NETWORK THERMODYNAMICS

AN OVERVIEW

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INTRODUCTION

Thermodynamics was one of Aharon Katzir-Katchalsky's great loves. To the physicists of the late nineteenth and early twentieth centuries thermodynamics epitomized the simplicity, generality, and symmetry one expected from a physical theory. Aharon, however, was well aware of its limitations when applied in the biological realm. He saw a need to extend the scope of thermodynamics in a new direction, in hopes of addressing the puzzle of biological organization and complexity from a phenomenological viewpoint. George Oster and I had the great privilege of collaborating with Aharon on this, his last major research effort. In this memorial symposium on thermodynamics and life it seems particularly appropriate to recount the history of what Aharon christened "network thermodynamics," and to discuss its relevance and potential in modern biophysics.

In 1968 Aharon brought to Berkeley news of Prigogine's work on dissipative structures (Prigogine, 1969). His enthusiasm for discovering the basis of life in temporal and spatial structuring was, as many of you know, quite contagious; George Oster, then a postdoctoral student, and I, then a graduate student, became infected. We understood how temporal oscillations in electrical and mechanical systems worked. If one had two energy storage devices, such as an inductor and capacitor, one could transfer energy between the devices periodically. Therefore, we began looking for chemical analogs of capacitors and inductors. We also realized that the mere presence of capacitors and inductors was not enough; their interconnection had to be precisely right. Thus, we also began searching for ways to quantitate the notion of topology in chemical systems. Graphical and network techniques naturally came to mind. The idea of applying concepts in electrical network theory to thermodynamics was not new, Meixner (1963, 1964, 1965, 1966*a*,*b*) had already proposed a nonequilibrium thermodynamic theory based on the general theory of linear passive systems. Out of a synthesis of concepts from thermodynamics, circuit theory, graph theory, and differential geometry, network thermodynamics was developed.

Unfortunately, Katchalsky did not live to see the work grow to fruition. During his lifetime we spent much time "putting old wine in new bottles" so to speak; much of nonequilibrium thermodynamics as applied to biophysics was reformulated in terms of network thermodynamics, theoretical results such as the Glansdorff-Prigogine $d_x P$ inequality and $\delta_x P$ stability criterion were given rigorous and elegant network formulations (Glansdorff and Prigogine, 1971; Oster and Desoer, 1971), and the framework for a nonlinear far-from-equilibrium theory of thermodynamic processes was created (Oster et al., 1971). Frankly, however, this period produced no significant new results.

Before discussing more recent work it is first worthwhile to explain in some detail what network thermodynamics is and why Aharon thought it worthwhile to translate known results into network thermodynamic terms.

WHAT IS NETWORK THERMODYNAMICS?

Great progress had been made in understanding simple thermodynamic systems using equilibrium thermodynamics, and nonequilibrium thermodynamics as developed by Onsager, Prigogine, deGroot, and Meixner. However, Aharon could see clearly that the conventional tools of irreversible thermodynamics were not suitable for treating the complex nonlinear biological processes which occur far from thermodynamic equilibrium. As an analogy consider the problem of analyzing or designing a radio. The basic physics is completely summarized in Maxwell's equations. One could, in principle, integrate these equations to obtain an overall system description. In practice, however, too much irrelevant information is required to integrate the equations over such a complex object. As the engineers have discovered, a lumped parameter approximation to Maxwell's equations—network theory—is the most convenient tool to use. Since the complexity of a biological organelle such as a membrane or chloroplast is more akin to a radio than an isotropic continuum, a lumped parameter approximation to the field equations or irreversible thermodynamics and continuum mechanics would seem to be the preferred description. Network thermodynamics is precisely such an approximation. By establishing an isomorphorism between the underlying mathematical structure of network theory and thermodynamics, problems in thermodynamics can be formulated and solved using network methods.

The advantages of a network approach are numerous. Engineering experience and network methods of solving large nonlinear systems can be brought to bear on thermodynamic problems. For example, complex systems can commonly be thought of as composite systems made up of interconnected subsystems. In many instances such systems can be "torn" or decomposed into their subsystems, the subsystems solved, and these solutions used to generate the solution to the whole system. Such a decomposition technique can be applied to network models of diffusion-reaction systems. Besides specific method of analysis, there are many network theorems that can be used to solve thermodynamic problems. One of the most important is Tellegen's theorem. This is a powerful theorem whose generality derives from the fact that it is independent of the nature of the network elements—that is, whether they are linear or nonlinear, reciprocal or nonreciprocal. All that matters is the network topology; that is, the way in which the elements are interconnected (Penfield et al., 1970).

Graphical representations similar to engineering circuit diagrams can be constructed for thermodynamic systems. Although the proverb that a picture is worth a thousand words may not be completely applicable, such diagrams do increase one's intuition about system behavior. Moreover, as in circuit theory, one can algorithmically read the algebraic and differential equations that describe the system directly from the diagram much more easily than they can be constructed directly. In this sense the diagram is just another notation for the equations themselves. However, in many instances manipulations on the diagram are much easier to perform than the corresponding operations on the equations; one can interact directly with the diagram and bypass the equations. Thus, a physiologist can sit at a computer terminal equipped with a graphical display and draw his system with a light pen, assign element values, and have the computer derive and solve the system equations. By utilizing a network framework for thermodynamics many existing engineering computer programs can be utilized directly, removing the need for a large programming effort.

