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Ion Transport and Displacement Currents with Membrane-Bound Carriers:

The Theory for Voltage-Clamp Currents, Charge-Pulse Transients and Admittance for Symmetrical Systems

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Summary. The standard carrier model for ion transport by a one-to-one mechanism is developed to predict the time-dependent currents for systems that are symmetrical at zero applied potential. The complete solution for ions and carriers bearing any charge is derived by assuming that the concentration of ions in the membrane is low and either that the applied potential is small or that the applied potential affects equally all of the association and dissociation reactions between the ions and the carriers. The response to an abruptly applied potential is then given by the sum of a constant and two declining exponential terms. The time constants of these relaxations are described by the equations derived for neutral carriers by Stark, Ketterer, Benz and Läuger in 1971 (*Biophys. J.* **11**:981). The sum of the amplitudes of the exponentials for small applied potentials obeys a relation like that first derived by Markin and Liberman in 1973 (*Biofizika* **18**:453). For small applied potentials expressions are also provided for the voltage transients in charge-pulse experiments and for the membrane admittance.

In the simplest version of the model, a carrier transports a substrate by binding it on one side of the membrane and crossing to the other side where the substrate is released. The carrier is then free either to pick up another passenger or to return to the original side. The model can be taken literally as in its application to the ion carriers, valinomycin and trinactin, or formally as when it is used to describe Patlak's (1957) variable conformation pore. It is assumed in either case that the carriers spend most of the time in just four states, i.e., adsorbed on one side or the other of the membrane either free or complexed, with the negligible remaining time spent in the transitions between these states. The rate of each of the transitions is proportional to the concentration of carriers in

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the original state, independent of the concentration in the final state, and dependent in some manner on the applied potential.

The equations that describe this carrier model have already been solved for the steady-state current when only one type of ion is present that can use the carrier (Hladky, 1972; Stark, 1973). However, a comparably general solution is not available when the currents vary with time. The principal purpose of this paper is to provide a solution for transients which is valid over a wide range of carried ion concentrations and which allows for the effects of the applied potential on the rates of all the steps in the transport cycle. As Markin and Lieberman (1973) and Ciani (1976) have also seen, when the applied potential is small, the solution for a symmetrical system can be obtained by expressing the concentrations of the carriers and complexes as power series in the potential. For sufficiently small potentials, the fluxes and hence the current may be calculated from the first-order terms in these series. The resulting expression for the time-dependent current in a voltage clamp is easily converted into a solution for the admittance of the membrane.

The Model and the Current in the External Circuit

The model, described in Fig. 1, has been discussed in many reviews (e.g., Haydon & Hladky, 1972; Ovchinnikov, Ivanov & Shkrob, 1974; Eisenman *et al.*, 1973; Markin & Chizmadzhev, 1974; Le Fevre, 1975; McLaughlin & Eisenberg, 1975; and Hladky, 1979). Any step in the cycle can transfer charge part of the way across the membrane. Even the transfer of a neutral carrier or complex across the membrane can entail the rotation of its own dipole moment and of dipoles in the membrane material, thus producing a charge displacement. It is therefore convenient to adopt a symbol for the amount of charge which moves in the external circuit as a result of each of the transitions which can occur. Thus at constant applied potential, transfer of a complex from left to right moves γ charges through the external circuit, transfer of a free carrier moves ψ charges, formation of a complex on the left moves ξ' charges, and dissociation of a complex on the right moves ξ'' charges. Since one complete cycle of the carrier system transfers one ion with charge z_i across the entire membrane, z_i charges move through the external circuit and

$$\gamma - \psi + \xi' + \xi'' = z_i. \tag{1}$$

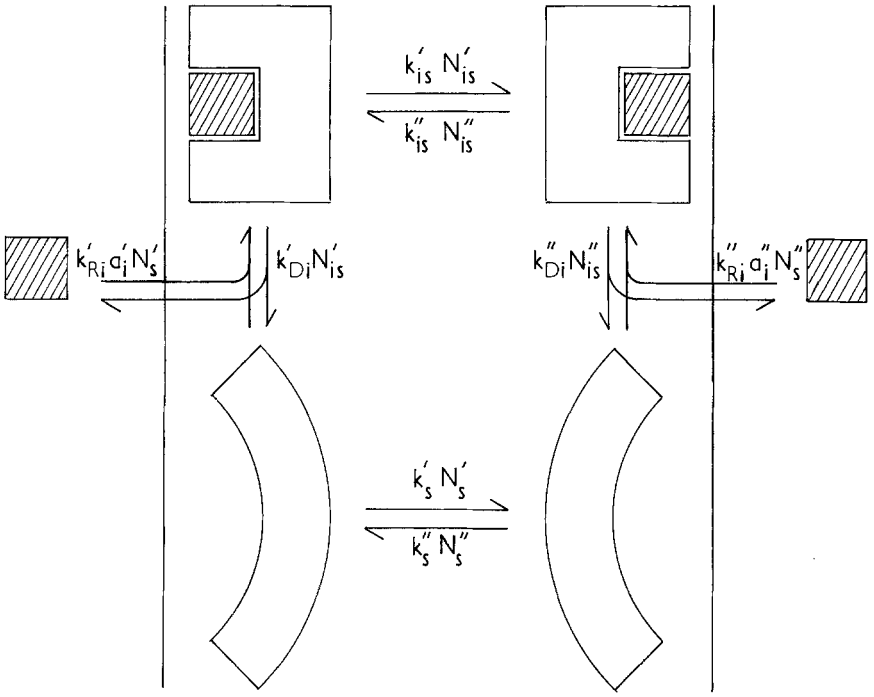

Fig. 1. The kinetic scheme for the standard carrier model. Adsorbed ion carrier complexes are present on either side of the membrane at surface concentrations N'_{is} and N''_{is}, respectively. These can cross the membrane (or undergo a conformation change exposing the binding site to the opposite solution) or dissociate, releasing the ion into solution. The free carriers present at surface concentrations N'_s and N''_s, may cross the membrane (or undergo a conformation change exposing the binding site to the opposite solution) or recombine with ions to form complexes. The rate constants, the k's, depend on the applied potential but at constant potential not on either the concentrations or the current

If the carrier molecules are small, are adsorbed near the surfaces, and produce only a small perturbation of the membrane, ξ' and ξ'' will be small, while the values of γ and ψ will be almost equal to the charges of the complex and free carrier, respectively. If, instead, the carrier spans the membrane and undergoes weakly potential-dependent conformation changes which expose its site to one solution or the other, then γ and ψ will be small and $\xi'+\xi''$ will be almost equal to z_i. At any instant the total current in the external circuit is the sum of the current in the absence of any of these transitions plus all the currents which flow as a consequence of the transitions. Thus the current per unit area of membrane may be written

$$I = -C\frac{d\Delta V}{dt} + F[\xi' J'_i + \xi'' J''_i + \gamma J_{is} + \psi J_s]. \tag{2}$$

In this equation, F is the Faraday, C is the capacitance per unit area of the membrane, strictly with the carriers present but not undergoing transitions, ΔV is the potential difference across the membrane,

$$J_i' = k_R' a' N_s' - k_D' N_{is}' \tag{3}$$

is the net rate of formation of complexes on the left as moles per unit area per unit time;

$$J_i'' = k_D'' N_{is}'' - k_R'' a'' N_s'' \tag{4}$$

is the net rate of dissociation on the right;

$$J_{is} = k_{is}' N_{is}' - k_{is}'' N_{is}'' \tag{5}$$

is the net rate of transfer of complexes from left to right; and

$$J_s = k_s' N_s' - k_s'' N_s'' \tag{6}$$

is the net rate of transfer of free carriers from left to right.

