

THERMODYNAMIC TREATMENT OF MEMBRANE TRANSPORT

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1. INTRODUCTION

The advances which have been made in the synthesis of polymeric films have led to the development of several industrial processes based on transport through selective membranes. Desalination techniques based on electro-dialysis and on reverse osmosis, and methods for the isolation of valuable substances from gaseous or liquid mixtures by filtration across suitable films, are well-known examples. The versatility of the new membranes also permits extensive experimental and theoretical studies of the physico-chemical characteristics of transport across simple and complex layers.

Major interest in membrane behaviour is still concentrated, however, on biological processes. The earliest investigators in physiology were already aware that cell and tissue covers regulate selective accumulation and excretion of necessary and waste materials. Studies indicated that the evolution of osmoregulatory membranes governed the transition of plants and animals from the primeval sea to sweet water and land; and it is now recognized that living membranes are true organs, which have made possible some of the remarkable adaptations to extreme conditions of life. Thus, the ability to survive in hot and salty environments is related to the development of powerful desalination mechanisms, such as the kidneys of the mammalia, the tear glands of reptiles and birds, and the secretion devices of plants.

Even more intriguing is the recent finding of the cell biophysicists that a high percentage of cellular material is organized in the form of intracellular membranes. These two-dimensional patterns of cellular organization seem to contribute the transition step between the unidimensional biopolymers and the three-dimensional structures of the cell as a whole.

Further progress in biological and technological membrane research depends to a large extent on mastery of the laws governing membrane transport. A convenient method of deriving these laws is through the study of synthetical model systems the structure of which is known and may be regulated at will. The thermodynamic discussion presented below, while primarily concerned with the behaviour of polymeric films, has an evident relevance to the interpretation of several biological phenomena.

2. THERMODYNAMIC BACKGROUND¹

2.1. The fundamental equation which served as starting point for numerous further developments is that of Nernst and Planck. It is based on the assumption that the steady velocity of transport in a viscous medium \vec{v} is directly

proportional to the driving force \vec{X}_i , the proportionality factor being the constant mobility ω . Thus,

$$\vec{v} = \omega \vec{X} \quad (1)$$

For diffusional flows

$$X_i = - \text{grad } \tilde{\mu}_i \quad (2)$$

where X_i is the force acting on the i th component and $\tilde{\mu}_i$ its electrochemical potential. The flux of the i th component (J_i) is the product of velocity and concentration, or,

$$\vec{J}_i = c_i \vec{v}_i = c_i \omega_i \vec{X}_i \quad (3)$$

In the case of unidirectional diffusion of a non-electrolyte, equation (3) yields readily the conventional equation of Fick. Assuming that the system is dilute in the i th component, and that ideality may be attributed to the chemical potential, $\mu_i = \mu_i^0 + RT \ln c_i$

$$X_i = - \frac{d\mu_i}{dx} = - \frac{RT}{c_i} \frac{dc_i}{dx} \quad (4)$$

Inserting (4) into (3) we obtain

$$J_i = RT\omega_i \left(- \frac{dc_i}{dx} \right) = D_i \left(- \frac{dc_i}{dx} \right) \quad (5)$$

where

$$D_i = RT\omega_i \quad (6)$$

is the coefficient of diffusion according to the well-known equation of Einstein.

For the flow of an electrolyte, the electrochemical potential, $\tilde{\mu}_i$, may be written as

$$\tilde{\mu}_i = \mu_i^0 + RT \ln c_i + z_i F \psi \quad (7)$$

where ψ is the local electrical potential and z_i the valency of the i th component. Inserting equation (7) into (2) we obtain

$$X_i = - \frac{d\mu_i}{dx} = - \left(\frac{RT}{c_i} \frac{dc_i}{dx} + z_i F \frac{d\psi}{dx} \right) \quad (8)$$

which upon insertion into (3) gives the renowned Planck expression

$$J_i = RT\omega_i \left[\left(- \frac{dc_i}{dx} \right) + \frac{c_i z_i F}{RT} \left(- \frac{d\psi}{dx} \right) \right] \quad (9)$$

Equation (9) has been tested extensively for diffusion in liquid and solid media and was applied successfully to membrane transport by Meyer and Sievers² and by Teorell³.

2.2. A serious limitation of equation (3), and the derived expressions (8) and (9), is that they deal with independent flows, i.e. with cases in which the transport of each component is not influenced by the concomittant flows passing through the system. It is known, however, since the pioneering work of Reuss in 1809⁴, that we should in general assume a *coupling* between flows, which may profoundly change the transport pattern. In his ingenious experiments on the electrokinetic behaviour of porous media, Reuss demonstrated that the flow of electricity is accompanied by a volume flow, while a flow of water, induced by a mechanical pressure head, results in a flow of electrical current. A series of other coupling phenomena were discovered during the XIXth century, such as thermoelectricity, thermo-osmosis and thermodiffusion. It is therefore evident that a comprehensive theory of membrane transport should treat explicitly the coupling between flows and should provide a measure for the transport interaction.

In the study of biological systems, there is a special interest in the interpretation of coupling between diffusional transport and metabolic processes taking place within the membrane or in its vicinity. Such coupling, known in physiology as *active transport*, which plays an important role in the regulatory function of cells and tissue, will be considered later.

2.3. A suitable theoretical introduction to the analysis of coupling phenomena is provided by the thermodynamics of irreversible processes. Although kinetic and statistical mechanical treatments are better suited for the visualization of the processes under consideration, the statistical mechanics of irreversible processes is still an inadequate tool for the description of condensed systems.

Despite its inherent limitation as a formal and 'empty' conceptual system, nonequilibrium thermodynamics has the advantages of simplicity and consistency in making its statements a useful guide in membrane study. It is indeed the apparent simplicity of the equation which misleads the inexperienced who may believe that the thermodynamic statements are trivial and 'self evident' . . .

A convenient starting point for the development of the phenomenology of nonequilibrium thermodynamics is the treatment of the total change in entropy, written in the form

$$dS = d_e S + d_i S \quad (10)$$

where $d_e S$ is the entropy exchanged with the surrounding and $d_i S$ is the entropy created within the system by all irreversible processes. In the terms of equation (10) the second law may be written as

$$d_i S \geq 0 \quad (11)$$

or, *the irreversible entropy change is positive definite*. $d_i S$ equals zero for equilibria and is positive for all irreversible processes.

The thermodynamic description of the rate processes is based on the increase in inner entropy per unit time or on the entropy formation $d_i S/dt$. For isothermal processes, it is convenient to use the dissipation function introduced by Lord Rayleigh, $\Phi = T(d_i S/dt)$, which measures the degradation of free energy per unit time due to irreversibility.

The work of Onsager, Prigogine, deGroot, Meixner and their coworkers⁵ led to the conclusion that for cases in which the equation of Gibbs, $dU = TdS - pdV + \sum \mu_i d\mu_i + \text{etc.}$, may be applied, i.e. for phenomena in which *local* equilibria may be assumed and the thermodynamic parameters of state maintain their validity, the dissipation function may be written as

$$\Phi = \sum J_i X_i \geq 0 \quad (12)$$

Here the J_i 's are the irreversible flows taking place in the system (such as diffusional, electrical, thermal and chemical flows) while the X_i 's are the conjugated thermodynamic forces. Some of the forces are well known, e.g. the electrical field intensity and the negative gradients of electrochemical potentials, while other forces are more sophisticated, such as the affinity of a chemical reaction

$$A = - \sum_k \nu_k \mu_k \quad (13)$$

which drives the flow of a chemical process. Equation (12) may be directly used by stipulating that the choice of flows and conjugate forces must be such that their product should have the dimension of dissipation per unit time. Only such flows and forces are applicable in the phenomenological relations discussed below.

Superficial consideration of equation (12) may give the impression that what it states is self-evident. If it is assumed that the direction of the flows is always the same as that of the conjugate forces, their product will evidently be always positive, whether the flows and forces are positive or negative. Equation (12), however, does not imply the positivity of all binary terms. It is only the sum total which has to be positive definite. Indeed, the more interesting cases are those in which part of the terms are negative, the overall positive dissipation being provided by other terms. A negative term means that the flow proceeds in a direction opposite to its own force and is a 'contragradiant' flow. Such processes may be regarded as *driven* by those forces which provide the dissipation. Numerous cases of this type are well known and are naturally formulated through the thermodynamics of irreversible processes.

Thus, for two concomittant diffusional flows,

$$\Phi = J_a^1 X_a^1 + J_a^2 X_a^2 \geq 0 \quad (14)$$

If flow (1) proceeds in a direction opposite to that of the negative gradient of the concentration of component (1), we have a case of incongruent diffusion. The driving process is here the diffusion of component (2) which provides the required dissipation.

Similarly, for two chemical coupled processes J_r^1 and J_r^2 , the dissipation function is

$$\Phi = J_r^1 A_1 + J_r^2 A_2 \geq 0 \quad (15)$$

where A_1 and A_2 are the affinities. Here again, equation (15) permits reaction (1) to proceed against its own affinity, if reaction (2) provides the dissipation. This is clearly the type of biochemical coupling in which the entropy

reducing synthetic processes are based on coupling with dissipation providing metabolic processes. Finally, the coupling of diffusional with chemical processes makes possible a contragradient transport which can be related to chemical-metabolic dissipation

$$\Phi = J_a X_a + J_r A \geq 0 \quad (16)$$

Equation (16) is thus a thermodynamic formulation of active transport.

2.4. In the further development of a thermodynamic treatment of flow processes, explicit relations have to be established between flows and forces. The simplest relation is given in equation (3) which may be rewritten as

$$\vec{J}_i = L_i \vec{X}_i, \quad (17)$$

$L_i = c_i \omega_i$

where

is the phenomenological coefficient relating J_i and X_i . It should be noted that L_i is not a constant, but a function of the parameters of the state. It is, however, independent of the flows and forces.

To extend the relation for all coupling possibilities, Onsager⁶ suggested the general set of linear equations

$$\begin{aligned} J_1 &= L_{11}X_1 + L_{12}X_2 + \dots + L_{1n} \\ L_2 &= L_{21}X_1 + L_{22}X_2 + \dots + L_{2n}X_n \\ J_n &= L_{n1}X_1 + L_{n2}X_2 + \dots + L_{nn}X_n \end{aligned} \quad (18)$$

or

$$J_i = \sum L_{ik} X_k$$

where the coefficients L_{ii} are straight coefficients and L_{ik} are the coupling coefficients relating the i th flow J_i to the k th force X_k .