The network approach brings to thermodynamics a degree of mathematical rigor and provides a unification of ideas with modern dynamical system and control theory (Oster and Perelson, 1973). There is a close formal similarity between Hamilton's equations in mechanics, the Brayton-Moser-Smale equations in network theory (Smale, 1972) and equations that Oster and I have devised to describe the dynamics of reaction and reaction-transport systems.

One of the more important aspects of network thermodynamics is that it highlights the importance of topological concepts. Prigogine has stressed the significance of the dissipative aspects of complex systems; but the topology of any system is also crucial to its overall behavior. A set of resistors, capacitors, and transistors may act as a radio when hooked up in one way, but with a minor change in the wiring may not operate at all. From the rate of entropy production one could not distinguish the difference. An analogous situation obtains in chemistry. A set of reactants in the presence of one catalyst may yield a specified set of products, but a slight change in the catalyst may select completely different reaction pathways. The relevance of topology in determining the stability of reaction networks has also been noted (Morowitz et al., 1964; Gardner and Ashby, 1970).

The development of network thermodynamics depends on three postulates:

(*1*) We make the usual local phase equilibrium assumption. That is, even though the system as a whole may be far from equilibrium, locally one can still describe the state of the system by thermodynamic variables, such as temperature, pressure, and chemical potential.

(*2*) Instead of viewing physical space as a continuum we treat it as discrete. This will generate finite dimensional models described by ordinary differential equations as opposed to the partial differential equation description of continuum theories. Indeed, there is a precise mathematical duality between these two structures available for describing dynamical systems. Continuum theories employ vector calculus whose operational structure arises from point set topology. The discrete counterpart of point set topology is algebraic topology; it is this latter structure that underlies the network approach (Branin, 1966).

(*3*) In every volume element of a physical system complex processes are occurring;

however, we assume that one can conceptually separate these processes into dissipative and nondissipative parts.

EQUILIBRIUM THERMODYNAMICS

In order to demonstrate the application of network thermodynamics we consider some examples. Let us start with equilibrium thermodynamics. Equilibrium thermodynamics regards a system as a "black box" that can be described by a finite number of external measurements. For example, the piston and cylinder shown in Fig. 1*a* can interact with the environment through the mechanical movement of the piston or by exchanging mass and heat. We can represent this system schematically as shown in Fig. 1*b*, where each mode of interaction has been represented by a line called a *port*. In circuit parlance this object is called an *n-port*. In classical thermodynamics one usually postulates the existence of a real valued function, the internal energy U, which depends on a set of thermodynamic displacements q_i which include the entropy, S, the volume, V, and the mole numbers, N_i. Then one usually defines a set of conjugate thermodynamic potentials by differentiating U. For example the chemical potential $\mu_i \equiv \partial U / \partial N_i$. We shall denote thermodynamic potentials e_i and call them *efforts*. In network thermodynamics we follow an approach to thermodynamics initiated by Brönsted in the 1930s. We focus on measureable quantities not on energy functions for reasons which become apparent when we treat irreversible processes. Thus e_i and q_i are taken as primitive variables in network thermodynamics and we postulate that the properties of any n-port can be described by relations between these port variables, called *constitutive relations* or "equations of state" (i.e., the local equilibrium postulate). An example is the relation $\mu_i = \mu_i(T, p, N_1, \cdots N_n)$. In general, a constitutive

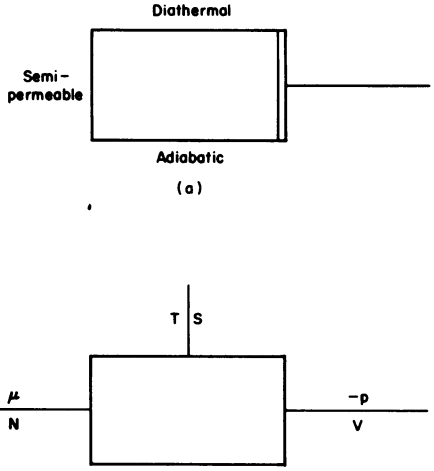

FIGURE 1 (*a*) Piston and cylinder. (*b*) Its n-port representation.

relation is a map **F** which assigns to a set of independent port variables the set of conjugate port variables:

$$\begin{aligned} \mathbf{F}:\ & R^n \rightarrow R^n \\ & \mathbf{x} \mapsto \mathbf{y} \end{aligned} \tag{1}$$

where **x** and **y** are vectors of port variables.

Next, consider two simple thermodynamic systems surrounded by rigid adiabatic walls and separated by a rigid semipermeable membrane as shown in Fig. 2. Conventionally, the equilibrium of this composite system is found by minimizing the total energy of the system subject to the constraint $N_1 + N_2 = \text{constant}$. One finds U is a minimum when $\mu_1 = \mu_2$.