In order to obtain a solution for the current, it is necessary to determine how the concentrations of the carriers and complexes change with time. So long as each individual experiment can be conducted at constant total concentration of adsorbed carrier N_T (i.e., the carrier is effectively membrane bound)

$$N_s' + N_s'' + N_{is}' + N_{is}'' = N_T \tag{7}$$

during the experiment, and the basic equations may be written

$$\begin{aligned} \frac{dN_{is}'}{dt} &= J_i' - J_{is} \\ \frac{dN_{is}''}{dt} &= J_{is} - J_i'' \\ \frac{dN_s'}{dt} &= -J_i' - J_s \end{aligned} \tag{8}$$

and

$$\frac{dN_s''}{dt} = J_s + J_i''.$$

The mathematical model is defined by Eqs. (1)–(8), which specify how the various fluxes and the current depend both on the explicitly stated concentrations of carried ions, carriers, and complexes and on the applied potential, which is stated implicitly in the values of the rate

constants k', k'', etc.[1] Markin and Liberman (1973), using a smeared charge model, have considered variations in the rate constants caused by changes in the concentration of charged carriers and complexes in the membrane. However, the increase in the range of concentrations adequately covered by the theory is not great (Andersen *et al.*, 1978; Hladky & Tsien, 1979; *see also Appendix A*) and for present purposes does not justify the required increase in the complexity of the model.

Relations between the Constants and the Applied Potential

There are several relations between the rate constants and the potential which can be derived from the predictions of the model when the current is zero in a gradient of a single species of permeant ion. Since all the net fluxes are then zero, each reaction and its reverse occur at the same rate, e.g., $k'_R a' N'_s = k'_D N'_{is}$, which implies under these particular conditions that

$$k'_R k'_{is} k''_D k''_s / k''_R k''_{is} k'_D k'_s = a''/a'. \tag{9}$$

The value of the potential for which Eq. (9) is satisfied is specified by the Nernst equation

$$a''/a' = e^{-z_i \Delta\phi} \tag{10}$$

where

$$\Delta\phi = F \Delta V / RT, \tag{11}$$

R is the gas constant and T is the absolute temperature. Since Eqs. (9) and (10) hold for arbitrary activity ratios and hence arbitrary zero-current potentials and in the model as it is treated here all of the constants are independent of the concentrations and currents,

$$k'_R k'_{is} k''_D k''_s / (k''_R k''_{is} k'_D k'_s) = e^{-z_i \Delta\phi} \tag{12}$$

holds for all applied potentials regardless of whether the current is zero or not (*cf.* Hodgkin & Huxley, 1952). For high concentrations of the adsorbed ions *(see Appendix A)* where the rate constants are no longer independent of the concentrations, this relation must hold when the current is zero, but not necessarily otherwise.

The Nernst equation (10) is a special case of the general equation for equilibrium, as is also

[1] These "rate" constants simply state the assumed proportionalities between fluxes and concentrations. Their use does not imply acceptance of any particular theory for how they vary with the applied potential

$$\frac{N''_{is}}{N'_{is}} = e^{-\Delta G^*/RT} \tag{13}$$

where ΔG^* is the standard Gibb's free energy of transfer of a mole of complexes from left to right. This free energy is equal to the work done by the external circuit (e.g., the voltage clamp), $\gamma F \Delta V$, when a mole of complexes is transferred from one side of the membrane to the other. Thus by the reasoning used to derive Eq. (12),

$$k'_{is}/k''_{is} = e^{-\gamma \Delta\phi} \tag{14}$$

$$k'_s/k''_s = e^{-\psi \Delta\phi} \tag{15}$$

$$k'_R(\Delta\phi)/k'_D(\Delta\phi) = [k'_R(o)/k'_D(o)]\, e^{-\xi' \Delta\phi} \tag{16}$$

and

$$k''_R(\Delta\phi)/k''_D(\Delta\phi) = [k''_R(o)/k''_D(o)]\, e^{+\xi'' \Delta\phi}. \tag{17}$$

From Eqs. (2), (12) and (14)–(17),

$$\frac{k'_R(o)\, k'_{is}(o)\, k''_s(o)\, k''_D(o)}{k''_R(o)\, k''_{is}(o)\, k'_s(o)\, k'_D(o)} = 1. \tag{18}$$

Comments on a General Solution

When the current and concentrations are constant, $J'_i = J_{is} = J''_i = -J_s$ and the current is just $I = z_i F J_{is}$. The steady-state solution for J_{is} from Eqs. (3)–(8) for arbitrary concentrations and applied potentials regardless of symmetry has been given previously (Hladky, 1972, Eq. (87); Stark, 1973). The general solution to Eqs. (1)–(8), (12) and (14)–(17) for a voltage-clamp experiment could be derived by standard means. Since there are three independent time variables, the current at any potential can be expressed as

$$I = I_\infty (1 + \alpha_1 e^{-\lambda_1 t} + \alpha_2 e^{-\lambda_2 t} + \alpha_3 e^{-\lambda_3 t}) \tag{19}$$

The theory specifies the seven functions of the potential and the concentrations in Eq. (19) in terms of four rate "constants", $k'_R(\Delta\phi)$, $k'_{is}(\Delta\phi)$, $k''_R(\Delta\phi)$, $k'_s(\Delta\phi)$, and seven true constants,[2] $k'_D(o)$, $k''_{is}(o)$, $k'_s(o)$, ξ', γ, ψ, and N_s, all of which must be determined from the data. Thus, unless the

[2] There is no guarantee that ξ', γ and ψ are constants independent of the applied potential. This complication does not occur in the limit of small applied potentials considered in later sections. It is ignored in all that follows

model can be simplified *a priori*, it will be necessary to resort to numerical curve fitting procedures to extract the rate "constants" from the data. Since such analysis is possible starting from the simple linear differential equations (7), there is little point in producing the complex general algebraic solution.

Carrier Systems Symmetrical at Zero Applied Potential

A dramatic simplification in the solution occurs when the system is symmetrical. It is then possible for small applied potentials to obtain the solution in a compact form without making any further assumptions. Of course, less information is available if the only data analyzed are obtained when the system is symmetrical and linear in the applied potential. In particular, there is then no way in which to determine the potential dependence of the individual rate constants. However, the information which is still contained in the data is more accessible.

