CARRIER MODEL FOR ACTIVE TRANSPORT OF IONS ACROSS A MOSAIC MEMBRANE

ALAN FINKELSTEIN
From the Department of Neurology, Albert Einstein College of Medicine, New York

ABSTRACT The central purpose of this paper is to elucidate in a well defined system the meaning of certain phenomena and concepts associated with the active transport of ions. To this end a specific model for a carrier system which actively transports a single ionic species is analyzed and discussed in detail. It is assumed in this model that the carrier-mediated ionic transport occurs in regions of the membrane physically separate from those regions in which free ionic movement takes place,—coupling between the active and passive regions of the membrane occurring through local current flows. The model is seen to display the following characteristics: (*a*) Starting from identical solutions on the two sides of the membrane, there is produced a redistribution of ions; (*b*) with identical solutions on the two sides of the membrane there exists a potential difference across the membrane, *i.e.*, the "pump" is electrogenic; (*c*) the "short circuit" current for symmetrical solutions is equal to the flux of the neutral ion carrier complex; (*d*) the rate of active transport (and hence of metabolism) is dependent on the ionic concentrations in the surrounding solutions. Throughout the paper comparison is made between features of the model and properties displayed by biological active transport systems, but there is no claim of an identity between the two.

INTRODUCTION

The ability of cells to perform active transport, *i.e.* their ability to utilize the energy of metabolism to move molecules and ions across the plasma membrane from a region of low electrochemical potential to one of high potential, has fascinated cellular physiologists for many years. While there is no question (any longer) that active transport is thermodynamically possible, the details of the process by which this is accomplished remain obscure. Of the general types of mechanisms postulated, the most popular one of recent years has been the "carrier" system. The essence of this theory (which can take many variations) is that there is confined to the plasma membrane a carrier molecule which can react with the species that is actively transported. At one interface these two react to form a complex; the complex then diffuses through the membrane to the other interface, where it dissociates; the undissociated carrier then diffuses back to the first interface, etc. It is understood that

the reaction at one or both interfaces is coupled to an exergonic system (*e.g.* ATP $\rightarrow$ ADP + P), thus accounting for the difference in the direction of the reactions at the two interfaces.

It is clear that if the transported species is an *uncharged* molecule, the above scheme can be invoked to explain active transport, although the actual chemistry involved in a specific transport system may be quite subtle and difficult to work out. It is not so obvious, however, how such a scheme will work if the transported species is an ion, since, from macroscopic electroneutrality, there cannot be a net transport of one ion without the movement of others. This immediately raises certain questions as to how a single ionic species can be actively transported; for example, the so called sodium "pump."

It is the purpose of this paper to discuss, in detail, a carrier model for the active transport of ions. We are motivated to do this for several reasons: First, we feel that it is instructive to see how the problems raised and hinted at in the previous paragraph can be resolved in a specific, well defined system. Second, we wish to clarify certain aspects of the electrical events associated with active ion transport. Since there has been considerable discussion in the literature as to whether a given ion "pump" is "electrogenic" or "neutral," we feel it may be useful to see explicitly in a particular system what these concepts mean. Third, we wish to see if certain of the features reported in the literature to be displayed by cells performing active transport can be accounted for by a simple carrier system.

Our fourth reason for undertaking this study is to develop further the concept of the plasma membrane as a mosaic structure. From the work of Hodgkin and Keynes (1955) on active transport in the cephalopod axon, it is apparent that in at least that system the active process is quite independent of "passive" ion movement. The most obvious way for the cell to realize this independence is for the regions in the membrane where active transport occurs to be physically separate and distinct from those regions where passive ion movement occurs; *i.e.*, for the membrane to be a mosaic structure.[1] In our model, therefore, we shall start from this assumption and then pursue the consequences of this feature.

We wish to emphasize at the outset that we are not claiming that our model necessarily corresponds to a biological carrier system, or for that matter that a carrier system is actually involved in cellular active transport. Our objective is to demonstrate with a relatively simple model, which is capable of explicit analysis, some of the features and concepts of cellular active transport. For this reason we shall frequently compare properties of the model to physiological phenomena, but it should be understood that this is done primarily for pedagogical reasons rather than as offering evidence of an identity between the model and the biological

[1] We have previously discussed some of the properties of a mosaic membrane with respect to passive ion movement (Finkelstein and Mauro, 1963) and have suggested that the plasma membrane is such a structure (Finkelstein, 1964).

system. We hope, however, that this study will stimulate physiologists into thinking in more concrete terms about active transport.

ANALYSIS AND DISCUSSION

A. *The Isolated Active Transport Element*

As stated in the Introduction, we shall take the active transport region of the membrane as physically separate from those regions in which passive ion movement occurs. For this reason, we first consider the active transport element by itself. After the current-voltage relations and ion flux properties of this isolated element have been worked out, it will be a relatively simple matter to couple this element to the passive regions.

1. *General Description of the Model.* The active transport element we shall consider is shown in Fig. 1. For the sake of concreteness we have taken Na^+

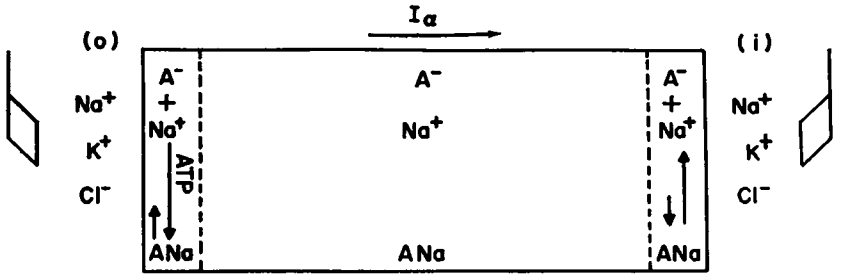

FIGURE 1 The isolated single ion active transport element. The bulk phase of the membrane is included between the dashed lines. The chemical reactions occur within the two narrow space-charge regions, which are highly exaggerated in size in the figure. A pair of electrodes for passing current are shown.

as the actively transported ion. The general aspects of the scheme depicted above are as follows: "Just within"[2] the membrane at the (o) interface Na^+ reacts with the negative carrier A^- (which is confined to the membrane phase) to form the neutral complex ANa; "just within" the membrane at the (i) interface, the neutral complex dissociates into Na^+ and A^-; within the body of the membrane are freely diffusing Na^+, A^-, and ANa. We have tacitly assumed that the association and dissociation reactions described above require the presence of some enzymes in order that they may occur at a reasonable rate, and that these enzymes are confined to the interfaces; thus for all practical purposes these reactions do not occur within the bulk of the membrane.[3] We have also assumed that the reaction at the left interface is

[2] By "just within" the membrane we shall mean the space-charge regions of the membrane near the interfaces. See section A. 2(c).

