THERMODYNAMICS OF FLOW PROCESSES IN BIOLOGICAL SYSTEMS

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INTRODUCTION

The role of classical thermodynamics in the natural sciences resembles that played by logics in the humanities. The limited number of its fundamental principles, the rigorosity of its laws and the simplicity of its mathematical apparatus endow thermodynamics with a generality and wide applicability similar to those of logics. Thermodynamics succeeded to impose the necessary and sufficient conditions on equilibrium processes; it correlated numerous observable quantities and predicted important relations between measurable data without asking for any information about the microscopic structure of the systems under consideration. The importance of thermodynamic characterization of the molecular constituents of cells and tissues and of equilibrium reactions in metabolic processes cannot be over estimated and need not be followed up here.

Thermodynamics found, however, only minor application in the description of overall processes in the living organism and exerted a small influence on the advancement of biological thought. This is due to the fact that classical thermodynamics is essentially a theory of equilibria and is largely concerned with closed systems which do not exchange matter with the surroundings. On the other hand, all living organisms are open systems (1) in a state of constant flux. For the description of biological processes one needs a thermodynamic theory of flow in open systems. Such a theory should define in a formal manner the character of the flow, isolate the pertinent driving forces and derive quantitative relations between the flows and the forces.

An important advancement towards this goal was made during the last three decades by the investigators of the thermodynamics of irreversible processes. Numerous elements of this new branch of science can be found in the writings of the nineteenth century. It is, however, only through the law of Onsager, published in 1931 (2) that the thermodynamics of irreversible processes obtained a solid foundation on which a coordinated system could be developed. The modern version of irreversible thermodynamics is due to the work of numerous workers notably

Prigogine (3), de Groot (4), Meixner (5) and others (6) who developed the operational method and applied it to numerous examples. The major effort at present is devoted to the clarification of physical foundations and to the derivation of irreversible thermodynamics from the statistical mechanics of flow processes. Very little has however been done to apply this theory to the analysis of biological phenomena and this fertile field is open to further exploration.

ENTROPY PRODUCTION AND THE DISSIPATION FUNCTION

The major step in the development was the explicit introduction of time—t— into the thermodynamic formalism. While the classical treatment led to the realisation that irreversible processes in isolated systems are characterized by an increase in entropy, reaching its maximum at equilibrium, the new approach deals directly with the change of entropy with time dS/dt. For the study of open systems the change in entropy is decomposed into a part d_eS derived from the interplay with the external world and into a part d_iS produced in the system itself by irreversible processes.

$$dS = d_eS + d_iS \tag{1}$$

While d_eS may be positive or negative, d_iS is positive definite, i.e.,

$$d_iS \geq 0 \tag{2}$$

for any part of the system under consideration. The local time derivative or the "inner entropy production" d_iS/dt was chosen as the fundamental magnitude characterizing irreversible process.

For isothermal processes it is often convenient to use another function

$$\Phi = T\frac{d_iS}{dt}$$

or the "dissipation function" introduced by Lord Rayleigh already at the end of the nineteenth century.

If the irreversible processes are sufficiently slow so that the use of ordinary thermodynamic functions is justified, it is possible to apply the Gibbs equation to any part of the system and to write

$$T\,dS = dU + p\,dv - \sum_i \mu_i\,dn_i \tag{3}$$

In these cases the dissipation function may be shown to consist of the sum of products of fluxes J_i and conjugated forces X_i

$$T\frac{d_iS}{dt} = \sum_i J_iX_i \tag{4}$$

The forces of irreversible thermodynamics are generalized forces and should not be identified with the forces of mechanics. Thus the force driving a flux of matter

(dn_i/dt) is the gradient of chemical potential $(\nabla\mu_i)$ or the difference of chemical potential across a membrane $\Delta\mu_i$; the force driving a volume flow of liquid (J_v) is the gradient of hydrostatic pressure ∇p; while the force conjugated to the flow of an electrical current (I) is the gradient of electrical potential (E). More sophisticated is the "force" driving the flow of a chemical reaction: the force driving the advancement of reaction or reaction rate $d\xi/dt$ is the "affinity" A defined by de Donder as

$$A = -\sum_i \nu_i \mu_i \tag{5}$$

The ν_i's in eq. (5) are the stoichiometric coefficients of the chemical change.

The choice of forces and fluxes is arbitrary to a certain extent and is dictated by their adequacy for a convenient description of the behavior of the system under investigation. However, the possible transformations of flows and forces are subject to two limitations. The product of any pair of conjugated flows and forces should have the dimensions of the entropy-production and the sum of all products should leave the entropy production invariant (Meixner).

Let us consider as an example the flow of a single solute and water through a membrane. The dissipation function for this case is

$$\Phi = T\frac{d_iS}{dt} = \frac{dn_s}{dt}\,\Delta\mu_s + \frac{dn_w}{dt}\,\Delta\mu_w \tag{6}$$

where the flows of solute and water per unit area $J_s = dn_s/dt$ and $J_w = dn_w/dt$ are conjugated to the forces $X_s = \Delta\mu_s$ and $X_w = \Delta\mu_w$ which are the differences of the corresponding chemical potentials across the membrane. Since chemical potentials are not readily determined experimentally, it is preferable to chose as forces the difference of hydrostatic pressure on both sides of the membrane (Δp) and the difference of osmotic pressure $(\Delta\pi_s)$. The corresponding flows are now the volume flow

$$J_v = \bar{V}_w\frac{dn_w}{dt} + \bar{V}_s\frac{dn_s}{dt}$$

and the exchange flow (7)

$$J_D = \frac{1}{c_s}\frac{dn_s}{dt} - \frac{1}{c_w}\frac{dn_w}{dt}$$

and where $\overline{V}_w$ and $\overline{V}_s$ are the partial molar volumes of water and solute. Now the transformed dissipation function assumes the more convenient form

$$\Phi = J_v\,\Delta p + J_D\,\Delta\pi_s \tag{7}$$

THE PHENOMENOLOGICAL EQUATIONS

In order to utilize the formalism outlined above, relations between flows and forces have to be established. On a priori grounds it is expected that for sufficiently slow processes in "aged" systems which are close to a state of equilibrium, the flows should depend linearly on the conjugated forces. Indeed, as early as 1811 Fourier assumed a linear dependence of heat flow on temperature gradient. A similar dependence of the diffusion flow on the gradient of concentration was shown by Fick and of electrical current on potential by Ohm.

It was realized, however, already in the ninteenth century that there are cases when flows are coupled to non conjugated forces. Thus in the Seebeck effect a temperature difference in a thermocouple produces a flow of electricity and in the electroosmotic flow, discovered in 1801, a volume flow of liquid is produced by an electrical driving force. It is worth noting immediately that the structure of the dissipation function allows for the coupling between processes, one process becoming possible on the account of the entropy production of another. Consider for example, the entropy production in a system in which two simultaneous reactions are taking place. The dissipation function is for this case $\Phi = A_1 d\xi_1/dt + A_2\, d\xi_2/dt$ (where the A's are the affinities and the $d\xi/dt$'s are the velocities of reactions 1 and 2.) For independent reactions we would expect each reaction to proceed in a direction prescribed by its own affinity, but the thermodynamic requirement, $\Phi > 0$, does not impose this restriction. There is thus also the possibility that a process would proceed in a direction opposite to that dictated by its affinity if another coupled process provides the necessary entropy production (8).

