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From Irreversible Thermodynamics to Network Thermodynamics*

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Whenever the subject of the thermodynamics of irreversible processes TIP is brought up among biologists, there seems to be a very polarized reaction: some have found it a useful tool, others reject it utterly, and for some reason which I do not understand, even fervently. For the present school, Professor Aharon Katchalsky had suggested that we try together to point out some ways in which TIP has been useful, to discuss limitations and shortcomings, and, finally, to show the direction and first results of present efforts, mainly in network thermodynamics[1]. It would have been my task to show you the darker side of the coin, but now Aharon is not with us to show you the shining side in his unique way, to carry you along with his enthusiasm. I believe it is in Aharon's spirit that I do not attempt to evaluate or commemorate his contributions and achievements, but just talk science and try to convey a little of what was at the center of his interest during the last years.

The contribution of TIP to membrane biology may be considered in two aspects, which we shall call the computational and the conceptual. The possible computational contribution is well defined: correlations derived from Onsager's reciprocity theorem may make it feasible to evaluate parameters which are important for the elucidation of mechanism and not accessible to measurement, from readily measurable ones. The conceptual contribution is much more difficult to formulate and document but, I feel, not less important. We all know that a clear question is often a significant step towards an answer. TIP has helped membrane biologists to ask new questions, though it has not always been possible to give an answer.

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[1] Professor A. Katchalsky had planned to give the lecture on Network Thermodynamics at this Membrane School. My lecture was originally to be devoted to the use of TIP in the study of biological membranes.

Without touching upon the profound issues of the relation between a highly structured organism and its surroundings, some concrete examples may help to clarify these two aspects. First, the set of equations which has so far been most widely applied to biological systems describing the flow of water and nonelectrolytes. For each of the equations separately,

$$J_v = L_p(\Delta p - \Delta \pi) \tag{1}$$

and

$$J_s = RT\Delta c_s + c_s(1-\sigma) J_v, \tag{2}$$

TIP is not at all required. Eq. (1) may be regarded as an empirical statement of two facts: (1) Volume flow is a linear function of Δp and $\Delta \pi$. (2) The proportionality coefficient for $\Delta \pi$ is opposite in sign and often smaller than that for Δp. Nevertheless, and in spite of the extensive experimental study of membranes, the general background of TIP was necessary to realize and state clearly that a stationary pressure head, different from the osmotic pressure difference, may exist (Staverman's reflection coefficient). In other words, it was necessary to ask first whether a finite pressure head at zero flow is always equal to the osmotic pressure, before experimental results were critically reviewed, and new experiments designed, on synthetic membranes, the red cell, and later many other cells and tissues.

When I was reading Aharon's recent manuscripts, I was guided not only by the typed text, but also by the annotations in the margin, in his familiar handwriting. Some of them, when he was very pleased or quite annoyed by something which his colleagues, or he himself, had written earlier, in Hebrew. But this effect, when things seem obvious once we are led through them, or, sometimes and in small steps, get through, he used to define by a succinct saying in Yiddish: Reason does not run—it crawls. His own moved, in fact, at a considerable pace. In the same tradition, he would be classified as the prototype of "a flying mind".

Coming back to water and solute flow: An equation of the form of Eq. (2), including solvent drag, was indeed written without TIP. Onsager's symmetry relation gives us independent information only for the correlation of Eqs. (1) and (2): If, and only if, we have chosen our flows and forces in accord with the thermodynamically defined dissipation function, this mutual influence can be characterized by a single coefficient. It turns out that in many cases, Eq. (1) provides the easier avenue for measurement.

It is instructive to compare Eqs. (1) and (2) on the one hand with Jacobs' membrane permeation equations, and on the other with the classical equation for pore (or capillary) flow. The implicit choice for σ there is either one or zero. The formalism of TIP emphasizes the possibility of intermediate values, of incompletely coupled flows.

This applies also to other processes, e.g., active transport. One need not necessarily assume that an electrogenic pump is analogous to a battery, so that any observed leaks must occur in some other pathways, totally independent of metabolism. Whatever the mechanism of the "slipping", Onsager's relation can help us to relate the affinity of the driving reaction to measurable quantities, without plugging the leak:

$$A = -\frac{I^{sc}}{\partial J_r / \partial \Delta \psi} \tag{3}$$

where A = affinity, I^{sc} = short-circuit current, J_r = rate of oxygen consumption, and $\Delta \psi$ = electric potential. In practice, many questions still have to be clarified, and assumptions justified before one can accept this as the determination of *the* affinity, but there seems to be a promising start.