[3] The fact that we can talk about interfacial regions of the membrane as opposed to a bulk region means that we are taking for our model a macroscopic system. How valid these considerations will be for the thin plasma membrane is an open question.

coupled to an exergonic system (which for the sake of example we have taken as the hydrolysis of ATP), thus accounting for the difference in the direction of the reactions (as indicated by the relative lengths of the arrows) at the two interfaces. Finally, we assume that the only ion in the two solutions bathing the membrane that can enter the membrane is Na^+. (We have included K^+ and Cl^- in the bathing solutions to indicate that all ions other than Na^+ are excluded from the membrane). The direction of positive current is from (o) to (i), the current being established by means of a pair of electrodes.

2. *Quantitative Formulation of the Basic Assumptions.* We restrict our analysis to the *steady state,* which is characterized by a constant flux, ϕ_j, of the j'th species at any point in the membrane.

(a) *Transport relations.* We shall now write the equations governing the transport of matter. The flux of each species is given by the flux equations:[4]

$$\phi_{Na} = -u\left[RT\frac{dc_{Na}}{dx} + Fc_{Na}\frac{d\psi}{dx}\right] \tag{1a}$$

$$\phi_A = -v\left[RT\frac{dc_A}{dx} - Fc_A\frac{d\psi}{dx}\right] \tag{1b}$$

$$\phi_{ANa} = -D_{ANa}\frac{dc_{ANa}}{dx} \tag{1c}$$

where,

u = the mobility of the sodium ion
v = the mobility of the carrier ion
D_{ANa} = the diffusion constant of the neutral ion-carrier complex
c_j = the concentration of the j'th species at any point x in the membrane.
ψ = the electrical potential at any point in the membrane, with a value of 0 "just within" the membrane at (o) and a value of $-\Psi$ "just within" the membrane at (i).
R = the gas constant
T = the absolute temperature
F = the Faraday constant

We further impose at every point in the membrane the condition of electroneutrality:

$$c_{Na} = c_A \equiv c \qquad \text{electroneutrality condition} \tag{2}$$

From the steady state condition we have, assuming carrier is conserved (see equation 6):

$$\phi_{ANa} = -\phi_A \qquad \text{steady state requirement} \tag{3}$$

[4] We assume throughout the paper that bulk water flow is negligible, and that activity coefficients are unity.

By definition, the current, I_a, flowing through the membrane is:

$$I_a \equiv \phi_{Na} - \phi_A \qquad \text{definion of current} \qquad (4)$$

and the total flux, Φ_{Na}, of sodium is defined by:

$$\Phi_{Na} \equiv \phi_{Na} + \phi_{ANa} \qquad \text{total flux of Na} \qquad (5)$$

Finally, we assume that carrier is conserved:

$$\int_0^i (c_{ANa} + c_A)\, dx \equiv A \qquad \text{conservation of carrier} \qquad (6)$$

where A is the total amount of carrier, as both ANa and A^-, in the membrane.

Remark. It is instructive to note an immediate consequence of these relations. Substituting equation (3) into equation (4) and comparing this with equation (5) we have:

$$\Phi_{Na} = I_a \qquad (7)$$

This states that the total flux of Na is equal to the current flow through the active transport region. This is a rather interesting result, since the total current is *not* carried exclusively by Na^+, but rather by both Na^+ and A^-. We see that the flux ϕ_{ANa} is behaving *as if* it, instead of $-\phi_A$, were contributing to the current; this is a formal consequence of the steady state requirement, equation (3). We shall comment further on this point a little later. We also note from equation (7) that when there is no current flow through the membrane the total sodium flux goes to zero, which is of course intuitively obvious. This does not mean, however, that both ϕ_{Na} and ϕ_{ANa} are zero. We can see heuristically (and we shall verify this quantitatively below) that because of the chemical reactions, we shall have:

$$(c_{ANa})_o > (c_{ANa})_i$$

$$(c_{Na})_o < (c_{Na})_i$$

where $(c_{ANa})_o$ is the concentration of ANa "just within" the membrane at the (o) interface, and similarly for the other terms. Thus, both ϕ_{Na} and ϕ_{ANa} will be finite, but they will be equal and of opposite sign. That is, Na will move from left to right as ANa and from right to left as Na^+, the net result being no total movement of sodium. The zero current condition is satisfied because $\phi_{Na} = \phi_A$. A qualitative plot of the concentration profiles within the membrane of the various species is shown in Fig. 2. For the case of free diffusion ($I_a = 0$), the relative value of the slopes of the lines in Fig. 2 will be determined by the relation:

$$(D_{ANa}/\delta)[(c_{ANa})_i - (c_{ANa})_o] = -(D/\delta)(c_i - c_o)$$

where,

$$D = \frac{2RTuv}{u + v}$$

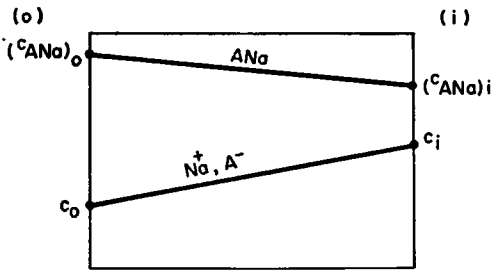

FIGURE 2 A qualitative plot of the steady state concentration profiles within the bulk phase of the active transport element of Fig. 1. Note that all profiles are linear.