The linear set of equations (18) holds rigorously only for slow flows, close to equilibrium. Its range of validity is, however, sufficiently wide as to make it useful in the treatment of numerous natural phenomena.

As shown by Onsager, the matrix of the coefficients L_{ik} is symmetrical, so that

$$L_{ik} = L_{ki} \quad (19)$$

This important theorem was checked experimentally in many fields of physics and physical chemistry and found to hold under a wide range of experimental conditions⁷. The main utility of equation (19) is in the possibility of deriving a large number of cross relations such as

$$\left(\frac{J_i}{X_k} \right)_{X_i=0} = \left(\frac{J_k}{X_i} \right)_{X_k=0} \quad (20)$$

(for all $i \neq k$) (for all $k \neq i$)

which play the same prominent role in thermodynamics of transport phenomena as the Maxwell relations in classical thermodynamics.

3. TREATMENT OF SIMPLE MEMBRANES

3.1. Let us now consider thermodynamically the simplest case of the transport of a binary solution, say that of a nonelectrolyte (s) in water (w), across a homogeneous membrane.

For the common case of stationary flows—i.e. when the parameters of state, such as temperature, pressure and concentration, do not change with time, although they may vary with position—it is found that the dissipation per unit area is given by

$$\Phi = J_s \Delta \mu_s + J_w \Delta \mu_w \quad (21)$$

It will be noted that, in this case, the flows J_s and J_w are constant throughout the membrane and equal to the flows of solute and water, as measured in the adjacent compartments. Other novel features of equation (21) are the overall forces, $\Delta \mu_s = \mu_s^0 - \mu_s^i$ and $\Delta \mu_w = \mu_w^0 - \mu_w^i$, which represent the difference in chemical potentials across the membrane, instead of the local gradients given in equations (4) and (8).

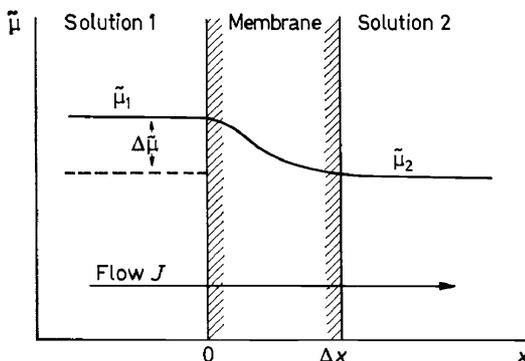


Figure 1

Equation (20) may be 'transformed' to another combination of forces and flows, provided that the dissipation function remains invariant. A convenient choice is that of a volume flow J_v driven by a hydrostatic pressure head Δp , and a diffusional flow J_D driven by the difference in osmotic pressure $\Delta \pi$ †. With this choice, we obtain for the dissipation function

$$\Phi = J_v \Delta p + J_D \Delta \pi \quad (22)$$

† Note: The relation between volume flow J_v and the flows of the components J_s and J_w is: $J_v = J_s \bar{V}_s + J_w \bar{V}_w$, where \bar{V}_s and \bar{V}_w are the partial molal volumes of s and w .

The diffusional flow is given by

$$J_D = \frac{J_s}{\bar{c}_s} - \frac{J_w}{\bar{c}_w}$$

and on the basis of equation (3) it may be written as $J_D = \vec{V}_s - \vec{V}_w$ i.e., the diffusional flow is the relative velocity of solute to solvent.

and the corresponding phenomenological equations⁸

$$\begin{aligned} J_v &= L_p \Delta p + L_{pD} \Delta \pi \\ J_D &= L_{Dp} \Delta p + L_D \Delta \pi \end{aligned} \quad (23)$$

The significance of the coefficients L_p , L_{pD} , L_{Dp} and L_D is readily understood. The application of a pressure head across a membrane separating two solutions of equal concentration ($\Delta \pi = 0$) causes a volume flow, linearly proportional to the pressure difference Δp ; L_p is therefore the filtration coefficient, given by

$$L_p = \left(\frac{J_v}{\Delta p} \right)_{\Delta \pi = 0} \quad (24)$$

Similarly, the coefficient L_D is a kind of diffusion coefficient relating the diffusional flow J_D to the difference in osmotic pressure, at zero pressure head

$$L_D = \left(\frac{J_D}{\Delta \pi} \right)_{\Delta p = 0}$$

The coupling coefficients are especially interesting, and have the following significance: the coefficient L_{pD} relates to the phenomenon that a volume flow across a membrane can be induced also by a difference in osmotic pressure, when $\Delta p = 0$, i.e.,

$$(J_v)_{\Delta p = 0} = L_{pD} \Delta \pi \quad (25)$$

This volume flow is the well-known⁹ osmotic flow, and L_{pD} is therefore *the coefficient of osmotic flow*. On the other hand, L_{Dp} relates the pressure head to the diffusional flow, which occurs through a membrane even if the adjacent solutions have equal concentrations, i.e.,

$$(J_D)_{\Delta \pi = 0} = L_{Dp} \Delta p \quad (26)$$

A fundamental observation in colloid chemistry is that of diffusional flow of solute and solvent with separation of components during filtration. The process is known as ultra-filtration. Thus, L_{Dp} is the *coefficient of ultra-filtration*, and Onsager's relation

$$L_{pD} = L_{Dp} \quad (27)$$

proves to be a non-trivial *physical* statement, namely, that the coefficient of osmotic flow equals that of ultra-filtration.

Inspection of equation (23) permits a better understanding of an ordinary osmotic experiment. The osmometric determination of molecular weights is based on the determination of molar concentrations through the measurement of the hydrostatic pressure (Δp) when volume flow stops (i.e., $J_v = 0$). From equation (23) we obtain:

$$(\Delta p)_{J_v=0} = -\frac{L_{pD}}{L_p} \Delta\pi \quad (28)$$

instead of the expected van't Hoff relation

$$\Delta p = \Delta\pi = RT\Delta c \quad (29)$$

which is generally used for the determination of Δc from known Δp . The difference between equations (29) and (28) is that equation (29) holds only for ideal, semipermeable membranes, through which no solute flow is allowed and a true osmotic equilibrium is established at $J_v = 0$. Equation (28), on the other hand, is valid for any membrane which allows both solute and solvent transport. The coefficient

$$-\frac{L_{pD}}{L_p} = \sigma \quad (30)$$

which determines the deviation of the membrane from semipermeability was named by Staverman¹⁰ the *reflection coefficient*—when $\sigma = 1$ the solute molecules are fully reflected from the membrane. It is an important parameter which may be regarded as an indicator for the selectivity of the membrane; it represents the ability of the membrane to distinguish between solute and solvent molecules. For $\sigma = 0$, the membrane does not distinguish between the components; for negative σ , as found for instance in electrochemical systems, the solute permeates more readily than the solvent. The introduction of equation (30) into (23) gives a useful equation for volume flow as a function of both osmotic and hydrostatic pressures

$$J_v = L_p(\Delta p - \sigma\Delta\pi) \quad (31)$$

This expression has been applied extensively to describe the behaviour of both biological and synthetic membranes used in reverse osmosis. A selection of values of L_p and σ for various systems is given in *Table 1*.

It is often advantageous to have an explicit expression for solute flows J_s , instead of the diffusional flows J_D . A straightforward calculation gives

$$J_s = \omega\Delta\pi + \bar{c}_s(1 - \sigma)J_v \quad (32)$$

where ω is a solute permeability coefficient, based on a combination of L_p , L_{pD} and L_D , and \bar{c}_s is an average solute concentration. The over-simple approach to solute permeability leads to the conventional expression $J_s = \omega\Delta\pi$, as found in many textbooks of physiology and physical chemistry. Equation (32) shows, however, that a direct proportionality between solute flow and osmotic difference holds only when $J_v = 0$. If volume flow accompanies the solute flow, solvent drag effects have to be taken into consideration and a suitable correction introduced. Column 4 of *Table 1* presents some values of ω , indicating its variation range. For the sake of completeness, it is worth mentioning that in the physiological literature the permeability coefficient is usually given as

$$P = RT\omega$$

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Table 1. Properties of membranes

Membrane	Solute	Solute permeability, ω [$10^{-15} \frac{\text{mole}}{\text{dyne sec}}$]	Reflection coefficient, σ	Filtration coefficient, L_p [$10^{-11} \frac{\text{cm}^3}{\text{dyne sec}}$]
Toad skin ^a	Acetamide	0.0041	0.89	0.4
	Thiourea	0.00057	0.98	
<i>Nitella translucens</i> ^b	Methanol	11	0.50	1.1
	Ethanol	11	0.44	
	Isopropanol	7	0.40	
	Urea	0.008	1	
Human red blood cell ^c	Urea	17	0.62	0.92
	Ethylene glycol	8	0.63	
	Melonamide	0.04	0.83	
	Methanol	122	—	
Visking dialysis tubing ^d	Urea	20.8	0.013	3.2
	Glucose	7.2	0.123	
	Sucrose	3.9	0.163	
Dupont 'wet gel' ^d	Urea	31.6	0.0016	9.7
	Glucose	12.2	0.024	
	Sucrose	7.7	0.036	

^a B. Andersen and H. H. Ussing, *Acta Physiol. Scand.* **39**, 228 (1957).

^b J. Dainty and B. Z. Ginzburg, *Biochim. Biophys. Acta* **79**, 102, 112, 122, 129 (1964).

^c Values of ω from unpublished data of D. Savitz and A. K. Solomon; σ from D. G. Goldstein and A. K. Solomon, *J. Gen. Physiol.* **44**, 1 (1960); L_p from V. W. Sidel and A. K. Solomon, *J. Gen. Physiol.* **41**, 243 (1957).