One may ask whether this whole approach, based on linearity of the flow equations, is at all realistic in biological systems, except perhaps for water flow. It turns out that in some investigations which were explicitly designed for the study of flow-flow and flow-force relations, amazing linearity was observed: for water and salt flow in intestine and other tissues, metabolism and ion-flow in frog skin, sodium and amino-acid flow in single cells, and others.

Clearly, many other processes are nonlinear, especially if one covers a large range of conditions; and for some, very important ones, nonlinearity is an essential requirement for their biological function.

The fundamental assumption of TIP is, that in a nonequilibrium system the entropy depends only on the same independent variables as at, or very near, equilibrium. The range of validity of this assumption may be much wider than that of the linear flow equations; and in the nonlinear thermodynamics dealing with this region, general theorems about evolution and stability criteria could be developed. However, the validity of the Onsager relation, the practical tool with which we are concerned here, is indeed restricted to the linear range. Within the formalism of conventional TIP one can cope with a limited kind of nonlinear membrane phenomena, using the equations for continuous systems: if the flows are linear functions of the local driving forces, and the membrane is in a stationary state, integration may be possible. Overall nonlinearity can result from linear local equations with coefficients depending on the concentration of some of the permeants, or on other state parameters. Such analysis led to an explanation of rectification by bipolar membranes and, more recently, to a quantitative theory of the flip-flop current in Teorell's membrane oscillator, without however treating the oscillation itself. In the network approach, nonlinearity and nonstationary time-dependent phenomena are a priori included. To illustrate the broadening of scope and the insight achievable through network representation, we shall discuss the description of coupling between processes, in TIP and in networks.

We start by retracing briefly the well-known description of a discontinuous system, a membrane separating two reservoirs which are accessible to experimentation .The changes in the reservoirs are followed by measuring state parameters at predetermined time intervals. From these one derives all the information on the processes which must take place in the membrane itself, with the aid of conservation laws and the assumption of local equilibrium. Concretely speaking, one follows, e.g., the concentration of a given solute in one, or both, compartments and, if the membrane is in a stationary state, the number of moles appearing on one side, or disappearing on the other, can be identified with the flow through the membrane. If a chemical reaction takes place in or on the membrane, the conservation law is appropriately modified. The forces driving these flows are also completely defined through the state parameters of the reservoirs: in our example the difference of the chemical potentials of the solute, or a sum of chemical potentials comprising the affinity of the reaction. For this we assume local equilibrium at the membrane surfaces, so that the chemical potential is continuous. In many systems the rates of change of different state parameters are found to be interdependent. In the usual terminology: the processes are coupled, and the coupling is quantitatively expressed by cross-coefficients in the flow equations.

Network thermodynamics start at once with the consideration of all parts of the system, and the processes taking place in them, not necessarily assuming a stationary state in any subsystem. The system is represented by an assembly of interconnected elements, thus the subdivision into volume elements is a natural part of this approach. However, the system is reticulated not only spatially, but also functionally. In general, in a time-dependent system, each volume element exchanges free energy with its surroundings, dissipating and storing it by various mechanisms. These are represented by capacitors and resistors, respectively. Since all the dissipation is separately represented, the capacitors are assumed to be charged and discharged reversibly, and thus this aspect of the process may be regarded as a "reversible flow". All irreversible subsystems are assumed to dissipate energy without storage.

In electrical networks, the meaning of these concepts is immediately clear, and there may even exist discrete physical entities approximating this idealized separation. The elements can be generalized to include the characterization of other flows: each volume element has a differential capacity for every substance i, defined by $C=(\partial n_i/\partial \mu_i)_{n_j,T,p}$, an expanding gas has a capacity $(\partial V/\partial p)_{T,n}$, etc. The reversible flow of i in the membrane element is

$$J_i^m = dn_i^m/dt = C_m\, d\mu_i^m/dt. \tag{4}$$

Resistances are defined by the response of effort (force) to flow. For diffusion: $\frac{\partial \Delta \mu_i}{\partial J_i}$ and the irreversible flow is

$$J_m^i = \frac{\Delta \mu_i}{R_i}. \tag{5}$$

The interdependence of displacements, flows and efforts is thus given by groups of constitutive relations, some of which we have indicated here. By this representation the various aspects of each part of the system are brought into a single framework in an intuitively appealing manner. The conservation laws and the assumption of local equilibrium are expressed by Kirchoff's current and voltage laws; the mathematical language of networks which was extensively developed for complex energy and information processing systems is put at the disposal of the biophysicist.