In network theory equilibrium is generally calculated by imposing the requirements of Kirchhoff's laws at the interconnection of two systems. This method, which does not require the introduction of an energy function, is equivalent to the usual thermodynamic method. The continuity of potential at system boundaries is Kirchhoff's voltage law (KVL). Conservation of thermodynamic displacements is a form of Kirchhoff's current law (KCL). For the system illustrated in Fig. 2

$$\mu_1 = \mu_2 \tag{2}$$

is KVL, while

$$N_1 + N_2 = \text{constant}, \tag{3A}$$

or

$$\dot{N}_1 + \dot{N}_2 = 0 \tag{3B}$$

is KCL. Since S and V are constant for systems 1 and 2

$$\mathrm{d}U = \mu_1 \mathrm{d}N_1 + \mu_2 \mathrm{d}N_2. \tag{4}$$

Eqs. 2 and 3 imply

$$\mathrm{d}U = (\mu_1 - \mu_2)\mathrm{d}N_1 = 0, \tag{5}$$

i.e., the system energy is at a minimum. In general, utilizing Kirchhoff's laws one can obtain all of the standard equilibrium conditions and, in fact, one can always show

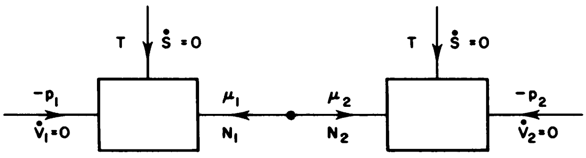

FIGURE 2 Two thermodynamic systems surrounded by rigid adiabatic walls and separated by a semipermeable membrane.

that the energy is minimal when Kirchhoff's laws apply. Of the three conditions: KVL, KCL, and minimum energy at equilibrium, any two imply the third.

By analogy with the electrical capacitor we shall call any system which is described by thermodynamic displacements and thermodynamic potentials a capacitor. Hence any equilibrium thermodynamic system is an n-port capacitor and shall be denoted symbolically by the capital letter C.

Reciprocity is the central characteristic of thermodynamic systems. In equilibrium thermodynamics Maxwell reciprocity is a constitutive assumption equivalent to postulating an energy function. It is easy to see that Maxwell reciprocity is just the statement that the incremental or linearized constitutive relation describing an n-port capacitor is symmetric (Oster and Perelson, 1973). For example, if the constitutive relation **F** of the piston-cylinder arrangement shown in Fig. 1 is given by the function $(S, V, N) \overset{\mathbf{F}}{\mapsto} (T, -p, \mu)$, then the linearized constitutive relation or Jacobian of **F** is

$$D\mathbf{F}(S,V,N) = \begin{bmatrix} (\partial T/\partial S)_{V,N} & (\partial T/\partial V)_{S,N} & (\partial T/\partial N)_{S,V} \\ -(\partial p/\partial S)_{V,N} & -(\partial p/\partial V)_{S,N} & -(\partial p/\partial N)_{S,V} \\ (\partial \mu/\partial S)_{V,N} & (\partial \mu/\partial V)_{S,N} & (\partial \mu/\partial N)_{S,V} \end{bmatrix} \tag{6}$$

The matrix $D\mathbf{F}$ is symmetric if and only if

$$\begin{aligned} -(\partial p/\partial S)_{V,N} &= (\partial T/\partial V)_{S,N} \\ (\partial \mu/\partial S)_{V,N} &= (\partial T/\partial N)_{S,N} \\ (\partial \mu/\partial V)_{S,N} &= -(\partial p/\partial N)_{S,V} \end{aligned} \tag{7}$$

Eqs. 7 are the familiar Maxwell relations (Callen, 1960, p. 118). Geometrically we can view the relations between the port variables as defining a constitutive surface in the space of all $2n$-port variables. Reciprocity then requires this surface to lie with a very special orientation in R^{2n} (Desoer and Oster, 1973).

Defining energy functions is a useful way of summarizing the constitutive information about simple homogeneous systems. However, in practice, trying to find an overall energy function for a radio is probably not as useful as simply applying Kirchhoff's laws. In network thermodynamics we have chosen to utilize the Kirchhoff approach.

NONEQUILIBRIUM THERMODYNAMICS

Next we consider an example from nonequilibrium thermodynamics: the steady-state transport of a single substance across a membrance. We can view the membrane as a 1-port device with a constitutive relation between the chemical potential difference across the membrane and the flow rate through the membrane as shown in Fig. 3 *a*. Mathematically this type of constitutive relation is identical to that of an electrical resistor.

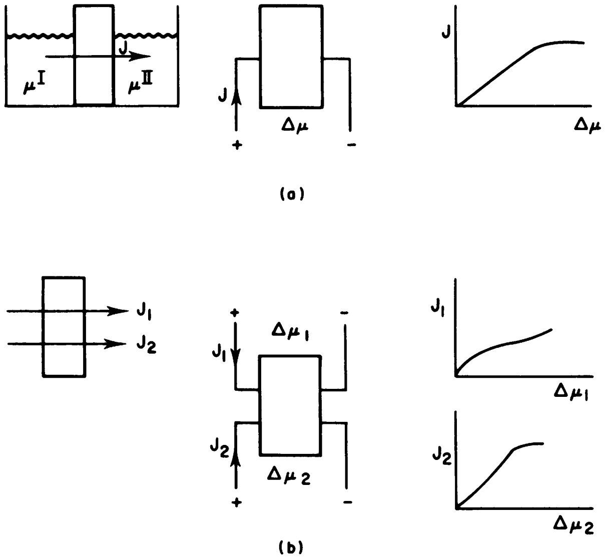

FIGURE 3 (*a*) The steady-state transport of a single species across a membrane viewed as a 1-port. (*b*) The steady-state transport of two species.

Irreversible thermodynamics is generally concerned with coupled flow phenomena. The obvious generalization is an *n*-port resistor defined by a constitutive relation between the flows of *n* solutes and the set of *n* chemical potential differences (Fig. 3*b*). We postulate that, whatever its internal transport mechanism, the observed behavior of the membrane in steady state can be completely characterized by a finite set of port variables. If this is not the case we must look for additional variables or assume that the membrane has not yet reach steady state. (This is the nonequilibrium equivalent of the "local state" postulate.)