^d B. Z. Ginzburg and A. Katchalsky, *J. Gen. Physiol.* **47**, 403 (1963).

so that

$$(J_s)_{J_v=0} = \omega \Delta \pi = P \Delta c_s$$

3.2. For systems involving electrolyte transport across a charged membrane we must *a priori* consider three flows driven by three conjugated forces. The flows may be chosen to be: the flow of salt, J_s , the flow of water, J_w , and the flow of electrical current I . The corresponding forces are $\Delta \mu_s$, $\Delta \mu_w$ and the electromotive force E , which is measured with reversible electrodes. Following the formalism developed heretofore, the dissipation function is

$$\Phi = J_s \Delta \mu_s + J_w \Delta \mu_w + I \cdot E \tag{33}$$

which may be transformed into other convenient forms. Whatever the dissipation function, the phenomenological equations are rather bulky, since the full matrix of coefficients relating flows to forces comprises nine terms, six of which are independent by Onsager's symmetry theorem. The determination of six coefficients requires six independent methods of measurement, generally an ungratifying task. We shall consider therefore only the simple case in which membranes permit no water transport and the dissipation function is reduced to¹¹:

$$\Phi = J_s \Delta \mu_s + I \cdot E \tag{34}$$

In this case, the phenomenological relations may be reduced to the following practical form

$$J_s = \omega \Delta\pi + \frac{t_1}{F} \cdot I \quad (35)$$

$$I = \kappa \left(E + \frac{t_1}{F} \Delta\mu_s \right)$$

Here, the flow of salt means the flow of the ion which does not participate in the electrode reaction. Thus, if the electrode is an Ag-AgCl electrode, the flow of the cations would be identified with J_s . The coefficient ω is again the salt-permeability coefficient, while the transport number t_1 is the coupling coefficient measured at $\Delta\pi = 0$

$$t_1 = \left(\frac{J_s F}{I} \right)_{\Delta\pi=0} \quad (36)$$

The straight coefficient κ is the conductance of the membrane, and may be determined at equal salt concentrations in the adjacent solutions, i.e. when $\Delta\mu_1$ for the cation, and $\Delta\mu_2$ for the anion equal zero.

It is often useful to substitute the reversible electromotive force E by the potential difference $\Delta\psi$ measured with two calomel electrodes. Inserting $\Delta\psi$ into equation (35) we obtain $I = \kappa[\Delta\psi + (1/F)(t_1\Delta\mu_1 - t_2\Delta\mu_2)]$ where 1 and 2 denote the cation and anion respectively.

We shall find in the following paragraphs that equations (35) and (36) are useful in the evaluation of the properties of complex membranes.

4. FACILITATED TRANSPORT

4.1. In the discussion on transport across simple membranes, it was assumed that the permeant passes the membrane matrix without interaction. In certain ion-exchange films, it can be assumed that the membrane may be approximated by a system of water-filled capillaries, the behaviour of which is adequately described by the methods of classical colloid chemistry. The permeability of most biological membranes and many polymeric films does not however fit the Helmholtz-Quincke and Gouy model¹² even to a rough approximation. It was found that biological covers may be highly permeable to substances which are of low solubility in the membranes and which should behave essentially as non-permeants. Furthermore, it is well established that the flow does not increase linearly with the concentration difference, but at sufficiently high concentrations it may reach a limiting value, or in general, exhibit flow saturation phenomena. The prevailing explanation of this behaviour is based on the assumption that a biological membrane contains a specific 'carrier' which combines readily with the permeant and facilitates its transport across media in which it dissolves with difficulty. Moreover, the carrier has a finite number of adsorption sites the saturation of which with the permeating substance puts a limit to the facilitation of transport. Although the mechanism of carrier

transport is unknown, and saturation phenomena may be observed also in two dimensional lattice models¹³, numerous attempts have been made to reproduce facilitated transport with synthetic systems. Several interesting models were described recently by Eisenman *et al.*¹⁴ and by Shean and Sollner¹⁵. J. Gabbay, in this laboratory¹⁶ obtained facilitated transport of amino-acids across ion-exchange membranes, the carrier being the hydrogen ion. He found that when a zwitterionic amino-acid enters through one surface of a sulphonated resin membrane in the hydrogen form, it reacts according to the scheme:



The form which passes readily the membrane is the carrier-substrate complex AH^+ . On the other surface, the complex dissociates and liberates the free amino-acid to the outer solution.

The last example serves as a model for the simple carrier mechanism which has been adequately studied by cell physiologists¹⁷.

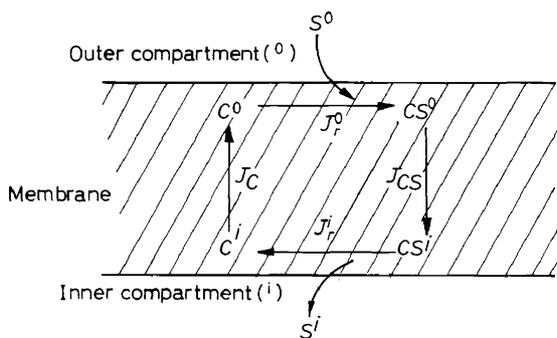


Figure 2. Schematic representation of carrier (C) mediated transport of the solute S . J_r^0 is the rate of adsorption of S^0 to the free carrier C^0 in the outer compartment to give CS^0 . J_r^i is the rate of solute desorption in the inner compartment. J_C is the flow of free carrier from the inner to outer compartment. J_{CS} the flow of the solute-loaded carrier from the outer to the inner compartment

We shall consider here the general case in which carrier and substrate combine and dissociate throughout the membrane phase¹⁸.

4.2. The continuity equation for the local change of concentration in every volume element is given by

$$\frac{\partial c_i}{\partial t} = - \frac{\partial J_i}{\partial x} + \nu_i J_r \quad (38)$$

where the diffusional flow J_i proceeds only in the x -direction, J_r is the local rate of chemical reaction (per unit volume) and ν_i the stoichiometric coefficient of the i th component. The reaction considered here is between permeant and carrier



where J_r is positive for association and negative for dissociation.

Thus

$$\left(\frac{\partial S}{\partial t}\right)_x = -\left(\frac{\partial J_s}{\partial x}\right)_t - J_r; \left(\frac{\partial C}{\partial t}\right)_x = -\left(\frac{\partial J_C}{\partial x}\right)_t - J_r$$

and

$$\left(\frac{\partial CS}{\partial t}\right)_t = -\left(\frac{\partial J_{CS}}{\partial x}\right) + J_r \tag{40}$$

In equation (40), S , C and CS denote the concentrations of substrate, carrier and carrier-substrate complex, respectively. A stationary state is characterized by time independence of all parameters of state, so that every $(\partial c_i / \partial t)_x = 0$. Hence,

$$-\frac{\partial J_s}{\partial t} = J_r; -\frac{\partial J_C}{\partial x} = J_r \text{ and } \frac{\partial J_{CS}}{\partial x} = J_r \tag{41}$$

Equation (41) leads immediately to some interesting observations on facilitated transport. Adding the second and third statements in equation (41) we obtain

$$\frac{\partial(J_C + J_{CS})}{\partial x} = 0 \text{ or, } J_C + J_{CS} = \text{const.} \tag{42}$$

Similarly, the addition of the first and third expressions in equation (41) gives

$$\frac{\partial(J_s + J_{CS})}{\partial x} = 0 \text{ or, } J_s + J_{CS} = \text{const.} \tag{43}$$

Now, facilitated transport is characterized by the requirement that the *total* turnover within the membrane must cancel out—the same substance has to enter and exit from the membrane. That is the association on one side has to be precisely compensated for by the dissociation on the other, or,

$$\int_0^{\Delta x} J_r dx = 0 \tag{44}$$

where 0 and Δx are the boundary values of the x coordinate at the membrane surfaces. Inserting into (44) the values of J_r from (41), we obtain

$$\int_0^{\Delta x} (\partial J_i / \partial x) dx = 0 \text{ or } J_i^0 = J_i^{\Delta x} \tag{45}$$

Since no external flow of carrier or carrier-substrate complex is permissible

$$J_C^0 = J_C^{\Delta x} = 0 \text{ and } J_{CS}^0 = J_{CS}^{\Delta x} = 0 \tag{46}$$

Inserting these expressions into equation (45) we obtain the important conclusion that

$$J_C + J_{CS} = 0 \quad (47)$$

Equation (47) shows that at every point within the membrane, the flow of carrier is compensated by a counter flow of carrier-substrate complex. The total carrier may, therefore, be regarded as a circulating vehicle transporting substrate from one coast to another. It is further apparent that

$$J_S + J_{CS} = J_S^0 = J_S^{Ax}$$

but since the permeant flow is continuous, $J_S^0 = J_S = J_S^{\text{ext}}$ where J_S^{ext} is the total solute flow measurable in the external solution. Thus,

$$J_S + J_{CS} = J_S^{\text{ext}} \quad (48)$$

indicating that although the permeant may move as a free component (J_S) or as a complex (J_{CS}), the total amount transported per unit time and unit area is constant throughout the membrane.

4.3. From a thermodynamic point of view, the dissipation of free energy due to the transport of a single component is given by

$$\Phi = J_S^{\text{ext}} \Delta\mu_s \quad (49)$$

whatever the mechanism of transport. It is, however, interesting to demonstrate that the detailed treatment of local carrier reaction introduces no changes into equation (48). The local dissipation for a volume element is given by

$$\phi = J_S \left(-\frac{d\mu_S}{dx} \right) + J_C \left(-\frac{d\mu_C}{dx} \right) + J_{CS} \left(-\frac{d\mu_{CS}}{dx} \right) + J_r A \quad (50)$$

where A is the affinity of reaction (39)

$$A = \mu_S + \mu_C - \mu_{CS} \quad (51)$$

Using equations (47), (48), (41) and (50) we obtain

$$\begin{aligned} \Phi &= J_S^{\text{ext}} \left(-\frac{d\mu_S}{dx} \right) + J_{CS} \frac{d}{dx} (\mu_S + \mu_C - \mu_{CS}) + J_r A \\ &= J_S^{\text{ext}} \left(-\frac{d\mu_S}{dx} \right) + J_{CS} \frac{dA}{dx} + \frac{dJ_{CS}}{dx} A \\ &= J_S^{\text{ext}} \left(-\frac{d\mu_S}{dx} \right) + \frac{d}{dx} (J_{CS} A) \end{aligned} \quad (52)$$

Equation (52) is readily integrated over the thickness of the membrane to give the total dissipation per unit area

$$\begin{aligned} \Phi &= \int \Phi dx = J_S^{\text{ext}} \int_0^{4x} \left(-\frac{d\mu_S}{dx} \right) dx + \int_0^{4x} \frac{d}{dx} (J_{CS}A) dx \\ &= J_S^{\text{ext}} \Delta\mu_S + (J_{CS}^{4x} A^{4x} - J_{CS}^0 A^0) \end{aligned} \tag{53}$$

Taking into account equation (46), equation (53) reduces however to equation (49), i.e., $\Phi = J_S^{\text{ext}} \Delta\mu_S$.

Q.E.D.