If the system is symmetrical at zero applied potential, then when the applied potential is zero $k'_{Ri}=k'_{Ri}=k_{Ri}$, $k'_{is}=k''_{is}=k_{is}$, $\xi'=\xi''=\xi$, etc., where the omission of the superscript on a concentration or rate constant is used to designate this value. For other applied potentials it is useful for each pair of functions of the potential such as k'_{Ri} and k''_{Ri} to define a new pair such that one, k^*_R, expresses the common variation of k'_R and k''_R with potential while the other, δ_R, expresses the difference. Thus

$$\begin{aligned} k^*_R &= (k'_R+k''_R)/2 \quad \text{and} \quad \delta_R=(k'_R-k''_R)/2; \\ k^*_D &= (k'_D+k''_D)/2 \quad \text{and} \quad \delta_D=(k'_D-k''_D)/2; \\ k^*_{is} &= (k'_{is}+k''_{is})/2 \quad \text{and} \quad \delta_{is}=(k'_{is}-k''_{is})/2; \end{aligned} \tag{20}$$

and

$$k^*_s=(k'_s+k''_s)/2 \quad \text{and} \quad \delta_s=(k'_s-k''_s)/2.$$

Defining further

$$K^*=(k'_R/k'_D+k''_R/k''_D)/2 \quad \text{and} \quad \delta_K=(k'_R/k'_D-k''_R/k''_D)/2 \tag{21}$$

it follows that

$$k^*_R=K^*k^*_D+\delta_K\delta_D \tag{22}$$

and

$$\delta_R-\delta_D K^*=\delta_K k^*_D. \tag{23}$$

From these equations, Eq. (12) and Eqs. (14)–(17), K^*, δ_K, δ_{is}/k_{is}^* and δ_s/k_s^* may be expressed in terms of the applied potential as

$$K^* = K\cosh(\xi\Delta\phi) \simeq K(1+\xi^2\Delta\phi^2/2+\ldots) \tag{24}$$

$$\delta_K = -K\sinh(\xi\Delta\phi) \simeq -K(\xi\Delta\phi+\ldots) \tag{25}$$

$$\delta_{is}/k_{is}^* = -\tanh(\gamma\Delta\phi/2) \simeq -\gamma\Delta\phi/2+\ldots \tag{26}$$

and

$$\delta_s/k_s^* = -\tanh(\psi\Delta\phi/2) \simeq -\psi\Delta\phi/2+\ldots \tag{27}$$

Since the starred functions are all symmetrical in $\Delta\phi$, their series expansions do not contain a linear term and as $\Delta\phi$ approaches zero they may be replaced by their limiting values.

The changes in the surface concentrations are defined by

$$\begin{aligned} \Delta'_{is} &= N'_{is} - N_{is}, \qquad \Delta''_{is} = N''_{is} - N_{is}, \\ \Delta'_s &= N'_s - N_s, \quad \text{and} \quad \Delta''_s = N''_s - N_s. \end{aligned} \tag{28}$$

Using these relations and Eqs. (2)–(7)

$$\begin{aligned} d(\Delta'_s+\Delta''_s)/dt = &-(k_D^*+k_R^* a)(\Delta'_s+\Delta''_s)+\delta_R a(\Delta''_s-\Delta'_s) \\ &+\delta_D(\Delta'_{is}-\Delta''_{is})+2k_D^*(K-K^*)aN_s-2\delta_K\delta_D N_s a. \end{aligned} \tag{29}$$

Whenever the applied field affects the association-dissociation reactions equally on the two sides of the membrane ($\delta_R=\delta_D=0$, $K^*=K$) and $a'=a''$, Eq. (29) becomes

$$d(\Delta'_s+\Delta''_s)/dt = -k_D^*(1+Ka)(\Delta'_s+\Delta''_s) \tag{30}$$

which has the trivial solution

$$\Delta'_s+\Delta''_s = 0 = \Delta'_{is}+\Delta''_{is} \tag{31}$$

for all applied potentials regardless of the values of k_s^*, k_{is}^*, k_D^*, δ_s and δ_{is}.

In general, as $\Delta\phi$ approaches zero the terms in Eq. (29), which include the factors $K-K^*$, $\delta_K\delta_D$, $\delta_R(\Delta''_s-\Delta'_s)$, and $\delta_D(\Delta'_{is}-\Delta''_{is})$, all approach zero at least as fast as $\Delta\phi^2$. Thus Eq. (30) and its solution Eq. (31) still apply. In other words, for a system symmetrical at $\Delta\phi=0$, the first order terms in the series expansions of $N'_{is}+N''_{is}$ and $N'_s+N''_s$ are zero and as stated by Markin and Liberman (1973), for small $\Delta\phi$, $N'_{is}+N''_{is}$ and $N'_s+N''_s$ are each constant. Thus for symmetrical starting conditions and either $\delta_R=\delta_D=K^*-K=0$ or small $\Delta\phi$, there are only two independent variables which can change with time. These can be chosen as N'_{is} and N'_s or

equivalently as Δ'_{is} and Δ'_s. It then follows that there are only two exponential terms in the time-dependent solutions for the surface concentrations and the observable current.[3]

The Steady-State

For small applied potentials, the steady-state current is described by the well-known expression (Markin *et al.*, 1969; Läuger & Stark, 1970; Hladky, 1972; Ciani *et al.*, 1975):

$$I_\infty = -z_i^2 F \Delta\phi\, 2N_s k_R a k_{is} k_s/(2k_D k_s + 4k_s k_{is} + 2k_R a k_{is}). \tag{32}$$

Alternatively, if $\delta_R = \delta_D = K^* - K = 0$, then the solution for all applied potentials is [*compare* Markin, 1972, Eq. (1)],

$$I_\infty = z_i F\, 4N_s k_R a(k_s^* \delta_{is} - k_{is}^* \delta_s)/(2k_s^* k_D^* + 4k_s^* k_{is}^* + 2k_R^* a k_{is}^*). \tag{33}$$

Initial Current in a Voltage Clamp

At $t = 0^+$ just after the abrupt application of a potential, none of the concentrations have had time to change. Thus

$$N'_s = N''_s = N_s \tag{34}$$

and

$$N'_{is} = N''_{is} = N_{is} = (k_R a/k_D) N_s.$$

From Eqs. (1)–(5) the external current is then

$$I_o = 2FN_s\{\xi[\delta_R - K\delta_D]a + \gamma K a \delta_{is} + \psi\delta_s\} \tag{35}$$

which can be rewritten for small potentials using Eqs. (24)–(27) as

$$I_o = -F\Delta\phi N_s\{2k_R a\xi^2 + (k_R a k_{is}/k_D)\gamma^2 + k_s\psi^2\}. \tag{36}$$

If it is assumed that

$$\gamma/\psi = z_{is}/z_s \tag{37}$$

[3] There are other conditions in which there are only two independent variables. Thus for $k'_s = k'_{is} = rk''_s = rk''_{is} = b$ where r and b are constants, $N'_s + N'_{is}$ is constant. From Eq. (12) $K' = K'' e^{-z_i \Delta\phi}$ and the binding constants on the left and right at zero potential must be the same. They can, however, be affected to different extents by the applied potential. Physically, this special case could correspond to a large "carrier" enclosing a fixed internal site which can be exposed to either side by conformational changes which do not depend on the applied field.

where z_{is} is the charge of the complex and z_s is the charge of the free carrier, then

$$\gamma = z_{is}(1-2\xi/z_i) \tag{38}$$

and Eq. (36) is equivalent to Eq. (20) of Markin and Liberman (1973), restricted to low concentrations of adsorbed ions.