We place no restriction on the form of resistive constitutive relations; they may be linear or nonlinear. Analogous to equilibrium systems we say that an *n*-port is reciprocal if the Jacobian matrix of its constitutive equation is symmetric. For linear constitutive equations this is the usual Onsager reciprocity. In the nonlinear case it is the obvious generalization. However, in general, we need make no assumption of reciprocity.

If all the resistors in the systems are 1-ports then it is easy to show that the system must be reciprocal (Brayton, 1971). Thus as we whall see in order to model the nonreciprocal nature of far-from-equilibrium chemical reactions one cannot use 1-ports.

In cases where the system is reciprocal, there always exists a potential function from which the constitutive relation can be derived and which is extremal at a steady state (Brayton and Moser, 1964, Stern, 1971; Oster and Desoer, 1971). For linear systems the potential is simply the entropy productions, while for nonlinear systems the potential function is called the "content" (Millar, 1951).

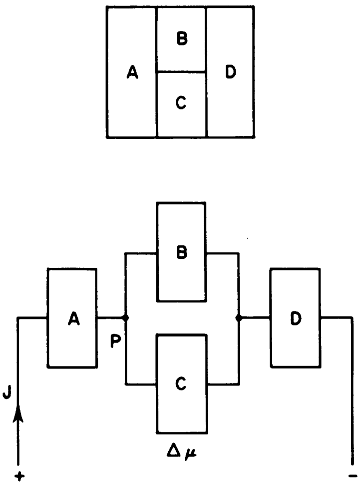

FIGURE 4

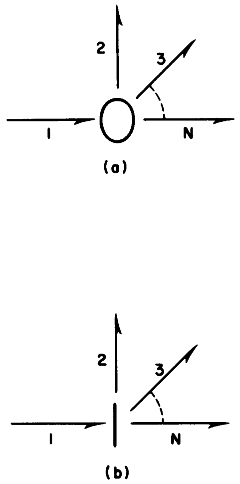

FIGURE 5

FIGURE 4 Transport across a composite membrane.
FIGURE 5 (*a*) 0-junction. (*b*) 1-junction.

INTERCONNECTION OF RESISTIVE AND CAPACITIVE N-PORTS

Reaction and transport processes involve only resistive and capacitive *n*-ports. Thus all that remains is to specify how to interconnect these devices. As before, at points of interconnection thermodynamic potentials are continuous and there is no loss of flow. These restrictions are just generalized statements of Kirchhoff's laws. What is needed is some systematic way of writing these laws for complex interconnections. For example, consider the composite membrane shown in Fig. 4. At point p the membranes A, B, and C are interconnected. Observe that since the membranes are all in contact the chemical potential of the substrate must be the same at the rightmost surface of A and the left surfaces of B and C, and whatever flows out of A must flow into B and C. This type of parallel interconnection can be represented by a special graphical symbol, the *0-junction* or *parallel junction*, shown in Fig. 5*a*. The lines incident on the junction are called *bonds* and represent perfect lossless connectors. Denoting generalized thermodynamic potentials or efforts by e_i and flows by f_i, a parallel junction is defined by

$$e_1 = e_2 = \cdots = e_N \tag{8}$$

$$\sum_{i=1}^{N} \sigma_i f_i = 0 \tag{9}$$

where

$$\sigma_i = \begin{cases} +1 \text{ if bond } i \text{ is oriented away from the junction} \\ -1 \text{ if bond } i \text{ is oriented towards the junction.} \end{cases} \qquad (10)$$

Membranes can also be connected in series. A series interconnection of elements can be represented by a *1-junction* or *series junction,* shown in Fig. 5 *b*, and defined by

$$f_1 = f_2 = \cdots f_N \qquad (11)$$

$$\sum_{i=1}^{N} \sigma_i e_i = 0. \qquad (12)$$

Parallel and series junctions can be considered special types of n-ports, "connection n-ports."[1] Their constitutive relations are simply Kirchhoff's laws corresponding to parallel and series interconnections. One can show that any interconnection, no matter how complex, can be constructed by combining these two junctions. Thus network models of thermodynamic systems require only four basic symbols R, C, 0, and 1. Graphical representations constructed from these symbols are known as *bond graphs.* Bond graph fundamentals are described in a variety of references including: Karnopp and Rosenberg (1968), Rosenberg and Karnopp (1972), Oster et al., (1973), and Perelson and Oster (footnote 1).

SIMPLE SYSTEMS

Now consider some models of simple transport systems such as the one shown in Fig. 6*a*. The membrane is first reticulated into volume elements each sufficiently large that a thermodynamic description is still appropriate. Each volume element is assumed to both store and transport material. The transport process is described by a constitutive relation between a flow and a difference in chemical potential and thus is a resistive n-port. The storage process is described by a relationship between concentration and chemical potential and hence is equivalent to an n-port capacitor. If we consider only one substrate transported isothermally and isobarically then the resistors and capacitors are 1-ports. One can easily establish that they must be interconnected as shown in Fig. 6*b*. This leads to the usual RC ladder network representation of one-dimensional diffusional processes. One can show that as the size of each volume element approaches zero the network equations approach the usual continuum differential equations. In the case of an ideal dilute solution capacitive constitutive relation and a linear resistive constitutive equation one obtains (Oster et al., 1973)

