, are nevertheless unfortunate, since, on theoretical grounds (because mechanical forces obey Kirchoff's current law), the roles of flow and effort are reversed (21). The "natural" assignment is still used by some authors, for example, Karnopp and Rosenberg (19). Displacements and momenta for various energy domains are summarized in Table 1.

2.3 Energy: Dissipation and Storage

Energy $E(t)$ is the time integral of power:

$$E(t) = \int^t P(t)\,dt \tag{5}$$

We may choose to classify energy in three forms—dissipative, $E_D(t)$, capacitative, $E_C(t)$, and inductive, $E_L(t)$—according to how we integrate Eq. 5.

$$E_D(t) = \int^t \mathbf{e}^T \mathbf{f}\,dt \tag{6a}$$

$$E_C(t) = E_C(0) + \int_{q(0)}^{q(t)} \mathbf{e}(\mathbf{q})\,\mathbf{dq} \tag{6b}$$

$$E_L(t) = E_L(0) + \int_{p(0)}^{p(t)} \mathbf{f}(p)\,dp \tag{6c}$$

Equation 6a represents energy dissipation by a resistive element. To perform the integration, and thus determine the energy dissipated, the constitutive relationships between effort and flow, which define a generalized resistance Φ_r, are required:

$$e = \Phi_r f \qquad \text{or} \quad f = \Phi_r^{-1} e \tag{7}$$

In the simplest case Φ_r is a constant resistance R, and Eq. 7 defines linear constitutive relationships such as Ohm's law ($V = Ri$) or for a chemical diffusion (in the simplest case of uncoupled flow) $e_i = R_i J_i$ where, as will be discussed later, $e_i = \Delta\mu_i$.

In Eq. 6b $E_C(t)$ represents energy stored by displacement in a capacitative element. For its evaluation, the relationship $e(q)$ (effort as a function of displacement) is required:

$$e = \Phi_C^{-1} q = \Phi_C^{-1} \int^t f\,dt \tag{8}$$

In Eq. 8 Φ_C is a generalized capacitance. When Φ_C is constant (C), the familiar relationship for an electrical capacitor is obtained:

$$e = q/C \qquad \text{or} \quad v = q/C \tag{9a}$$

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Table 1 **Efforts, Flows, Momenta, and Displacements for Common Energy Domains**

Domain	Flow	$f(t)$	Effort	$e(t)$	Momentum	$p(t)$	Displacement	$q(t)$
Chemical								
Diffusion	Molar flow	J_i	Chemical potential	μ_i	—	—	Number of moles	n_i
Reaction	Reaction rate	J^R	Affinity	A	—	—	Degree of advancement	ξ
Electrical	Current	i	Voltage	v	Flux	ϕ	Charge	q
Hydraulic	Volume flow rate	Q	Pressure	p	Pressure momentum	Γ	Volume	V
Mechanical								
Translation	Force	F	Velocity	V	Displacement	x	Momentum	p
Rotation	Torque	τ	Angular velocity	ω	Angular displacement	θ	Angular momentum	p_τ

$$f = C\,(de/dt) \qquad \text{or} \quad i = C\,(dv/dt) \tag{9b}$$

(The relationships on the right are specifically electrical.)

The form of Eq. 8 shows that effort is stored in the capacitor by integrating the flow over a time interval (t). This implies that flow is the natural input (or independent) variable. As we shall see, this natural or preferred form of the capacitance relationship is indicated by a "causal" stroke on the bond to the capacitor, indicating that flow is the source of capacitance (Section 2.4).

By similar reasoning, the energy $E_L(t)$ of Eq. 6c is obtained by evaluating flow as a function of momentum $f(p)$:

$$f = \Phi_L{}^{-1}\,p \qquad \text{or} \quad df/dt = \Phi_L{}^{-1}\,e \tag{10}$$

The natural, independent input to an inductor is effort. Again, by analogy with electrical systems with constant inductance $\Phi_L = L$ and Eq. 10 defines Henry's law:

$$di/dt = v/L \qquad \text{or} \quad v = L\,(di/dt) \tag{11}$$

with constant inductance L.

The three expressions for energy derived from Eq. 6 define three fundamental elements of the bond graph: the resistor R, capacitor C, and inductor L. Their application is now extended far from their original meanings as components of electrical circuits. In electrochemical systems the inductor is not represented by any known process. This is unfortunate (as we shall see) because as in electrical circuits a capacitor coupled to an inductor oscillates naturally. Chemical and membrane oscillators operate by much less obvious interactions (Section 3.6). Atlan and Weisbuch (22), however, have suggested a mechanism by which inductancelike effects may occur in chemical reactions.