In a general way it is thus plausible to assume with Onsager that every flow is linearly dependent on all the forces operative in the system, i.e.,

$$\begin{aligned} J_1 &= L_{11}X_1 + L_{12}X_2 + \cdots + L_{1n}X_n \\ J_2 &= L_{21}X_1 + L_{22}X_2 + \cdots + L_{2n}X_n \\ J_n &= L_{n1}X_1 + L_{n2}X_2 + \cdots + L_{nn}X_n \end{aligned} \tag{8}$$

The set of equations (8) states that each flow J_i is dependent on its conjugate force X_i through a straight coefficient L_{ii}, which is always positive, and in addition it may also be coupled to non-conjugated forces X_j through the coupling coefficients $L_{ij}(i \neq j)$ which may be positive, negative or zero. The coefficients L_{ij} need not be constant but have to be independent of the forces X_j.

The phenomenological equations became a powerful tool of research on the basis of an important law formulated by Onsager in 1931. It states that the matrix of the coefficients is symmetrical or that the cross coefficients are related by

$$L_{ij} = L_{ji} \tag{9}$$

Onsager's proof of the validity of relation in equation (9) is based on an extension of the theory of fluctuations. It has by now become verified in a large number of cases and the recent review of Miller (1960) (9) on the existing material shows that it may be accepted as an experimentally founded law of nature.

To demonstrate the usefulness of Onsager's law for a particular example, let us consider again the transport of a single solute and a solvent through a membrane. The phenomenological equations corresponding to the dissipation function in equation (7) are

$$\begin{aligned} J_v &= L_p\,\Delta p + L_{pD}\,\Delta\pi_s \\ J_D &= L_{Dp}\,\Delta p + L_D\,\Delta\pi_s \end{aligned} \tag{10}$$

The meaning of the coefficients is the following: If we keep the osmolar concentration on both sides of the membrane equal ($\Delta\pi_s = 0$) and subject the system to a hydrostatic pressure head Δp, a volume flow will result, determined by the coefficient L_p, i.e. $J_v = L_p\,\Delta p$. It is clear that the straight coefficient L_p is the filtration coefficient of the membrane. At the same time in a selective membrane a difference in the flows of solute and solvent will be observed and the exchange flow, $J_D = L_{Dp}\,\Delta p$, will be determined by the ultrafiltration coefficient L_{Dp}. On the same membrane, another experiment may be carried out: the hydrostatic pressure Δp is now zero but solutions of different concentration are put on both sides of the membrane, $\Delta\pi_s \neq 0$. In this case, a different exchange flow will take place, $J_D = L_D\,\Delta\pi_s$ but at the same time an osmotic volume flow will be observed, $J_v = L_{pD}\,\Delta\pi_s$. The law of Onsager now states that the coefficient of ultrafiltration equals that of osmotic flow, i.e., $L_{pD} = L_{Dp}$. This example demonstrates that Onsager's law is not a mathematical theorem on the matrix of the coefficients but a physical law on the relation between coupled phenomena. Moreover our system is defined by three coefficients, instead of the four introduced originally. It should, however, be noted that three is the minimum number of coefficients and no unequivocal description of the system by a smaller number of coefficients is possible. Numerous attempts by physiologists to describe the permeability of cell and tissues by two coefficients—one coefficient for volume flow and another for solute flow—lead therefore, to inconsistencies and inner contradictions. These earlier attempts have missed the important cross coefficient introduced by Staverman (10).

Consider an osmotic experiment in which the membrane system is left for a sufficiently long time to ensure a stationary state in which the volume flow disappears. In this state

$$J_v = 0 = L_p\,\Delta p + L_{pD}\,\Delta\pi_s \quad \text{or} \quad \Delta p = -\frac{L_{pD}}{L_p}\,\Delta\pi_s \tag{11}$$

If the membrane is ideally semipermeable we expect according to van't Hoff $\Delta p = \Delta\pi_s$ or $L_p = -L_{pD}$. For leaky membranes $\Delta p < \Delta\pi_s$ and for a fully permeable membrane $\Delta p = 0$. Hence

$$-L_{pD} \leq L_p \tag{12}$$

Staverman introduced the concept of a reflection or selectivity coefficient

$$\sigma = -\frac{L_{pD}}{L_p} \tag{13}$$

For an ideal semipermeable membrane $\sigma = 1$, but usually it lies between 0 and 1. Its determination is valuable for the characterization of membrane selectivity. Solomon et al. (11) were the first to introduce the study of σ into biological research and used it for the evaluation of the equivalent pore radius in the membrane.

Numerous transformations of the phenomenological equations into more convenient forms are possible as a consequence of their linearity. Thus we may write the forces as linear functions of the flows.

$$\begin{aligned} X_1 &= R_{11} J_1 + R_{12} J_2 + \cdots + R_{1n} J_n \\ X_2 &= R_{21} J_1 + R_{22} J_2 + \cdots + R_{2n} J_n \\ X_n &= R_{n1} J_1 + R_{n2} J_2 + \cdots + R_{nn} J_n \end{aligned} \tag{14}$$

and the coefficients R_{ij} again obey Onsager's law

$$R_{ij} = R_{ji} \tag{15}$$

This mode of writing is particularly instructive since the R_{ij}'s have the character of frictional coefficients as was observed already by Lord Rayleigh. Equation (14) is useful for the translation of the Onsager coefficients into frictions operative in the membrane.

There are also other transformations and it will be often found that it is convenient to use equations in which the flows are expressed as mixed functions of flows and forces. Thus again in the case of the permeation of a single non-electrolyte in aqueous solution one usually considers the volume flow J_v and solute flow J_s. In this case the pertinent phenomenological equations are:

$$\begin{aligned} J_v &= L_p \, \Delta p - \sigma L_p \, \Delta\pi_s \\ J_s &= c_s(1 - \sigma) J_v + \omega \, \Delta\pi_s \end{aligned} \tag{16}$$

It will be observed that in equation (16) the solute flow is a function of the volume flow J_v and the force $\Delta\pi_s$. In this transformation a new coefficient, ω, was introduced instead of the diffusion coefficient L_D. The coefficient

$$\omega = (J_s/\Delta\pi_s)_{J_v=0}$$

is the conventional solute permeability coefficient at zero volume flow. It derives its usefulness from the fact that for non-electrolytes it is often independent of solute concentration.

STATIONARY STATES

Among the irreversible processes a special role is played by those in which the state variables of the system are independent of time. These may be called non-equilibrium stationary states. If no restraints are imposed on the system it achieves, after a sufficiently long time, a state of equilibrium. On the other hand, if a number of constant restraints are imposed, such as a constant gradient of temperature, a constant gradient of chemical or electrical potential, a steady state is attained. In the steady state all flows corresponding to the forces on which no restraint was imposed—vanish, while the flows corresponding to the fixed forces assume a constant value independent of time. In a steady state all functions of the state become independent of time and hence the change of entropy of the system with time vanishes, i.e.

$$\frac{dS}{dt} = \frac{d_eS}{dt} + \frac{d_iS}{dt} = 0 \quad \text{or} \quad \frac{d_eS}{dt} = -\frac{d_iS}{dt} \tag{17}$$

but since for any state of the system $d_iS/dt > 0$, $d_eS/dt < 0$. This conclusion means that the entropy production in a stationary system must be compensated by the liberation of entropy to the surroundings. In other words, non-equilibrium steady states cannot occur in isolated systems which do not permit exchange of entropy with the suroundings.

In an interesting analysis of the approach to the steady state Prigogine (12) has shown that during an irreversible process taking place in a system the entropy production assumes the minimal value compatible with the restrictions imposed on the system. Moreover, if, as a result of some fluctuation, the system deviates from the steady state the internal changes tend to bring it back to its initial state. Thus we have a situation analogous to that observed in stable equilibria which are governed by Le Chatelier's principle of moderation (13). The stationary processes are therefore in a stable state.

