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A Binding Site Model of Membrane Transport: Binary and Cooperative Flows

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Summary. The flows of solute molecules in a membrane under the influence of concentration gradients are considered within the framework of classical physical theories. A lattice model is constructed in which the binding sites represent potential minima and the flows are regarded as a result of molecules' making discrete transitions between the binding sites.

Expressions for two-component currents are derived from certain descriptions for the transition mechanism. Where the molecular movement is given the crudest description, permeability coefficients are identical for both components and there is no current coupling. Where the molecular movement is given some finer detail, the permeability coefficients differ and positive coupling of flows appears. Our result applies to a combination of flows of tracer and abundant species as well as, more generally, to any combination of flows of two components which are distinguishable yet kinetically similar.

Also considered are binary currents whose transport mechanism is further controlled by allosteric cooperativity. Whether the cooperative control is short or long ranged, permeability coefficients and fluxes differ appreciably from those without cooperative control. Thus, unlike in the case of channel flow, current coupling here may be either positive or negative, depending on the strength and nature of cooperative coupling. Numerical evidence suggests that the permeability and coupling may have discontinuous behavior, possibly indicating the existence of phase transitions. Our lattice model, from which the formulations for the flows are obtained, is compatible with current concepts of membrane structure.

I. Introduction

Consider a thin, sheet-like membrane separating two baths, A and B, both filled with some solutions differing only in their concentrations,

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denoted respectively by c_A and c_B. The two baths are separately connected to their own reservoirs so that at all times the concentration difference $\Delta c = c_A - c_B$ is maintained at a fixed level at some given temperature. We shall assume that the system is near equilibrium, i.e., $|\Delta c| \ll c$, where c is the mean concentration defined as $c = \frac{1}{2}(c_A + c_B)$, and that the solutions are dilute, i.e., $c \approx 0$. For this work it is not necessary to specify the nature of the species (i.e., charge, geometry, etc.) forming the solutions. We shall assume for convenience that the transported species are neutral molecules with some regular shape. One can also consider charged as well as irregularly-shaped species with appropriate forces governing their interactions with the surroundings [7]. The above system, which can be thought of as representing an ideal limit of a number of real systems, is amenable to theoretical analysis.

With well-stirred solutions and in the absence of active transport, the flow of molecules, or the molecular current J, arises from the overall concentration gradient Δc. In a *linear* theory, the two macroscopic quantities J and Δc can be parametrically related by

$$J = \Omega \Delta c \tag{1}$$

where the coefficient Ω is a macroscopic parameter characterizing the permeability of the membrane with respect to the transport of a given species at a fixed temperature. The coefficient may be a function of the mean concentration. Equation (1) might be considered to represent an ideal flow.

One traditional method of studying the permeability is through the addition of tracer species to the solution which are easily detectable radioactive isotopes of the abundant species [20]. If the abundant and tracer currents do *not* interact or couple, one can also write an ideal form for the isotopic current J_o^* as

$$J_o^* = \Omega_o^* \Delta c^*. \tag{2}$$

If the mass difference between abundant and tracer species is negligible, one can assume that

$$\Omega_o^* = \Omega. \tag{3}$$

If the two currents *do* couple, then the isotopic current J^* is expected to satisfy a nonideal relation

$$J^* = \Omega^* \Delta c^* + \mu \Delta c. \tag{4}$$

In this case, permeability differentiation (i.e., $\Omega^* \neq \Omega$) and current coupling (i.e., $\mu \neq 0$) presumably arise from interaction of the two currents within the membrane [8].

Essig, Kedem, and Hill [4] have used simple models to study conditions for which Eqs. (1)–(4) can be realized. They consider the membrane as a regular lattice of sites where the permeating molecules are to be singly bound. In this picture, the current is then a sum of discrete transitions between neighboring sites. The transition rates are given *a priori* [10] (i.e., they are taken as parameters to be determined experimentally or to be deduced from a more fundamental theory). Essig *et al.* have studied only the analytically soluble cases of one and two component flows in the lattice model. Their solutions for mixed species, for example, are valid if, and only if, the concentration and concentration gradient of the tracer species are negligible compared with those of the abundant species. The transport mechanism employed in their work is also perforce of the simplest type.