2.4 One-Port Elements and Causality

The three possible methods for integration of power to obtain energy (Eq. 6) correspond to three mathematical (and in some cases discrete physical) entities, the resistor, capacitor, and inductor. They are represented in bond graph notation as one-port (1-port) or two-terminal devices, because the function of each is defined by one effort and one flow, and so by one bond. Their bond graphs, which are given later, are symbolic representations of their constitutive relationships, defined in Section 2.3 (Eqs. 7, 8, and 10). In electrical circuits these elements take concrete form as specific components of the circuit. In other energy domains, their presence does not take such tangible form.

The resistor's role is purely dissipative and, since it is the *only* seat of dissipation, all irreversible processes must have resistors in their bond graph representation. Electrical, hydraulic, and chemical diffusion examples are seen in Figure 2.

The capacitor, on the other hand, stores energy without dissipation and so operates reversibly. Figure 3 presents capacitors with bond graphs. The chemical capacitor is more conceptual than its electrical or mechanical analogs (Figures 3*c*, 3*d*), although it has much in common with the hydraulic example (Figure 3*e*). The chemical capacitor is just a volume element in a chemical or biological system which accumulates molecules that raise their own chemical potential (effort) in that volume: should any local volume receive more molecules by inflow (J_i') than are removed by outflow (J_i''), the resultant net accumulation of chemical species would raise its local concentration and so raise its chemical potential, as seen in Figure 4. In the steady state all state variables, including local chemical potential, are time invariant. In consequence the capacitors within such a system will not contribute or detract from flows and may, in that specific situation, be ignored. Further discussion of the chemical capacitor is deferred to Section 3.1.

The bond graph of an element is simply a symbolic representation of the

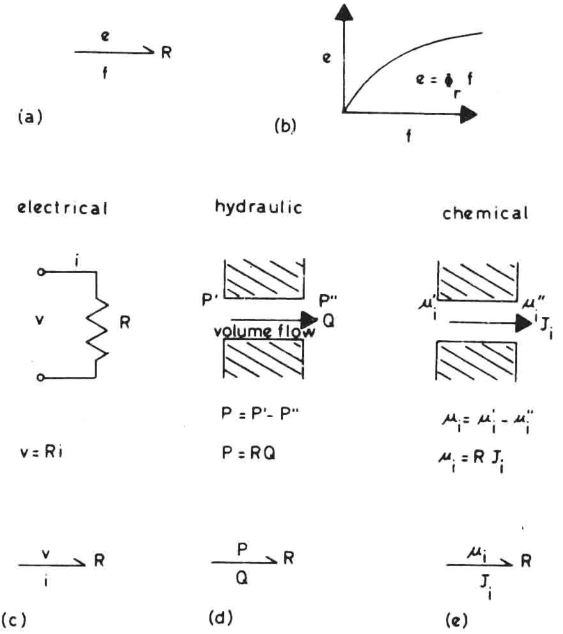

Figure 2 The resistor: (*a*) bond graph; (*b*) constitutive relationship (nonlinear); (*c*, *d*, *e*) resistors in electrical, hydraulic, and diffusional systems.

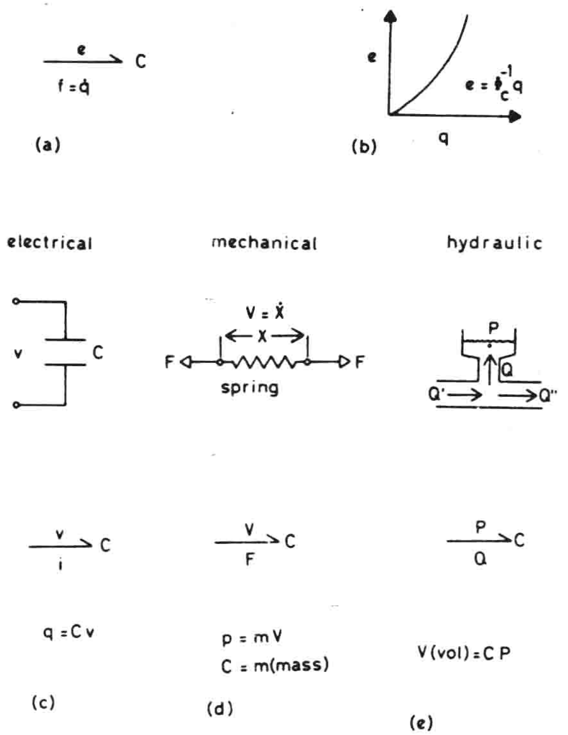

Figure 3 The capacitor: (*a*) bond graph; (*b*) constitutive relationship (nonlinear); (*c*, *d*, *e*) capacitors in electrical, mechanical, and hydraulic systems. Note that velocity V and force F are effort and flow, respectively, in mechanical systems (Section 2.3, Table 1).