Numerous speculations have been made by various authors on the applicability of the principle of minimum production of entropy to living systems. There is little doubt that a mature organism may be regarded as a restricted open system in which the irreversible processes have reached a stationary state. From a more sophisticated point of view, it may be said that the homeostasis of all self regulating systems is another expression for the stability of the steady state and its tendency to return from a perturbed state to that of highest stability compatible with the restriction imposed by biological requirements.

The stationary states allow a new interdependence between flow processes. Some striking examples were considered by Hearon (14) who has shown how the coupling of irreversible processes in the steady state may contribute to our understanding of active transport. A very simple case was treated in the illuminating monograph of Prigogine (3): Consider an open system which receives a component M from the environment and transforms it into component N, which is then returned to the environment. The system receives also another "inert" component O which does not take part in any chemical reaction but whose flow is coupled frictionally with that of M only. The flow equations are under isothermal conditions, the following:

$$\begin{aligned} J_M &= L_{11}\,\Delta\mu_M + L_{12}\,\Delta\mu_0 \qquad & J_N &= L_N\,\Delta\mu_N \\ J_0 &= L_{21}\,\Delta\mu_M + L_{22}\,\Delta\mu_0 \qquad & \frac{d\xi}{dt} &= L_{ch}\,A \end{aligned} \tag{18}$$

The stationary conditions for the concentrations of M, N and O in the system are

$$\frac{dN_M}{dt} = J_M - \frac{d\xi}{dt} = 0 \quad \text{or} \quad J_M = \frac{d\xi}{dt}$$

$$\frac{dN_N}{dt} = J_N + \frac{d\xi}{dt} = 0 \qquad J_N = -\frac{d\xi}{dt}$$

$$\text{and} \quad \frac{dN_0}{dt} = J_0 = 0$$

where N_i is the number of moles of component i in the cell. Solving the equations we get, among other results, the interesting expression

$$\Delta\mu_0 = -\frac{L_{12}/L_{22}}{L_{11} - (L_{12})^2/L_{22}} \frac{d\xi}{dt} \tag{19}$$

This expression states that the difference in chemical potential of the inert component $O - \Delta\mu_0$—which expresses the ratio of O inside and outside the open system—is determined by the rate of the chemical reaction of component M. In other words, a change in the rate of reaction may cause either the accumulation or the expulsion of O from the system. Such stationary couplings may cause an unequal distribution of matter between cell and surroundings by an amount determined by the rate of metabolic reaction (15).

In the following we shall consider some problems of membrane permeability mainly under conditions of stationary flow in the membrane. During a short time interval, as compared with times of relaxation for the system as a whole, a steady state is reached within the membrane. The steady state requires constant flows throughout the thickness of a single membrane or throughout a composite membrane. As shown by Kirkwood, (16) if the flows are constant, the phenomenological equations assume a simpler form. It is possible then to proceed and elucidate the meaning of the phenomenological coefficients in terms of frictions and to predict new correlations between the observables.

TRANSCRIPTION OF THE ONSAGER COEFFICIENTS IN TERMS OF FRICTIONAL COEFFICIENTS

The classical attempt to express the phenomenological coefficients in terms of frictions was followed up recently by Klemm (17), by Laity (18) and especially by Spiegler (19). We have extended this treatment which correlated explicitly the measurable quantities outside the membrane with some inner membrane parameters. The frictional treatment has admittedly less generality than the pure thermodynamic approach, it gives, however, a new insight into the transport magnitudes (20).

The equations to be used for aqueous solution of a single solute are the phenomenological equations where the forces are expressed as functions of the flows.

$$\begin{aligned} X_s &= R_s J_s + R_{sw} J_w \\ X_w &= R_{ws} J_s + R_w J_w \end{aligned} \tag{20}$$

In this consideration equations (20) represent the local forces and local flows at a point x in the membrane. For the derivation of the measurable macroscopic coefficients an integration of equation (20) has to be carried out. The three basic assumptions underlying the integration are:

1. The processes in the membrane are steady and the magnitudes of the flows are independent of x (Kirkwood) (16).
2. The chemical potentials on the bounding surfaces are equal to those in the adjacent solutions (Teorell (21), Meyer and Sievers (22).
3. Mechanical equilibrium of driving and frictional forces exists in every point of the membrane (Spiegler) (19).

The last assumption states that each of the driving forces (X_i) is counter-balanced by frictional forces acting between solute and water (X_{sw}) and between solute or water and the membrane (X_{sm}, X_{wm}). Thus $X_s = X_{sw} + X_{sm}$ and $X_w = X_{ws} + X_{wm}$. As is known from hydrodynamics the frictional forces of a steady flow can be expressed as products of a frictional coefficient f_{ij} and a relative velocity $v_i - v_j$

$$X_s = f_{sw}(v_s - v_w) + f_{sm}(v_s - v_m)$$

and if the membrane is taken as the frame of reference, $v_m = 0$

$$\begin{aligned} X_s &= v_s(f_{sw} + f_{sm}) - v_w f_{sw} \\ X_w &= -v_s f_{ws} + v_w(f_{ws} + f_{wm}) \end{aligned} \tag{21}$$

Upon expressing the velocities in terms of flows and converting the concentrations in the membrane to external concentrations by means of suitable partition coefficients (K), an integration of equation (21) across the membrane of thickness Δx can be carried out.

The result of such a calculation for the coefficient of solute permeability is

$$\omega = \frac{K}{\Delta x(f_{sw} + f_{sm})} \tag{22}$$

To apprehend the significance of the terms in equation (22) let us compare the membrane under consideration with a system of parallel capillaries of length Δx perpendicular to the membrane surface. If the volume fraction of water in the membrane is φ_w, we shall assign a fraction φ_w to the surface of the capillary system. According to Fick's law the diffusion of solute through the capillary system is given by

$$J_s = \varphi_w D \frac{\Delta c_s}{\Delta x}$$

where $D = RT/f_{sw}{}^0$ is the diffusion constant of solute in free solution, and $f_{sw}{}^0$ the corresponding friction coefficient of solute and water.

Hence

$$J_s = \varphi_w \frac{RT \, \Delta c_s}{f_{sw}{}^0 \, \Delta x} = \varphi_w \frac{\Delta \pi_s}{f_{sw}{}^0 \, \Delta x}$$

According to the definition of ω

$$\omega = \frac{J_s}{\Delta\pi_s} = \frac{\varphi_w}{f_{sw}{}^0\,\Delta x} \tag{23}$$

A comparison of equations (22) and (23) reveals the new features introduced by the present treatment: First it will be observed that instead of the frictional coefficient of free diffusion $f_{sw}{}^0$ we have now the sum of two coefficients. The term f_{sw} will generally differ from $f_{sw}{}^0$ although the difference becomes negligible in highly swollen membranes. The interesting term is the second coefficient f_{sm} which expresses the hydrodynamic interaction of the solute with the membrane matrix. It should be realised that f_{sm} need not be the friction of solute with fine capillary walls but may be the friction of solute dissolved in the matrix. In cases of dissolution f_{sm} may assume large values and decrease ω appreciably. To be sure f_{sm} will also achieve prominence in the case of large molecules which have a high friction with fine capillaries.

The other difference between ordinary diffusion in a capillary system and the penetration through the membrane is in the distribution coefficient K. In the case of capillary permeability the overall concentration of solute in the membrane will be proportional to the volume fraction of water in the capillary φ_w. However, if the solute dissolves in the membrane matrix, as is the case with numerous lipophilic solutes, the strong increase of K may overcome the simultaneous increase of f_{sm} and produce high permeability coefficients. The dependence of the permeability coefficient on the distribution coefficient was recognised by some of the earlier cell physiologists, notably by Overton (22), and later treated quantitatively by Osterhout et al (24) and by Longsworth (25).