Of special interest to us is the nature of the molecular movement within the membrane. Evidently, the molecular motions are not free as in solution but restricted owing to membrane structure. Thus, the membrane structure must manifest itself ultimately in the permeability.[1]

One prevailing picture of the membrane structure is that, at the grossest level, it is a grid-like arrangement formed primarily by units of lipid. Whatever constituents of the membrane are mainly responsible for the molecular movement (according to one current view, they are globular-shaped integral membrane-protein imbedded in a lipid matrix), this basic matrix-like structural pattern must influence transport. The lattice model (further described and discussed in Sections II and IV) represents this coarse picture of real membranes with a 3-dimensional regular network of binding sites. Now starting from the general lattice model, one can obtain various possible flows mentioned, e.g., single-file flows [6], by imposing some suitable controls on the transition mechanism (*see* Section II). One does not, of course, expect real membranes to exhibit periodicity as crystalline solids do. The lattice model, however, is a reasonable first approximation for membranes, especially for considering their transport properties.

We shall elaborate on the solutions of Essig *et al.* to bring out the physical significance of the lattice model. Our work includes a derivation

[1] In earlier days it was the tendency, perhaps owing to lack of information, to smooth out the structural details of the molecular movement within the membrane. *See*, for example, Zwolinski, B. J., *et al.*, 1949, *J. Phys. Colloid. Chem.* **53**:1426.

of the transport equations for two component flows. We have also included for the transport mechanism certain additional biological features such as allosteric cooperativity. These steps, it is hoped, will provide us with ideas for constructing a microscopic theory where the transport is considered truly at the molecular level. Finally, it is shown that the fomulations presented are compatible with current concepts of membrane structure.

In Section II, the current composed of two similar species is considered as a function of transition rates between sites in adjacent layers. In Section III, a special form of cooperativity is introduced in the transition mechanism. In Section IV, we discuss the physical significance of our transition mechanism. Some further justifications for the lattice model, including its biological relevance, are also given.

II. The Lattice Model and Two-Component Current

The membrane, which separates baths A and B, is viewed as being composed of n identical homogeneous layers. These layers will be labelled by l in the sequence $l=\{1,2,\ldots,n\}$, where the first ($l=1$) layer represents the layer immediately adjacent to bath A and the nth layer the layer immediately adjacent to bath B. Each layer is considered to be a two-dimensional lattice of N fixed sites whose positions are labelled by $\mathbf{r}$. Thus, the membrane is represented by a lattice of regular sites denoted by $\{l,\mathbf{r}\}$. According to the classical view, solute molecules are stationary about these lattice sites; and discrete transitions that the molecules make in going from the sites of one layer to the sites of a *neighboring* layer produce a flow in the system.

Let both solutions of baths A and B be made of two similar components I and II, such as isotopes, which are distinguishable but with essentially identical thermodynamic and kinetic characteristics. The state of a given site $\{l,\mathbf{r}\}$ is represented by $x_{l\mathbf{r}}^{(\nu)}$, where ν denotes the component I or II. If we assume that these sites can be occupied by single molecules only (no multiple occupancy), then $x_{l\mathbf{r}}^{(\nu)}=1$ or 0 depending on whether the site is occupied by the ν-component or not. The fraction of occupied sites in a given layer l is

$$x_l=\frac{1}{N}\sum_{\nu}\sum_{\mathbf{r}}x_{l\mathbf{r}}^{(\nu)} \tag{5}$$

where N is the total number of sites in each layer.

Each physical event at a site is associated with a kinetic coefficient. The rate coefficients for adsorption for the component v from baths A and B onto the surfaces are denoted, respectively, by $\alpha_A^{(v)}$ and $\alpha_B^{(v)}$, which are assumed to be proportional to their concentrations. This assumption is generally valid for low concentrations. The rate coefficient for desorption from an outer layer into the solution is denoted by β. Finally, the transition rate coefficient for going from a site of one layer to a site of an adjacent layer is denoted by k. Transitions within a given layer are ignored since they cannot contribute to the overall current in our homogeneous system. The transition coefficients depend on the nature of the surface and bulk states of the system arising from interaction between solute molecules and the membrane. In classical theories these rate coefficients cannot be calculated *ab initio* but must be given as parameters for the system.