(*b*) *Chemical terms.* "Just within" the membrane at the (*o*) and (*i*) interfaces occur the reactions:

$$A^- + Na^+ \underset{k_{-1}}{\overset{k_1(ATP)}{\rightleftarrows}} ANa \qquad \text{at } (o) \text{ interface}^5$$

$$A^- + Na^+ \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} ANa \qquad \text{at } (i) \text{ interface}$$

where k_j is the rate constant for the indicated reaction. The rate of change of concentration of the species at the interfaces due to these reactions (that is, the "chemical flux" of the species) is given by:

$$J_{(Na)_o} = J_{(A)_o} = -J_{(ANa)_o} = -k_1(c_{Na})_o(c_A)_o + k_{-1}(c_{ANa})_o \tag{8a}$$

$$J_{(Na)_i} = J_{(A)_i} = -J_{(ANa)_i} = -k_2(c_{Na})_i(c_A)_i + k_{-2}(c_{ANa})_i \tag{8b}$$

where, $J_{(Na)_o}$ is the rate of change of Na^+ concentration at the (*o*) interface due to the chemical reactions, and similarly for the other *J*'s. Note that the "constant" k_1 is a function of ATP concentration, going to zero if the ATP concentration goes to zero (as will be nearly the case after prolonged metabolic inhibition). In order for a steady state to exist we must have at the (*o*) interface:

$$J_{(ANa)_o} = \phi_{ANa} \qquad \text{steady state requirement} \tag{9a}$$

$$J_{(A)_o} = \phi_A \tag{9b}$$

$$J_{(Na)_o} = \phi_{Na} - \Phi_{Na} \tag{9c}$$

and at the (*i*) interface:

$$J_{(ANa)_i} = -\phi_{ANa} \qquad \text{steady state requirement} \tag{10a}$$

$$J_{(A)_i} = -\phi_A \tag{10b}$$

$$J_{(Na)_i} = \Phi_{Na} - \phi_{Na} \tag{10c}$$

[5] A more complete way of writing this reaction would be:

$$A^- + Na^+ + ATP \underset{k'_{-1}}{\overset{k'_1}{\rightleftarrows}} ANa + ADP + P$$

Thus,

$$k_1 = k'_1[ATP]; \qquad k_{-1} = k'_{-1}[ADP][P]$$

Note that equations (9*b*) and (9*c*) follow from equation (9*a*) and the previous relations. Similarly equations (10*b*) and (10*c*) follow from equation (10*a*).

(*c*) *Boundary conditions.* We shall assume that the kinetics of the boundary processes at the two membrane-solution interfaces are so rapid that essentially a state of equilibrium exists there at all times. This means that the electrochemical potential of Na^+ is the same in free solution as it is "just within" the membrane. These assumptions are essentially those made by Teorell (1951, 1953) in his treatment of the fixed-charge membrane and by Kirkwood (1954). Because A^- is confined to the membrane and all other ions except Na^+ are excluded from the membrane, there will be space-charge regions set up at the two interfaces. We do not worry about these explicitly, however, but, following Teorell, treat these transitions as essentially being discontinuous. If the standard chemical potential of Na^+ is assumed the same in the membrane as in free solution, then we have for the interfacial emf's, π_o and π_i:

$$\pi_o = -\frac{RT}{F} \ln \frac{(c_{Na})_o}{(a_{Na})_o} \tag{11a}$$

$$\pi_i = \frac{RT}{F} \ln \frac{(c_{Na})_i}{(a_{Na})_i} \tag{11b}$$

where, $(a_{Na})_o$ and $(a_{Na})_i$ are the concentrations of Na^+ in solutions (o) and (i), respectively. The emf's given in equation (11) are analogous to the "Donnan emf's" in the Teorell fixed-charge membrane. Combining equations (11*a*) and (11*b*) we have for the total boundary emf, π, of the membrane:

$$\pi = \frac{RT}{F}\left[\ln \frac{c_i}{c_o} + \ln \frac{(a_{Na})_o}{(a_{Na})_i}\right] \tag{12}$$

where because of the electroneutrality conditions we have written:

$$c_o \equiv (c_{Na})_o = (c_A)_o$$

$$c_i \equiv (c_{Na})_i = (c_A)_i$$

3. *Membrane Potential and Fluxes.* We shall now use the equations of the previous section to develop expressions for the total membrane potential and the fluxes of Na^+, A^-, and ANa, in terms of the boundary[6] concentrations c_o, c_i, $(c_{ANa})_o$, and $(c_{ANa})_i$.

It is clear that given c_o and c_i, we are dealing with nothing more complicated than the single salt case of a Planck diffusion regime of ions. It immediately follows then from equations (1*a*), (1*b*), and (2) that:

$$\Psi_D = \frac{RT}{F}\left(\frac{u - v}{u + v}\right) \ln \frac{c_i}{c_o} \tag{13}$$

[6] By boundary concentrations we mean the concentrations "just within" the membrane; that is, the concentrations immediately following the discontinuous "jumps" from the free solutions.

$$R_{\text{total}} = \frac{\delta}{F(u+v)(c_i - c_o)} \ln \frac{c_i}{c_o} \tag{14}$$

where,

Ψ_D is the diffusion emf of the regime, R_{total} is its integral resistance, and δ is the membrane thickness (see Finkelstein and Mauro, 1963). The potential difference between the two ends of the membrane, excluding the boundary emf's, is then the sum of equation (13) and the $I_\alpha R$ drop within the membrane; thus,

$$\Psi = I_\alpha \frac{\delta}{F(u+v)(c_i - c_o)} \ln \frac{c_i}{c_o} + \frac{RT}{F}\left(\frac{u-v}{u+v}\right) \ln \frac{c_i}{c_o} \tag{15}$$

Combining this with equation (12) we then have for the total potential difference, Ψ_{total}, across the membrane:

$$\Psi_{\text{total}} = \pi - \Psi = \pi - \Psi_D - I_\alpha R$$

$$\Psi_{\text{total}} = \frac{RT}{F}\left[\ln \frac{c_i}{c_o} + \ln \frac{(a_{\text{Na}})_o}{(a_{\text{Na}})_i}\right] - \frac{RT}{F}\left(\frac{u-v}{u+v}\right) \ln \frac{c_i}{c_o} - I_\alpha \frac{\delta}{F(u+v)(c_i - c_o)} \ln \frac{c_i}{c_o} \tag{16}$$