4.4. The advantage of a ‘microscopic’, detailed, treatment lies therefore not in the possibility of overcoming the severe limitations imposed by the ‘macroscopic’, external view, but in providing means to interpret the relation between flows and forces which the thermodynamic treatment leaves undetermined. Thus, the phenomenological equation for single component facilitated transport is

$$J_S^{\text{ext}} = L \Delta\mu_S \tag{54}$$

which does not provide any information on facilitation or saturation flow with increasing concentration. The aim of our ‘microscopic’ analysis is therefore to make the coefficient L meaningful and to give it an explicit formulation. A fuller treatment is given elsewhere (Blumenthal and Katchalsky)¹⁸. We shall consider here only a simple case which suffices to illustrate the essential features.

It is assumed that S , C and CS are moving in a matrix or solution in such a manner that the main frictional resistance to flow is due to interaction with the medium. In this case, hydrodynamic coupling between the components may be neglected and the independent flows can be described by the classical equation of Fick:

$$J_S = D_S \left(-\frac{dS}{dx} \right); J_C = D_C \left(-\frac{dC}{dx} \right) \text{ and } J_{CS} = D_{CS} \left(-\frac{dCS}{dx} \right) \tag{55}$$

where the D_{is} are constant. From the second and third equations of (55) and equation (47) we obtain

$$-\frac{d}{dx} (D_C C + D_{CS} CS) = 0 \quad \text{or} \quad D_C C + D_{CS} CS = C^{\text{tot}}, \text{ a const.} \tag{56}$$

The first and third equations of (55) inserted into (48) give:

$$J_S^{\text{ext}} = D_S \left(-\frac{dS}{dx} \right) + D_{CS} \left(-\frac{dCS}{dx} \right)$$

and, upon integration across the membrane,

$$J_S^{\text{ext}} = D_S \frac{\Delta S}{\Delta x} + D_{CS} \frac{\Delta CS}{\Delta x} \quad (57)$$

An appreciable simplification is obtained if, following the procedure of Wilbrandt and Rosenberg, it is assumed that surface equilibria exist between permeant and carrier. Then

$$\frac{C_0 S_0}{C S_0} = \frac{C_{\Delta x} S_{\Delta x}}{C S_{\Delta x}} = K_s \quad (58)$$

where K_s is an equilibrium constant. Using equations (56) and (58), we obtain

$$\begin{aligned} \Delta CS &= C S_0 - C S_{\Delta x} = C^{\text{tot}} K_s D_C \frac{(S_0 - S_{\Delta x})}{(K_s D_C + S_0 D_{CS})(K_s D_C + S_{\Delta x} D_{CS})} \\ &= C^{\text{tot}} K_s D_C \frac{\Delta S}{(K_s D_C + S_0 D_{CS})(K_s D_C + S_{\Delta x} D_{CS})} \end{aligned} \quad (59)$$

The final expression is therefore

$$J_S^{\text{tot}} = \left(D_S + \frac{K_s D_C D_{CS} C^{\text{tot}}}{(K_s D_C + S_0 D_{CS})(K_s D_C + S_{\Delta x} D_{CS})} \right) \frac{\Delta S}{\Delta x} \quad (60)$$

The first term in equation (60) is that of regular transport, $D_S (\Delta S/\Delta x)$, and requires no further comment. It is in the second term that the facilitation is expressed: If it is assumed that $S_{\Delta x} = 0$, facilitated transport will be given by

$$\frac{D_{CS} C^{\text{tot}} S_0}{(K_s D_C + S_0 D_{CS}) \Delta x}$$

which for $S_0 D_{CS} \ll K_s D_C$ is linear in S_0 . On the other hand, for $S_0 D_{CS} \gg K_s D_C$, the facilitated flow reaches the limiting value of $C^{\text{tot}}/\Delta x$ and becomes saturated.

To compare equations (60) and (54), we may write

$$\Delta \mu_s = (\mu_s^0 + RT \ln S_0) - (\mu_s^0 + RT \ln S_{\Delta x}) = RT \ln \frac{S_0}{S_{\Delta x}} = RT \frac{\Delta S}{\bar{S}} \quad (61)$$

where \bar{S} is defined by equation (61) and approaches $\bar{S} = (S_0 + S_{\Delta x})/2$ for small values of S . Thus,

$$J_S^+ = \frac{RTL \Delta S}{\bar{S}} = \left(\frac{D_s \bar{S}}{\Delta x} + \frac{K_s D_C D_{CS} C^{\text{tot}} \bar{S}}{\Delta x (K_s D_C + S_0 D_{CS})(K_s D_C + S_{\Delta x} D_{CS})} \right) \frac{\Delta S}{\bar{S}}$$

and hence

$$L = \frac{RT}{4x} \bar{S} \left(D_S + \frac{K_S D_C D_{CS} C^{\text{tot}}}{(K_S D_C + S_0 D_{CS})(K_S D_C + S_{4x} D_{CS})} \right) \quad (62)$$

Equation (62) concludes our treatment of facilitated transport. It shows how the phenomenological coefficient may be interpreted and demonstrates that it comprises both facilitation and saturation properties of the process.

5. COMPLEX MEMBRANES¹⁹

5.1. For many purposes, it is sufficient to study the behaviour of single membranes. There exist, however, industrial processes, such as desalination by electrodialysis, which are based on the utilization of membrane stacks, composed of alternating positive and negative membranes, the mastery of which requires an understanding of the operation of composite membrane systems. The evaluation of the rules of transport through an array of membrane elements is particularly important in biology, where every cellular and tissue cover is a complex system made up of several layers characterized by different permeabilities for electrolytes and nonelectrolytes. In this section, the significance of some of the basic features of complex membranes composed of elements arranged in series will be evaluated. We shall consider in some detail the well-investigated 'bilayer' composed of two permselective elements, one of which carries fixed positive charges and has a selective permeability to anions, and the other of which is negatively charged and has a preferred cation permeability.

It can be readily shown that when a regime of stationary flow is attained and no chemical interaction takes place either in the membranes or in the intermembrane space, the flows become constant and assume the same value throughout the system. At the same time, the overall forces acting across the composite system may be decomposed into partial forces acting on each membrane element and the total force is found to be the sum of all individual forces.

With these simple concepts, we may approach the treatment of a bilayer in the special case that no water flow accompanies the transport of salt and electrical current across the complex membrane. If we denote all parameters and coefficients for one layer by α and those for the other by β we may apply directly equations (53) with the restrictions of stationary flow described in the previous paragraph.

$$J_s^\alpha = \omega_\alpha \Delta\pi_\alpha + \frac{t_1^\alpha}{F} I_\alpha \quad J_s^\beta = \omega_\beta \Delta\pi_\beta + \frac{t_1^\beta}{F} I_\beta \quad (63)$$

$$I^\alpha = \kappa_\alpha \left[\Delta\psi_\alpha + \frac{1}{F} (t_1^\alpha \Delta\mu_1^\alpha - t_2^\alpha \Delta\mu_2^\alpha) \right];$$

$$I^\beta = \kappa_\beta \left[\Delta\psi_\beta + \frac{1}{F} (t_1^\beta \Delta\mu_1^\beta - t_2^\beta \Delta\mu_2^\beta) \right] \quad (64)$$

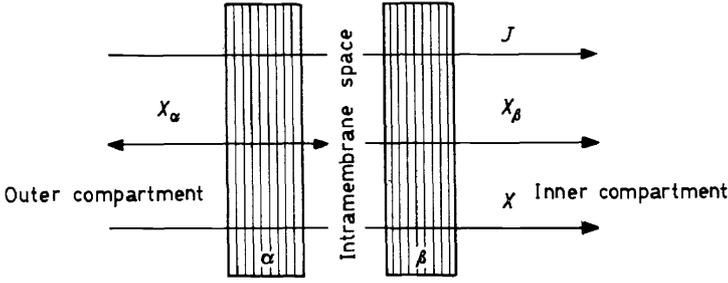


Figure 3. Scheme of a composite membrane composed of a series array of membrane elements α and β . The total force X acting across the composite membrane is additive in the forces acting on each element $X = X^\alpha + X^\beta$. In stationary cases the flows J are continuous across the system

$$J_s^\alpha = J_s^\beta; \quad I^\alpha = I^\beta \quad (65)$$

$$\Delta\psi^{\text{tot}} = \Delta\psi_\alpha + \Delta\psi_\beta; \quad \Delta\pi^{\text{tot}} = \Delta\pi_\alpha + \Delta\pi_\beta \quad (66)$$

$$\Delta\mu_1^{\text{tot}} = \Delta\mu_1^\alpha + \Delta\mu_1^\beta; \quad \Delta\mu_2^{\text{tot}} = \Delta\mu_2^\alpha + \Delta\mu_2^\beta$$

The implications of equations (66) may be shown as follows: let us consider explicitly the intramembrane space, the volume of which may be very small but nonvanishing. Let the concentration of the permeating salt in the intermembrane space be c^* .

$$\Delta\pi_\alpha = 2RT(c_1 - c^*); \quad \Delta\pi_\beta = 2RT(c^* - c_2) \quad (67)$$

and

$$\Delta\pi^{\text{tot}} = \Delta\pi_\alpha + \Delta\pi_\beta = 2RT(c_1 - c_2).$$

Similarly,

$$\Delta\mu_1^\alpha = RT \ln \frac{c_1}{c^*}; \quad \Delta\mu_1^\beta = RT \ln \frac{c^*}{c_2} \quad (68)$$

and

$$\Delta\mu_1^{\text{tot}} = \Delta\mu_1^\alpha + \Delta\mu_1^\beta = RT \ln \frac{c_1}{c_2}$$

An equivalent expression holds for $\Delta\mu_2$.