constitutive relationship it obeys. For any 1-port element the constitutive law may either define effort as a function of flow or vice versa (Eqs. 7–11). The convention is that the independent variable (input) is on the right-hand side of the constitutive equation. Since the bond graph of a dynamic system is itself an algorithm by which the constitutive laws of all the elements may be combined to give the dynamic behavior of the whole, it is essential not only to assign positive directions for power flow (which has been done, using the half-arrow as in Figures 1–8) but, additionally, to assign the natural, independent power variable—either effort or flow—to each. Paynter (16) has discussed this problem and augmented the bond graph with "causal" strokes to assign the independent input variable for each element. The causal stroke is placed at the end of the bond to which effort (defined as input) is directed. In consequence, the end without the causal stroke is the end to which flow is directed (as input) to some adjacent element of the bond graph. As an example, $\vdash\!\rightharpoonup$ R signifies that flow into the resistance is the independent variable, defining output effort and the constitutive form, $e = \Phi_r f$. By the reverse

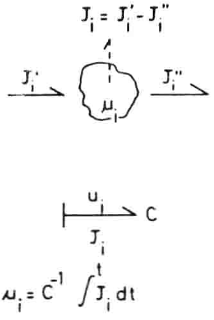

Figure 4 The chemical capacitor.

argument $\rightharpoonup\!|$ R signifies input effort defining output flow and the inverse form of the resistance equation, $f \Leftarrow \Phi_r^{-1} e$. Causality may be assigned arbitrarily to resistors, because the relationship between flow and effort is purely algebraic and does not involve integration or differentiation. Step functions for effort or flow therefore do not involve infinite power pulses, which, as we shall see, is a problem for both capacitors and inductors.

For a capacitor, which is naturally defined as an integrator of flow, generating effort (Eq. 8), the preferred causality will be $|\!\rightharpoonup$ C. The alternative $\rightharpoonup\!|$ C signifies the inverse relationship, $f = d(\Phi_C e)/dt$ and a step in effort would require flow and hence power to become infinite (8, 19). By similar reasoning, the natural causality for an inductor will be $\rightharpoonup\!|$ L, indicating the constitutive relationship

$$f = \Phi_L^{-1} \int e \, dt$$

Causal strokes must be assigned to the bond graph before it is analyzed and causal considerations for the remaining bond graph elements will be discussed as they are introduced. A very useful logic for causal assignments has been developed by Karnopp and Rosenberg (19). Since the causal implications of capacitors and inductors are of such importance, they are assigned their preferred causalities first and those causal implications are used to extend assignments to the whole bond graph.

The only other 1-port elements are the sources of constant flow $S(f)$ and constant effort $S(e)$. Their symbols and causalities, which are obligatory in their definitions, are shown in Figure 5. The only other possible source or sink for power is the capacitor. This may be an adjacent reservoir of limited volume of either a concentrated solution from which molecules will flow or a more dilute solution into which molecules will flow. In the process, however, it will be continuously depleted (or concentrated) and so will act as a variable source (or sink) for power.

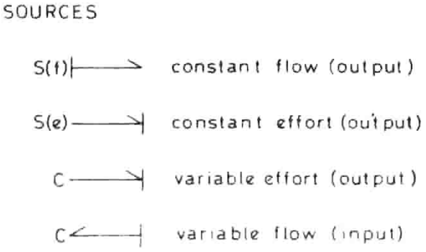

Figure 5 Sources: $S(f)$, constant flow; $S(e)$, constant effort and capacitors, which represent variable sources or sinks.

2.5 Two-Port Elements

There are only three fundamental 2-port elements: the transformer, —TF—, transducers, —TD—, and gyrators, —GY—. In all cases they conserve power, so that the power entering by one bond, $(e_1 f_1)$, will equal that leaving by the second, $(e_2 f_2)$, as seen in Figure 1. In Figures 6 and 7 the through-power convention indicates that power is considered to flow through the 2-port. Transformers and transducers alter the outgoing effort and flow in inverse proportion, as determined by the modulus r according to the constitutive laws:

$$e_1 = (r)e_2 \qquad \vdash\xrightarrow{e_1}\mathrm{TF}\vdash\xrightarrow{e_2} \tag{12a}$$

Since, by definition, power is conserved $(e_1 f_1 = e_2 f_2)$, Eq. 12 also implies a second relationship:

$$f_1 = f_2/(r) \qquad \xrightarrow[f_1]{}\dashv \mathrm{TF}\xrightarrow[f_2]{}\dashv \tag{12b}$$

The causal implications of Eqs. 12a and 12b are given above. Although the distinction is not universally observed it seems better to reserve the term "transformer" for a device that operates within one energy domain, such as an electrical transformer, a lever, or a gear (Figure 6). The term "transducer" is reserved to indicate identical constitutive relationships in which energy is converted from one domain to another or even from one chemical component to another. Transducers occur in bond graphs for chemical reaction schemes (Section 4) and in such common examples as electric motors (electromechanical), heat engines (thermomechanical), and a large number of biophysical processes such as muscle action (mechanochemical).

The third 2-port is the gyrator GY, in which the effort of one port is proportional to the flow of the other. The constitutive relationships are given in

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