Biophysical Chemistry 9 (1979) 111–120
© North-Holland Publishing Company

ENERGY-BARRIER MODELS FOR MEMBRANE TRANSPORT

L.F. Del CASTILLO * and E.A. MASON
Brown University, Providence, Rhode Island 02912, USA

and

Larry A. VIEHLAND
Parks College of Saint Louis University, Cahokia, Illinois 62206, USA

Received 19 July 1978

Energy-barrier models are analyzed to find hidden assumptions and establish ranges of validity. The analysis proceeds by comparison with integrated results for model continuum membranes. The main conclusions are that a simple energy-barrier model has a wide range of validity, is remarkably accurate even when its conditions of validity are not strictly met, and is almost always superior to the analogous equations of irreversible thermodynamics. Its major limitations are a possible nonphysical divergence at high electric fields or volume flows caused by breakdown of the transition-state approximation, and the inability to treat multicomponent mixtures except in a pseudobinary (Nernst-Planck) approximation.

1. Introduction

Because details of membrane structures are often known only poorly, if at all, there have been many attempts to describe transport through membranes whereby the membrane is represented as a "black box" or by some simple but general model. A well-known example of the former is Kedem and Katchalsky's treatment of membrane transport according to the irreversible thermodynamics of discontinuous systems [1,2], and of the latter is the use of generalized "frictional coefficients" by Spiegler, Kedem, and Katchalsky to formulate transport equations [2–5]. Both of these procedures have been widely used in discussing membrane transport phenomena. An alternative model, in which the membrane is represented as an energy barrier or series of barriers which a permeating substance must surmount, has been much less widely used. This energy-barrier model is the subject of the present investigation, and we argue that it shows several distinct advantages over other phenomenological or black-box models that have enjoyed much greater popularity. We also argue, however, that it must be used with caution at high values of applied electric field or of volume flow. In this connection it is important to draw a clear distinction between the energy-barrier model itself and approximate solutions for the model based on so-called transition-state or absolute rate theory given by Eyring and co-workers [6,7].

The background is briefly as follows. An energy-barrier model for membranes was proposed long ago by Danielli [8], and a number of specific applications were worked out by Eyring and coworkers [9–13], using the methods of transition state theory [6,7]. A simplified formalism involving only a single barrier was later introduced by Markin [14]. Single barriers were added to each side of a continuum bulk membrane by deLevie and Abbey [15] for the purpose of describing interfacial effects at the membrane surfaces. Manning [16] showed how nonzero volume flow could be introduced into the formalism, thereby greatly extending the possible range of applicability of the model.

The relation of energy-barrier models to irreversible thermodynamics was considered by Manning [16] and by Hogg and Williams [17], who derived the linear transport equations of irreversible thermodynamics [1,

---

* On leave during 1977–78 from Centro de Investigación de Materiales, Universidad Nacional de México, Mexico City.

2] from energy-barrier models in the limit of small differences of pressure and concentration across the membrane. The connection between thermodynamic and kinetic (energy-barrier) descriptions was also discussed by Schlögl [18], who integrated the linear thermodynamic equations across a membrane under a number of idealizations, and obtained integrated nonlinear equations similar to those from a suitable energy-barrier model. Thus there is no inconsistency between energy-barrier model descriptions of membrane transport and irreversible thermodynamics. By implication, there is also no inconsistency with frictional-model equations, since these have been shown to be mathematically equivalent to the thermodynamic equations [2–5]. Complete consistency in general is limited to the linear regime, however.

A recent critique [17] of energy-barrier models stresses three advantages over irreversible thermodynamics: (1) a form of membrane model is provided, in contrast to a "black box"; (2) a temperature dependence for membrane transport coefficients is suggested; (3) an indication is given of the range of validity of linear transport equations. The third point is particularly interesting — it results from the fact that the equations from the energy-barrier model are nonlinear. They apply to transport across the membrane as a whole, and are not just local differential equations, valid only in a small region, that must be integrated across the membrane. From the standpoint of local transport equations in a continuum membrane, this feature means that the energy-barrier model has in fact performed an integration of local differential equations. Since this is in general not possible without some knowledge of the membrane structure and the boundary conditions, some hidden assumptions must be involved in the use of the energy-barrier model.

The purpose of this paper is to ferret out such assumptions by careful analysis of the energy-barrier model, especially comparison of its results with results obtained by integration of local differential equations for model continuum membranes. Our approach is thus somewhat similar in spirit to that of Manning [16,19], but the details are quite different. We begin with the simplest cases in order to isolate the basic strengths and weaknesses of the model. Complex situations can then be accommodated more readily.

2. Transition-state treatment

The basic picture behind the energy-barrier model is the jumping of molecules over a potential energy barrier. We consider first the case where the jumping of the molecules of interest is independent of the behavior of any other molecular species in the solution, except through the possible mechanism of overall volume flow. If the concentration of molecules on one side of a barrier is c_0, then the number of molecules eligible to leap the barrier is equal to $c_0\lambda_0$, where λ_0 is a characteristic jump distance. The actual number jumping the barrier per unit time is $c_0\lambda_0 k_0$, where k_0 is a specific rate coefficient. Similarly, the number jumping the barrier in the opposite direction is $c_1\lambda_1 k'_1$, where the subscript 1 refers to values on the other side of the barrier and the prime on k indicates passage in the opposite direction. Thus the net transport Q across the barrier in unit time is $(c_0\lambda_0 k_0 - c_1\lambda_1 k'_1)$. For a number of barriers in series, Q is the same for all in a steday state, and we can write

$$
\begin{aligned}
Q &= c_0\lambda_0 k_0 - c_1\lambda_1 k'_1 \\
Q &= \qquad\qquad c_1\lambda_1 k_1 - c_2\lambda_2 k'_2 \\
&\;\;\vdots \\
Q &= \qquad\qquad\qquad\qquad c_{n-1}\lambda_{n-1}k_{n-1} \\
&\quad - c_n\lambda_n k'_n \,.
\end{aligned}
\tag{1}
$$