Inserting equations (63) into (65) we obtain,

$$2RT \omega_\alpha (c_1 - c^*) + \frac{t_1^\alpha}{F} I = 2RT \omega_\beta (c^* - c_2) + \frac{t_2^\beta}{F} I \quad (69)$$

and hence

$$c^* = \frac{\omega_\alpha c_1 + \omega_\beta c_2}{\omega_\alpha + \omega_\beta} + \frac{(t_1^\alpha - t_1^\beta) I}{2RT(\omega_\alpha + \omega_\beta) F} \quad (70)$$

Equation (70) shows some remarkable features which deserve consideration. The most important is that the intramembrane concentration c^* is seen to be a function of the electrical current. In the case of the two semi-infinite compartments, adjacent to the simple membrane considered

previously, we could assume that the external parameters of the state were independent of the flows. Now we encounter a small finite volume the parameters of which are functions of the flow pattern. When $I = 0$, c^* assumes the value

$$\bar{c}^* = \frac{\omega_\alpha c_1 + \omega_\beta c_2}{\omega_\alpha + \omega_\beta} \quad (71)$$

which is a weighted average of the external concentrations. If $t_1^\alpha - t_1^\beta$ is positive, as is the case in *Figure 3*, c^* will increase with increasing I until a breakthrough of the permselectivity occurs. More interesting however, is the case in which I decreases and assumes negative values. Ultimately, a limiting value I_0 will be reached which makes c^* zero:

$$0 = \bar{c}^* = \frac{t_1^\alpha - t_1^\beta}{2RT} \frac{I_0}{(\omega_\alpha + \omega_\beta) F}$$

or

$$\frac{I_0}{F} = \frac{2RT \bar{c}^* (\omega_\alpha + \omega_\beta)}{t_1^\alpha - t_1^\beta} \quad (72)$$

Equation (72) is a simplified expression for the desalination process in a cell with walls made of oppositely charged permselective membranes. There is, however, another important aspect revealed by equation (72). Since no negative concentrations are known, I_0 is the most negative current which can flow through the membrane systems (i.e. before breakdown of the water molecules occurs). Thus positive electro-osmotic forces may increase both I and c^* ; negative electro-osmotic forces, however lead to a *limiting flow of current* which does not change with decreasing E . The presence of the intramembrane space transforms therefore a composite membrane into a rectifier. Even if Ohm's law is expected to hold in the range of layer positive I s, it breaks down when $I \rightarrow I_0$.

Equations (70), (71) and (72) may be condensed to a single expression

$$c^* = \bar{c}^* \left(1 + \frac{I}{I_0} \right) \quad (73)$$

5.2. The rectification properties are cast into a quantitative form by utilizing equations (64), (65) and (68).

$$\begin{aligned} \frac{I}{\kappa_\alpha} &= \Delta\psi_\alpha + \frac{1}{F} (t_1^\alpha \Delta\mu_1^\alpha - t_2^\alpha \Delta\mu_2^\alpha) = \Delta\psi_\alpha + \frac{RT}{F} (t_1^\alpha - t_2^\alpha) \ln \frac{c_1}{c^*} \\ \frac{I}{\kappa_\beta} &= \Delta\psi_\beta + \frac{1}{F} (t_1^\beta \Delta\mu_1^\beta - t_2^\beta \Delta\mu_2^\beta) = \Delta\psi_\beta + \frac{RT}{F} (t_1^\beta - t_2^\beta) \ln \frac{c^*}{c_2} \end{aligned}$$

Upon adding these expressions and noting that $t_1^\alpha + t_2^\alpha = t_1^\beta + t_2^\beta = 1$ we obtain

$$\begin{aligned} I \left(\frac{1}{\kappa_\alpha} + \frac{1}{\kappa_\beta} \right) &= \Delta\psi + \frac{RT}{F} [(t_1^\alpha - t_2^\alpha) \ln c_1 - (t_1^\beta - t_2^\beta) \ln c_2] \\ &\quad + \frac{2RT}{F} (t_1^\beta - t_1^\alpha) \ln c^* \end{aligned}$$

or, inserting (73),

$$\Delta\psi = -\frac{RT}{F} [(t_1^\alpha - t_2^\alpha) \ln c_1 - (t_1^\beta - t_2^\beta) \ln c_2] + \frac{2RT}{F} (t_1^\alpha - t_1^\beta) \ln \bar{c} + \frac{2RT}{F} (t_1^\alpha - t_1^\beta) \ln \left(1 + \frac{I}{I_0}\right) + I \left(\frac{1}{\kappa_\alpha} + \frac{1}{\kappa_\beta}\right) \quad (74)$$

The first two terms on the right-hand side of the equation are independent of the electrical current I and may be identified with the 'resting potential' $\Delta\psi_0$. $(1/\kappa_\alpha) + (1/\kappa_\beta) = \rho$ is the total electrical resistance of both membranes (excluding the intramembrane space). Inserting $\Delta\psi_0$ and ρ into equation (74) a lucid and suggestive equation is obtained:

$$\Delta\psi - \Delta\psi_0 = (t_1^\alpha - t_1^\beta) \frac{2RT}{F} \ln \left(1 + \frac{I}{I_0}\right) + I \cdot \rho \quad (75)$$

At higher values of I , the contribution of the logarithmic term becomes of lesser importance, so that $\Delta\psi - \Delta\psi_0 \rightarrow I \cdot \rho$, i.e., Ohm's law holds once more. On the other hand, for small values of I which tend to I_0 , the term $I \cdot \rho$ becomes negligible and

$$\Delta\psi - \Delta\psi_0 = \frac{2RT}{F} \ln \left(1 + \frac{I}{I_0}\right) \quad (76)$$

In most synthetic ion-exchange membranes, ρ is sufficiently small to make $I \cdot \rho$ negligible over a wider range. It is clear that for $I \rightarrow -I_0$, $\Delta\psi$ tends to $-\infty$, or, expressed in another way, $-I_0$ is the limiting value of the current in the rectification processes of the membrane system.

5.3. Equation (76), which has a form similar to Tafel's equation for overvoltage, was found to represent adequately the experimental data found in the literature²⁰ and accumulated in this laboratory^{21, 22}. *Figure 4*

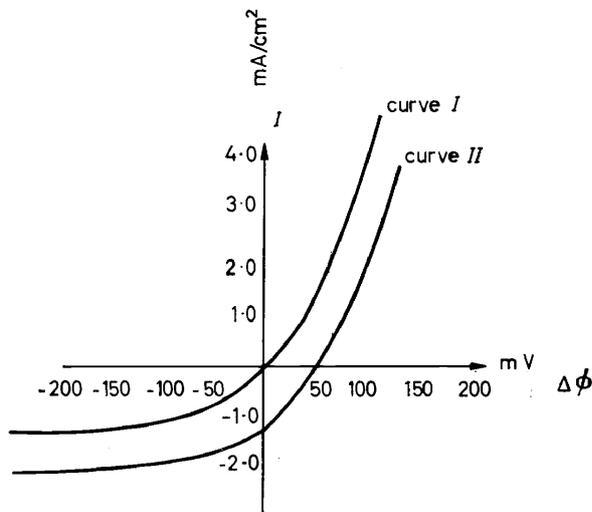


Figure 4. Rectification with a double membrane composed of cation and anion permselective membrane elements. Curve I for equal salt concentrations in outer and inner compartments. (Note that at $I = 0$ at $\Delta\psi = 0$.) Curve II for unequal salt concentrations. (Calculated by Richardson¹⁹)

gives an example of an experimental set of $\Delta\psi$ versus I values and their analysis by equation (76)†.

It is rather interesting to observe that many biological membranes exhibit a rectification behaviour which closely resembles that of a synthetic bilayer. The dependence of current on potential for non-excited muscle and nerve membranes is represented in *Figure 5*.

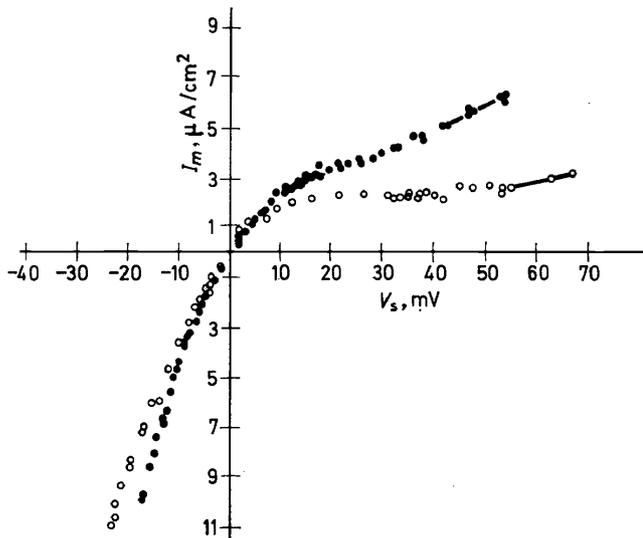


Figure 5. Relation between electrotonic membrane potential and current density for fibre 1 (○) and fibre 4 (●) [R. H. Adrian and W. H. Frey Gang, *J. Physiol.* **163**, 109 (1962)]

Although there is no reason to assume that biological membranes are structurally related to the composite permselective layer described above, it is plausible to assume that their rectification properties rest on an electrical anisotropy of cell or tissue covers. The study of membrane anisotropy is of fundamental importance for the thermodynamic grasp of active transport and will occupy our attention in the following paragraphs. The feature which emerges from the present analysis is that electrophysiological rectification studies may be a useful tool for the interpretation of anisotropic distribution of charges in complex biological structures.

An insight into the complex structure of organismic covers may be obtained also from the resting potential $\Delta\psi_0$ and its dependence on concentration. For the sake of lucidity we shall assume that both layers α and β of *Figure 3* are highly permselective. In this case, $t_1^\alpha = 1$, $t_2^\alpha \simeq 0$ while $t_1^\beta \simeq 0$, $t_2^\beta \simeq 1$. Hence:

$$\Delta\psi_0 = \frac{RT}{F} [-\ln c_1 c_2 + \ln (\bar{c}^*)^2] = \frac{RT}{F} \ln \frac{(\omega_\alpha c_1 + \omega_\beta c_2)^2}{c_1 c_2 (\omega_\alpha + \omega_\beta)^2} \quad (77)$$

† In the calculation given above we neglected the dependence of the ω s, t s and κ s on the average salt concentration. In certain cases this dependence is very pronounced and should be considered explicitly. A detailed analysis of these properties based on a frictional model can be found in the recent thesis of Richardson¹⁹.

Equation (77) should be compared with the well-known equation of Nernst and Planck

$$\Delta\psi_0 = \frac{2RT}{F} \ln \frac{c_1}{c_2} \tag{78}$$

or with the equation of Taylor for a liquid junction potential. If we keep c_2 constant and vary c_1 , equation (78) predicts a linear dependence of $\Delta\psi_0$ on $\ln c_1$ with a constant slope of RT/F , which was verified experimentally in numerous cases. On the other hand, $(\partial\Delta\psi/\partial \ln c_1)_{c_2}$ is neither constant nor equal to RT/F , but given by the expression

$$\left(\frac{\partial\Delta\psi}{\partial \ln c_1} \right)_{c_2, T} = \frac{RT}{F} \frac{\omega_\alpha c_1 - \omega_\beta c_2}{\omega_\alpha c_1 + \omega_\beta c_2} \tag{79}$$

It is clear that when $\omega_\alpha c_1 \gg \omega_\beta c_2$, $(\partial\Delta\psi/\partial \ln c_1)_{c_2} = RT/F$, corresponding to equation (78). When, however, $\omega_\beta c_2 \gg \omega_\alpha c_1$, the slope is $-RT/F$ and there is a point, $\omega_\alpha c_1 = \omega_\beta c_2$, at which $\partial\Delta\psi/\partial \ln c_1 = 0$, or the potential does not change with $\ln c_1$. This remarkable behaviour is depicted in *Figure 6* from Richardson's work.