$$\partial c_i/\partial t = -(\partial J_i/\partial x) \qquad (13)$$

$$J_i = -D_i(\partial c_i/\partial x) \qquad (14)$$

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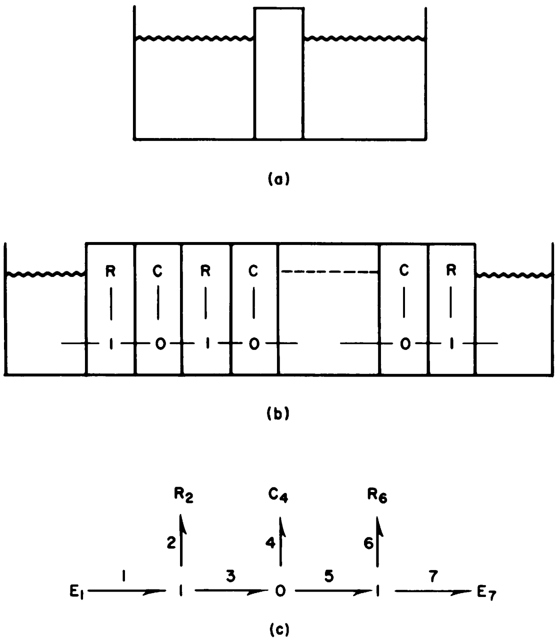
[1] Perelson, A., and G. Oster. 1975. Bond graphs and linear graphs. Submitted for publication.



(a)

(b)

(c)

FIGURE 6 (*a*) Membrane transport system. (*b*) Network representation.

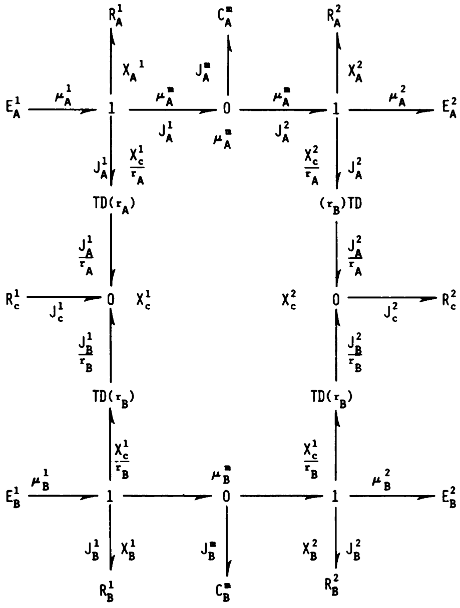


FIGURE 7 Coupled nonstationary transport of two species.

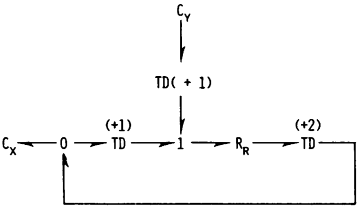


FIGURE 8

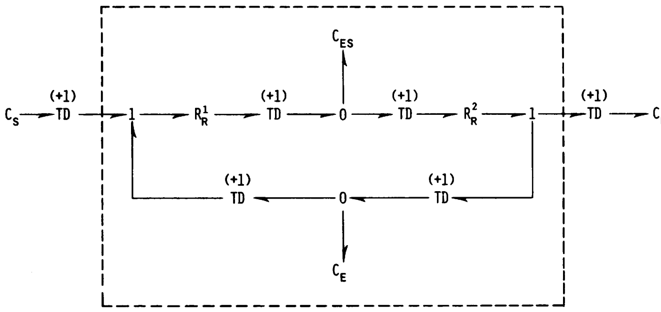


FIGURE 9

FIGURE 8 The autocatalytic reaction $X + Y \rightleftharpoons 2X$.
FIGURE 9 An enzymic reaction $S + E \overset{1}{\rightleftharpoons} ES \overset{2}{\rightleftharpoons} E + P$.

where D_i, J_i, and c_i are the diffusion coefficient, diffusive flux, and concentration of species i, respectively.

Fig. 7 shows the coupled transport of two species. The chemical potential difference that causes a flow of A also influences B and can cause its transport.

Chemical reactions can also be represented in network terms. Here we assume that the isothermal reaction mixture is well mixed and maintained homogeneous so that spatial considerations are unimportant. The network represents purely topological relationships between the dissipative and storage aspects of a reaction. Fig. 8 shows the representation of an autocatalytic reaction. The stoichiometry of a reaction represent various scalings that are occurring e.g., 2 mol of X must appear every time 1 mol of X and 1 mol of Y combine. In mechanical systems this type of scaling is performed by gears, while in electrical systems transformers are used. Thus, in representing reactions one must use scaling transducers to represent stoichiometry. Observe that Fig. 8 contains a positive feedback loop, indicating that autocatalytic reactions could contribute to the instability of a reaction system. Fig. 9 represents an enzymic reaction. Notice that the network diagram clearly illustrates that the enzyme cycles back and forth between free and combined forms. Although these diagrams look complex they can be generated algorithmically from conventional biochemical diagrams as shown in Fig. 10 (Morowitz, 1973). Other workers have used standard network representations for reactions (Hess et al., 1972; Busse and Hess, 1973).[2]

Reaction networks contain only resistors, capacitors, and transducers, making the prediction of oscillations a difficult task. However, Atlan and Weisbuch (1973) have shown that the effects of time delays in the reaction process can be approximated by adding inductors.