It is worth noting that the interesting research of Danielli (26) who applied the principles of the theory of absolute rate processes to the analysis of membrane phenomena leads to a similar result. Eyring and his co-workers (27) have introduced a series of kinetic parameters which find their counterpart in the coefficients derived from the frictional model. From equations (21), it is also possible to obtain an expression for the reflection coefficient σ.

$$\sigma = 1 - \frac{\omega \bar{V}_s}{L_p} - \frac{K f_{sw}}{\varphi_w (f_{sw} + f_{sm})} = 1 - \frac{\omega \bar{V}_s}{L_p} - \frac{\omega f_{sw}\,\Delta x}{\varphi_w} \tag{24}$$

Equation (24) shows an interesting relation between the permeability coefficient ω and the reflection coefficient σ. When ω goes to zero and the membrane becomes impermeable to the solute, σ goes to unity as expected for an ideally semipermeable membrane. On the other hand, it can be readily shown that for a coarse, non selective membrane $\sigma = 0$.

If solute and water penetrate the membrane through different routes there is no solute-water interaction in the membrane and $f_{sw} = 0$. This leads to a value of σ

$$\sigma = 1 - \frac{\omega \bar{V}_s}{L_p} \tag{25}$$

THE PERMEATION OF SALT THROUGH CHARGED MEMBRANES

The quantitative study of ion permeability through charged membranes goes back to the pioneering work of Michaelis. The theory of Teorell (10) and of Meyer-Sievers (21) elucidated numerous factors which determine the ion transport and led to valuable correlations between the phenomena observed.

Within the formal framework of the thermodynamics of irreversible processes the transport of ions introduces the possibility of the operation of an additional force—that of the gradient of electrical potential E—and an additional flow, the electrical current I (29). If the potential is applied through electrodes reversible to one of the ions, the dissipation function for the flow of water, single electrolyte and electrical current assumes the form

$$\Phi = J_w \, \Delta\mu_w + J_s \, \Delta\mu_s + IE \tag{26}$$

The three phenomenological equations include in this case six independent Onsager coefficients. This makes the detailed study of the system a rather formidable task. The choice of the coefficients useful in experimental research is a matter of convenience and in accord with common practice, we suggest to add to the triple L_p, ω and σ another set of three electrical coefficients. One set of coefficients is obtained by working at equal salt concentration on both sides of the membrane ($\Delta\pi_s = 0$) and maintaining the volume flow at zero ($J_v = 0$). The coefficients for this case are the following: The specific conductance,

$$\kappa = \left(\frac{I}{E}\right)_{\substack{\Delta\pi_s = 0 \\ J_v = 0}};$$

the transport number of the ion which does not interact with the reversible electrode,

$$\tau = \nu z F \left(\frac{J_s}{I}\right)_{\substack{\Delta\pi_s = 0 \\ J_v = 0}}$$

where z is the valency of the ion, ν the number of ions of this kind per salt molecule and F the Faraday or 96500 coulomb; and the electro osmotic pressure P_E developed at zero volume flow per unit potential

$$P_E = \left(\frac{\Delta p}{E}\right)_{\substack{\Delta\pi_s = 0 \\ J_v = 0}}.$$

With these coefficients the expressions for the three flows passing the membrane assume the following form (30):

$$J_v = L_p \, \Delta p - \sigma L_p \, \Delta\pi_s - \frac{P_E L_p}{\kappa} \cdot I$$

$$J_s = c_s(1 - \sigma) J_v + \omega \, \Delta\pi_s + \frac{\tau}{\nu z F} I \tag{27}$$

(*continued on next page*)

$$I = -P_E J_s + \frac{\kappa\tau}{\nu z F}\frac{\Delta\pi_s}{c_s} + \kappa E$$

Under other experimental conditions it may, however, be more convenient to keep the pressure head Δp zero, while J_v assumes the value corresponding to the restrictions imposed. The electrical coefficients suitable for this case are the conductance at $\Delta\pi_s = 0$ and $\Delta p = 0$;

$$\kappa' = \left(\frac{I}{E}\right)_{\substack{\Delta\pi_s=0\\ \Delta p=0}};$$

the transference number of the ion which does not interact with the reversible electrode,

$$\tau' = \nu z F\left(\frac{J_s}{I}\right)_{\substack{\Delta\pi_s=0\\ \Delta p=0}};$$

and the coefficient of electroosmotic flow β, i.e., the volume of liquid transported through the membrane per unit current at $\Delta\pi_s = 0$ and $\Delta p = 0$;

$$\beta = \left(\frac{J_v}{I}\right)_{\substack{\Delta\pi_s=0\\ \Delta p=0}}.$$

Maintaining the pressure head at zero, it is convenient to define also an alternative solute permeability coefficient ω',

$$\omega' = \left(\frac{J_s}{\Delta\pi_s}\right)_{\substack{\Delta p=0\\ I=0}}$$

instead of the usual permeability coefficient

$$\omega = \left(\frac{J_s}{\Delta\pi_s}\right)_{\substack{J_v=0\\ I=0}}.$$

The phenomenological equations for this set of coefficients are:

$$\begin{aligned} J_v &= L_p\,\Delta p - \sigma L_p\,\Delta\pi_s + \beta I \\ J_s &= c_s(1-\sigma)L_p\,\Delta p + \omega'\,\Delta\pi_s + \frac{\tau'}{\nu z F}\,I \qquad (28) \\ I &= \kappa'\beta\,\Delta p + \kappa'\left(\frac{\tau'}{\nu z F c_s} - \beta\right)\Delta\pi_s + \kappa' E \end{aligned}$$

The full equations (27) and (28) are necessary when discussing the behavior of composite membranes (31). Here we shall consider only the simple case where no electrical current flows through the membrane ($I = 0$). The equations reduce in this case to the simpler form of equation (16) and both volume and solute flow may be described by only three coefficients. Upon transcribing L_p, ω and σ in terms of frictional coefficients we realize however that it is impossible to ascribe a simple friction to the salt molecules and we have to investigate separately the frictional contributions of the counter ions (1) and the coions (2). The number of frictional coefficients increases to six, f_{1w}, f_{1m}, f_{12}, f_{2w}, f_{2m} and f_{wm} whose meaning is self explanatory. The calculations simplify considerably if we treat a highly charged membrane in which the Donnan exclusion effect makes the concentration of the coions negligible as compared to that of the counter ions. In this case the salt permeability coefficient ω assumes a form similar to that obtained for non electrolytes. For a uni-uni valent electrolyte

$$\omega = \frac{K}{\Delta x(f_{2w} + f_{2m})} \tag{29}$$

A closer investigation, however, shows the similarity to be only superficial. It will be observed that the frictions which determine ω are not of the salt as a whole but only those of the coions. A more important difference is in the nature of the distribution coefficient K which in the case of electrolytes is strongly dependent on concentration. This can be seen by applying our equation to the model of Teorell and of Meyer and Sievers: This model treats a rather loose membrane of water content φ_w and constant charge density X. It is assumed that in this case the distribution of salt between membrane and external solution is governed by Donnan's ideal equation, whence at high charge density

$$K = \frac{c_s \varphi_w^{\,2}}{X} \tag{30}$$

or K increases linearly with the average salt concentration.