If we eliminate all the intermediate concentrations $c_1 ... c_{n-1}$ from this set of equations, we obtain

$$
\begin{aligned}
&Q\left(1+\frac{k'_1}{k_1}+\frac{k'_1k'_2}{k_1k_2}+\ldots+\frac{k'_1\ldots k'_{n-1}}{k_1\ldots k_{n-1}}\right) \\
&\quad = \lambda_0 k_0\left(c_0-\frac{\lambda_n}{\lambda_0}\,\frac{k'_1k'_2\ldots k'_{n-1}k'_n}{k_0k_1\ldots k_{n-1}}c_n\right).
\end{aligned}
\tag{2}
$$

For simplicity, suppose all the barriers have the same height and are otherwise identical, except possibly the first and last, as shown in fig. 1. All the essential features of the treatment can be illustrated by this simple case. If external forces and volume flow are absent, then $k'_i = k_i$ for the intermediate barriers and $\lambda_0 = \lambda_n$, $k'_n = k_0$ for the first and last barriers, so that eq. (2) reduces to the conventional result,

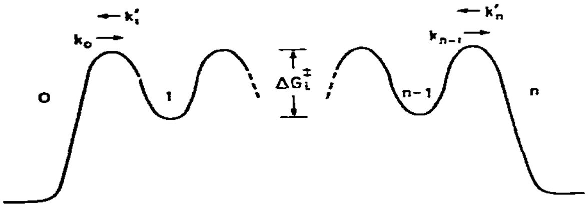

Fig. 1. Schematic diagram of uniform barriers in series.

$$Q = (\lambda_0 k_0/n)(c_0 - c_n) \equiv -P\Delta c\,, \tag{3}$$

where $\Delta c = c_n - c_0$ and P is a permeability coefficient.

The above treatment merely gives formal definitions of rate coefficients. Interesting physical content occurs only when some specific properties of the k's are introduced. According to transition-state theory [6,7], the rate coefficient in the absence of external forces and volume flow, denoted by a superscript ^{0}, is

$$k_i^0 = \kappa_i (k_B T/h) \exp(-\Delta G_i^{\ddagger}/RT)\,, \tag{4}$$

where κ_i is a transmission coefficient, k_B is Boltzmann's constant, h is Planck's constant, $\Delta G_i^{\ddagger}$ is the Gibbs free energy (per mole) necessary for the molecules to move from their equilibrium position on one side of the barrier to the top of the barrier, and R and T have their usual meanings. The traditional assumption behind this expression is that of an equilibrium or quasi-equilibrium between molecules at the side and at the top of the barrier. Although this particular assumption can be weakened or avoided [20,21], some sort of quasi-equilibrium assumption always seems necessary, a point to which we shall return later. According to this equilibrium assumption, if an external force F_i acts in the vicinity of position i, the effect is to change $\Delta G_i^{\ddagger}$ by an amount equal to the extra work necessary to carry the molecules from the side to the top of the barrier [9]. For the symmetrical barriers of fig. 1, the result is

$$k_i = k_i^0 \exp(\phi_i/2RT)\,, \tag{5a}$$

$$k'_i = k_i^0 \exp(-\phi_i/2RT)\,, \tag{5b}$$

where k_i^0 is given by eq. (4), and

$$\phi_i = 2 \int_{z_i}^{z_i+\lambda/2} F_i(z)\,\mathrm{d}z\,, \tag{6}$$

the coordinate z being measured in the direction of transport.

Several forms of external forces can be considered. A usual one is the electrical force on charged particles,

$$F_i = Z\mathcal{F}\mathcal{E}_i\,, \tag{7}$$

where Z is the charge number, $\mathcal{F}$ the faraday constant, and $\mathcal{E}_i$ the electric field strength. Similar expressions hold for gravitational and centrifugal forces. Thermodynamic "forces" are also sometimes considered, such as the change in free energy due to a hydrostatic pressure gradient ∇p_i [17],

$$F_i = -\overline{V}\nabla p_i\,, \tag{8}$$

where $\overline{V}$ is the partial molar volume of the molecular species crossing the barrier. A thermodynamic "force" due to the variation of activity coefficient with position can also be included [9]. Volume flow can be included by means of an effective frictional "force" of the flow on the molecules, as shown by Manning [16],

$$F_i = \zeta_i Q_v\,, \tag{9}$$

where Q_v is the volume flow per unit time over the same cross-sectional area that applies to Q, and ζ_i is a frictional coefficient that must be determined by experiment.