Turning now to the flux of the various species, we have for the concentration and potential profiles within the membrane from equations (1*a*), (1*b*), and (2):

$$c = (c_i - c_o)(x/\delta) + c_o \tag{17a}$$

$$\psi = -[1/F(u+v)][I_\alpha \delta/(c_i - c_o) + RT(u-v)] \ln \left[\frac{(c_i - c_o)(x/\delta) + c_o}{c_o}\right] \tag{17b}$$

and substituting these relations back into equations (1*a*) and (1*b*) we obtain:

$$\phi_{\text{Na}} = -\frac{u}{u+v}\left[\frac{2RTv(c_i - c_o)}{\delta} - I_\alpha\right] \tag{18a}$$

$$\phi_{\text{A}} = -\frac{v}{u+v}\left[\frac{2RTu(c_i - c_o)}{\delta} + I_\alpha\right] \tag{18b}$$

while integration of equation (1*c*) gives:

$$\phi_{\text{ANa}} = -(D_{\text{ANa}}/\delta)[(c_{\text{ANa}})_i - (c_{\text{ANa}})_o] \tag{18c}$$

Remarks. With equations (16) and (18) we have all of the relevant properties of the isolated active transport element before us; that is, we have the voltage-current characteristic of the element and the fluxes of Na^+, A^-, and ANa from one interface to the other, as functions of I_α. As they stand, however, these equations do not give explicitly the dependence of these quantities on I_α, since c_o, c_i, $(c_{\text{ANa}})_o$ and $(c_{\text{ANa}})_i$ are all functions of I_α. We therefore must solve for these concentrations in terms of I_α in order to complete our treatment of the isolated active transport element. There are several qualitative features of the system, however, that can be deduced from the results we already have, without knowing the detailed dependence

of these quantities on I_a, and so we shall discuss these features first, as it will give us further physical insight into the properties of the model.

The first point to note is that Ψ_{total}, ϕ_{Na}, and ϕ_{ANa} will be highly non-linear functions of I_a. At first glance this might appear rather strange, since, as was pointed out above, we are dealing with the single salt case of a Planck diffusion regime, which, as is well known, is the one case which is perfectly linear. The basis for the non-linearity, however, arises from the fact that c_o and c_i are not constant, as is the case in the classical Planck constrained boundary diffusion, but instead are functions of I_a. For positive I_a, c_o increases and c_i decreases, as a consequence of A^- accumulating and depleting at the (o) and (i) interfaces respectively, and conversely c_o decreases and c_i increases for negative I_a. As a result of the change in concentrations of Na^+ and A^- at the interfaces, the concentration of ANa at the interfaces is also affected, and hence ϕ_{ANa}. Thus we have the somewhat unusual phenomenon of current flow altering the flux of a neutral species.[7]

The second point of interest is that there generally will be a potential difference across the membrane, in the absence of current flow, with *identical* solutions on the two sides of the membrane. To see this, let us consider equation (16). With $(a_{\text{Na}})_o = (a_{\text{Na}})_i$ and $I_a = 0$, it reduces to:

$$\Psi_{\text{total}} = \frac{RT}{F} \ln \frac{c_i}{c_o} - \frac{RT}{F} \left(\frac{u - v}{u + v} \right) \ln \frac{c_i}{c_o} \tag{16a}$$

where from the direction of the reactions it is intuitively obvious that:

$$c_o < c_i$$

The first term in equation (16*a*) is the sum of the two boundary emf's, while the second term is the diffusion emf arising from the mobility difference between Na^+ and A^-. From equation (16*a*) we have for the various limiting cases:

$$\Psi_{\text{total}} \approx \frac{2RT}{F} \ln \frac{c_i}{c_o} \qquad (u \ll v)$$

$$\Psi_{\text{total}} \approx \frac{RT}{F} \ln \frac{c_i}{c_o} \qquad (u \approx v)$$

$$\Psi_{\text{total}} \approx 0 \qquad (u \gg v)$$

Thus the diffusion emf can either add or subtract from the boundary emf. We see, however, that in general Ψ_{total} is finite and positive, going to zero only in the limiting case of $u \gg v$. In other words, to put it in physiological terminology, our "pump" is electrogenic.

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[7] Note that the properties of the membrane discussed in this paragraph would still be present even if the transport element of Fig. 1 were not active; that is, if:

$$k_1/k_{-1} = k_2/k_{-2}$$

The third point to discuss is the so called "short circuit" current of the membrane with *identical solutions* on the two sides. Since, as we have shown above, there is a positive potential existing across the "open circuited" membrane with identical solutions on the two sides, it is clear that if we bring the membrane potential to zero (short circuit the membrane), there will be a finite positive current flowing through the membrane. Setting $\Psi_{\text{total}} = 0$ and $(a_{\text{Na}})_o = (a_{\text{Na}})_i$ in equation (16), we obtain for its value:

$$(I_a)_{\Psi_{\text{total}}=0} = \frac{2RTv}{\delta}(c_i - c_o) \qquad \text{short circuit current} \qquad (19)$$

Note that the short circuit current is independent of the mobility of Na^+. This we could have predicted intuitively. For with equal concentrations of Na^+ on the two sides of the membrane, when Ψ_{total} is brought to zero, the electrochemical potential of Na^+ is the same on the two sides of the membrane, and hence ϕ_{Na} (but not Φ_{Na}) must be zero. [We obtain this result formally by substituting equation (19) into equation (18*a*)]. Thus the current cannot depend on u, since no current is carried by Na^+. Hence, all of the short circuit current must be carried by A^-; that is,

$$(I_a)_{\Psi_{\text{total}}=0} = -\phi_{\text{A}} \qquad (20)$$

[This is obtained formally by substituting equation (19) into equation (18*b*)]. But substituting equation (3) into equation (20) gives:

$$(I_a)_{\Psi_{\text{total}}=0} = \phi_{\text{ANa}} \qquad (21)$$

Equation (21) is a rather remarkable expression. It states that the short circuit current for symmetrical solutions is equal to the flux of the neutral ANa species. This is of course an algebraic artifice, since ANa, being neutral, does not carry current; [compare this with the Remark in section A. 2(*a*)]. In fact in this case all of the current is actually carried by A^-. In the short circuit experiments on frog skin, Ussing and Zerahn (1951) reasoned from the equality of electrochemical potential of all species on the two sides of the membrane, that the current must be a reflection of the active transport process. We see that in our model this is indeed true, and we also see that this occurs in a rather subtle manner. We shall comment further on the short circuit current in the next section.