For very low salt concentrations $K \to 0$ and $\omega \to 0$, and hence the charged membrane behaves as an ideal semipermeable structure. Upon increasing c_s, K and ω increase, and the membrane becomes more and more leaky. This behavior has also a profound influence on σ. In terms of frictions the value of σ for a uni-univalent salt solution has the same form as that obtained for non electrolytes:

$$\sigma = 1 - \frac{\omega \bar{V}_s}{L_p} - \frac{K(f_{1w} + f_{2w})}{\varphi_w(f_{2w} + f_{2m})} = 1 - \frac{\omega \bar{V}_s}{L_p} - \frac{\omega f_{sw}\, \Delta x}{\varphi_w} \tag{31}$$

where

$$f_{sw} = f_{1w} + f_{2w}$$

For the model of Teorell and Meyer and Sievers (TMS model) equation (31) can be made more explicit. It will be observed that in the loose network considered in this model the friction of the coion with the membrane matrix (f_{2m}) can be neglected as compared with its friction with water (f_{2w}). Thus the frictional term in σ becomes $(f_{1w} + f_{2w})/f_{2w}$ and since according to this theory the frictions are not influenced by the membranes

$$\frac{f_{1w} + f_{2w}}{f_{2w}} = \frac{f_{1w}^{\,0} + f_{2w}^{\,0}}{f_{2w}^{\,0}} = \frac{1}{t_1^{\,0}} \tag{32}$$

where t_1^0 is the transport number of the counter ion in free solution. Introducing further equations (30) and (32) into (31) we get the interesting approximate expression

$$\sigma = 1 - \frac{\omega \bar{V}_s}{L_p} - \frac{\bar{c}_s \varphi_w}{X t_1^0} = 1 - \frac{\omega \bar{V}_s}{L_p} - \frac{\bar{c}_s}{X' t_1^0} \tag{33}$$

where $X' = X/\varphi$ is the charge concentration in the water filled capillaries. It is readily seen that at very low salt concentration both $\omega \bar{V}_s / L_p$ and $c_s/X' t_1^0$ are negligible, $\sigma \rightarrow 1$, and the membrane acts as an ideal semipermeable membrane. Upon increasing the salt concentration both terms increase and σ decreases, indicating an increasing leakiness. The decrease in σ will occur at lower concentrations if the transference number of the counter ion is lower. If t_1^0 is sufficiently small there will be a certain concentration at which σ vanishes and beyond it assumes negative values. We would like to recall that σ was defined as the ratio of hydrostatic pressure developed at a stationary state (Δ p) to the osmotic pressure difference ($\Delta\pi_s$), i.e., $\Delta p = \sigma \Delta \pi_s$. Negative values of σ mean that in the osmotic cell a negative pressure will develop or a pressure will have to be applied to the external solution to prevent water from flowing out of the cell. Similarly at zero pressure difference, an osmotic flow from the concentrated to the dilute solution will occur. This phenomenon, known since the work of Dutrochet in the first half of the nineteenth century as negative anomalous osmosis obtains a simple and quantitative explanation through equation (33). Several years ago Schlögl (32) found, that for very low values of t_1^0 anomalous osmosis is to be expected.

A comparison with experimental results is given in the two following figures. The first figure represents the experimental values of σ derived from the measurements

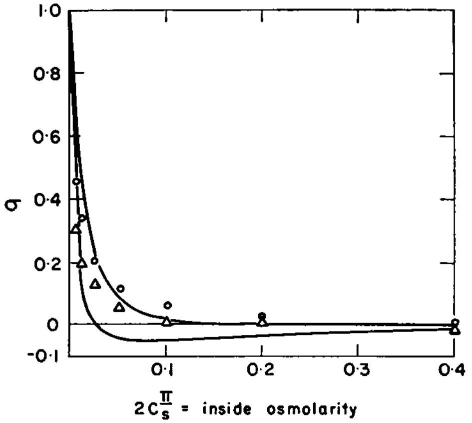

FIGURE 1 Reflection or selectivity coefficient (σ) of a positively charged membrane for mono-mono valent salts derived from the measurements of Grim and Sollner. 0 experimental points for KCL solutions. Δ experimental points for K 0_3 solutions. Upper curve calculated for mono-monovalent salt $t_1^0 = 0.5$. Lower curve calculated for mono-monovalent salt $t_1^0 = 0.35$. In all experiments the concentration of the outer salt solution was half the concentration of the inner salt solution.

of Grim and Sollner (33) on collodion membranes made permselective by the adsorption of either haemoglobin or protamin. The full lines are calculated from equation (33). The overall agreement is good although the quantitative correspondence at high salt concentration is less than expected, presumably due to the fact that the charge is not spread homogeneously over the membrane.

The second figure represents the experimental data of Loeb (34) on anomalous osmotic flow of a sodium chloride solution through a collodion membrane. Δh is the capillary rise after a given time, while $\Delta\pi_s/RT$ is the osmolarity of the inner solution. The full curve is calculated and represents rather closely Loeb's results.

It might be of interest to calculate σ for the TMS model, also for polyvalent salt permeating through charged membranes. The results of the calculation are given in Fig. 3. It will be observed that a divalent coion increases the selectivity of the membrane while a divalent counter ion, which is more effective in decreasing the effect of the charges fixed on the membrane matrix, diminishes σ.

COMPLEX MEMBRANES—CIRCULATION AND POLARITY

We can now pass to the treatment of more complex systems in which membranes of different characteristics are joined into composite structures, for which new relations between flows and forces are to be expected. The simplest modes of combination are those of a parallel and of a series array of homogeneous membrane elements. From these two, other compositions may be obtained.

The assumptions underlying the theoretical analysis of composite membranes are the following:

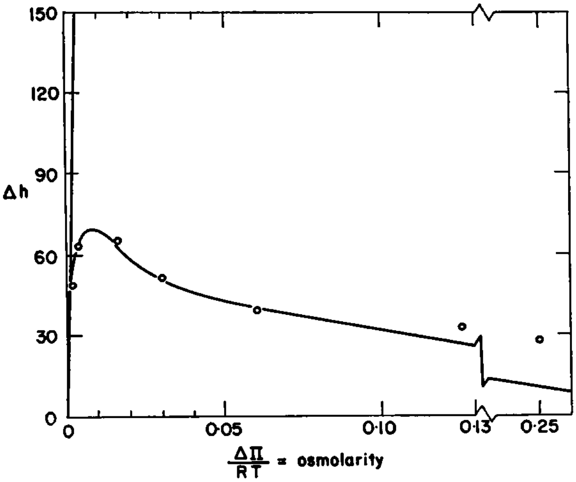

FIGURE 2 Theoretical curve of anomalous osmotic flow for the experimental data of Loeb. O experimental results of Loeb with sodium chloride solution permeating a collodion membrane.—calculated curve for a mono-monovalent salt with transference number of counterion $t_1{}^0 = 0.4$; Δh the capillary rise after a given time. $\Delta\pi/RT$ osmolarity of the salt solution in the membrane bag.

In the parallel array the same total force operates on each element. The flows passing through the elements may differ according to the coefficients characterizing each constituent.

On the other hand, in the series arrangement the flows passing each element will be the same as required for a stationary state. In this case the forces acting on each element will differ, while their sum total will represent the observable macroscopic force. The thermodynamic potentials are assumed to be continuous throughout the structure.

With these assumptions it can be readily shown that the transport of non electrolyte through an array of elements is essentially governed by coefficients whose form is to be expected from the laws of electrical networks (35, 36). Thus for mechanical and solute permeability in a series array

$$\frac{1}{L_p} = \frac{1}{L_{p1}} + \frac{1}{L_{p2}} \tag{34}$$

and

$$\frac{1}{\omega} = \frac{1}{\omega_1} + \frac{1}{\omega_2} \tag{35}$$

Figure 3 (*a*) to (*c*) The dependence of apparent osmolarity (per unit charge concentration in the membrane) $\sigma\Delta\pi/RTX'$ on the real osmolarity (per unit charge concentration in the membrane) $\Delta\pi/RTX'$, calculated from the model of Teorell and of Meyer and Sievers.