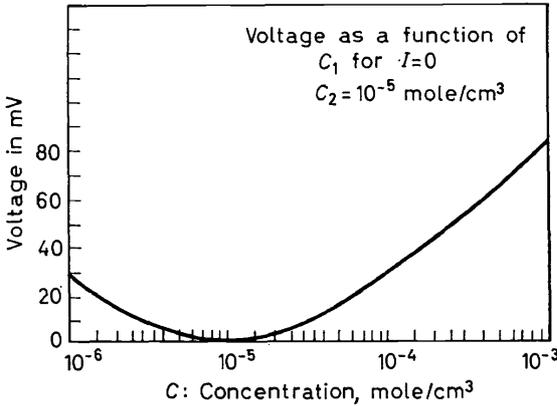


Figure 6. The resting potential $\Delta\psi$ for a complex membrane composed of two highly permeable elements. The concentration on side 2 is kept constant ($c_2 = 10^{-5}$ moles/cm³) while the concentration c_1 is varied. The flow of electrical current is zero ($I = 0$). Calculated by Richardson¹⁹

It is rather gratifying to find that those biological membranes which show a non-linear dependence of electrical current on potential exhibit also a non-linear dependence of potential on the logarithm of ion concentration. *Figure 7* is taken from Tasaki's study of the nerve membrane of perfused axons of the squid. The data resemble those found in synthetic bilayers and described theoretically by equations (77) and (79).

6. COMPLEX MEMBRANES WITH CHEMICAL INTERACTION

6.1. Anisotropic membrane structures, stressed in the previous section, are of particular importance for interpretation of the coupling phenomena underlying active transport. As pointed out in section 2.3, active transport

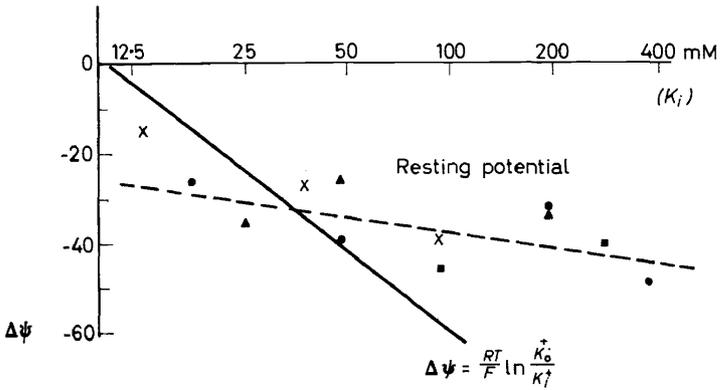


Figure 7. Effect upon the resting potential of diluting the K-perfusing fluid with isotonic sucrose solution. The ratio of Na^+/K^+ concentration was fixed at 1/10. The abscissa represents the K^+ concentration in the perfusing solution. (Temp: 22°C .) (From Tasaki and Takenaka)

requires the possibility of coupling between diffusional and chemical flows. Some sixty years ago, Pierre Curie²³ announced, however, a principle which cast doubt on the physical possibility of such coupling. Curie's principle, introduced by Prigogine²⁴ into non-equilibrium thermodynamics, states that in isotropic media, coupling between flows can take place only if the flows are of the same tensorial order. Since a chemical reaction is scalar while a diffusional flow is vectorial, no active transport could occur within an isotropic medium. On the other hand, in an anisotropic space coupling is possible, and hence the anisotropic structure of biological membranes is an essential condition for the utilization of metabolic processes to drive selective diffusional flows.

Under stationary conditions there exists however another coupling possibility, denoted by Prigogine²⁵ as 'stationary state coupling', which does not require anisotropy and does not violate Curie's principle even in isotropic media. Stationary state coupling is not sufficient to account for the rapid, non-stationary relaxation processes going on in the living cell; it is, however, satisfactory for the treatment of chemical reactions going on in complex systems of synthetic membranes, to be discussed below.

6.2. Consider a narrow space, bounded by two permselective membranes, facing two corresponding external semi-infinite compartments. Each of the compartments contains a solution of a uni-univalent salt, with cations 1 and anions 2, and a non-electrolyte. The non-electrolyte may undergo catalytic breakdown resulting in the formation of ions 1 and 2. The catalyst is, however, confined to the narrow intramembrane space, so that a chemical process takes place only there. Such a system was studied by Blumenthal *et al.*²⁶, who used amides of organic acids as the non-electrolyte, which, upon hydrolytic breakdown, forms ammonium and carboxylate ions.

The change in ion concentration in the narrow space is given by the evident equation:

$$dc_1^*/dt = J_1^\alpha - J_1^\beta + J_r; \quad dc_2^*/dt = J_2^\alpha - J_2^\beta + J_r$$

where J_1 and J_2 are the flows of cation and anion per unit area of membrane,

and J_r is the rate of the chemical process, calculated per unit area of the inner space.

A stationary state will be established when $dc_1^*/dt = dc_2^*/dt = 0$ and it is then that the ionic flows become coupled with the chemical process

$$J_1^\alpha - J_1^\beta = -J_r \quad (80.1)$$

$$J_2^\alpha - J_2^\beta = -J_r \quad (80.2)$$

It is worth noting that while J_1 and J_2 undergo a discontinuity, equal to $-J_r$, when passing through the inner cell, the flow of electricity remains continuous, for equations (80.1), (80.2) show that

$$I^\alpha = (J_1^\alpha - J_2^\alpha) F = I^\beta = (J_1^\beta - J_2^\beta) F = I \quad (81)$$

We assume that ion 2 participates in the reversible electrode reaction, while the flow of ion 1, J_1 , is considered as the flow of salt J_s . Equation (81) may therefore be rewritten

$$J_s^\alpha - J_s^\beta = -J_r$$

Inserting the expression J_s from equation (35), we obtain

$$\omega_\alpha \Delta\pi_\alpha + (t_1^\alpha/F) I - \omega_\beta \Delta\pi_\beta - (t_1^\beta/F) I = -J_r \quad (82)$$

Assuming, again, ideal behaviour we may write:

$$\Delta\pi_\alpha = 2RT(c_1 - c^*) \quad \text{and} \quad \Delta\pi_\beta = 2RT(c^* - c_2)$$

which upon insertion into (82) gives for c^*

$$\begin{aligned} c^* &= \frac{\omega_\alpha c_1 + \omega_\beta c_2}{\omega_\alpha + \omega_\beta} + \frac{(t_1^\alpha - t_1^\beta) I/F}{2RT(\omega_\alpha + \omega_\beta)} + \frac{J_r}{2RT(\omega_\alpha + \omega_\beta)} \\ &= \bar{c}^* + \frac{1}{2RT(\omega_\alpha + \omega_\beta)} \left[(t_1^\alpha - t_1^\beta) \frac{I}{F} + J_r \right] \end{aligned} \quad (83)$$

Equation (83) is an evident extension of equation (70); here, too, rectification is expected and there should exist a limiting current $-I_0$ at which the salt concentration c^* in the inner cell becomes zero. The magnitude of I_0 is, however, dependent on the rate of reaction, so that variation in the activity of the catalyst will shift I_0 to higher or lower values. If the bilayer may be regarded as a rectifying diode, the intramembrane chemical reaction may be regarded as a 'grid' the catalytic activity of which may amplify electrical flows. . . .

Following the procedure of section 5.1, we may now evaluate the dependence of I on $\Delta\psi$ for a bilayer with intramembrane chemical reaction. The

basic equation

$$\Delta\psi = -\frac{RT}{F} [(t_1^\alpha - t_2^\alpha) \ln c_1 - (t_1^\beta - t_2^\beta) \ln c_2] + \frac{2RT}{F} (t_1^\alpha - t_1^\beta) \ln c^* + I \cdot \rho \quad (84)$$

holds in the present case, as well as in that discussed in section 5.2. The main difference lies in the value of c^* which is now given by equation (83). Equation (84) can be cast in different useful forms: thus we may write c^* as:

$$c^* = \left[\bar{c}^* + \frac{J_r}{2RT(\omega_\alpha + \omega_\beta)} \right] \left(1 + \frac{I}{I_0} \right) \quad (85)$$

The dependence of I on $\Delta\psi$ then becomes identical with that given in equation (75)

$$\Delta\psi - \Delta\psi_0 = \frac{2RT}{F} (t_1^\alpha - t_1^\beta) \ln \left(1 + \frac{I}{I_0} \right) + I \cdot \rho \quad (86)$$

It should however be borne in mind that, in equation (86), the limiting current I_0 is a function of the chemical process (J_r) and that $\Delta\psi_0$ —the potential at zero current—differs from that discussed above. If we denote the resting potential at zero chemical reaction by $\Delta\psi_0^0$ it is easily shown that

$$\Delta\psi_0 = \Delta\psi_0^0 + \frac{2RT}{F} \ln \left(1 + \frac{J_r}{2RT\bar{c}^*(\omega_\alpha + \omega_\beta)} \right) \quad (87)$$

Now, if the concentrations on both sides of the composite membrane are equal, i.e., $c_1 = c_2 = c$, \bar{c}^* also become c and $\Delta\psi_0^0 = 0$, whatever may be the values of t_1^α and t_2^β . On the other hand, the resting potential does not vanish but becomes

$$\Delta\psi_0 (c_1=c_2) = \frac{2RT}{F} \ln \left(1 + \frac{J_r}{2RTc(\omega_\alpha + \omega_\beta)} \right) \quad (88)$$

Thus the biological observation that a resting potential is maintained even when the salt concentrations are equal on both sides of the membrane is an indication that an ion-forming or ion-reducing process goes on in the membrane.