The final point that we wish to comment upon is the interrelationship between metabolism and electrical properties. As noted in section A. 2(*b*), the rate "constant" k_1 is a function of ATP concentration, and hence of metabolism. If the system is metabolically poisoned, then k_1 will decrease with time until finally $k_1/k_{-1} = k_2/k_{-2}$. Clearly, then, with symmetrical solutions on the two sides of the membrane, there will be no potential difference across the system. This system will behave as a fixed-charge membrane of sorts, except that the "fixed" charge (that is, A^-) is mobile (and capable of reacting with Na^+ to form ANa). Hence, even in the absence

of active transport, the element will have a highly non-linear voltage current characteristic.

Of perhaps more interest, however, is the fact that current flow will affect the rate of the reactions, and hence the metabolic activity. As mentioned above, positive I_a increases c_o and negative I_a decreases c_o. Since the rate of the metabolically coupled reaction is given by $k_1 c_o^2$, it is clear that positive I_a will increase the rate of ATP hydrolysis and hence stimulate metabolic activity, while for large negative I_a, the metabolic activity associated with active transport will cease. We shall return to this point later, when we consider the coupling of the active element to passive regions.

4. *The Boundary Concentrations.* Let us now proceed to complete our treatment of the isolated active transport element by finding the functional dependence of the boundary concentrations on I_a. Substituting equations (18*b*) and 18*c*) into equation (3) we get:

$$-(D_{\mathrm{ANa}}/\delta)[(c_{\mathrm{ANa}})_i - (c_{\mathrm{ANa}})_o] = (v/u + v)[(2RTu/\delta)(c_i - c_o) + I_a] \qquad (22a)$$

Putting equation (17*a*) and the analogous expression for c_{ANa} into equation (6) we obtain:

$$c_i + c_o + (c_{\mathrm{ANa}})_i + (c_{\mathrm{ANa}})_o = 2A/\delta \qquad (22b)$$

Substituting equations (8*a*) and (18*c*) into equation (9*a*), and equations (8*b*) and (18*c*) into equation (10*a*) we get:

$$k_1 c_0^{\,2} - k_{-1}(c_{\mathrm{ANa}})_o = -(D_{\mathrm{ANa}}/\delta)[(c_{\mathrm{ANa}})_i - (c_{\mathrm{ANa}})_o] \qquad (22c)$$

$$k_2 c_i^{\,2} - k_{-2}(c_{\mathrm{ANa}})_i = (D_{\mathrm{ANa}}/\delta)[(c_{\mathrm{ANa}})_i - (c_{\mathrm{ANa}})_o] \qquad (22d)$$

Equations (22*a-d*) determine c_o, c_i, $(c_{\mathrm{ANa}})_o$, and $(c_{\mathrm{ANa}})_i$ as functions of I_a (and also as functions of the parameters u, v, D_{ANa}, k_1, k_{-1}, k_2, k_{-2}). The problem now is simply the algebraic one of solving four simultaneous equations in four unknowns. Because of the messiness of the algebra, we make the simplifying assumptions:

$$k_{-1} = 0 \qquad \text{simplifying assumptions} \qquad (23a)$$

$$k_2 = 0 \qquad (23b)$$

We wish to emphasize that we are doing this purely for mathematical and aesthetic reasons, and that if necessary the equations could be solved without any such approximations. For the problems that really interest us, however, we do not expect relations (23*a*) and (23*b*) to drastically affect the final results.[8] In order that the

[8] An exception to this statement is the tracer flux properties of the membrane, which can be significantly affected by equations (23*a*) and (23*b*). We shall defer, however, a discussion of tracer fluxes in homogeneous, mosaic, and active transporting membranes for a future communication.

active transport system function efficiently, it is clear that we should have:

$$k_1 \gg k_{-1}$$

$$k_{-2} \gg k_2,$$

so that equations (23) are good approximations to the situations of physiological importance.

Solving equations (22*a-d*) we obtain:

$$c_i = \frac{k_1(u+v)\delta}{2RTuv} c_0^2 + c_0 - \frac{I_a \delta}{2RTu} \tag{24a}$$

$$(c_{\mathrm{ANa}})_o = \frac{1}{2}\left\{k_1\left[\frac{\delta}{D_{\mathrm{ANa}}} - \frac{(u+v)\delta}{2RTuv}\right]c_o^2 - 2c_o + \left(\frac{2A}{\delta} + \frac{I_a\delta}{2RTu}\right)\right\} \tag{24b}$$

$$(c_{\mathrm{ANa}})_i = \frac{1}{2}\left\{-k_1\left[\frac{\delta}{D_{\mathrm{ANa}}} + \frac{(u+v)\delta}{2RTuv}\right]c_o^2 - 2c_o + \left(\frac{2A}{\delta} + \frac{I_a\delta}{2RTu}\right)\right\} \tag{24c}$$

and

$$c_o = \frac{-1 + \sqrt{1 + \beta\gamma k_1}}{\beta k_1} \tag{24d}$$

where,

$$\beta \equiv \frac{(u+v)\delta}{2RTuv} + \frac{\delta}{D_{\mathrm{ANa}}} + \frac{2}{k_{-2}} \tag{25a}$$

$$\gamma \equiv \frac{2A}{\delta} + \frac{I_a\delta}{2RTu} \tag{25b}$$

Remarks. Equations (24*a-d*) give us the explicit dependence of the boundary concentrations on I_a. Substitution of these into equations (16) and (18) then gives the voltage-current characteristics of the active transport element, the fluxes ϕ_{Na}, ϕ_{A}, ϕ_{ANa}, and any other relevent quantities that we care to know. Let us therefore examine some of the features of our results.