The steady-state current for component v, directed from bath A to bath B, is then given by

$$J^{(v)} = \sum_{\mathbf{r}\mathbf{r}'} k(l\mathbf{r}; l'\mathbf{r}')[x_{l\mathbf{r}}^{(v)} \bar{x}_{l'\mathbf{r}'} - \bar{x}_{l\mathbf{r}} x_{l'\mathbf{r}'}^{(v)}] \tag{6}$$

where

$$\bar{x} = 1 - \sum_{v} x^{v}. \tag{7}$$

Here, l and l' are any pairs of adjacent layers (i.e., $|l-l'|=1$), r and r' are positions of sites in layer l and l', respectively. The expression for the current is valid if the states of sites are all independent, i.e., there exists no cooperativity (*see* Section III). Equation (6) can describe channeled or single-file flows as well as diffusive flows depending on the form of the transition coefficients k. To obtain the current from Eq. (6) it is necessary to evaluate the x's. For steady-state conditions it is possible to express the x's in terms of the kinetic coefficients and thereby to obtain the current as a function of the parametric coefficients.

Generally, the transition coefficients are functions of the intersite separation distances and certain other configurational factors of the sites. The most probable transitions for molecules may be those between nearest-neighbor (*n.n.*) sites in adjacent layers. If molecules are allowed to make such transitions only, then the resulting current has one-dimensional (or single-file) pathways. If molecules are allowed to make transitions to any vacant sites of neighboring layers, the resulting current is no longer one dimensional. If the transition probability is independent of relative intersite distances, then one obtains a mean-field-like picture for

the flow. It is evident that the transition mechanism as manifested in the form of transition coefficients k determines the nature of the flow uniquely. In the following we shall consider the two limiting cases (i.e., *n.n.* and mean-field) and deduce the resulting forms for the permeability.

A. Mean-field Description and Ideal Flows

The simplest and crudest form of the transition mechanism is

$$k(l\mathbf{r}; l'\mathbf{r}') = k/N \tag{8}$$

for all r and r' of adjacent layers. Then, under steady-state conditions, one can solve for the states of sites $x_i^{(v)}$ and the current $J^{(v)}$. For either component $v=I$ or $v=II$, the resulting current per site $j^{(v)}=J^{(v)}/N$ may be given as [1]

$$j_{MF}^{(v)} = \Omega_{MF} \Delta c^{(v)} \tag{9}$$

with

$$\Omega_{MF} = \frac{\beta k}{(\alpha+\beta)(\alpha+\beta+2k)} \tag{10}$$

where

$$\alpha = \alpha^I + \alpha^{II} \tag{11}$$

and

$$\alpha^v = \tfrac{1}{2}(\alpha_A^v + \alpha_B^v). \tag{12}$$

In obtaining the above form, it is assumed that $\alpha_i^{(v)} = g\, c_i^{(v)}$, where $c_i^{(v)}$ is the v-component concentration of ith bath ($i=A,B$), and g is a proportionality constant. This assumption is known to be valid for dilute solutions. We have ignored the possibility that the constant g may be weakly solution- or component-dependent and furthermore we set $g=1$ by adopting an appropriate set of units.

We observe that both currents behave ideally, i.e., the flow of one component has no effect on the flow of the other component. The permeability, furthermore, is uniquely defined, independent of the component label. The ideal form of the currents (Eq. (9)) may be understood from the nature of the approximation employed for the transition mechanism. The mean-field description masks finer details of the molecular transitions and each component thereby appears to behave as if the other is not present.

B. Nearest-Neighbor Description and Channeled Flows

The form of the transition mechanism which gives rise to channeled or single-file flows is

$$k(l\mathbf{r};l'\mathbf{r}')=k\delta_{\mathbf{r}\mathbf{r}'}, \tag{13}$$

for sites between adjacent layers ll', where $\delta_{rr'}=1$ if $r=r'$ and $\delta_{rr'}=0$ if otherwise. Under steady-state conditions, the resulting current for component $v=I$ is [1]

$$j^I_{NN}=\Omega^I_{NN}\Delta c^I+\mu^I_{NN}\Delta c^{II} \tag{14}$$

where

$$\Omega^I_{NN}=\Omega_{MF}\left[1-\frac{2k\alpha^{II}}{(\alpha+\beta)(\alpha+2\beta+4k)}\right] \tag{15}$$

and

$$\mu^I_{NN}=\Omega_{MF}\left[\frac{2k\alpha^I}{(\alpha+\beta)(\alpha+2\beta+4k)}\right]. \tag{16}$$

The current for component II follows directly from the above expressions through the exchange of the labels I and II.

We observe that the resulting current (Eq. (14)) is no longer ideal, depending on the other component explicitly. The departure from the ideal form of a current implies that the two components interact with one another within the channels, leading one current to be coupled to the other current. The strength of the coupling is indicated by the new coefficient μ, which we shall term the current coupling coefficient. Since μ is positive, we refer to the current coupling as positive; i.e., an increase in Δc^{II}, increasing j^{II}_{NN}, will also increase j^I_{NN}. The permeability is also changed from the ideal case by the presence of the other component and is no longer uniquely definable as in the mean-field case. The magnitude of the permeability, which is maximum for the ideal flow, is reduced.