Let us finally insert c^* from equation (83) into (84) and introduce $\Delta\psi_0^0$. The expression obtained is

$$\Delta\psi - \Delta\psi_0^0 = \frac{2RT}{F} (t_1^\alpha - t_1^\beta) \ln \left[1 + \frac{(t_1^\alpha - t_1^\beta)}{2RT\bar{c}^*(\omega_\alpha + \omega_\beta)} \cdot \frac{I}{F} + \frac{J_r}{2RT\bar{c}^*(\omega_\alpha + \omega_\beta)} \right] + I \cdot \rho \quad (89)$$

There is a special interest in cases of slow flows, for which a formulation on the basis of non-equilibrium thermodynamics is applicable. In these cases, both

$$\frac{t_1^\alpha - t_1^\beta}{2RT\bar{c}^* (\omega_\alpha + \omega_\beta)} \frac{I}{F} \quad \text{and} \quad \frac{J_r}{2RT\bar{c}^* (\omega_\alpha + \omega_\beta)}$$

are smaller than unity and the logarithmic term may be expanded to give

$$\begin{aligned} \Delta\psi - \Delta\psi_0^0 = I \left[\rho + \left(\frac{t_1^\alpha - t_1^\beta}{F} \right)^2 \frac{1}{\bar{c}^* (\omega_\alpha + \omega_\beta)} \right] \\ + J_r \frac{t_1^\alpha - t_1^\beta}{F\bar{c}^* (\omega_\alpha + \omega_\beta)} = I \cdot R_{11} + J_r \cdot R_{12} \end{aligned} \quad (90)$$

Equation (90) shows that if the flows are sufficiently slow, the electrical force $\Delta\psi - \Delta\psi_0^0$ becomes a linear function of the flows I and J_r . Moreover, it demonstrates that there exists not only a straight coefficient—the resistance, R_{11} , which relates the potential to the electric current—but that also we may expect the existence of a non-vanishing coupling coefficient R_{12} , which relates $\Delta\psi - \Delta\psi_0^0$ to the chemical flow, J_r .

According to the structure of the composite membrane, which determines whether $t_1^\alpha - t_1^\beta \geq 0$, R_{12} may be either positive or negative. On the other hand, as required by the rules of the thermodynamics of irreversible processes, R_{11} is positive definite. It will be further observed that, in accord with Curie's principle, no coupling is possible if the membrane system is isotropic, for in this case $t_1^\alpha = t_1^\beta$ and the coupling coefficient R_{12} vanishes.

Equation (90) may be regarded as a special case of an equation proposed by Kedem²⁷ for the description of active transport:

$$X_i = \sum J_k R_{ik} + J_r R_{ir} \quad (91)$$

This expression indicates that the force X_i is related linearly to all the diffusion flows J_k passing through the system, in accordance with the phenomenological equation (18). The novel feature is the chemico-diffusional coefficient R_{ir} which makes active transport possible in anisotropic systems. In the last section we shall make use of equation (91) for some models of active transport worked out in this laboratory.

7. OBSERVATIONS ON CARRIER MEDIATED ACTIVE TRANSPORT

7.1. The discussion of active transport is furthest from the main subject of this lecture. Its inclusion is justified in that it provides the possibility of introducing additional aspects of the thermodynamic description of membrane behaviour and because of the possible relation of active transport to macromolecular contractility within active membranes.

It is not possible to sketch even in outline the scope of biological phenomena based on active transport. It embraces the operation of tissues and cells, is closely related to the metabolic transformations, and encompasses

the exchange of electrolytes and non-electrolytes as well as the transport of liquids and gases. Although it is not established unequivocally whether all cases of active transport described in the literature are membrane-bound phenomena, there are several cases where chemical-diffusional coupling was clearly shown to be present in membranes. The best investigated case is that of red blood cell membranes which will serve as a model for further discussion. It is well known that red blood cells actively accumulate potassium within the cell and expel sodium into the surroundings. If the cells are haemolysed carefully, empty cells free of haemoglobin, called ghosts, may be obtained. These are essentially osmometric sacks surrounded by intact cell membranes. The remarkable property of erythrocyte ghosts is that despite their emptiness, they may accumulate K^+ and expel sodium, as long as ATP is present within the cells. This observation indicates that at least in the erythrocytes, active transport of cations is carried out by the membrane—as long as the hydrolysis of ATP provides the energy for the process.

From the point of view of our previous discussion, it is rather interesting that active transport in the erythrocyte is based on a chemical anisotropy of the membrane. Electron micrographs of the membranes do not reveal any visual anisotropy and seem to substantiate the 'unit membrane' concept, which supposes that the membrane is composed of a lipid bilayer, the external and internal surfaces of which are covered with protein layers. Physiological studies indicate, however, that the molecular composition is different on both surfaces. Several years ago, Glynn, Post and their co-workers²⁸ showed that the ATPase activity of the membrane requires the presence of both Na^+ and K^+ in the reaction medium. Later, Whittam²⁹ showed in haemolytic experiments that the site of action of the ions is different: while Na^+ and ATP must be present within the cell, K^+ must be in the external solution to enable enzymatic breakdown of ATP to take place. The evidence is rather convincing that Na^+ combines with the inner membrane surface while K^+ binds selectively to the outer surface, and it is this anisotropic binding which permits active transport to proceed.

There are indications that the operation of other biological membranes is also related to structural anisotropy. Thus the exciting technique of Baker, Hodgkin and Shaw³⁰ in England and of Tasaki *et al.*³¹ in the U.S.A. led to the preparation of relatively pure nerve membranes from the axon of squids. These tubular membranes are 'active' since they are excitable and are capable of numerous responses to an external stimulus. If a proteolytic enzyme is applied externally to such membranes it has little influence on the excitability of the preparation. On the other hand, enzymatic attack on the internal membrane proteins causes rapid and irreversible damage with abolition of excitability. Another anisotropic effect is shown by the fish poison tetrodotoxin. While the application of nanomoles (10^{-9} moles) of tetrodotoxin to the external surfaces of the squid axon inhibits excitability, the introduction of the poison into the intramembrane liquid leaves the membrane intact. These physiological findings, together with the electrical rectification and potential dependence on concentration discussed previously support the view that active transport takes place in complex membrane systems, with anisotropic, vectorial properties.

There is additional evidence that transport in biomembranes make use of carrier facilitation. It is not only that saturation phenomena are found to be prevalent, but recent experiments of Glynn³² on isotope exchange in red blood cell membranes are readily explicable on the assumption that transport of sodium is based on the shuttling of a carrier back and forth in the membrane. The following discussion has therefore to make use of all the conceptual framework developed above.

7.2. The formal thermodynamic description of the sodium and potassium flows coupled with the metabolic process gives for the dissipation function

$$\Phi = J_{\text{Na}}\Delta\tilde{\mu}_{\text{Na}} + J_{\text{K}}\Delta\tilde{\mu}_{\text{K}} + J_r A \quad (92)$$

If the flows of sodium and potassium may be regarded as representing a true ion-exchange process, i.e. $J_{\text{Na}} = -J_{\text{K}}$, then the dissipation function reduces to the interesting form

$$\begin{aligned} \Phi &= J_{\text{Na}} (\Delta\tilde{\mu}_{\text{Na}} - \Delta\tilde{\mu}_{\text{K}}) + J_r A \\ &= J_{\text{Na}}\Delta\mu_{\text{exch}} + J_r A \end{aligned} \quad (93)$$

In reality, the two flows are not exactly equal in magnitude—but for our schematic representation, we shall consider the consequences of equation (93) for the simple case of equal flows.

The new force $\Delta\mu_{\text{exch}}$ which appears in equation (93) is related to the ion distribution coefficient Γ

$$\Gamma = \frac{c_{\text{K}}^1/c_{\text{Na}}^1}{c_{\text{K}}^0/c_{\text{Na}}^0}$$

by the evident expression

$$\Delta\mu_{\text{exch}} = -RT \ln \Gamma \quad (94)$$

The phenomenological equations corresponding to equation (93) are

$$\begin{aligned} J_{\text{Na}} &= L_{11}\Delta\mu_{\text{exch}} + L_{12}A \\ J_r &= L_{21}\Delta\mu_{\text{exch}} + L_{22}A \end{aligned} \quad (95)$$

where L_{11} and L_{22} are the straight coefficients, and L_{12} and L_{21} are the coupling coefficients expected to obey Onsager's relation $L_{12} = L_{21}$. For resting cells $J_{\text{Na}} = 0$ and hence

$$\Delta\mu_{\text{exch}} = -\frac{L_{12}}{L_{11}} A. \quad (96)$$

Inserting the ion distribution coefficient Γ from equation (94) we obtain the important relation

$$\Gamma = \exp\left(\frac{L_{12}}{L_{11}} \frac{A}{RT}\right) \quad (97)$$

which shows that if the coupling coefficient $L_{12} \neq 0$, a chemical reaction may maintain an unequal ion distribution across an anisotropic membrane.

The value of Γ for human red-blood cells at 37°C is ~ 220 , which is larger by two orders of magnitude than the selectivity coefficients found with technical ion-exchangers.

When the erythrocytes are cooled to 0°C the rate of the chemical process is reduced appreciably and $\Delta\mu_{\text{exch}}$ tends to zero. On heating the cells again to 37°C , an ion flow sets in which re-establishes the original distribution. Now, the initial value of J_{Na} (at $\Delta\mu_{\text{exch}} = 0$) may be readily related to the rate of the chemical process

$$\left(\frac{J_{\text{Na}}}{J_r}\right)_{\Delta\mu_{\text{exch}}=0} = \frac{L_{12}}{L_{22}} \quad (98)$$

Since an equilibrium mixture of ATP, ADP and inorganic phosphate could be introduced into a haemolysing cell, it is possible to test the membrane behaviours at $A = 0$. In this case

$$\left(\frac{J_r}{J_{\text{Na}}}\right)_{A=0} = \frac{L_{21}}{L_{11}} \quad (99)$$

and if the Onsager relation holds, we should obtain from (96) and (99)

$$\left(\frac{J_r}{J_{\text{Na}}}\right)_{A=0} = - \left(\frac{\Delta\mu_{\text{exch}}}{A}\right)_{J_{\text{Na}}=0} \quad (100)$$

Relations of the type given by equation (100) were studied by Blumenthal *et al.*²⁶ on synthetic membrane systems comprising a chemical process. A similar analysis is, however, still unavailable for the test of thermodynamic theory of active transport in biological membranes.

7.3. As pointed out previously, there is no possibility of making any thermodynamic statement on the phenomenological coefficients L_{ij} and their dependence on the parameters of state. Even the orthodox thermodynamicist, who follows precisely the commandment 'thou shalt have no graven image', is compelled to construct models which would allow quantitative correlations between flows and forces in active membranes, beyond the Onsager relation. On the basis of existing data, and following the pioneering work of several biophysical groups, we shall consider herewith an oversimplified model, which does not pretend to describe adequately all experimental findings but which is readily analysed by a physical chemist. It leans heavily on the treatment of Rosenberg and Wilbrandt, who separate the inner reaction from the outer reaction on the internal and external membrane surfaces.