Returning now to the uniform barrier model of fig. 1, we apply the foregoing results to eq. (2) and obtain

$$Q(1 + \mathrm{e}^{-\phi_1/RT} + \mathrm{e}^{-\phi_1/RT}\mathrm{e}^{-\phi_2/RT} + \ldots) = \lambda_0 k_0^0 \times (c_0 \mathrm{e}^{+\phi_0/2RT} - c_n \mathrm{e}^{-\phi_1/RT}\mathrm{e}^{-\phi_2/RT}\ldots\mathrm{e}^{-\phi_n/2RT}) \tag{10}$$

where

$$\phi_i = 2 \int_{z_i}^{z_i+\lambda/2} (Z\mathcal{F}\mathcal{E}_i - \overline{V}\nabla p_i + \zeta_i Q_v)\,\mathrm{d}z\,. \tag{11}$$

If all the ϕ_i's are equal, the series in eq. (10) can be summed to yield [9]

$$Q\left(\frac{1 - \mathrm{e}^{-n\phi/RT}}{1 - \mathrm{e}^{-\phi/RT}}\right) = \lambda_0 k_0^0 \mathrm{e}^{\phi/2RT}(c_0 - c_n \mathrm{e}^{-n\phi/RT})\,. \tag{12}$$

It is convenient to rewrite this expression in terms of an effective total potential across the membrane, ϕ, defined as

$$\Phi \equiv n\phi/RT\,, \tag{13}$$

and an effective total permeability, P, defined as

$$P \equiv \lambda_0 k_0^0/n \, . \tag{14}$$

Eq. (12) can then be written in the form,

$$Q = P\Phi \left(c_0 - \frac{\Delta c}{e^{\Phi} - 1} \right) B_n(\Phi) \, , \tag{15}$$

where $\Delta c = c_n - c_0$, and

$$B_n(\Phi) = (2n/\Phi) \sinh(\Phi/2n) \, . \tag{16}$$

It is this factor $B_n(\Phi)$ that distinguishes the transition-state result from results obtained with continuum models of membrane transport. We shall later argue that it leads to nonphysical results, namely exponential divergence at large Φ unless n is also large, but that the transition-state treatment nevertheless almost always leads to results with a wider range of validity than those from linear irreversible thermodynamics.

When $\Phi \to 0$, we can expand terms and take $B_n(\Phi) = 1 + \ldots$ and $e^{\Phi} = 1 + \Phi + \ldots$, whereby eq. (15) reduces to $Q = -P\Delta c$, the same result as eq. (3), as expected. For Φ small but not zero, consistency requires that terms in Φ^2 also be included in the expansion of e^{Φ}, and eq. (15) becomes

$$Q = -P(\Delta c - \Phi \bar{c}) \, , \tag{17}$$

$$\bar{c} = \tfrac{1}{2}(c_0 + c_n) \, . \tag{18}$$

This is the result anticipated from irreversible thermodynamics [2,22]. For large Φ, the term involving Δc in eq. (15) becomes negligible; this simply means that diffusion is unimportant when the driving forces are large, as would be expected. However, the actual asymptotic form taken by Q when $\Phi \gg 1$ depends on the relation between Φ and n, as follows:

$$Q = P\Phi c_0 \qquad \text{for } \Phi \gg 1 \text{ and } \Phi \ll 2n \, , \tag{19}$$

$$Q = nPc_0 e^{\Phi/2n} \text{ for } \Phi \gg 1 \text{ and } \Phi \gg 2n \, . \tag{20}$$

As discussed in the next section, the second result is regarded as a consequence of the failure of the transition-state approximation, not as a physical result.

3. Comparison with continuum treatment

The continuum equations for isothermal transport through a membrane, as derived from general statistical-mechanical considerations [23], are

$$\sum_{\beta} \frac{x_\alpha x_\beta}{D_{\alpha\beta}} (u_\alpha - u_\beta) + \frac{x_\alpha}{D_{\alpha\mathrm{M}}} u_\alpha = -\frac{x_\alpha}{RT} (\nabla \mu_\alpha - X_\alpha) - \frac{x_\alpha B_0}{\eta D_{\alpha\mathrm{M}}} (\nabla p - cX) \, , \tag{21}$$

where x_α is the mole fraction of species α, u_α its transport velocity (flux density divided by concentration) and μ_α its chemical potential, $D_{\alpha\beta}$ is the mutual diffusion coefficient for species α and β in the membrane and in the presence of the other species in the solution, $D_{\alpha\mathrm{M}}$ is the membrane diffusion coefficient for α, X_α is the external force on species α (per mole), η is the viscosity of the solution, B_0 is a geometrical constant of the membrane that characterizes its viscous-flow properties, ∇p is the gradient of the external pressure, and $cX = \Sigma_\alpha c_\alpha X_\alpha$ (c is the concentration in moles per unit volume of solution) is the total external force per unit volume. The summation in eq. (21) runs over all species. It is important to recognize that X_α is a true external body force like the electrical force of eq. (7), and does *not* include "effective forces" of a thermodynamic or frictional character, such as those in eqs. (8) and (9) for the energy-barrier model. Such "effective forces" are taken care of by other terms in eq. (21); e.g., the pressure-diffusion "force" $\bar{V}_\alpha \nabla p$ appears as part of $\nabla \mu_\alpha$. It will be convenient to absorb the viscous-flow term, the one containing B_0/η, into the diffusion terms; this can be done by purely mathematical manipulation, yielding [23,24]

$$\sum_{\beta} \frac{x_\alpha x_\beta}{E_{\alpha\beta}} (u_\alpha - u_\beta) + \frac{x_\alpha}{E_{\alpha\mathrm{M}}} u_\alpha = -\frac{x_\alpha}{RT} (\nabla \mu_\alpha - X_\alpha) \, , \tag{22}$$

where

$$E_{\alpha\mathrm{M}} = D_{\alpha\mathrm{M}} \left(1 + \frac{cB_0 RT}{\eta} \sum_{\gamma} \frac{x_\gamma}{D_{\gamma\mathrm{M}}} \right) , \tag{23}$$

$$1/E_{\alpha\beta} = 1/D_{\alpha\beta} + cB_0 RT/\eta E_{\alpha\mathrm{M}} D_{\beta\mathrm{M}} \, . \tag{24}$$