From equations (24*a*) and (24*b*) we have:

$$c_i = 2A/\delta; \qquad c_o = 0, \quad \text{when} \quad I_a = -4RTuA/\delta^2 \tag{26}$$

The current $I_a = -4RTuA/\delta^2$ is the largest negative current that can be put through the element. Substitution of equation (26) into equation (16) gives:

$$\Psi_{\mathrm{total}} \to +\infty \quad \text{as} \quad I_a \to -4RTu(A/\delta^2) \tag{27}$$

We note that Ψ_{total} becomes infinite on two accounts. First, because π, the boundary emf, becomes infinite; and second, because R_{total}, the total integral resistance of the element, becomes infinite, thus making the IR drop infinite. Note that the sign of π and IR are the same. (The diffusion emf, Ψ_D, also becomes infinite and will add or subtract from the other two quantities depending on whether $u < v$ or $u > v$; for

$u = v$, $\Psi_D = 0$). The analogous expression to equation (26) for the positive current that makes $c_i = 0$ can also be obtained, but is a little more cumbersome. If we make the arbitrary relation between the constants:

$$\frac{(u + v)\delta}{2RTuv} = \frac{\delta}{D_{ANa}} + \frac{2}{k_{-2}} \tag{28}$$

then this current turns out to be:

$$I_a = +4RTu(A/\delta^2)$$

For this current, $c_i \to 0$, and $\Psi_{total} \to -\infty$ for the same reasons it went to $+\infty$ when $c_o \to 0$. In Fig. 3 we see plotted the $\Psi_{total} - I_a$ characteristic of the active trans-

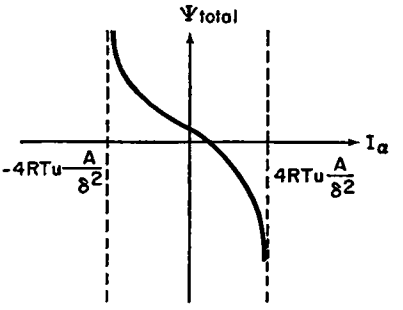

FIGURE 3 A qualitative plot of the steady state voltage-current characteristic of the active transport element of Fig. 1.

port element for an arbitrary choice of parameters. (The essential nature and shape of the curve are not dependent on the particular values of the parameters and would be the same even if A^- did not react with Na^+.) We therefore have confirmed our earlier qualitative prediction that the voltage-current characteristic would be highly non-linear. This non-linearity arises from the fact that both the resistance (R_{total}) and intrinsic emf ($E_a \equiv \pi - \Psi_D$) of the element are voltage (current)-dependent. The equivalent circuit for this element will therefore consist of an emf and resistance in series, both being voltage-dependent (see Fig. 4).

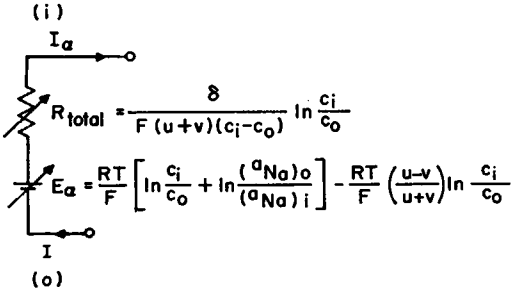

FIGURE 4 Equivalent circuit for the active transport element of Fig. 1. Note that both the resistance and the emf are voltage-dependent.

Turning to the fluxes, we have upon substituting equation (24*a*) into equations (18*a*) and (18*b*), and using equation (3):

$$\phi_{Na} = I_a - k_1 c_o^2 \tag{29a}$$

$$\phi_A = -k_1 c_o^2 \tag{29b}$$

$$\phi_{ANa} = k_1 c_o^2 \tag{29c}$$

where it should be remembered that c_o is a function of I_a as given by equation (24*d*). These equations are interesting in that they display the dependence of the individual fluxes on metabolism, as reflected in the rate constant k_1.

Let us finally return to the problem of the short circuit current when there are symmetrical solutions on the two sides of the membrane. Substituting equation (24*a*) into equation (19) we have on comparison with equation (29*c*):

$$(I_a)_{\psi_{total}=0} = k_1 c_o^2 = \phi_{ANa} \tag{30}$$

which we could also have obtained by comparing equations (21) and (29*c*). We see now explicitly the relationship between the short circuit current and metabolism, as evidence by the dependence of the short circuit current on k_1. With this we conclude our treatment of the isolated active transport element.

B. *Coupling of the Active Transport Element to Passive Elements*

In this part of the paper, we shall consider the consequences of placing various regions of specific (passive) permeability in parallel with our active element. Note that current, I_a, will flow through the active element even in the absence of an external pair of electrodes (that is, in the absence of net current flow across the membrane) because of local current loops between it and the passive regions. Since, however, the active element has no "knowledge" of how I_a is created, the equations of the previous sections will still be valid.

1. *Coupling to a Passive K Element.* The first situation we consider is that arising when a region exclusively permeable to K^+ is in parallel with the active transport element. It is obvious that for such a membrane, the equivalent circuit of Fig. 5 can be drawn, and that this circuit gives a physically realistic representation of the manner in which ions cross the membrane, namely, through local current flow

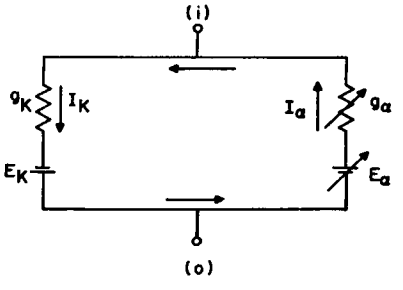

FIGURE 5 Equivalent circuit for a mosaic membrane consisting of some active transport regions of the type shown in Fig. 1 and other regions exclusively (passively) permeable to K^+.