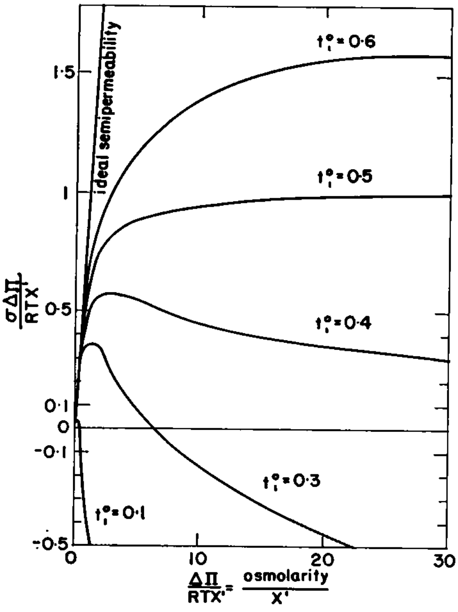

Figure 3 (a) The permeant salt is mono-monovalent. The curves are for salts with the following transference numbers (t_1^0) of the counter ion $t_1^0 = 0.1, 0.3, 0.4, 0.5, 0.6$.

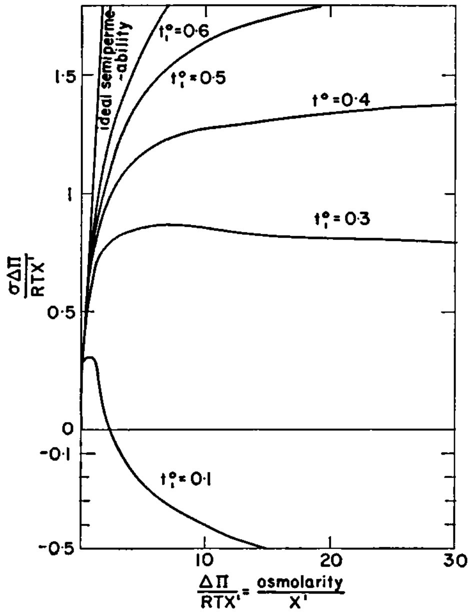

FIGURE 3 (b) The permeant salt is mono-divalent. The transference numbers of the monovalent counter ion are $t_1^0 = 0.1, 0.3, 0.4, 0.5, 0.6$.

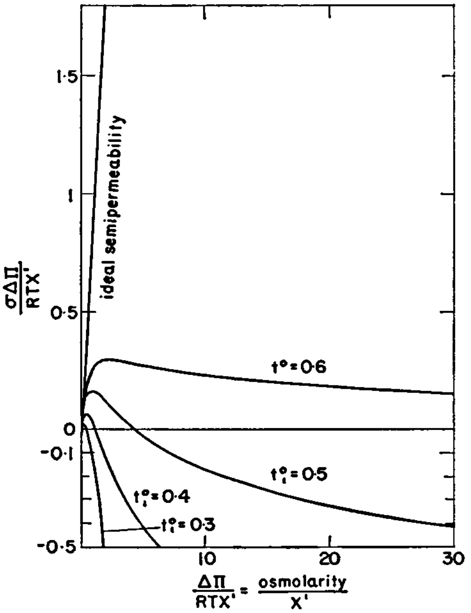

FIGURE 3 (c) The permeant salt is di-monovalent. The transference numbers of the divalent counter ion (t_1^0) are $t_1^0 = 0.3, 0.4, 0.5, 0.6$.

If we recall that L_p is essentially a mechanical conductance and $1/L_p = R$ is the resistance to mechanical flow, equation (34) is $R = R_1 + R_2$, which is the membrane equivalent to Ohm's law for a series of resistances. In a similar manner denoting the resistance to solute flow by ρ, equation (35) states that $\rho = \rho_1 + \rho_2$. The selectivity of a membrane composed of elements in series is more specific:

$$\sigma = \sigma_1 \frac{\rho_1}{\rho} + \sigma_2 \frac{\rho_2}{\rho} \tag{36}$$

i.e., the total selectivity coefficient is the sum of the elementary selectivities each weighted by the fraction of the resistance to solute flow offered by the corresponding element. Thus as already observed by Durbin (37) even a highly selective element will contribute only a little to the overall selectivity if it presents only a small resistance to solute flow.

Passing to non electrolyte transport through a parallel array of elements we again find for the mechanical filtration coefficient a simple law of additivity.

$$L_p = \gamma_1 L_{p1} + \gamma_2 L_{p2} \tag{37}$$

where γ_i is the fraction of the area occupied by the i'th element. Denoting $1/\gamma_1 L_{p1} = R_1$ we get $1/R = 1/R_1 + 1/R_2$ which is the membrane equivalent to the total electrical resistance exerted by resistances in parallel. Similarly for the permeability ω' measured at zero pressure head

$$\omega' = \gamma_1\omega_1' + \gamma_2\omega_2' \tag{38}$$

A new phenomenon appears however upon considering the solute permeability at zero volume flow. In this case $\omega \neq \gamma_1\omega_1 + \gamma_2\omega_2$ but is given by the expression

$$\omega = \gamma_1\omega_1 + \gamma_2\omega_2 + c_s \frac{(\sigma_1 - \sigma_2)^2}{R_1 + R_2} \tag{39}$$

The new term appearing in equation (39)—$c_s\ (\sigma_1 - \sigma_2)^2/R_1 + R_2)$—is due to the circulation of solvent through the elements. In order to keep overall volume flow zero, the flow through one element is compensated by an opposite flow passing the other. Circulation vanishes when $\sigma_1 = \sigma_2$ and evidently goes to zero when the mean concentration $c_s \rightarrow 0$. The existence of circulation increases the production of entropy and leads to higher values of ω.

The effect of circulation is still more pronounced when we pass to the permeation of ions through charged membranes. In this case the gradient of salt concentration may produce a circulation of an electrical current even if the overall current is zero. Thus consider a parallel arrangement of positive and negative permselective elements. A stream of cations will pass through one element and an equivalent flow of anions through the other. The direction of the electrical current will be opposite in the two elements and the effect will be that of circulation at zero flow of current. This effect increases the solute permeability as seen in the following expression

$$\omega' = \gamma_1\omega_1' + \gamma_2\omega_2' + \alpha_1\alpha_2\kappa'\left(\frac{\tau_1' - \tau_2'}{\nu z F}\right)\left[\frac{\tau_1' - \tau_2'}{c_s \nu z F} - (\beta_1 - \beta_2)\right] \tag{40}$$

It will be observed that the ionic circulation effect is determined by the difference in the transport numbers τ'. The transport number is closely related to the potential which will develop across a membrane at zero electrical current, and thus, the current will not vanish simultaneously in the elements with different τ'. For an ideally permselective membrane τ' is either 1 or 0. The circulation transport will be maximal when $\tau_1' = 1$ and $\tau_2' = 0$. In addition the electrical transport is clearly dependent on the conductance of the membrane elements. As $\alpha_1 = \gamma_1 \kappa_1'/\kappa'$ denotes the fractional conductance of the 1'st element and α_2 of the second, the circulation effect will vanish if one of the elements does not conduct. The term $\beta_1 - \beta_2$ expresses a secondary effect of the drag of the ions by the electroendosmotic flux of volume.

The circulation effect was first observed and analysed by Neihof and Sollner (38). They found that for oppositely charged permselective membranes the circulation term is much more important than the straight terms $\gamma_1\omega_1' + \gamma_2\omega_2'$, which were regarded only as a leakage through the membranes.