A third type of element is necessary to treat chemical reactions which transform one substance into another, and also the coupling between processes which transforms one type of power (rate of energy supply) into another. This is, of course, the transducer.

For the specific subject of our discussion, the description of coupling, let us return once more to TIP, for an interpretation of the flow equations.

If we want to learn or to state something about the mechanism of coupling, we must open the black box, go from the reservoirs into the membrane. One way of doing this was indicated earlier; if all local equations are supplied by a detailed model, it may be possible to express the overall coefficients in terms of model quantities. But before forming any molecular picture, a very general question poses itself: If we had complete thermodynamic information not only about the reservoirs but also about the membrane, with instantaneous maps of local concentrations, potentials, etc., at all times, equilibrium properties of membrane constituents and permeants, including their mutual influence, would we automatically know the mechanism of coupling? Would we find that the macroscopic coupling is brought about only by the overall organization of process, by the creation of gradients so that at any point and any given moment each microscopic process can go downhill, and none needs to be dragged along against its gradient? The answer is: sometimes, but certainly not always.

The two general possibilities are easiest explained by examples from large-scale energy conversion. In a Carnot machine, only spontaneous, downhill, processes take place at any given time. The overall coupling between the entropy flowing downhill (heat flow from high to low temperature) and mechanical work against some external load is made possible by the property of the gas to expand appreciably with an increase in temperature. As a consequence of its equation of state, the gas can transduce the two energy types which are the input and output of the machine, TS and PV. In the gas, $(\partial p/\partial T)_v \neq 0$, $(\partial S/\partial V)_T \neq 0$, etc., and the coefficients are correlated by Maxwell's relations.

On the other hand, no such equation of state or interdependence can be found in a hydro-electric station. The wheel turns when the water flows, because this is the way which was provided for the water to flow downhill, but no thermodynamic (thermostatic) analysis of the constituents reveals this.

Returning to the biological membrane, the unspecific mutual drag between water and solutes is usually attributed to frictional interaction, which can not be derived from the thermodynamic properties of the substances. Some models for active transport belong to the first type: a reaction on a carrier takes place on one side, driven by its own affinity. The new compound adsorbs the transported species, to equilibrium, the complex diffuses along the membrane under its own concentration gradient, there the group added before splits off, again in a spontaneous reaction, and the transported species is desorbed. But there are also models of the other type, built on direct coupling between elementary steps.

For coupled chemical reactions taking place on membranes this broad classification is a hotly disputed issue, though not necessarily formulated in this manner. Biochemists have traditionally assumed implicitly that reactions are coupled exclusively via common intermediates. According to this view, reactions only appear to us to be coupled because we do not know enough. Given detailed information, the coupling would disappear, and we would observe each reaction following its own affinity. However, the possibility is being suggested that in some cases the intermediate has not been found because it does not exist. On highly organized enzyme structures, reactions might be coupled because the path of the complex reaction does not allow the spontaneous one to run its natural course without taking along the other one, uphill.

The formalism of TIP does not provide a way to express such general classifications of models. To go beyond the matrix of L_{ij}'s, one has to have a full model calculation.

In network terms, on the other hand, the story told above can be put into a brief statement: coupled processes may be connected by transducers through capacitors, so that the discharge of one charges the other, or through resistances, so that part of the effort is diverted to another flow. The latter type was termed kinetic coupling. A common intermediate, for example, provides a transducer-capacitor link in the pattern of charge-discharge which leads from all the reactants to all the products. Frictional drag is represented by a coupling connection between the resistors representing the irreversible flows of *i* and *j*.

The point is, that before we have a model in molecular terms, the way a system is "hooked up" is extremely important information. Network thermodynamics may lead us towards a new class of questions and, hopefully, answers. So far, the main effort on network thermodynamics was directed towards conceptual clarification and definition of procedures. If this is indeed the right and natural direction, specific results on biological systems will be forthcoming.

For Aharon, the striving for a clearer and broader picture, the wrestling at each step, were an expression of his belief in science. In his own words: "The driving force of quantitative biological study is our mystical conviction that 'Nature' is one and that future generations will comprehend life within an integrated 'Natural Philosophy of the Physical World' ".