(Finkelstein and Mauro, 1963). We note that the conductance and emf of the active region are voltage-dependent (see Fig. 4) while by assumption the conductance and emf of the passive region are constants. Thus:

$$E_K \equiv \frac{RT}{F} \ln \frac{(a_K)_o}{(a_K)_i} \tag{31a}$$

$$g_K \equiv a \text{ constant} \tag{31b}$$

$$E_\alpha \equiv \pi - \Psi_D = \frac{RT}{F}\left[\ln \frac{c_i}{c_o} + \ln \frac{(a_{Na})_o}{(a_{Na})_i}\right] - \frac{RT}{F}\left(\frac{u-v}{u+v}\right) \ln \frac{c_i}{c_o} \tag{32a}$$

$$g_\alpha \equiv \frac{1}{R_{total}} = \frac{[F(u+v)/\delta](c_i - c_o)}{\ln c_i/c_o} \tag{32b}$$

and from the circuit we obtain:

$$I \equiv I_K + I_\alpha \tag{33}$$

$$\Psi_{total} = E_K - I_K \frac{1}{g_K} = E_\alpha - I_\alpha \frac{1}{g_\alpha} = -I \frac{1}{g_K + g_\alpha} + \frac{g_K E_K + g_\alpha E_\alpha}{g_K + g_\alpha} \tag{34}$$

In the absence of net current flow,[9] we have from equation (33):

$$I_K = -I_\alpha \tag{35}$$

that is, the net flux of sodium from (o) to (i) equals the net flux of potassium from (i) to (o). Thus, for example, if initially the membrane separates identical solutions, with time the sodium (postassium) concentration will rise (fall) in (i) and fall (rise) in (o). When will this redistribution of ions cease? Clearly when,

$$I_K = -I_\alpha = 0 \tag{35a}$$

Substituting this into equation (34) we have:

$$\Psi_{total} = E_K = E_\alpha \tag{36}$$

Putting equation (31a) and (32a) into this we have:

$$\frac{(a_{Na})_i}{(a_{Na})_o} = [(c_i/c_o)^{2v/u+v}] \frac{(a_K)_i}{(a_K)_o} \tag{37}$$

Equation (37) gives the relationship between the "equilibrium"[10] ratio of sodium concentrations to the ratio of potassium concentrations. In a completely passive

[9] For the remainder of this paper we shall be treating the case of zero net current flow across the membrane.

[10] We use the term "equilibrium" because in this state, equation (35a) holds, and thus there is no dissipation of free energy due to current flow. It is not a true equilibrium, however, but rather a steady state, since in order to maintain this state free energy must be continually dissipated by the reactions in the active transport element. It is somewhat similar to what Conway (1957) calls the "balanced state."

system (no metabolic reactions) instead of equation (37) we would obviously have a true equilibrium system:

$$\frac{(a_{Na})_i}{(a_{Na})_o} = \frac{(a_K)_i}{(a_K)_o} = 1 \tag{38}$$

Now from equation (24*d*) we have:

$$c_o \to 0 \quad \text{as} \quad k_1 \to \infty$$

Thus we have from equation (37) that for large k_1,

$$\frac{(a_{Na})_i}{(a_{Na})_o} \gg \frac{(a_K)_i}{(a_K)_o}$$

which is quite different from the passive situation as reflected in equation (38).[11] In short, our model is capable of producing a large redistribution of ions.

Remarks. The relatively simple membrane represented by the circuit of Fig. 5 possesses several features which are rather instructive and which may also be of physiological relevance.

(*a*) *Electromotive feature of the system.* Suppose we have metabolically stopped the active transport (for example by anoxia) and allowed the system to run down until all ion concentrations are equal on the two sides of the membrane. If we now readmit oxygen so as to start the "pump" up again, there will be "immediately" seen a potential difference across the membrane resulting from the emf, E_a, associated with the "pump." The magnitude of this potential will of course be determined by the relative values of the conductances g_K and g_a. Note that this potential difference occurs before there is any significant change in ion concentrations from their anoxic values; it is in this sense that we mean "immediate."

To illustrate the above remarks, let us assume that in the run down anoxic state:

$$(a_{Na})_o = (a_{Na})_i = (a_K)_o = (a_K)_i$$

Then in the "equilibrium" state after recovery from anoxia (and for that matter at all times) we have:

$$(a_K)_o/(a_K)_i = (a_{Na})_i/(a_{Na})_o$$

Substituting this into equation (37) gives:

$$\ln (a_{Na})_o/(a_{Na})_i = -(v/u + v) \ln c_i/c_o$$

and putting this into equation (16) and remembering that $I_a = 0$ in the "equilibrium" state, we have:

$$(\Psi_{total})_{t=\infty} = \frac{RT}{F}\left[\frac{v}{u+v} \ln \frac{c_i}{c_o}\right] \qquad \text{potential at "equilibrium"} \tag{39}$$

[11] It should be remembered in using equation (37) that c_i and c_o are dependent on the parameters u and v. This does not alter our above remarks except for the limiting case in which $v = 0$ for this degenerate case there is no ionic redistribution.

where c_i and c_o are obtained from equations (24*a*) and (24*d*) with $I_a = 0$. On the other hand we have from equation (34) for the potential "immediately" following readmission of oxygen:

$$(\Psi_{\text{total}})_{t=0} = \frac{RT}{F}\left[\frac{F(c_i - c_o)(2v \ln c_i/c_o)}{g_K\delta \ln c_i/c_o + F(u+v)(c_i - c_o)}\right] \quad \text{"immediate" potential} \qquad (40)$$

where c_i and c_o are not the same as in equation (39), since if g_K is finite, I_a is not zero. For illustrative purposes, however, let us take $g_K \approx 0$; then equation (40) becomes:

$$(\Psi_{\text{total}})_{t=0} = \frac{RT}{F}\left[\frac{2v}{u+v} \ln c_i/c_o\right] \qquad \text{"immediate" potential for } g_K \approx 0 \qquad (40a)$$

where now c_i and c_o are the same as in equation (39). Comparing equations (40*a*) and (39), we see that the "immediate" potential is larger than the final "equilibrium" potential. Thus, our model is capable of displaying *postanoxic overshoot* (Lorente de Nó, 1947).