It is clear that in a series arrangement of charged layers no circulation can take place, however, another important phenomenon comes to light—the phenomenon of polarity. Such a membrane system will respond in a different manner according to the direction of applied force. We shall consider here only the relation between current and potential in a series array of membrane elements. In the experimental determination of conductance identical salt solutions are introduced on both sides of the complex membrane so that $\Delta\pi_s = 0$. As pointed out however at the beginning, the total force in this case is the sum of the forces operating on the elements. In the case that the electrochemical potential remains continuous across the membrane even during the passage of electrical current we may therefore assume an effective $\Delta\pi_s$ operating on each membrane so that on one membrane element the force will be $\Delta\pi_s'$ and on the other, $-\Delta\pi_s'$. A simple calculation shows that

$$\Delta\pi_s' = \frac{\tau_2 - \tau_1}{\omega_2 + \omega_1} \frac{I}{\nu z F} \tag{41}$$

i.e. the intermittent osmotic difference is non vanishing and both its magnitude and size depend on the difference between the transport numbers and on the direction of the current. Thus if $\tau_2 - \tau_1 > 0$ and $I > 0$, $\Delta\pi_s' > 0$, and an accumulation of salt between the membranes will occur, increasing the conductance. In the opposite case of $\tau_2 - \tau_1 > 0$ and $I < 0$, $\Delta\pi_s' < 0$ and there will be a depletion of salt with concommitment decrease in conductance. This effect if of course well known from the study of desalting systems composed of positive and negative permselective membranes. In the double membrane however the value of $\Delta\pi_s'$ is fully determined by the electric current, which builds up a concentration extremum on the surface of contact between the membranes. Introduction of $\Delta\pi_s'$ into the expression for conductance gives

$$\frac{1}{\kappa} = \frac{1}{\kappa_1} + \frac{1}{\kappa_2} + \frac{[(\tau_1 - \tau_2)/\nu z F]^2}{c_s(\omega_1 + \omega_2)} \tag{42}$$

If the current goes in the desalting direction c_s diminishes strongly, the term

$$\frac{[(\tau_1 - \tau_2)/\nu z F]^2}{c_s(\omega_1 + \omega_2)}$$

increases and κ diminishes. The ordinary Ohmic resistances $1/\kappa_1$ and $1/\kappa_2$ become negligible as compared with the polarity term. On the other hand, if accumulation of salt takes place in membranes where selectivity is based on Donnan exclusion, the permselectivity breaks down, $\tau_1 - \tau_2$ decreases, ω_1 and ω_2 increase, the Ohmic resistances decrease too and the conductance reaches appreciable values.

Introducing this relation into the dependence of I on E we find a pronounced rectification effect as demonstrated clearly in the following figure.

The figure was calculated numerically for the TMS model on the assumption that the complex membrane is composed of a negative and positive membrane, separating two identical solutions of KCl.

The time required to reach a steady state in the membrane is strongly dependent on its thickness. In very thin membranes the times of relaxation should be sufficiently short to permit rectification of ordinary alternating current.

These "valve effects" may play a role in the function of the nerve membrane. Further examination of this point requires an analysis of displacement currents.

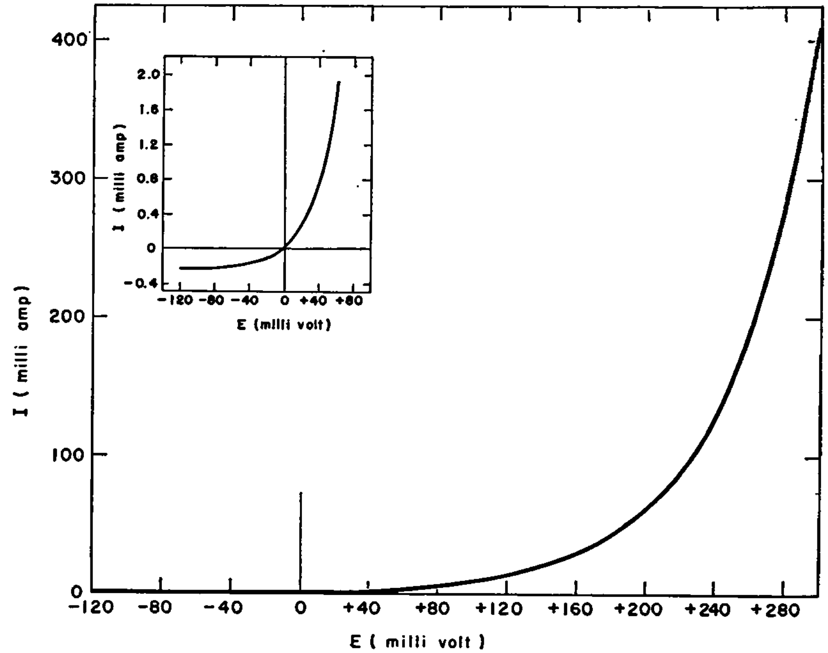

FIGURE 4 Calculated dependence of the electrical current I on the e.m.f. E for a double membrane—composed of a positive and negative membrane in series. The calculation is based on a Teorell and Meyer and Sievers model for membranes of effective thickness 10^{-3} cm and charge density $X' = 0.1$ moles/liter.

The discussion of transport through charged and complex membranes requires the treatment of several simultaneous flows governed by a large number of coefficients. It is now possible to extend the consideration to another important domain in which we deal with several flows—to the field of active transport. It is clear a priori that even in the simplest case—that of the transport of a solution with single solute—we have to consider here not only the flows of solute and solvent with their conjugated forces but we have to include into the treatment also the flow of a metabolic reaction, whose driving force is the affinity defined above.

In the attempt to write phenomenological equations which include the chemical flows we encounter however a difficulty arising from the violation of a principle announced many years ago by Curie. This principle states that coupling can take place only between flows of the same tensorial order. Hence a diffusional flow which has a vectorial character and is a tensor of the first order cannot be coupled with the flow of a chemical reaction which is scalar in nature and is a tensor of zeroth order. Indeed, no direct coupling was ever observed between solute flow and chemical reaction proceeding in a homogeneous medium. On the basis of Curie's principle Jardetzki (39) stated rather categorically that no direct coupling is possible between metabolic processes and membrane permeability, although an indirect coupling—through the modification of chemical driving potentials by chemical reaction—was not excluded.

In the sodium pump proposed by Conway (40) active transport of the sodium is based on the coupling between the flow of the ion and the flow of a circulating carrier in the membrane. In such a model Curie's theorem would hold at any point in the membrane phase, yet the phenomenological effect is that of a direct coupling between the sodium flow across the membrane and the chemical reaction. A concrete case of transport by a circulating carrier was analysed by Hokin (41).

Mitchell (42) stressed the importance of a highly specific and anisotropic structure of the membrane, which may create a direct coupling between the passage of ions and a metabolic reaction catalysed by an oriented enzyme.

Recently Langeland (43) showed that Curie's principle applies only to isotropic media but not to an anisotropic membrane capable of active transport. The metabolic reaction taking place in the membrane may therefore be included in the array of interacting flows and forces.

Kedem (44) wrote the explicit equations for the direct coupling of metabolic reaction with permeation flow in the following form

$$
\begin{aligned}
X_i &= \sum_j R_{ij} J_j + R_{ir} J_r \\
A &= \sum_i R_{ri} J_i + R_{rr} J_r
\end{aligned}
\tag{43}
$$

In these equations the flows of solutes and water are the J_j's while $J_r = d\xi/dt$ is the advancement of the chemical reaction. The forces X_i are the gradients of chemical potential driving the permeation flows and $A = \Sigma_i \nu_i \mu_i$ is the affinity driving the chemical reaction. The metabolically induced transport of a species i is thus determined by the cross coefficient R_{ir} and hence

$$R_{ir} \neq 0 \tag{44}$$

may be regarded as a criterium for active transport. It should however be pointed out that a significant difference exists between R_{ij} and R_{ir}. Since both X_i and J_j are vectors the ordinary coefficients are scalars dependent on frictional coefficients and concentrations. On the other hand, J_r is a scalar so that the R_{ir}'s are vectors, incorporating the directional anisotropy of membrane structure. The products are scalars, as is the driving force A. Similarly, the straight chemical coefficient R_{rr} is a scalar quantity.