It should be apparent that the network representations for reaction and transport processes can be combined to form complex models of chemico-diffusional systems.

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[2] Network analogs of chemical systems based on kinetic rather than thermodynamic models have been developed by Seelig (1970, 1971), Seelig and Göbber (1971), Seelig and Denzel (1972), and Rössler (1974, 1975).

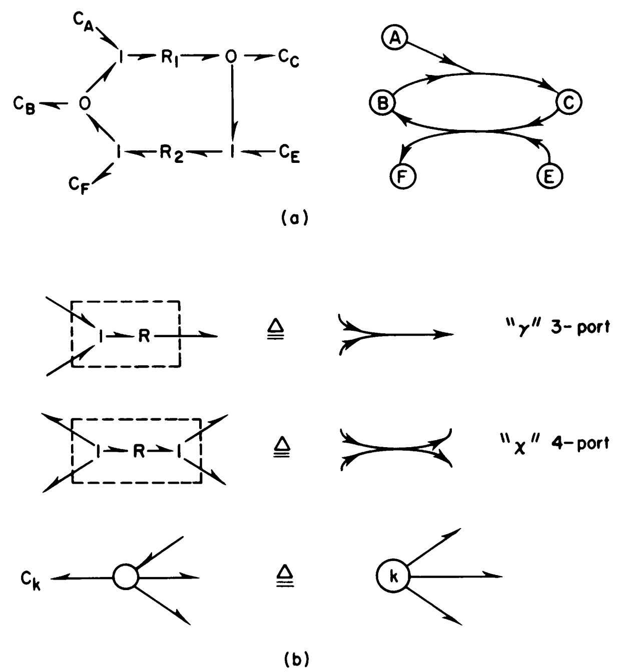

FIGURE 10 (*a*) Bond graph and conventional biochemical representations of a reaction network. (*b*) Equivalences used to interconvert the two representations.

Fig. 11 illustrates a model of facilitated transport. The membrane contains a carrier, *C*, which reacts with a permeant substrate, *S*, to form a complex, *CS*. Both *S* and *CS* are transported across the membrane. The complex then dissociates releasing *C* and *S*. *S* exits from the membrane and *C* is free to diffuse back across the membrane and combine with more *S*. Network models of a diffusion-coupled oscillatory chemical system have also been discussed by Busse and Hess (1973).

Other complex processes of biophysical interest including transport of nonelectrolytes and transport through series and parallel arrays of membranes have been modeled using network methods (Oster et al., 1973).

The important point to be made here is that by utilizing network thermodynamic methods one can translate problems in thermodynamics and in the modeling of biophysical systems into problems in network theory. Once this is done all of the practical and theoretical tools that engineers have developed for analyzing complex systems become available to the biophysicist. Studies of the temporal behavior of complex nonlinear transport systems, a subject usually ignored in irreversible thermodynamic treatments, become possible.

I emphasize that we have not simply found equivalent circuits for the equations describing thermodynamic processes. Given a set of equations there are many possible equivalent circuits. In network thermodynamics a unique graphical model is generated whose topology and elements are determined by the individual physical pro-

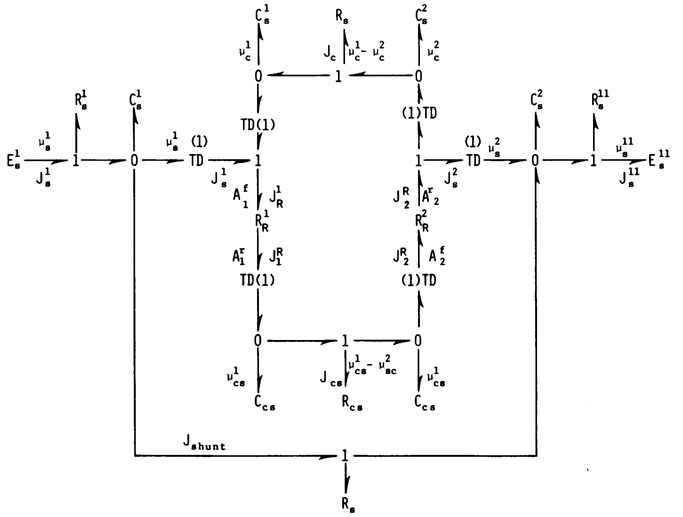

FIGURE 11 Facilitated transport.

cesses governing the operation of the system. The model thus totally reflects the thermodynamic description.

CHEMICAL REACTION NETWORKS

Besides extending the range of linear irreversible thermodynamics, network ideas can be applied to theoretical problems in chemistry to provide new insights into the structure of large chemical systems.

Chemical kinetics deals with the problem of determining rates of chemical reactions. Assuming temperature and pressure are maintained constant, and that the volume change due to reaction is negligible, the "state" of a chemical system is determined by the number of moles of each component. The equations of chemical kinetics describe the vector field that propels the state point through concentration space. One frequently assumes that this vector field is given by the law of mass action. Thus one is faced with the very difficult problem of solving large systems of nonlinear differential equations. In each set of reactions a different system of equations results and thus it has been very difficult to establish any general properties for reaction systems. I like to think of this approach as analogous to using Newton's equations in mechanics—a given problem may be easy to solve but general theorems are difficult to come by.

By using network thermodynamic methods one can formulate a generic set of differential equations to describe reaction dynamics that are in some sense analogous to Hamilton's equations in mechanics. Although these equations are valid for nonlinear far-from-equilibrium reactions I shall illustrate how they are derived by examining the simpler near equilibrium case.