It is often convenient experimentally to measure currents relative to an internal standard, usually the steady-state current. For small applied potentials

$$\frac{I_o}{I_\infty} = \frac{(k_D k_s + 2k_s k_{is} + k_R a k_{is})(2k_R a k_D \xi^2 + k_R a k_{is} \gamma^2 + k_s k_D \psi^2)}{z_i^2 k_R a k_{is} k_D k_s}. \tag{39}$$

Thus the ratio of the currents approaches ∞ as the ion activity approaches zero, as it must, since I_∞ then approaches zero while I_o includes a finite term due to transfer of the free carrier. The ratio goes through a minimum for some finite activity, then approaches infinity again as the ion activity becomes infinite.

For $\delta_R = \delta_D = \mathrm{K}^* - \mathrm{K} = 0$ and any $\Delta\phi$,

$$I_o = 2FN_s[\gamma K a \delta_{is} + \psi \delta_s] \tag{40}$$

and

$$\frac{I_o}{I_\infty} = \frac{(k_D^* k_s^* + 2k_s^* k_{is}^* + k_R^* a k_{is}^*)(\gamma k_R^* a \delta_{is} + \psi k_D^* \delta_s)}{z_i k_R^* a k_D^* (k_s^* \delta_{is} - k_{is}^* \delta_s)}. \tag{41}$$

The Relaxation Time Constants

Whenever $N_s' + N_s''$ is constant, the solution for the changes in the concentrations will take the form

$$\Delta_{is}' = {}^\infty\Delta_{is} + {}^1\Delta_{is} e^{-\lambda_1 t} + {}^2\Delta_{is} e^{-\lambda_2 t}$$

and

$$\Delta_s' = {}^\infty\Delta_s + {}^1\Delta_s e^{-\lambda_1 t} + {}^2\Delta_s e^{-\lambda_2 t}. \tag{42}$$

The fluxes can be expressed in terms of these changes using Eqs. (3)–(6) and thus

$$I = I_\infty + I_1 e^{-\lambda_1 t} + I_2 e^{-\lambda_2 t}. \tag{43}$$

For $\delta_R = \delta_D = \mathrm{K}^* - K = 0$ and arbitrary $\Delta\phi$, Eq. (8) can be rewritten as

$$d\Delta_{is}'/dt = k_R^* a \Delta_s' - (k_D^* + 2k_{is}^*)\Delta_{is}' - 2\delta_{is} K^* a N_s$$

and

$$d\Delta_s'/dt = k_D^* \Delta_{is}' - (k_R^* a + 2k_s^*)\Delta_s' - 2\delta_s N_s \tag{44}$$

while if only the first order terms in $\Delta\phi$ are considered

$$d\Delta'_{is}/dt = k_R a \Delta'_s - (k_D + 2k_{is})\Delta'_{is} + (\delta_K k_D a - 2\delta_{is} K a) N_s$$

and (45)

$$d\Delta'_s/dt = k_D \Delta'_{is} - (k_R a + 2k_s)\Delta'_s - (\delta_K k_D a + 2\delta_s) N_s.$$

The time-dependent terms in both Eqs. (44) and (45) are the same as those in Eqs. (A-10) and (A-11) in Hladky (1975), and thus for either set the two reciprocal time constants are given by the expressions originally provided by Stark *et al.* (1971):

$$\lambda_1 = 1/\tau_1 = A - B$$

and

$$\lambda_2 = 1/\tau_2 = A + B$$

where (46)

$$2A = 2k_s^* + k_R^* a + 2k_{is}^* + k_D^*$$

and

$$2B = \{(2k_{is}^* + k_D^* - 2k_s^* - k_R^* a)^2 + 4k_R^* a k_D^*\}^{\frac{1}{2}}.$$

Another relation useful in later calculations is

$$\lambda_1 \lambda_2 = 2k_s^* k_D^* + 4k_s^* k_{is}^* + 2k_{is}^* k_R^* a. \tag{47}$$

Thus for either $\delta_R = \delta_D = \mathrm{K}^* - \mathrm{K} = 0$ or small applied potentials, and symmetrical initial conditions, the reciprocal time constants depend on the rate constants in the manner stated above regardless of the charges of the carrier and complex.

The Relaxation Amplitudes

Since the objective of the derivation is to obtain expressions for the current, it is useful to express the various amplitudes in terms of the steady-state flux, J_∞. At time $t = 0^+$ the concentrations have not had time to change and thus from Eq. (42)

$$-{}^\infty\Delta_{is} = {}^1\Delta_{is} + {}^2\Delta_{is}$$

and (48)

$$-{}^\infty\Delta_s = {}^1\Delta_s + {}^2\Delta_s.$$

From Eqs. (6), (20) and (28),

$$J_\infty = -J_s^\infty = -2k_s^* {}^\infty\Delta_s - 2\delta_s N_s. \tag{49}$$

For small applied potentials this equation with Eqs. (27), (32) and (47), implies that

$$^1\Delta_s + {}^2\Delta_s = (J_\infty/2k_s)\,[1+\psi\lambda_1\lambda_2/(2z_i k_R a k_{is})]. \tag{50}$$

Similarly from Eq. (5),

$$J_\infty = J_{is}^\infty = 2k_{is}\,{}^\infty\Delta_{is} + 2\delta_{is}N_{is} \tag{51}$$

and

$$^1\Delta_{is} + {}^2\Delta_{is} = -(J_\infty/2k_{is})\,[1-\gamma\lambda_1\lambda_2/(2z_i k_D k_s)]. \tag{52}$$

The equations to be solved for the first-order terms are thus Eqs. (50), (52) and, from Eq. (44),

$$-\lambda_1\,{}^1\Delta_{is} = k_R a\,{}^1\Delta_s - (k_D + 2k_{is})\,{}^1\Delta_{is} \tag{53}$$

and

$$-\lambda_2\,{}^2\Delta_{is} = k_R a\,{}^2\Delta_s - (k_D + 2k_{is})\,{}^2\Delta_{is}. \tag{54}$$

After straightforward algebra, the solutions are

$$^1\Delta_{is} = \frac{\lambda_2 J_\infty}{\lambda_2-\lambda_1}\left\{\frac{2\xi}{z_i}\frac{\lambda_1-2k_s}{4k_s k_{is}} + \frac{\psi}{z_i}\frac{1}{2k_{is}} + \frac{\gamma}{z_i}\frac{k_R a + 2k_s - \lambda_1}{2k_s k_D}\right\} \tag{55}$$

and

$$^2\Delta_{is} = \frac{\lambda_1 J_\infty}{\lambda_2-\lambda_1}\left\{\frac{2\xi}{z_i}\frac{2k_s-\lambda_s}{4k_s k_{is}} - \frac{\psi}{z_i}\frac{1}{2k_{is}} + \frac{\gamma}{z_i}\frac{\lambda_2 - k_R a - 2k_s}{2k_s k_D}\right\}. \tag{56}$$