The existence of direct coupling does not preclude the possibility of indirect coupling, say, through an intermittent carrier. In this case R_{ir} may be zero, however-there has to exist a non vanishing coupling coefficient $R_{ij} \neq 0$ to the flow of the carrier J_j and there should exist a coupling coefficient $R_{rj} \neq 0$ between the carrier and the chemical reaction. From this point of view, the case of stationary coupling in active transport described by Hearon and discussed above may give rise to indirect coupling.

To demonstrate some of the consequences of the phenomenological equations (43), let us consider a simple case analyzed by Kedem: Assume an active transport of a mono-monovalent salt under conditions of zero volume flow $J_v = 0$ or, which is approximately the same condition, at zero water flow $J_w = 0$. In this case we have to consider three flows: that of the cation J_1, that of the anion J_2 and the flux of the chemical reaction J_r. For the sake of simplicity we shall assume that only the flow of the cation is coupled to that of the chemical reaction, i.e., $R_{jr} \neq 0$ while $R_{2r} = 0$. Such a case was considered by Ussing and Zerahn (45) for the transport of sodium chloride through the frog skin where it was shown that only the transport of sodium is coupled to the rate of biological oxidation.

The phenomenological equations for this case are:

$$\begin{aligned} \Delta\tilde{\mu}_1 &= R_{11} J_1 + R_{1r} J_r \\ \Delta\tilde{\mu}_2 &= R_{22} J_2 \\ A &= R_{r1} J_1 + R_{rr} J_r \end{aligned} \tag{45}$$

Now let us impose the further condition that the salt concentration is equal on both sides of the membrane. Two reversible electrodes are introduced and short circuited (45) so that the potential E is zero and the current I flowing in the circuit is measured. Under these conditions $X_1 = X_2 = 0$ and hence also $J_2 = 0$.

The electrical current, which is given by $I = (J_1 - J_2)F$, is in this case $I = J_1F$.

From equation (45) the relation between the electrical current and the flow of chemical reaction is given by

$$I = -\frac{R_{1r}}{R_{11}} J_r F \tag{46}$$

It is worth noting the minus sign in equation (46): since R_{11}, J_r and F are positive, I will be positive for negative R_{1r}. This is to be expected since the existence of coupling in active transport diminishes the force required to drive the flow J_1 and hence the term $R_{1r}J_r$ should be negative.

Additional information on the coupling coefficient can be obtained under other conditions. The experiment is now carried out so that no electrical current is allowed to flow through the membrane. When a steady state for salt flow is obtained, $J_1 = 0$, and hence also $J_1 = J_2 = 0$. The salt accumulation on one side of the membrane is now given by the following expression:

$$\Delta\mu_s = \Delta\tilde{\mu}_1 + \Delta\tilde{\mu}_2 = R_{1r} J_r \tag{47}$$

and since for an ideal case

$$\Delta\mu_s = RT \ln c_s^I / c_s^{II}$$

where c_s^{I} is the salt concentration on one side and c_s^{II} on the other side of the membrane

$$RT \ln c_s^I / c_s^{II} = R_{1r} J_r \tag{48}$$

Equation (48) shows that in the case when no salt or water flow take place and the unequal distribution of salt cannot be attributed to a mechanical drag it is the coefficient R_{ir} which determines salt accumulation. This justifies the assumption that R_{ir} may be regarded as the coupling coefficient characterizing direct active transport.

CYCLIC IRREVERSIBLE PROCESSES

All the processes discussed hitherto were slow processes close to a state of equilibrium. The formalism of irreversible thermodynamics fails for rapid processes, and there is little doubt that fast chemical reactions, such as many of the metabolic changes, have to be treated by more general methods than by the simple phenomenological equations described above. A stationary state may of course be attained also in rapid processes if external restrictions are kept constant, however, often the linear dependence between flows and forces will not hold, the matrix of the coefficients will not be symmetrical and will not obey Onsager's law. Generally speaking, if linearity and symmetry of coefficients do not hold it is also impossible to predict whether the system will reach, in time, a stationary state and will obey the requirement of minimum production of entropy.

Recent theoretical studies of Prigogine and Balescu (46) on rapid processes far removed from a state of equilibrium led to a remarkable conclusion. It was shown that one can envisage a stable cyclic process, in the vicinity of a stationary state, which may repeat an infinite number of times without passing to the stationary state itself. Moreover, a fluctuation from the stationary process will transfer the system into the more probable state of cyclic repetition. The thermodynamic analysis led to the conclusion that there is the possibility of observing repeating irreversible processes which produce entropy in every cycle, in contrast to the classical reversible and cyclic processes.

These theoretical findings are related to the recent work of Teorell (47) on the oscillatory transport of fluid across a charged loose membrane. Teorell found that a constant electric current in a loose membrane develops a periodically changing potential with concomitant changes in the membrane conductance and with an oscillating electroendosmotic pressure. He succeeded to describe these phenomena quantitatively and it would be interesting to compare his results with the predictions of a more general thermodynamic theory. Similar observations were made on denser permselective membranes (48) and it seems that there are numerous circular motions resembling some important biological phenomena which are now falling within the realm of the formalism of an extended theory of irreversible thermodynamics.

FOOTNOTE

The equation for salt permeability in charged membranes

$$\omega = \frac{K}{\Delta x(f_{2w} + f_{2m})}$$

reduces for the model of Teorell and Meyer and Sievers to the more explicit equation

$$\omega = \frac{\bar{c}_s \varphi_w}{X' \, \Delta x f_{2w}{}^0}.$$

Teorell obtained for the permeation of a uni-univalent salt the following expression

$$-\Phi\pm = \frac{2RT}{\delta} \frac{uv}{u+v} \left(c_2{}^+ - c_1{}^+ - \frac{\varphi_2 - \varphi_1}{50.4} X' \right)$$

where

$$-\phi\pm = J_s/\varphi_w$$

is the flux of the salt through the membrane capillaries and $\delta = \Delta x$ is the thickness of the membrane, $u = 1/f_{1w}{}^0$ and $v = 1/f_{sw}{}^0$ are the mobilities of the counter and coions respectively, and $c_2{}^+$, $c_1{}^+$ are the membrane concentrations of the coions on both surfaces. The difference in diffusion potentials $\varphi_2 - \varphi_1$ is given by the Henderson equation

$$\varphi_2 - \varphi_1 = \frac{(u - v)RT}{(u + v)F} \ln \frac{c_1{}^+ u + c_1{}^- v}{c_2{}^+ u + c_2{}^- v}$$

while the factor $50.4 = 2\,RT/F$. The values of $c_1{}^+$, $c_1{}^-$ are readily substituted by external concentrations making use of the Donnan equation. Introducing the expressions for $c_2^+ - c_1^+$ and for $\varphi_2 - \varphi_1$ and noting that at large values of X' the logarithmic term in the potential difference may be expanded, we get from Teorell's equation

$$\frac{J_s}{\varphi_w} = \frac{c_s 2RT\ \Delta c_s}{X'\ \Delta x f_{2w}{}^0}$$

Noting that for a uni-univalent salt $\Delta\pi_s = 2\ RT\ \Delta\ c_s$

$$J_s = \frac{c_s\ \Delta\pi_s \varphi_w}{X'\ \Delta x f_{2w}{}^0} \quad \text{and since} \quad \omega = \frac{J_s}{\Delta\pi_s}$$

Teorell's equation is seen to be identical with our expression under the conditions of the TMS model.

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