For each reaction we can define an *extent* or *advancement of reaction,* ξ_k. If we can determine how the reaction extents change with time then the law of definite proportions

$$n_i(t) = n_i(0) + \sum_k \nu_{ik}\xi_k \tag{15}$$

determines how the mole numbers of each species change in time. Thus it suffices to find a differential equation in the extents.

For a set of M chemical reactions occurring among N chemical species, let $\mathcal{N} = R^N$ be the *species space* and let $\mathcal{M} = R^M$ be the *reaction space*. (In Oster and Perelson [1974*a*, *b*], a more general treatment is given in which $\mathcal{N}$ and $\mathcal{M}$ can be nonlinear spaces; i.e. differentiable manifolds.) The mole numbers $n_1, n_2, \ldots n_N$ can be assembled into a vector $\mathbf{n} \in \mathcal{N}$, and the reaction extents $\xi_1, \xi_2, \ldots \xi_M$ collected into a vector $\xi \in \mathcal{M}$. The law of definite proportions provides a map between the species and reaction spaces. Let ν be the $N \times M$ stoichiometric matrix, then

$$\nu: \mathcal{M} \longrightarrow \mathcal{N} \tag{16}$$

$$\xi(t) \longmapsto \mathbf{n}(0) + \nu\xi(t) = n(t). \tag{17}$$

By differentiating this map we obtain a relation between the rate of change of mole numbers, $\dot{\mathbf{n}}(t)$, and the rate of reaction $\mathbf{j} = d\xi/dt \equiv \dot{\xi}$ given by

$$\mathbf{n}(t) = \nu\dot{\xi}(t) = \nu\mathbf{j}. \tag{18}$$

To construct the equations of motion on the reaction space $\mathcal{M}$ we must introduce the constitutive equations for the species capacitors and reaction resistors. The former are defined by the map

$$\mathbf{n} \longmapsto \mu(\mathbf{n}) \tag{19}$$

on $\mathcal{N}$, where $\mu(\mathbf{n}) = [\mu_1(\mathbf{n}), \mu_2(\mathbf{n}), \ldots \mu_N(\mathbf{n})]$ is the vector of chemical potentials. The reactions are characterized by a nonlinear constitutive map Λ defined on $\mathcal{M}$

$$\alpha \longmapsto \Lambda(\alpha) = \mathbf{j}, \tag{20}$$

where α is the vector of chemical affinities ($\alpha = -\nu^T\mu$) and $\mathbf{j}$ is the reaction rate vector. The driving forces in species space μ and the driving forces in reaction space α are related by the law of definite proportions. In fact α is uniquely determined, given μ and the law of definite proportions, by the operation of pulling back a covector field along a map (see Oster and Perelson, 1974*b* for the details of this technical point).

By composing the constitutive relation and law of definite proportion maps the equations of motion can be constructed. The law of definite proportions (Eq. 15) determines $\mathbf{n}$ as a function of ξ. The capacitive constitutive relation (Eq. 19) assigns a unique chemical potential vector μ to $\mathbf{n}$, and then as indicated above the law of definite portions ($-\nu^T$) can be used to map μ into α. The reaction constitutive relation $\Lambda(\cdot)$ finally determines the reaction rate. Symbolically

$$\dot{\xi} = \Lambda(-\nu^T \mu[\mathbf{n}(0) + \nu\xi]) \tag{21 A}$$

$$= \mathbf{F}(\xi). \tag{21 B}$$

Once the equations have been solved the trajectories $\xi(t)$ can be mapped back to species space via $\mathbf{n}(t) = \mathbf{n}(0) + \nu\xi$.

If Λ is a linear map, as it must be sufficiently near equilibrium, then Eqs. 21 are just the conventional equations of irreversible thermodynamics written in an unconventional way. The difficulty with this formulation is that far-from-equilibrium the rate of reaction is not a unique function of the thermodynamic affinity; i.e., reaction resistors are not 1-ports. If this were the case one could easily show that all reactions must be reciprocal arbitrarily far from equilibrium.

For a large class of reactions including those described by mass-action and Michaelis-Menten kinetics one can formulate the reaction constitutive relation as a nonreciprocal 2-port with two independent driving forces: a forward affinity which depends only on the chemical potentials of the reactants and a reverse affinity which depends on the product chemical potentials. By appropriately modifying the stoichiometric matrix and the reaction extent vector one can incorporate this 2-port reaction constitutive relation into the previous derivation, and generate a generic set of differential equations valid for any reaction process, no matter how complex. Their form is similar to the above equations in that they show explicit dependence on three aspects of a reaction: (*a*) the equilibrium properties of the reaction mixture $\mu(\cdot)$, i.e., the chemical environment in which the reaction takes place, (*b*) the topology of the reaction network, ν, and (*c*) the dissipative aspects of the reaction process, $\Lambda(\cdot)$. The equations are generic in the same sense as Hamilton's equations except here one needs to specify three maps μ, Λ, and ν instead of one scalar Hamiltonian in order to determine the system.