For $\delta_R = \delta_D = K^* - K = 0$ and any $\Delta\phi$, similar algebra leads to

$$^1\Delta_{is} = \frac{\lambda_2 J_\infty}{\lambda_2-\lambda_1}\left\{\frac{k_D^*\delta_s + (k_R^* a + 2k_s^* - \lambda_1)\,\delta_{is}}{2k_D^*(k_s^*\delta_{is} - k_{is}^*\delta_s)}\right\} \tag{57}$$

and

$$^2\Delta_{is} = \frac{\lambda_1 J_\infty}{\lambda_2-\lambda_1}\left\{\frac{-k_D^*\delta_s + (\lambda_2 - k_R^* a - 2k_s^*)\delta_{is}}{2k_D^*(k_s^*\delta_{is} - k_{is}^*\delta_s)}\right\}. \tag{58}$$

Under either set of conditions, the current components in Eq. (43) can be expressed in terms of the concentration changes by using Eqs. (1)–(6), (53) and (54)

$$I_1 = F\left[\gamma\,2k_{is}^* + 2\xi(2k_{is}^* - \lambda_1) + \psi\frac{2k_s^*(k_D^* + 2k_{is}^* - \lambda_1)}{k_R^* a}\right]{}^1\Delta_{is} \tag{59}$$

and

$$I_2 = F\left[\gamma\,2k_{is}^* + 2\xi(2k_{is}^* - \lambda_2) + \psi\frac{2k_s^*(k_D^* + 2k_{is}^* - \lambda_2)}{k_R^* a}\right]{}^2\Delta_{is}. \tag{60}$$

Equation (43) with the expressions for I_∞ [Eq. (32)], I_1 [Eqs. (59) and (55)], I_2 [Eqs. (60) and (56)] and the reciprocal time constants λ_1 and λ_2 [Eq. (46)] contains the complete solution for the time-dependent currents for a carrier system, provided the applied potential is small, the concentration of adsorbed ions is low *(see Appendix A)*, and the system is symmetrical at zero applied potential.

The theory for small transients in systems symmetric at $\Delta\phi=0$ thus connects the five experimentally determined functions of concentration I_∞, $\alpha_1=I_1/I_\infty$, $\alpha_2=I_2/I_\infty$, λ_1 and λ_2 with seven true constants, k_{is}, k_s, k_R, k_D, γ, ψ and N_s.

The Equivalent Circuit and the Membrane Admittance

The response [Eq. (43)] to a step change in potential for an initially symmetrical system is the same as that obtained from the equivalent circuit shown in Fig. 2. The small signal admittance of the membrane

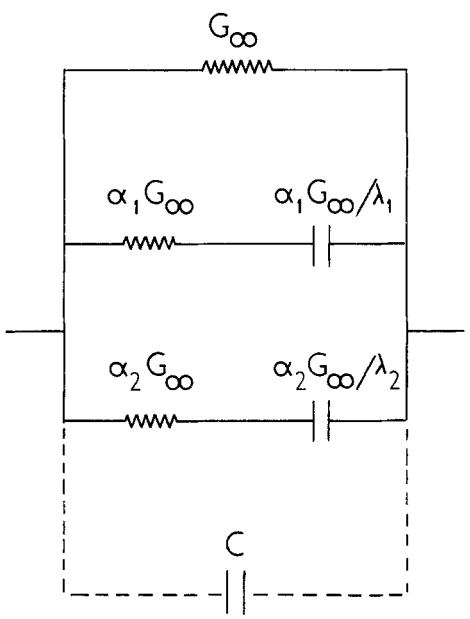

Fig. 2. The equivalent circuit for the small signal response of a carrier system symmetric at zero applied potential is shown by the elements connected with solid lines. The electrical connection with the capacitance of the bare membrane is shown by the dotted lines. G_∞ is the steady-state conductance, C the bare membrane capacitance, λ_1 and λ_2 are the reciprocal time constants seen in voltage-clamp experiments, and α_1 and α_2 are the respective relaxation amplitudes

with carrier, $Y(\omega)$, may be calculated from this equivalent circuit or with less effort from the transfer function for the carrier system

$$\Phi(s) = -L[I(t)]/L[V(t)] = -I(s)/V(s) \tag{61}$$

where $L[\ ]$ denotes a Laplace transform (Bracewell, 1965). (The minus sign enters as a result of the conventions that V increases to the right and positive current flows towards the right.)

After defining $G_\infty = -I_\infty/\Delta V$, it follows by standard procedures that

$$\Phi(s) = G_\infty[1 + \alpha_1 s/(\lambda_1 + s) + \alpha_2 s/(\lambda_2 + s)] \tag{62}$$

and

$$\begin{aligned} Y(\omega) = \Phi(\mathrm{j}\omega) + \mathrm{j}\omega C &= G_\infty \left[1 + \frac{\alpha_1 \omega^2}{\lambda_1^2 + \omega^2} + \frac{\alpha_2 \omega^2}{\lambda_2^2 + \omega^2}\right] \\ &+ \mathrm{j}\omega \left[C + G_\infty \left(\frac{\alpha_1 \lambda_1}{\lambda_1^2 + \omega^2} + \frac{\alpha_2 \lambda_2}{\lambda_2^2 + \omega^2}\right)\right]. \end{aligned} \tag{63}$$

Thus the low frequency conductance is just the steady-state conductance, the low frequency capacitance is the membrane capacitance plus the total charge transferred in the transient per unit voltage, the high frequency capacitance is the membrane capacitance, and the high frequency conductance equals the initial conductance. If a complete dispersion curve can be measured, then the four voltage clamp constants and the steady-state conductance are obtainable from the locations of the two dispersions, centered at $\omega = \lambda_1$ and $\omega = \lambda_2$, their amplitudes, and either the low or high frequency conductance.

Explicit expressions in terms of the rate constants have been given by Aityan, Markin & Chizmadzhev (1973) for the low and high frequency limits of $Y(\omega)$ whenever either ψ or λ is equal to zero. The complete function $Y(\omega)$ has been given by Markin & Chizmadzhev (1974) whenever $\xi = 0$ and either ψ or γ equals zero.[4]

Charge Pulse Transients

In a charge pulse experiment, the membrane is rapidly charged to an initial voltage, $V_o = Q/C$, the external charging circuit is replaced by a voltage measuring circuit, and the subsequent decay is monitored as the charge is conducted across the membrane. While the analysis of such

[4] In Eq. (3.30) of Markin & Chizmadzhev (1974) the v_T which multiplies $(i\omega\lambda + k_4 + 2v_L)$ and the v_L which multiplies $(i\omega\lambda + k_3 A + 2v_T)$ should be squared.

transients is more complicated than that for voltage-clamp experiments, this technique allows considerably faster transients to be measured. Benz and Läuger (1976) have derived equations for neutral carriers, low applied potentials, symmetrical initial conditions, and only k'_{is} and k''_{is} voltage dependent which allow the rate constants to be calculated from the values of the amplitudes and time constants obtained by fitting

$$V(t)=V_o[a_1\,e^{-\varepsilon_1 t}+a_2\,e^{-\varepsilon_2 t}+a_3\,e^{-\varepsilon_3 t}] \tag{64}$$

to experimental data.