A simple case corresponding to the energy-barrier example in the preceeding section is the one-dimensional transport of an ideal binary mixture through a homogeneous, homoporous membrane. We write $u_\alpha = J_\alpha/c_\alpha$, where J_α is flux density, $\mathrm{d}\mu_\alpha = RT \, \mathrm{d} \ln x_\alpha + \bar{V}_\alpha \mathrm{d}p \approx RT \, \mathrm{d} \ln c_\alpha + \bar{V}_\alpha \mathrm{d}p$, $X_\alpha = Z_\alpha \mathcal{F} \mathcal{E}$ and eliminate J_β through the volume-flow velocity, defined as

$$J_\mathrm{v} = \bar{V}_\alpha J_\alpha + \bar{V}_\beta J_\beta \, . \tag{25}$$

After some algebra, the result can be arranged into the form of a Nernst–Planck equation,

$$J_\alpha = -\bar{D}_\alpha\left(\frac{\mathrm{d}c_\alpha}{\mathrm{d}z} + \frac{c_\alpha \bar{V}_\alpha}{RT}\frac{\mathrm{d}p}{\mathrm{d}z} - \frac{c_\alpha Z_\alpha \mathcal{F}\mathcal{E}}{RT}\right) + g_\alpha c_\alpha J_\mathrm{v}\,, \tag{26}$$

where

$$1/\bar{D}_\alpha = (1/c\bar{V}_\beta E_{\alpha\beta}) + (1/E_{\alpha\mathrm{M}})\,, \tag{27}$$

$$g_\alpha = \bar{D}_\alpha/c\bar{V}_\beta E_{\alpha\beta}\,. \tag{28}$$

The coefficient g_α measures the coupling of the diffusion to the volume flow, through the relative importance of $E_{\alpha\mathrm{M}}$ and $E_{\alpha\beta}$. If $E_{\alpha\mathrm{M}} \gg E_{\alpha\beta}$, the transport of α is dominated by mutual diffusion, which couples strongly to volume flow, and $g_\alpha = 1$. But if $E_{\alpha\mathrm{M}} \ll E_{\alpha\beta}$, the transport of α is dominated by the diffusion of α through the membrane, independent of the transport of the other component, and $g_\alpha = 0$. Eq. (26) can be put in closer correspondence with the transition-state result after integration. To this end we define a total flux of α as $Q_\alpha = AJ_\alpha$, and a total volume flow as $Q_\mathrm{v} = AJ_\mathrm{v}$, where A is the area of the membrane open to transport, and rearrange eq. (26) to the form

$$\frac{\mathrm{d}c_\alpha}{\mathrm{d}z} - (\Phi_\alpha/d)c_\alpha + Q_\alpha/A\bar{D}_\alpha = 0\,, \tag{29}$$

where

$$\frac{\Phi_\alpha}{d} \equiv \frac{Z_\alpha \mathcal{F}\mathcal{E}}{RT} - \frac{\bar{V}_\alpha}{RT}\frac{\mathrm{d}p}{\mathrm{d}z} + \frac{g_\alpha Q_\mathrm{v}}{A\bar{D}_\alpha} \tag{30}$$

and d is the membrane thickness. It is easy to integrate eq. (29) if Φ_α can be taken as constant; the result is

$$Q_\alpha = \left(\frac{A\bar{D}_\alpha}{d}\right)\Phi_\alpha\left(c_0 - \frac{\Delta c}{\mathrm{e}^{\Phi_\alpha} - 1}\right)\,. \tag{31}$$

This has the same form as eq. (15) for the transition-state method if $B_n(\Phi) = 1$, in which case we can readily identify coefficients as

$$P = A\bar{D}_\alpha/d\,, \tag{32}$$

or

$$\bar{D}_\alpha = \lambda_0^2 k_0^0/A \qquad \text{if } d = n\lambda_0\,, \tag{33}$$

and

$$\zeta = g_\alpha RT/A\bar{D}_\alpha = RT/c\bar{V}_\beta A E_{\alpha\beta}\,. \tag{34}$$

Eq. (34) has the frictional coefficient ζ directly proportional to RT and inversely proportional to a diffusion coefficient, as would be expected from the Einstein relation [25].

Two conclusions would appear to follow from the foregoing comparison. First, the simple closed-form expressions for Q given by eq. (15) or eq. (31) can be obtained only if Φ is constant throughout the membrane, otherwise the series in eq. (10) from the transition-state treatment cannot be summed, or the differential eq. (29) from the continuum treatment cannot be integrated. Second, the transition-state and continuum treatments lead to the same result only when $B_n(\Phi) \to 1$. However, the first conclusion is not entirely correct, and the second conclusion is not as restrictive as it might seem. The constancy of Φ is indeed required as far as the electric-field component $\mathcal{E}$ is concerned, as has long been known [13,26], but is not required for the volume-flow component Q_v. We shall demonstrate this for the continuum treatment, and then show under what circumstances it also holds for the transition-state treatment. That is, we shall show that the basic form of eq. (31) for the flux remains unchanged even if A and $\bar{D}_\alpha$ are arbitrary functions of z, provided that volume flow is the only external "force" operating and that g_α can be taken as constant. This somewhat surprising result corresponds to membranes stacked in series, and is very special; it does not depend simply on the fact that eq. (29) is a first-order differential equation of the form $y' + p(z)y + q(z) = 0$. Although the solution of such an equation can always be written formally in terms of integrals, the integrals cannot in general be evaluated unless $p(z)$ and $q(z)$ are known explicitly. But if $p(z)$ and $q(z)$ have the same z-dependence, in the sense that $p(z)/q(z) = \text{constant}$, then the explicit dependence on z need not be known. We indicate the proof below, since the result does not seem to be widely known.