Furthermore, if we assume that g_K greatly increases upon recovery from anoxia,[12] then in the recovered state the membrane would behave as a potassium electrode. This would offer a possible reconciliation of the ionic theory of membrane potentials (Hodgkin, 1958) with the opposing view that the membrane potential results directly from metabolism (Lorente de Nó, 1947). Thus, it would account for the "immediate" recovery of the potential in frog nerve upon readmission of oxygen to a prolonged anoxic preparation (Lorente de Nó, 1947), and still be consistent with the fact that the "normal" nerve behaves very similarly to a potassium electrode (Huxley and Stämpfli, 1951).

(*b*) *Dependence of "pump" activity on* $(a_{Na})_o$. Because it is exclusively permeable to sodium, the activity of the isolated active transport element is independent of $(a_{Na})_o$; this is no longer so, however, when it is coupled to a passive element, as in the present system. For if $(a_{Na})_o$ is increased, I_a become more positive. This increases c_o and hence the rate of the reaction:

$$A^- + Na^+ \xrightarrow{k_1(ATP)} ANa$$

(See last paragraph in section A.3). Thus, increasing $(a_{Na})_o$ indirectly (through local currents) increases c_o and consequently the rate of metabolism. The same effect is produced by decreasing $(a_K)_o$. Our model, therefore, can explain the increased "pumping" action of nerve that follows tetanic stimulation (Connelly, 1959); that is, that follows an elevation of internal sodium (and decrease of internal potassium) concentration in the fiber. [Our side (*o*) corresponds to the inside of the fiber.]

(*c*) *On obligatory Na+—K+ coupling.* In the system represented by Fig. 5,

[12]The plasma membrane conductance of several biological systems is reversibly affected by metabolism (Blinks, 1955; Rehm *et al.*, 1962; Finkelstein, 1964).

there is a one-for-one exchange of sodium for potassium, while the carrier is only involved with sodium. Even if the membrane contained regions of exclusive permeability to other ions, this would still be essentially true provided $g_K \gg g_{\text{other ions}}$. We mention this in order to point out that the intimate coupling of Na^+ and K^+ fluxes observed in several biological systems is not, *by itself,* proof that Na^+ and K^+ are linked through a common carrier.

2. *Coupling to a Passive Na Element.* This system is identical with the one just discussed, except that the passive element is exclusively permeable to Na^+ instead of K^+. It is essentially a trivial situation, since analogous to equation (35):

$$I_{Na} = -I_\alpha \tag{41}$$

Thus the net flux of sodium through the passive branch is equal and opposite to the net flux of sodium through the active branch, resulting in no net flux across the membrane.

3. *Coupling to a Passive Cl^- Element.* In this system the passive region is exclusively permeable to an anion, Cl^-. The elements of the circuit are analogous to those in Fig. 5 except that:

$$E_{Cl} \equiv -\frac{RT}{F} \ln \frac{(a_{Cl})_o}{(a_{Cl})_i} \tag{42}$$

the minus sign arising because chloride is an anion. Once again the "equilibrium" condition will be characterized by:

$$\Psi_{\text{total}} = E_{Cl} = E_\alpha$$

$$I_{Cl} = -I_\alpha = 0$$

and analogous to equation (37) there is the "equilibrium" relation

$$\frac{(a_{Na})_i}{(a_{Na})_o} = [(c_i/c_o)^{2\nu/u+v}] \frac{(a_{Cl})_o}{(a_{Cl})_i} \tag{43}$$

The membrane "pumps" NaCl from solution (o) to solution (i) until equation (43) is satisfied; at this point "equilibrium" is reached, and the continued activity of the "pump" maintains this situation.

Although we have refrained throughout this paper from considerations of water movement, it is perhaps interesting to note that along with the movement of NaCl from (o) to (i) there will be net transport of water in the same direction (even before there is any significant change in NaCl concentration) due to electroosmosis in the active and passive regions. The movement of water along with salt is well known in biological secretory systems (Curran and Solomon, 1957; Diamond, 1962).

4. *Coupling to Several Elements.* For the sake of concreteness we shall take the case when the active region is in parallel with the three passive regions

considered above. Without going through the complete circuit analysis, it is clear that in the final steady state:

$$I_K = I_{Cl} = 0 \tag{43a}$$

$$I_{Na} = -I_\alpha \tag{43b}$$

$$\Psi_{total} = E_K = E_{Cl} \tag{43c}$$

If $g_K \gg g_{Cl}$, then starting from symmetrical solutions across the membrane, this final steady state is reached as follows: Initially there will be a one-for-one exchange of Na for K until:

$$\Psi_{total} \approx E_K$$

Then along with the K exchange for Na, Cl^-, will move with Na^+ until finally equation (43*c*) is satisfied. Thus, at first the system behaves as if Na^+ and K^+ are obligatorily coupled, but later it is seen that both K^+ and Cl^- are redistributing.

It should be noted that, in general, equation (43*c*) is not satisfied by most biological systems. For example, in the squid axon, although the ion being "pumped" is presumably Na^+, Cl^- is *not* in electrochemical equilibrium across the membrane (Mauro, 1953; Keynes, 1963) as is demanded by equation (43*c*), nor is K^+, although it is not too far off. This must mean either that these systems never are in a true steady state, or that each of the ions not in electrochemical equilibrium is actively transported (Keynes, 1963; Hodgkin and Keynes, 1955).

C. *Concluding Remarks*

In this paper we have discussed in some detail the significant properties of a particular carrier model for active transport.[13] Our main aim, as we stated previously, has been to demonstrate how many of the attributes (and the terms used to describe them) of biological ionic active transport are realized *explicitly* in a well-defined carrier model. To this end we have dwelt on such topics as the dependence of active transport rate (and hence, metabolic rate) on solution concentrations, the nature of the "short circuit" current, the concept of "obligatory coupling" of ion fluxes, the meaning and implication of an "electrogenic pump," etc., and have shown what these involve in a particular model system. We hope that in so doing we have helped to clarify for physiologists some of the problems of active transport, and that this study will serve to stimulate further thought and analysis of both hypothetical models and actual biological systems.

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[13] We have not discussed the important phenomenon of tracer fluxes; this subject will be treated in a separate communication.

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