For carriers charged or uncharged, symmetrical initial conditions and small charge pulses, the voltage *vs.* time will in general show three declining exponentials and thus the Laplace transform will be

$$V(s)=V_o\left[\frac{a_1}{s+\varepsilon_1}+\frac{a_2}{s+\varepsilon_2}+\frac{a_3}{s+\varepsilon_3}\right]. \tag{65}$$

During the decay of the voltage, the current and the potential must always obey

$$-C\,\frac{dV}{dt}+I(t)=0 \tag{66}$$

which, in terms of the transformed functions, becomes

$$V(s)=\frac{CV_o}{sC+\Phi(s)}=\frac{CV_o}{sC+G_\infty[1+\alpha_1 s/(s+\lambda_1)+\alpha_2 s/(s+\lambda_2)]}. \tag{67}$$

The two expressions for $V(s)$, Eqs. (65) and (67), must coincide for all values of s. The necessary and sufficient conditions are

$$\begin{aligned}
&1=a_1+a_2+a_3\\
&\lambda_1+\lambda_2=(\varepsilon_2+\varepsilon_3)\,a_1+(\varepsilon_1+\varepsilon_3)\,a_2+(\varepsilon_1+\varepsilon_2)\,a_3\\
&\lambda_1\lambda_2=\varepsilon_2\varepsilon_3 a_1+\varepsilon_1\varepsilon_3 a_2+\varepsilon_1\varepsilon_2 a_3\\
&\lambda_1\lambda_2 G_\infty/C=\varepsilon_1\varepsilon_2\varepsilon_3\\
&\lambda_1+\lambda_2+(G_\infty/C)(1+\alpha_1+\alpha_2)=\varepsilon_1+\varepsilon_2+\varepsilon_3
\end{aligned} \tag{68}$$

and

$$\lambda_1\lambda_2+(G_\infty/C)[\lambda_1(1+\alpha_2)+\lambda_2(1+\alpha_1)]=\varepsilon_1\varepsilon_2+\varepsilon_1\varepsilon_3+\varepsilon_2\varepsilon_3.$$

It is of some interest to have expressions for the amplitude and time constant of the final decay of the voltage when this process is much slower than the relaxations observed in voltage-clamp experiments (Feld-

berg & Kissel, 1975; Feldberg & Nakadomari, 1977). If the small reciprocal time constant is designated ε_3, then for

$$\varepsilon_3 \ll \lambda_1, \lambda_2 \tag{69}$$

it follows that, for

$$\begin{aligned} &(\lambda_1+\lambda_2)\,t \gg 1, \\ -d\ln V/dt &= \varepsilon_3 = \lambda_1\lambda_2 G_\infty/(C\varepsilon_1\varepsilon_2) \\ &\simeq (G_\infty/C)\Big/\left[1+(G_\infty/C)\left(\frac{1+\alpha_2}{\lambda_2}+\frac{1+\alpha_1}{\lambda_1}\right)\right] \end{aligned} \tag{70}$$

which differs in the denominator from the expression given by Feldberg and Nakadomari [1977, Eq. (*A*.5)]. Since

$$a_3 = (\lambda_1\lambda_2 - \varepsilon_3(\lambda_1+\lambda_2)+\varepsilon_3^2)/[(\varepsilon_1-\varepsilon_3)(\varepsilon_2-\varepsilon_3)] \tag{71}$$

It also follows that

$$a_3 \simeq \left[1+(G_\infty/C)\left(\frac{1+\alpha_2}{\lambda_2}+\frac{1+\alpha_1}{\lambda_1}\right)\right]^{-1} \tag{72}$$

and thus [Feldberg & Nakadomari, 1977, Eq. (29)]

$$-\frac{d\ln V}{dt} = a_3 G_\infty/C. \tag{73}$$

Reduction of the Solutions to Simpler Cases

(1) *Neutral carrier with* $\delta_s = 0$. For small applied potentials the relaxation amplitudes are given by

$$\alpha_1 = \frac{\lambda_2 k_{is}}{k_s k_D}\left\{\frac{k_R a + 2k_s - \lambda_1}{\lambda_2 - \lambda_1}\right\}\left\{1-\frac{\xi\lambda_1}{z_i k_{is}}\right\}^2$$

and

$$\alpha_2 = \frac{\lambda_1 k_{is}}{k_s k_D}\left\{\frac{\lambda_2 - k_R a - 2k_s}{\lambda_2 - \lambda_1}\right\}\left\{1-\frac{\xi\lambda_2}{z_i k_{is}}\right\}^2. \tag{74}$$

For arbitrary applied potentials and $\delta_R = \delta_D = \mathrm{K}^* - \mathrm{K} = 0$, the expressions are the same except that $\xi = 0$ and all of the rate constants are starred. These equations are then a minor extension of those derived by Stark *et al.* (1971). A simpler derivation and expressions valid for $k_R^* a + 2k_s^* \gg k_D^* + 2k_{is}^*$ and $k_D^* + 2k_{is}^* \gg k_R^* a + 2k_s^*$ were given by Hladky (1975).

(2) *Neutral complex with* $\delta_{is}=0$. For small applied potentials the relaxation amplitudes are

$$\alpha_1=\frac{\lambda_2 k_s}{k_{is}k_R a}\left\{\frac{k_D+2k_{is}-\lambda_1}{\lambda_2-\lambda_1}\right\}\left\{1-\frac{\xi\lambda_1}{z_i k_s}\right\}^2$$

and (75)

$$\alpha_2=\frac{\lambda_1 k_s}{k_{is}k_R a}\left\{\frac{\lambda_2-k_D-2k_{is}}{\lambda_2-\lambda_1}\right\}\left\{1-\frac{\xi\lambda_2}{z_i k_s}\right\}^2.$$

For arbitrary applied potentials and $\delta_R=\delta_D=\mathrm{K}^*-\mathrm{K}=0$, the expressions are the same except that $\xi=0$ and all of the rate constants are starred.

(3) *Variable conformation pore with* $\delta_{is}=\delta_s=0$. For small applied potentials

$$\alpha_1=\frac{\lambda_2(2k_{is}-\lambda_1)(\lambda_1-2k_s)}{4k_{is}k_s(\lambda_2-\lambda_1)}$$

and (76)

$$\alpha_2=\frac{\lambda_1(2k_{is}-\lambda_2)(2k_s-\lambda_2)}{4k_{is}k_s(\lambda_2-\lambda_1)}.$$

(4) *Interfacial equilibrium for small applied potentials.* With the assumption that

$$k_R a+k_D \gg \max\left\{2k_{is}, 2k_s, \left|\frac{\gamma}{\xi}k_{is}\right|, \left|\frac{\psi}{\xi}k_s\right|\right\} \tag{77}$$

Eqs. (46), (55), (56), (59) and (60) reduce to

$$\lambda_2=k_R a+k_D+\frac{2k_s k_R a+2k_D k_{is}}{k_R a+k_D} \tag{78}$$

$$I_2=-F\Delta\phi\xi^2 2N_s k_R a \tag{79}$$

$$I_\infty=-z_i^2 F\Delta\phi N_s\frac{k_R a k_{is}k_s}{k_s k_D+k_{is}k_R a} \tag{80}$$

$$\lambda_1=\frac{2k_R a k_{is}+2k_s k_D}{k_R a+k_D} \tag{81}$$

and

$$\alpha_1=\frac{k_{is}k_R a}{k_s k_D}\left[\frac{\gamma}{z_i}+\frac{\xi}{z_i}\frac{k_D}{k_{is}}\frac{2k_{is}-2k_s}{k_R a+k_D}+\frac{\psi}{z_i}\frac{k_D k_s}{k_{is}k_R a}\right]^2. \tag{82}$$

For low concentrations of adsorbed ions Markin and Liberman's (1973) Eqs. (22)–(24) are equivalent if γ and ψ obey Eqs. (37) and (38).