The proof is simple. Eq. (29) simplifies to

$$\frac{\mathrm{d}c_\alpha}{\mathrm{d}z} - \frac{g_\alpha Q_\mathrm{v}}{A\bar{D}_\alpha}c_\alpha + \frac{Q_\alpha}{A\bar{D}_\alpha} = 0\,. \tag{35}$$

An integrating factor can be obtained from

$$\int_0^z \frac{g_\alpha Q_\mathrm{v}}{A\bar{D}_\alpha}\,\mathrm{d}z' = g_\alpha Q_\mathrm{v}\int_0^z \frac{\mathrm{d}z'}{A(z')\bar{D}_\alpha(z')} \equiv g_\alpha Q_\mathrm{v} f(z)\,, \tag{36}$$

where $f(z)$ has the properties,

$$f(0) = 0\,, \qquad \mathrm{d}f/\mathrm{d}z = 1/A\bar{D}_\alpha\,, \tag{37}$$

$$f(d) = \int_0^d \frac{\mathrm{d}z'}{A(z')\bar{D}_\alpha(z')} \equiv \frac{1}{P} = \text{constant}\,. \tag{38}$$

Multiplication by $\exp[-g_\alpha Q_\mathrm{v} f(z)]$ converts eq. (35) into an exact differential that can be explicitly integrated without specifying the functional form of $f(z)$; the result is

$$Q_\alpha = g_\alpha Q_\mathrm{v}\left(c_0 - \frac{\Delta c}{\mathrm{e}^{g_\alpha Q_\mathrm{v}/P} - 1}\right), \tag{39}$$

which is the same as eq. (31) with $\Phi_\alpha = g_\alpha Q_\mathrm{v}/P$. The final integration to obtain eq. (39) requires an implicit assumption that c_α is a continuous function of z – that is, there is no internal concentration polarization in the membrane. Another implicit assumption is contained in eq. (38), namely that the dependence of D_α on z is independent of Q_v. This means that $\bar{D}_\alpha$ should depend on z directly through the local structure of the membrane, and not indirectly through any dependence on c_α. The variation of c_α with z will be altered by a change in Q_v, whereas the membrane structure presumably will not. Eq. (38), which defines the overall permeability coefficient P, also contains the rule for combining permeabilities of discrete membranes stacked in series, namely

$$1/P = 1/P_1 + 1/P_2 + \ldots\,. \tag{40}$$

The proof follows directly from breaking the integration of eq. (38) into discrete steps.

A special case of the foregoing general result is already known through the use of a model membrane consisting of pores in an otherwise impermeable plate. For this model it has been shown that the equation for a pathway consisting of open pores in series is identical with the equation for a single uniform pore [27], with the permeability given by eq. (40).

A similar result does not hold in general for the transition-state treatment of the energy-barrier model. Not only do different barriers in series give results of a different mathematical form than for a single barrier, but the results depend on the order in which the barriers occur. The problem can be illustrated by considering the example of n_1 barriers of overall permeability P_1 followed by n_2 barriers of overall permeability P_2. Eq. (15) is applied to each set of barriers, and then the resulting two equations are combined to eliminate the intermediate concentration between the two sets of barriers. If volume flow is the only external "force", an Einstein relation between ζ_i and P_i can be used to show that $P_1\Phi_1 = P_2\Phi_2 = gQ_\mathrm{v}$ = constant, and then the resulting equation can be manipulated into the form

$$Q = P\Phi\left[c_0(1-\beta_1) - \frac{\Delta c(1+\beta_1)}{\mathrm{e}^\Phi - 1}\right]B_1\,, \tag{41}$$

where $P^{-1} = P_1^{-1} + P_2^{-1}$ as in eq. (40), $B_1 = B_{n1}(\Phi_1)$, and

$$\Phi = \Phi_1 + \Phi_2\,, \tag{42}$$

$$\beta_1^{-1} = (1 - B_1/B_2)^{-1}(\mathrm{e}^{\Phi_2} - 1)^{-1}(\mathrm{e}^\Phi - 1) - 1\,. \tag{43}$$

The relation for P is similar to that for electrical resistances in series. This result resembles eq. (15), but clearly is not identical to it. Moreover, if the two sets of barriers are interchanged, the equation for Q is also changed, as is easily shown by interchanging the subscripts 1 and 2 in eqs. (41)–(43). Only in the special case of $B_1 = B_2$ does eq. (41) take the same form as eq. (15); this will usually happen only if $B_1, B_2 \to 1$, in which case the result is the same as for the continuum model.

We may now enquire about the degree of agreement between the transition-state and continuum results when $B_n(\Phi) \neq 1$. Comparison of eqs. (15) and (31) shows that they differ *only* through the deviation of $B_n(\Phi)$ from unity. From eq. (16) it is easy to calculate that the difference will be less than 5% as long as $\Phi/2n < 0.55$; this translates to $\phi_i < 1.1\,RT$, or the work per barrier by the external "force" should not exceed approximately RT. (For the difference to be less than 10%, the condition per barrier is $\phi_i < 1.5\,RT$.) This is a plausible result, in that the transition-state derivation involves an assumption of quasi-equilibrium, either between reactants and "activated complexes" [6,7], or, more generally, between reactants and some degrees of freedom that act as a thermal "reservoir" [20,21]. If the external "force" is large, the reactant energy distribution function will no longer approximate an equilibrium thermal distribution, and the transition-state method may be expected to fail. This sort of failure is known and understood in some detail for the case of ions moving through an electrically neutral gas in the presence of a strong electrostatic field [28, 29], where deviations from the thermal Maxwell–Boltzmann distribution are large, and where, for example, the Einstein relation between the ion mobility and the diffusion coefficient breaks down. We suggest, therefore, that the exponential behavior of the transition-state result when $\phi_i \gg RT$ or $\Phi \gg 2n$, as given in eq. (20), is not physically correct. This is obvious when the driving "force" is volume flow, since the flow cannot carry more solute than is present in the upstream concentration. It is less obvious when the driving force is an electric field, since nonlinear behavior at high electric fields is well-known experimentally. The explanation of such high-field nonlinearities, however, must presumably be sought in details of membrane structure or in large deviations from equilibrium (as in the gaseous ion case) [30,31], and *not* from a transition-state theory whose fundamental assumptions probably break down just where these nonlinearities begin, even though the theoretical formulas can be adjusted to give a mathematical fit of experimental data [15].