It is assumed that ion transport is based on a carrier molecule C which shuttles in the membrane. The carrier may be free, and has then a selective affinity for potassium ions, which are transported as the complex CK ; or it may be phosphorylated by ATP to the form CP , acquiring a strong affinity to sodium ions which are transported as a $CPNa$ complex. *Figure 8* shows clearly that the phosphorylation reaction J_r^i takes place on the inner

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surface ($CK^i + ATP \rightarrow CPK^i + ADP$) while dephosphorylation take^s place on the outer surface $CPK^0 \rightarrow CK^0 + P_{inorganic}$. Ion-exchange reaction^s take place on both surfaces ($CPK^i + Na^i \rightarrow CPNa^i + K^i$ and $CPNa^0 + K^0 \rightarrow CPK^0 + Na^0$), the overall result being transport of Na^+ to the external solution by the carrier flow J_{CPNa} , and an influx of K^+ by the carrier flow J_{CK} . The overall process is that of ion exchange, although counter gradient flow is allowed by the chemical reaction.

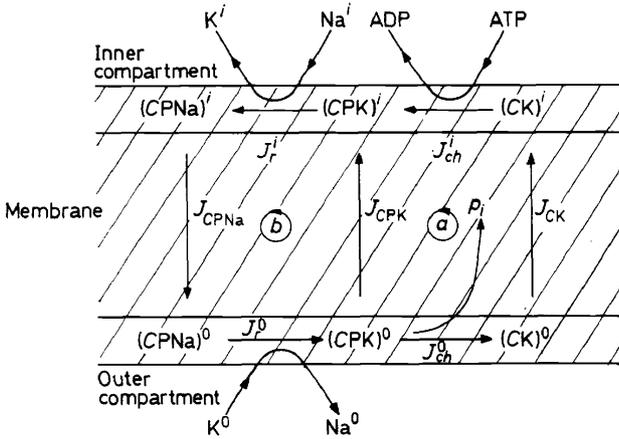


Figure 8. Schematic representation of carrier mediated, active, exchange of $Na^+—K^+$. J_{ch}^i is the rate of the chemical process which transforms the free carrier (CK^i) into a phosphorylated carrier (CPK^i) ($CK^i + ATP \rightarrow CPK^i + ADP$). J_{ch}^0 represents the rate of dephosphorylation which regenerates the free carrier ($CPK^0 \rightarrow CK^0 + P_i$). J_r^i is the rate of exchange of potassium by sodium on the inner side of the membrane ($CPK^i + Na^i \rightarrow CPNa^i + K^i$). J_r^0 represents the rate of sodium liberation to the outer solution through exchange with external potassium ($CPNa^0 + K^0 \rightarrow CPK^0 + Na^0$). J_{CK} , J_{CPK} and J_{CPNa} are the rates of flow of the different carrier forms across the membrane

The scheme presented here is similar to that used by Heckmann and by Hill and Kedem¹³ in their treatment of facilitated and active transport by a lattice model. The common feature is the separation of the process into a chemical cycle (a) and an ion exchange cycle (b) which may be readily evaluated.

It is unnecessary to present the detailed calculation, which follows the method outlined above for facilitated-carrier mediated transport; only the final equations will be reproduced.

$$J_{Na} = L_{11}(1 - \Gamma) + L_{12} \left(K \frac{C_{ATP} \cdot C_{H_2O}}{C_{ADP} \cdot C_{P_i}} - 1 \right) = L_{11}X_{exch} + L_{12}X_r \quad (101)$$

$$J_r = L_{21}(1 - \Gamma) + L_{22} \left(K \frac{C_{ATP} \cdot C_{H_2O}}{C_{ADP} \cdot C_{P_i}} - 1 \right) = L_{21}X_{exch} + L_{22}X_r$$

The kinetic treatment underlying equations (101) makes the flows J_{Na} and J_r linearly dependent on a new pair of forces,

$$X_{exch} = 1 - \Gamma \text{ and } X_r = K \frac{C_{ADP} \cdot C_{H_2O}}{C_{ADP} \cdot C_{P_i}} - 1$$

where K is the equilibrium constant for the hydrolysis of ATP. These forces reduce, however, within a factor of RT to the thermodynamic forces $\Delta\mu_{\text{exch}}$ and A used in section 7.2 when the system approaches equilibrium. Indeed if $(\Delta\mu_{\text{exch}}/RT) \ll 1$, equation (94) gives immediately

$$\frac{\Delta\mu_{\text{exch}}}{RT} = 1 - \Gamma = X_{\text{exch}} \quad (102)$$

Similarly, we find for the affinity A

$$\begin{aligned} A &= \mu_{\text{ATP}} + \mu_{\text{H}_2\text{O}} - \mu_{\text{ADP}} - \mu_{\text{P}_i} = (\mu_{\text{ATP}}^0 + \mu_{\text{ADP}}^0 - \mu_{\text{P}_i}^0) + \\ &\quad RT \ln \frac{c_{\text{ATP}} \cdot c_{\text{H}_2\text{O}}}{c_{\text{ADP}} \cdot c_{\text{P}_i}} \\ &= RT \ln K + RT \ln \frac{c_{\text{ATP}} \cdot c_{\text{H}_2\text{O}}}{c_{\text{ADP}} \cdot c_{\text{P}_i}} \end{aligned}$$

Close to equilibrium $(A/RT) \ll 1$, and hence

$$\frac{A}{RT} = K \frac{c_{\text{ATP}} \cdot c_{\text{H}_2\text{O}}}{c_{\text{ADP}} \cdot c_{\text{P}_i}} - 1 = X_r \quad (103)$$

Upon inserting equations (102) and (103) into equations (101), we regain equations (95); the model treatment provides us, however, with an explicit expression for L_{11} , L_{12} and L_{22} and verifies kinetically the validity of Onsager's theorem. As expected the coefficients are linearly proportional to the amount of carrier and its mobility, and exhibit saturation properties ascribed to facilitated transport.

The explicit dependence of the L_{ij} s on the parameters of the state permits a quantitative description of several aspects of active transport, as will be found in the paper of Blumenthal, Katchalsky and Ginzburg³³.

7.4. The model treatment leaves open the problem of the mechanism of carrier transport across the membrane. Although in the formal description of the carrier flows it was assumed that we may write $J_K = P(C_K^0 - C_K^t)$, there is little doubt that neither the free nor the phosphorylated carrier move according to the rules of free diffusion. Study of erythrocyte membranes shows that they have a tough structure displaying a viscoelastic behaviour resembling that of swollen nylon³³. Rapid transport through such a medium would require a special mechanism which differs in essence from the random movement of small molecules. Recent studies of Post *et al.*³⁴ and of Hokin *et al.*³⁵ indicate that the carrier of erythrocyte membranes consists of protein molecules which undergo phosphorylation. It is an attractive hypothesis that the conformational change which is expected to accompany the phosphorylation would develop sufficient forces to transport the permeant across the membrane. A model demonstration of such a possibility is provided by the mechanochemical engines built in this laboratory³⁶ (Figure 9).

These engines utilize the reversible contractility of regenerated and cross-linked collagen fibres (product of the Ethicon Co., New Jersey, U.S.A.)

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which contract to about half their length by interaction with strong salt solutions such as LiBr and expand reversibly upon washing with water. The original fibre is constructed of highly stretched triple helices of collagen molecules. Upon interaction with salt the helices undergo a conformational change to a random coiled structure which behaves as an ideal rubber³⁷. Since the contraction process develops large forces sufficient to be utilized for the conversion of chemical energy into mechanical work, it is plausible to suppose that in the living membranes also conformational changes of biopolymers may serve as the molecular basis for carrier-mediated transport.

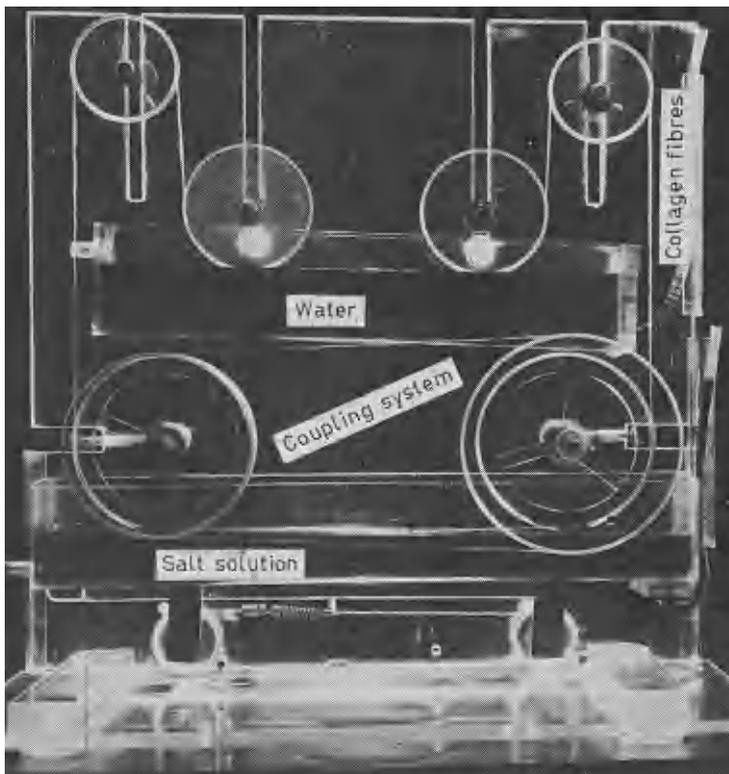


Figure 9

A tentative corroboration of this assumption is based on the following consideration of the rate of the transport in the red blood cell membrane: the sodium flow at room temperature $J_{Na} = 10^{-13}$ mole/cm²sec. Since the area of a red blood cell membrane is 1.5×10^{-6} cm² the number of Na⁺ ions passing across the membrane is

$$10^{-3} \cdot 1.5 \times 10^{-6} \cdot 6 \cdot 10^{23} \simeq 10^5 \text{ ions/sec red blood cell.}$$

Various estimates lead to the conclusion that the number of sites involved in the transport is on the average $5 \cdot 10^3$. Hence, if each site comprises

one carrier molecule and each carrier molecule takes up a single ion per movement across the membrane, the macromolecule has to make

$$\frac{10^5}{3 \cdot 10^8} = 30 \text{ cycles/sec.}$$

This is a reasonable number for macromolecular conformational change and is not far from the macroscopic contraction rates observed in collagen fibres.

Thus a deeper analysis of the performance of membranes brings us back to the study of macromolecular systems, the conformational changes and dynamic properties of which underlie the intriguing behaviour of biological systems.

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