If $\xi=0$, then clearly the inequality [Eq. (77)] used above fails. The reduction is, however, then even simpler, assuming only $k_R a + k_D \gg \max\{2k_{is}, 2k_s\}$. The time constants are the same, $\alpha_2 \to 0$, and α_1 is given by Eq. (82) with $\xi=0$.

(5) *Limiting behavior as the concentration of the carried ions approaches zero.* For small applied potentials the reciprocal time constants and amplitudes are:

$$\begin{aligned}
\lambda_s = 2k_s; \quad \alpha_s &= \left(\frac{\psi}{z_i}\right)^2 \left[\frac{k_s(k_D+2k_{is})}{k_R a k_{is}} - \frac{2k_s^2 k_D}{k_{is}(2k_{is}+k_D-2k_s)^2}\right] \\
&\quad + \left(\frac{\psi}{z_i}\right) \frac{2k_{is}+k_D}{2k_{is}+k_D-2k_s} \left[\frac{2\gamma}{z_i} + \frac{4\xi}{z_i} \frac{2k_{is}-2k_s}{2k_{is}}\right] \\
\lambda_{is} &= 2k_{is}+k_D; \\
\alpha_{is} &= \frac{2k_{is}}{k_D} \left[\frac{\gamma}{z_i} - \frac{2\xi k_D}{z_i 2k_{is}} + \frac{\psi k_s k_D}{z_i k_{is}(2k_s-2k_{is}-k_D)}\right]^2.
\end{aligned} \tag{83}$$

Either relaxation may be the faster. If $2k_s = 2k_{is}+k_D$, then for $k_R a = 0$, the two time constants are both equal to $2k_s$, $I_o = -F\psi^2 N_s k_s \Delta\phi$ and $I_\infty = 0$. If $\psi=0$, then $\alpha_s=0$ and

$$\alpha_{is} = \frac{2k_{is}}{k_D}\left[1 - \frac{2\xi}{z_i}\left(1+\frac{k_D}{2k_{is}}\right)\right]^2 \tag{84}$$

which is the equation derived by Ciani (1976). Eq. (*A*-29) from Hladky (1975) and the statement following it are incorrect.

(6) *Limiting behavior at high ion concentrations.* For small applied potentials, the steady-state current, reciprocal time constants, and amplitudes are

$$\begin{aligned}
I_\infty &= -F\Delta\phi z_i^2 N_s k_s \\
\lambda_1 &= 2k_{is}, \qquad \alpha_1 = \frac{\gamma^2}{z_i^2} \frac{k_{is} k_R a}{k_D k_s} \\
\lambda_2 &= 2k_s + k_R a + k_D, \quad \text{and} \quad \alpha_2 = \left(\frac{2\xi}{z_i}\right)^2 \frac{k_R a}{2k_s}.
\end{aligned} \tag{85}$$

The amount of charge transferred in the slow transient

$$\frac{I_\infty \alpha_1}{\lambda_1} = -F\Delta\phi\gamma^2 N_s k_R a/2k_D, \tag{86}$$

will be much greater than that transferred in the fast transient

$$I_\infty \alpha_2/\lambda_2 = -F\Delta\phi(2\xi)^2(N_s/2) \tag{87}$$

unless γ approaches zero.

In Eq. (A-32) of Hladky (1975) the right-hand side should be multiplied by γ.

Discussion

This paper reports an extension of the theory for current transients using the symmetrical version of the standard carrier model (*see* Fig. 1) developed by Markin *et al.* (1969), Läuger and Stark (1970), Stark *et al.* (1971), Hladky (1972), Markin and Liberman (1973), Aityan *et al.* (1973), Ciani (1976) and Benz and Läuger (1976). Stark *et al.* (1971) solved the equations for transients, assuming that the carrier is neutral and that only the rate of transfer of complexes is affected directly by the applied field. They and others have used this solution with some success to interpret data obtained with the ionophores trinactin and valinomycin (for references, *see* Hladky, 1979). However, while it has been generally recognized that the values of the rate constants derived from the curve fitting would have been different if a different simplifying assumption had been made (Hladky, 1975; Knoll & Stark, 1975), no estimate of the size of these discrepancies has been available. Markin and Liberman (1973) developed the model to allow all the steps in the carrier process to depend on the potential and provided solutions for certain special cases at low applied potentials. However, the special conditions they imposed were too restrictive for their solutions to be used in the analysis of the data for the systems available.

In all previous attempts to provide solutions for the time-dependent currents, which are more general than those derived by Stark *et al.* (1971), the membrane has been treated as a layered structure and the ions as usually adsorbed at the boundaries between these layers (*see* Markin & Liberman, 1973; Ciani, 1976; Benz, Läuger & Janko, 1976). When an ion moves, the current in the external circuit is then calculated as the sum of the ionic current and the Maxwell displacement current, $\partial D/\partial t$ across any one of these layers. This method of calculation leads to a notation and algebraic expressions which are considerably more cumbersome than those provided here. Presumably for this reason, neither Markin and Liberman nor Ciani provide a general solution for their three layer carrier models. Even were such a solution available, it would be restricted to cases where either the free carriers and complexes adsorb

at the same depth into the membrane (i.e., Eqs. (37) and (38) must apply) or the movements of one or the other results in no charge displacement.

In the present formulation the current is calculated not from the sum of the ionic and Maxwell displacement currents across a plane within the membrane, but rather as the sum of the charge movements caused in the external circuit by the changes which occur within the membrane. Thus, instead of specifying the location of the boundaries separating the layers, in this formulation one must specify the amount of charge transferred in the external circuit for each type of transition which can occur. The principal computational advantage of this notation arises since the amount of charge transferred in the external circuit for a transition between two states determines the amount of work done by the external circuit (e.g., the voltage clamp) during the transition. This work is, in turn, equal to the change in standard free energy for the transition which determines the equilibrium constant between the states. For small applied potentials, low concentrations of adsorbed ions and systems symmetrical at zero applied potential, no further information about the potential dependence of the rate constants is required or available.

The present formulation has one further advantage. The parameters γ, ψ and ξ describe not the movements of the ions themselves, but rather the sum of all the movements of charge which occur as a consequence of the movement of the ions and neutral molecules. As S. Simon and J. Hall (*personal communication, see* Hladky, 1979) have emphasized, the adsorption of a large ion or ion carrier complex, or even a neutral molecule, will perturb the structure of the membrane in that region. Any dipole rotations which occur as a consequence will be seen as part of the charge movement.