Of more practical interest is the agreement at small, rather than large, values of Φ. Near $\Phi = 0$, Q is linear in both Δc and Φ, as shown by eq. (17). This is the same result as obtained from irreversible thermodynamics [2,22], but it has been pointed out that the range of validity of this linear result may be severely limited [32,33]. It is thus of interest to see whether the energy-barrier model is more accurate with respect to the continuum model than is irreversible thermodynamics. A comparison is shown in fig. 2, where Q/Pc_0 versus Φ for $c_0 = c_0$, $c_n = 0$ (or $\Delta c/c_0 = -1$) is shown for five cases: (linear) irreversible thermodynamics, eq. (17); continuum model, eq. (31); and the transition-state energy-barrier result, eq. (15), for $n = 1$, 5, and 10. The energy-barrier model is accurate over a much wider range than the thermodynamic result except for the case of a single barrier ($n = 1$), where the accuracies are comparable, both deviating from the continuum result by 5% at about $\Phi = 1$.

We conclude that the transition-state treatment of the energy-barrier model will be accurate, and superior to the thermodynamic treatment, as long as $n > 1$ and $\phi_i < RT$ (per barrier). These conditions are not very restrictive [18]. Consider an extreme case of a very thin lipid membrane; if we take $d = 50$ Å, then the number of barriers is at least $n = 10$ even if the diffusion jump distance is as large as $\lambda_0 = 5$ Å. The maximum electric field strength sustainable without dielectric breakdown is about 3×10^5 V/cm; this corresponds to a total potential drop across the membrane of 250 mV, and a value of $\phi_i/RT = 1.0$ with $\lambda_0 = 5$ Å. Thus the model will be accurate even for these rather extreme conditions. However, it would be wrong to treat such a membrane as a single barrier, because then $\phi_i/RT = 10$ and the model fails.

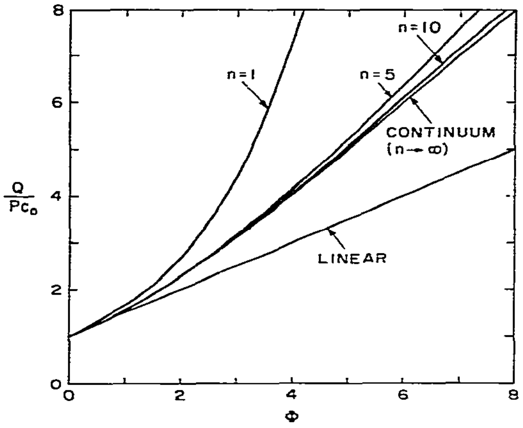

Fig. 2. Comparison of flux versus dimensionless driving potential for linear irreversible thermodynamics, continuum model, and transition-state energy-barrier model.

4. Barriers in series and in parallel

Within the range of accuracy of the transition-state treatment as discussed in the preceding section, namely $n > 1$ and $\phi_i/RT < 1$ (per barrier), the energy-barrier model shows several interesting and useful properties, especially when volume flow is the only external "force". We shall here mention two of them.

The first property concerns sets of barriers in series, with no other external force then volume flow. If all have the same value of B_n (not necessarily unity), then the flux Q is the same as if the arbitrary collection of barriers were replaced by a single set of uniform barriers of an overall permeability given by eq. (40). The proof is a straightforward generalization of the calculation given in the preceding section for two sets of barriers in series, or is a direct adaptation of the corresponding proof for open pores in series [27], and need not be repeated here.

The second property concerns sets of barriers in parallel. It is also ananlgous to a result first obtained for a pore model [27], but is here generalized to include other external forces than volume flow. In this case the flux Q as a function of Φ is not invariant in form as in the series case, but depends on the distribution of barrier heights among the parallel paths. Instead of a simple equation of the form of eq. (15), we have a complicated equation obtained by summing the contributions to Q from all the parallel paths (denoted here by a subscript j),

$$Q = \sum_j Q_j = \sum_j P_j \Phi_j \left(c_0 - \frac{\Delta c}{e^{\Phi_j} - 1} \right) B_j \, . \tag{44}$$

Results from this equation are not invariant, depending on the distribution of the P_j's, but definite mathematical bounds can be put on the possible values that Q may assume. In particular, we can obtain a lower bound by assuming that Q is represented by an expression like eq. (15), that is by one "average" term of the summation in eq. (44).