The analogy with Hamilton's equations is instructive. Hamilton's equations can be written in the form

$$\dot{\mathbf{x}} = \mathbf{J}\nabla_x H(\mathbf{x}), \tag{22}$$

where the real valued function $H: R^{2n} \longrightarrow R$ is the Hamiltonian, $\mathbf{x} = (\mathbf{q}, \mathbf{p})$ is the vector of positions and momenta and

$$\mathbf{J} = \begin{bmatrix} \mathbf{O} & \mathbf{I} \\ -\mathbf{I} & \mathbf{O} \end{bmatrix}$$

is the symplectic matrix (Malcev, 1963; Arnold and Avez, 1968). Because μ is the

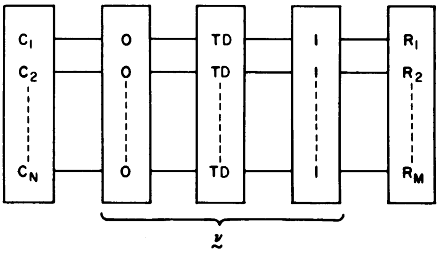

FIGURE 12 Generalized bond graph representation of a reaction system.

gradient of the Gibbs free energy, G, the equations of motion of a chemical system can be written

$$\dot{\xi} = \Lambda \nabla_{\xi} \phi(\xi), \tag{23}$$

where $\phi(\xi) \overset{\Delta}{=} -G[\mathbf{n}(0) + \nu\xi]$ is a scalar potential defined on $\mathcal{M}$, i.e., $\phi\colon \mathcal{M} \longrightarrow R$. The form of the two sets of equations is superficially similar. They are identical only if $\mathcal{M}$ is even dimensional and $\Lambda = \mathbf{J}$.

The generic equations (21) can be given a network interpretation (Perelson and Oster, 1974). Fig. 12 shows a general bond graph representation of any reaction system. With the capacitor constitutive relation given by $\mu(\,)$ and the resistor constitutive relation $\Lambda(\cdot)$, the equations describing this network are precisely Eqs. 21. The capacitors represent species space, the resistors represent reaction space and the set of junctions and transformers representing the network topology correspond to the reaction stoichiometry ν (Oster and Perelson, 1974*a*).

Using the network representation as a guide the equations of chemical dynamics can be extended in many ways. First, the generalization to open reaction systems can be derived by simply adding sources to the network (Perelson and Oster, 1974). Next, the biologically interesting situation in which there are a collection of cells communicating with each other and their environment via the transport of material across their outer boundaries can be modeled by a network which is formally identical to a reaction network. Here however, the resistors exhibit the dissipation due to transport and the capacitors represent the storage of chemical species in N cells instead of the storage of N species in one cell. This model can then be further generalized to include multiple species undergoing chemical reaction within each cell. The generic differential equations for this complex transport-reaction system can be easily derived from the network (Perelson and Oster, 1974); they are a generalization of the equations dealt with by Othmer and Scriven (1971) in studying instabilities and dynamic patterns in cellular networks.

FUTURE OF NETWORK THERMODYNAMICS

The analysis of large chemical systems is far from complete. Eq. 21 which described the dynamics of reaction systems needs to be thoroughly examined under a variety of constitutive assumptions. For example, by fixing the capacitive and resistive constitutive equations one can study the effects of changes in reaction topology. Are there certain topologies such as the positive feedback loop of autocatalytic reactions that make oscillations more probable? Alternatively, one can hold the topology and the reaction constitutive relation fixed and vary the capacitance. Some effects of capacitance variation on system stability and bifurcations to periodic solutions have been investigated (Luss, 1974).[3] Given a system of known reactions and equilibrium properties one can study the qualitative behavior of systems in which the nonlinearity of the reaction constitutive relations are restricted. For example monotone, passive, or quasi-linear (Duffin, 1946), resistive constitutive relations can be studied. Also the asymptotic behavior and the number of maxima or minima in the constitutive relation can be specified. Perelson and Oster (1974) consider the reciprocal, passive, and locally passive cases.

The graphical techniques developed to represent thermodynamic systems need to be exploited. Since the graphs are just another notation for the dynamic equations one may be able to find graphical criteria for stability and oscillations. The decomposition or "tearing" of a complex system into subsystems has been utilized in treating one reaction-transport system (Perelson and Oster, 1974). This technique should prove useful in analyzing a variety of large systems.

The ease of interfacing bond graph models with computer systems can be exploited in a classroom situation. Experience at Berkeley in teaching both undergraduates and graduates has shown that students with no previous computer experience can formulate and solve complex physiological modeling problems. Thus an intuitive understanding of complex system behavior can quickly be attained by students with little or no experience in nonlinear systems. The biophysics can be emphasized while submerging the formal mathematics.

Let me end by mentioning an area in which I foresee future growth of network thermodynamics. The goal of biophysics is to understand how biological systems work. Traditionally we have approached this problem through reductionist analyses. However, when we have isolated every enzyme and catalogued every reaction that occurs in a cell will we understand how the system works? I think not, for there are complex dynamic interactions that impart to matter the property that we call life. However, if we can design and synthesize systems which have these dynamic characteristics we will have made significant progress towards understanding them. Engineers have enormous experience in synthesis and design, and it is my hope that through network thermodynamics, these techniques can be applied to synthesize chemical networks with prescribed behaviors.

Network thermodynamics is based upon an idea of great simplicity—that the logical foundation of finite-dimensional thermodynamic models is formally identical to that of network theory. It was Aharon's hope that this similarity could be exploited to

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[3] Perelson, A. 1975. A note on the qualitative theory of lumped parameter systems. *Chem. Eng. Sci.* In press.

enrich thermodynamics and to provide a practical tool for the experimental biophysicist.

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