In the preceding sections the general solution for the current in a voltage clamp has been derived for low adsorbed ion concentrations, symmetrical starting conditions, and either low applied potentials or an equal effect of the applied potential on all four of the association and dissociation rate constants. The current after the abrupt application of a potential is given by

$$I = I_\infty (1 + \alpha_1 e^{-t/\tau_1} + \alpha_2 e^{-t/\tau_2}) \tag{43}$$

where the time constants are related to the rate constants by the equations (46) first derived for neutral carriers by Stark *et al.* (1971). The sum of the relaxation amplitudes, i.e., $\alpha_1 + \alpha_2$, obeys a relation [Eq. (36)] similar to that derived from the three-layer model by Markin and Liberman (1973). The individual amplitudes are stated explicitly in Eqs.

(55)–(60). The simpler equations which apply to a number of special cases have then been obtained from the general solution by reduction. Wherever alternative derivations of these cases have been available, the solutions have been compared. Solutions for the voltage transient in a charge pulse experiment [Eq. (65) and (68)] and for the membrane admittance [Eq. (63)] have been obtained from the solution for the current in a voltage clamp experiment [Eq. (43)] by Laplace transform.

A similar development of the theory for lipid soluble ions is included in Section *II* and *Appendix A* of Hladky (1979).

The theory developed here makes no assumptions about the charge of the carried ion or the carrier. In later papers it is intended to give further consideration to the theory as it describes carriers of particular charges and the use of the theory in the analysis of experimental data. Application to the neutral carriers trinactin and valinomycin has been discussed elsewhere (Hladky, 1979) based on the assumption that movement of the free carrier does not displace charge.

While the particular examples of carriers cited above are carriers in the literal, mechanistic sense, it should be emphasized that the equations used here describe a broader class of systems. For instance, the same equations could describe a large protein which contains a fixed site and which by changes in conformation opens a route of access from one solution or the other. Kinetically this system would be a carrier, mechanistically it might more accurately be described as a pore. Indeed if the conformation change were strongly dependent on potential, it might be indistinguishable from a gated channel.

I should like to thank R.H. Adrian, S. Simon, and R.Y. Tsien for helpful suggestions.

Appendix A

The condition that the potential seen by one ion in the membrane is not altered by the presence of others necessarily restricts the range of concentrations to which the present theory can apply. An underestimate of this range for carriers such as trinactin and valinomycin can be provided using the three capacitor model of Markin, Grigoryev and Yermishkin (1971) in which the adsorbed charges are assumed to be smeared out in two adsorption layers with charge densities σ' and σ''. The capacitance between one of these layers and the adjacent solution is C_1, that between the two layers is C_2. Thus, considering for simplicity

only one species of ion in the membrane, the extra energy of one ion resulting from the potential drop across C_1 due to the other adsorbed ions, must be small compared to kT. Since $\sigma = zFN$, and the potential drop is $\Delta V = \sigma/C_1$, the condition required is

$$N \ll \frac{RTC_1}{z^2F^2}.$$

For $C_1 = 4 \times 10^{-6}$ F/cm^2, $RT/F = 25$ mV, $F = 10^5$ C/mole, $z = 1$, this condition requires that $N \ll 10^{-12}$ moles/cm^2. Acceptable concentrations probably approach this limit closely since (i) the boundary capacitance has been underestimated, and (ii) the smeared charge model used in the calculation provides an upper limit for the possible interaction between the ions (*see* Andersen *et al.*, 1978, and Hladky & Tsien, 1979).

The second necessary condition is that rearrangement of the adsorbed ions in response to an applied potential must not perturb the potential drop across the central capacitance, C_2. By elementary electrostatics, the potential drop across the center is

$$\Delta V_2 = \frac{C_1}{C_1 + 2C_2}\Delta V_a + \frac{2(zFN - \sigma')}{C_1 + 2C_2}$$

where ΔV_a is the applied potential. The change in the adsorbed charge due to the applied potential can be estimated from the quilibrium shift which would be produced by ΔV_a,

$$zFN - \sigma' = zFN \tanh[zF\Delta V_a/(2RT)]$$

which for small potentials becomes

$$zFN - \sigma' = -z^2F^2N\Delta V_a/2RT.$$

Thus, again the condition to be satisfied is

$$N \ll \frac{RTC_1}{z^2F^2}.$$

The restriction that the adsorbed ion densities must be kept below 10^{-12} moles/cm^2 does not preclude a significant effect of the ion transfer on the membrane capacitance. Thus for low frequencies and 10^{-13} moles/cm^2, the additional capacitance of the membrane [Eq. (63)] is

$$C_A = \frac{\Delta Q}{\Delta V_a} \simeq \frac{z^2FN\Delta\phi}{2\Delta V_a} = 0.4\,\mu\text{F/cm}^2$$

which is of the same order as the capacitance of the bare membrane.

Notation

Superscripts:

refers to the left; $''$ refers to the right

Subscripts:

- is – complex
- s – carrier
- i – carried ion
- R – association (recombination)
- D – dissociation

Symbols:

- a_i – ion activity
- a_1, a_2, a_3 – relaxation amplitudes in charge pulse experiments
- C – membrane capacity
- d – membrane thickness
- F – the Faraday constant
- G_∞ – steady-state, low voltage conductance
- I – current
- I_o – initial current
- I_∞ – steady-state current
- J_i, J_{is}, J_s – fluxes (moles/(area × time)) of ions across the boundary and of complexes and free carriers across the membrane core
- $j=\sqrt{-1}$
- k – rate constant – omission of superscript implies the value for $\Delta V=0$. See Fig. 1.
- k^* – symmetric part of k – e.g., $k^*_{is}=(k'_{is}+k''_{is})/2$
- K – equilibrium binding constant
- N – surface concentration (moles/area), *see* Fig. 1.
- R – gas constant
- s – Laplace transform variable
- T – temperature
- t – time
- V, V_0 – potentials in charge pulse experiments
- z – number of protonic charges on the species indicated
- α_1, α_2 – slow and fast voltage clamp relaxation amplitudes
- α_s, α_{is} – voltage clamp relaxation amplitudes corresponding to τ_s and τ_{is}
- $\delta_R, \delta_D, \delta_s$ – antisymmetric part of a rate constant, e.g. $\delta_{is}=(k'_{is}-k''_{is})/2$
- Δ_s, Δ_{is} – changes in surface concentrations
- ΔV – applied potential
- γ – charge displacement in the transfer of a complex
- $\varepsilon_1, \varepsilon_2, \varepsilon_3$ – reciprocal time constants in charge pulse experiments
- λ_1, λ_2 – slow and fast voltage-clamp reciprocal time constants
- λ_s, λ_{is} – reciprocal time constants related to k_s and k_{is} regardless of which process is slower
- ξ – charge displacement in formation of a complex (on the left)
- τ – time constant $=1/\lambda$
- ψ – charge displacement in transfer of a carrier
- ω – angular frequency

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