To form the lower bound, we first define an average permeability $\bar{P}$ by considering a measurement in the pure diffusion limit, where the voltage drop, the pressure drop, and the volume flow are all zero, so that $\Phi_j \to 0$. Eq. (44) then becomes

$$Q = -\sum_j P_j \Delta c \equiv -\bar{P} \Delta c \, , \tag{45}$$

which determines $\bar{P}$, in analogy to the rule that conductances add for electrical circuits in parallel. We next formally define an average total potential across the membrane, $\bar{\Phi}$, as

$$\bar{\Phi} \equiv \sum_j P_j \Phi_j / \bar{P} \, , \tag{46}$$

by analogy with the rule for current additivity in parallel electrical circuits. For an experimental definition of $\bar{\Phi}$ we refer back to eqs. (11) and (13) and note that each Φ_j consists of three terms, proportional to the voltage drop across the membrane, the pressure drop across the membrane, and the volume flow through the jth path, respectively. The voltage and pressure drops will be the same for each parallel path, and we can write the third term as proportional to the total volume flow,

$$\bar{\Phi} = (Z\mathcal{F}/RT)\Delta V - (\bar{V}/RT)\Delta p + \bar{g} Q_{\mathrm{v}} / \bar{P} \, , \tag{47}$$

where ΔV is the voltage drop, Δp is the pressure drop, and $\bar{g}$ is a mean coupling coefficient between volume flow and diffusion, defined by analogy with the g_α of the Nernst–Planck eq. (26). From eqs. (11), (13), and (46), the formal definition of $\bar{g}$ is obviously

$$\bar{g} \equiv \sum_j P_j \zeta_j Q_{\mathrm{v}j} d_j / Q_{\mathrm{v}} \, , \tag{48}$$

where ζ_j is the frictional coefficient and d_j the length of the jth path. An experimental determination of $\bar{g}$ can be made by setting ΔV and Δp equal to zero and measuring Q as a function of Q_{v} in the limit of almost pure diffusion – expansion of eq. (44) for this case of all Φ_j small but not zero yields

$$Q = -\bar{P} \Delta c + \overline{cg} \, Q_{\mathrm{v}} \, , \tag{49}$$

where $\bar{c} = (c_0 + c_n)/2$. Having defined $\bar{P}$ and $\bar{\Phi}$ both formally and experimentally we can now write the lower bound as follows (taking the $B_j = 1$ for simplicity):

$$Q \geqslant \bar{P} \bar{\Phi} \left(c_0 - \frac{\Delta c}{e^{\bar{\Phi}} - 1} \right) . \tag{50}$$

The proof of this inequality follows from the observation that Q_j as a function of Φ_j is concave upwards; for such functions, Jensen's inequality [34] states that the average of the function is always greater than or equal to the function of the average value of the independent variable. Eq. (50) is a direct statement of this inequality.

An upper bound for Q as a function of $\bar{\Phi}$ can be obtained by the same arguments used for the pore model [27]. It consists of a straight line that passes through the pure diffusion limit and is parallel to the asymptote approached by eq. (44) when all Φ_j are large. When $\bar{\Phi}$ acts in the same direction as the concentration difference ($\bar{\Phi} > 0$), the result is

$$Q = -\bar{P} \Delta c + c_0 \bar{P} \bar{\Phi} \, , \tag{51}$$

and when $\bar{\Phi}$ acts against the concentration difference ($\bar{\Phi} < 0$), the result is

$$Q = -\bar{P} \Delta c + c_n \bar{P} \bar{\Phi} \, . \tag{52}$$

These lower and upper bounds put strong restrictions on the numerical values allowed for Q. In fact, unless the distribution of permeabilities is rather peculiar, the value of Q will usually be within a few percent of the lower bound given by eq. (50). Numerical examamples of this assertion are given in ref. [27], where it is shown that the maximum possible error of the lower bound is 23%.

As a final comment, it can be shown [27] that the same bounds apply to internally connected sets of barriers arranged in series-parallel arrays.

5. Multicomponent mixtures

Thus far we have considered only the special case where the crossing of a barrier by one molecular species is independent of the behavior of any other species, except possibly the solvent (which couples through volume flow). The results are thus strictly applicable only to binary solutions, and it is pertinent to ask whether they can be extended to multicomponent mixtures. In principle the extension can be done by letting the $\Delta G_i^{\ddagger}$ at position i be different for different species. Such a generalization will require that the value of $\Delta G_i^{\ddagger}$ for one species depends also on the concentration distributions of all the other species in the vicinity of position i. Unfortunately, this generalization is likely to be only a formal trick of little practical utility, since the nature of such dependence is usually completely unknown. The nature of the problem may be clarified by consideration of the continuum case again, and the difficulty of integrating the transport equations, say eq. (22) for definiteness, for multicomponent mixtures. Even if all the coefficients $E_{\alpha M}$ and $E_{\alpha\beta}$ are taken as constants, the equations are highly coupled and analytical integration for more than two components is difficult [35]. A frequent approximation is to rewrite (22) so that the equations resemble those for a binary mixture, e.g. eq. (26), with some sort of "intrinsic" or "effective" diffusion coefficients. Such pseudobinary Nernst–Planck equations are only approximations to the full multicomponent equations, as is clear because fewer coefficients are involved. Although Nernst–Planck equations may be satisfactory approximations in some circumstances [23,24], they completely discard a number of striking effects that do not occur with binary mixtures, but only with three or more components. Examples are diffusion of a species against its concentration gradient, and development of density inversions with resultant convection (e.g., "salt fingers") [36]. Such effects can be formally retained in the Nernst–Planck equations by allowing the effective diffusion coefficients to depend on the gradients, but then the equations are at least as difficult to handle as were the original multicomponent equations.

We therefore regard the energy-barrier equations for multicomponent mixtures as analogous to the Nernst-Planck equations — they are useful only when a pseudobinary approximation is permissible. A special multicomponent case that is readily handled by this approximation is one that fortunately also occurs frequently in practice, namely a solution in which one component is in large excess. Each of the other components interacts only with the excess component (solvent) to a good approximation, and the solution acts like a collection of simple binary solutions.

6. Discussion

The most important conclusion from the present analysis is that the energy-barrier model has wide validity as a phenomenological model for membrane transport. It should almost always be preferred over the equations from irreversible thermodynamics, which are forced to be linear. Attempts to extend irreversible thermodynamics into nonlinear regimes are usually based on Taylor series expansions that introduce new transport coefficients. In contrast, the equations of the energy-barrier model give accurate results far into the nonlinear regime without the introduction of new coefficients. This success can be viewed as the result of an approximate integration via the transition-state treatment, subject to some simplifying assumptions. However, even when the conditions for the validity of such assumptions are not met, the results can still be quite accurate. In particular, the representation of a complex membrane by an equivalent collection of uniform barriers leads to an equation that gives a lower bound — eq. (50) with operational definitions of variables and coefficients from eqs. (45)–(40).

Two caveats on the use of an energy-barrier model should be noted. First, the transition-state treatment may introduce a nonphysical divergence at high electric fields or volume flows. This should cause no difficulty as long as $n > 1$ and $\phi_i < RT$ (per barrier), which are not very restrictive conditions. The explanation of real high-field nonlinearities must be sought outside the transition-state procedure. Secondly, the energy-barrier model for practical purposes cannot deal properly with general multicomponent mixtures. It is likely to be useful for systems describable by Nernst–Planck equations (i.e., pseudobinary mixtures), but otherwise has only formal significance.

Acknowledgement

This research was supported in part by the National Science Foundation under Grant ENG-76-07415.

References

[1] O. Kedem and A. Katchalsky, Biochim. Biophys. Acta 27 (1958) 229.
[2] A. Katchalsky and P.F. Curran, Nonequilibrium thermodynamics in biophysics (Harvard University Press, Cambridge, Mass., 1967) Ch. 10.
[3] K.S. Spiegler, Trans. Faraday Soc. 54 (1958) 1408.
[4] O. Kedem and A. Katchalsky, J. Gen. Physiol. 45 (1961) 143.
[5] K.S. Spiegler and O. Kedem, Desalination 1 (1966) 311.
[6] S. Glasstone, K.J. Laidler and H. Eyring, The theory of rate processes (McGraw-Hill, New York, 1941).
[7] H. Eyring and E.M. Eyring, Modern chemical kinetics (Reinhold, New York, 1963).
[8] H. Davson and J.F. Danielli, The permeability of natural membranes (Cambridge University Press, London, 1943) pp. 56–58 and Appendix A.
[9] B.J. Zwolinski, H. Eyring and C.E. Reese, J. Phys. Colloid Chem. 53 (1949) 1426.
[10] H. Eyring, R. Lumry and J.W. Woodbury, Rec. Chem. Prog. 10 (1949) 100.
[11] R.B. Parlin and H. Eyring, in: Ion transport across membranes, eds. H.T. Clarke and D. Nachmansohn (Academic Press, New York, 1954) pp. 103–118.
[12] F.H. Johnson, H. Eyring and M.J. Polissar, The kinetic basis of molecular biology (Wiley, New York, 1954) Ch. 14.
[13] H. Eyring, in: Molecular biology, ed. D. Nachmansohn (Academic Press, New York, 1960) pp. 77–85.
[14] V.S. Markin, Molek. Biol. 3 (1969) 610. [English translation, Molec. Biol. 3 (1969) 481].
[15] R. de Levie and K.M. Abbey, J. Theor. Biol. 56 (1976) 151.
[16] G.S. Manning, J. Chem. Phys. 49 (1968) 2668.
[17] J. Hogg and E.J. Williams, Proc. Roy. Soc. Edinburgh A70 (1971–72) 197.
[18] R. Schögl, Quart. Rev. Biophys. 2 (1969) 305.
[19] G.S. Manning, J. Phys. Chem. 76 (1972) 393.
[20] J.H. Gibbs, J. Chem. Phys. 57 (1972) 4473.
[21] J.H. Gibbs and P.D. Fleming III, J. Stat. Phys. 12 (1975) 375.
[22] G.S. Manning, Science 166 (1969) 1438.
[23] E.A. Mason and L.A. Viehland, J. Chem. Phys. 68 (1978) 3562.
[24] G.D. Mehta, T.F. Morse, E.A. Mason and M.H. Daneshpajooh, J. Chem. Phys. 64 (1976) 3917.
[25] A. Einstein, Z. Elektrochem. 14 (1908) 235; English translation in Investigations on the theory of the Brownian movement, ed. R. Fürth (Dover, New York, 1956).
[26] D.E. Goldman, J. Gen. Physiol. 27 (1943) 37.
[27] R.P. Wendt, E.A. Mason and E.H. Bresler, Biophys. Chem. 4 (1976) 237.
[28] E.W. McDaniel and E.A. Mason, The mobility and diffusion of ions in gases (Wiley, New York, 1973) Chs. 1 and 5.
[29] L.A. Viehland and E.A. Mason, Ann. Phys. (N.Y.) 110 (1978) 287.
[30] M.C. Mackey, Biophys. J. 11 (1971) 75, 91.
[31] M.C. Mackey and M.L. McNeel, Biophys. J. 11 (1971) 664, 675; 13 (1973) 733.
[32] E.H. Bresler and R.P. Wendt, Science 166 (1969) 1438.
[33] E.A. Mason, R.P. Wendt and E.H. Bresler, J. Chem. Soc. Faraday Trans. II 68 (1972) 1938.
[34] T.S. Ferguson, Mathematical statistics (Academic Press, New York, 1967).
[35] E.L. Cussler, Multicomponent diffusion (Elsevier, Amsterdam, 1976).
[36] J.S. Turner, Ann. Rev. Fluid [illegible] (1974) 37.