It is useful to consider our solutions (Eqs. (14)–(16)) in some different limits. If we take the limit $\alpha\approx\alpha^I$, i.e., the second component has a tracer concentration only, then the permeability [Eq. (15)] reduces to the ideal form but the current coupling [Eq. (16)] still persists. The reduced expressions are both identical to those earlier obtained by Essig *et al.* Now if the two components are totally indistinguishable, i.e., $I=II$, the current is reduced to

$$j_{NN}=\Omega_{MF}\Delta c. \tag{17}$$

The same result is also obtained if the second component is not present at all, i.e., $c^{II}=0$. Actually it is a general result that whenever there exists

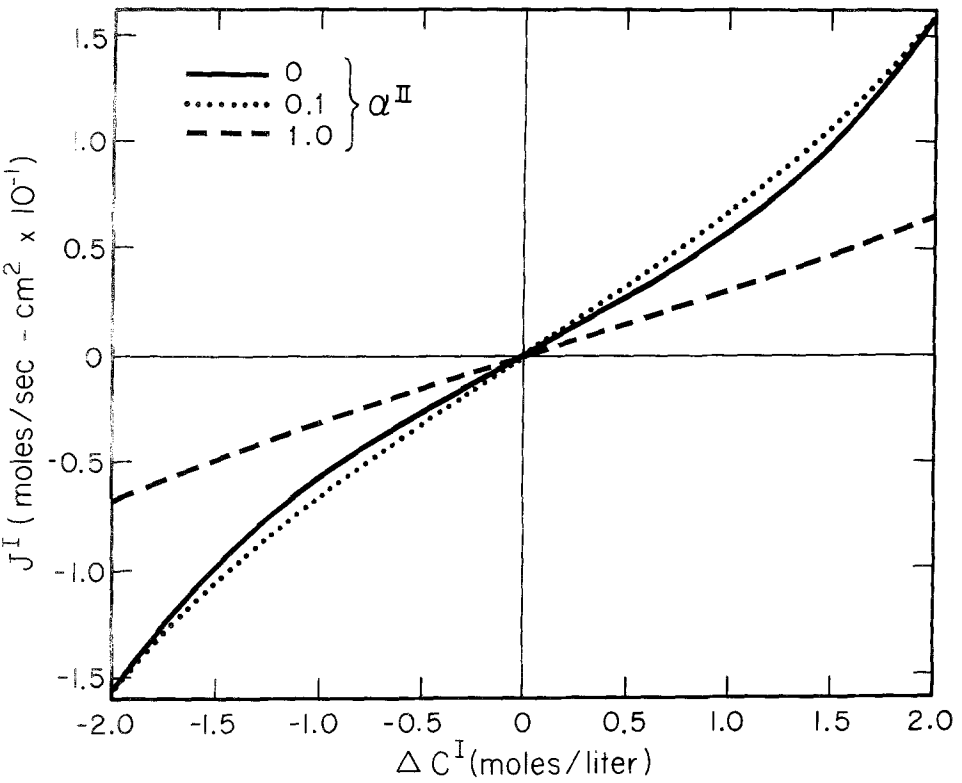

Fig. 1. J^I vs. Δc^I at $\Delta c^{II}=0$ for three values of α^{II} using the nearest-neighbor form of the transition mechanism. The permeability Ω^I_{MN} is given by the slope at $\Delta c^I=0$

only one component, both the mean-field and nearest-neighbor forms of the transition mechanism give formally the same ideal expression for the current [10].

An inclusion of additional layers in our treatment (which is limited to two layers) is expected to give a nonideal form of the current having the same general structure given by Eqs. (14)–(16). The form of the transition mechanism considered here thus can provide a complete description of single-file flows [5]. Biological examples of positive coupling may be found in the transport of Na^+, sugar, and amino acid [18].

The above analytic solutions are valid only in the linear regime, i.e., $|\Delta c| \ll c$. Outside this regime, one can obtain numerical solutions for the current. In Figs. 1 and 2, examples of numerical solutions for the current with the nearest-neighbor form of the transition mechanism are shown. We show in particular j^I and j^{II}, both as a function of Δc^I. For computational convenience we use for the rate coefficients the following

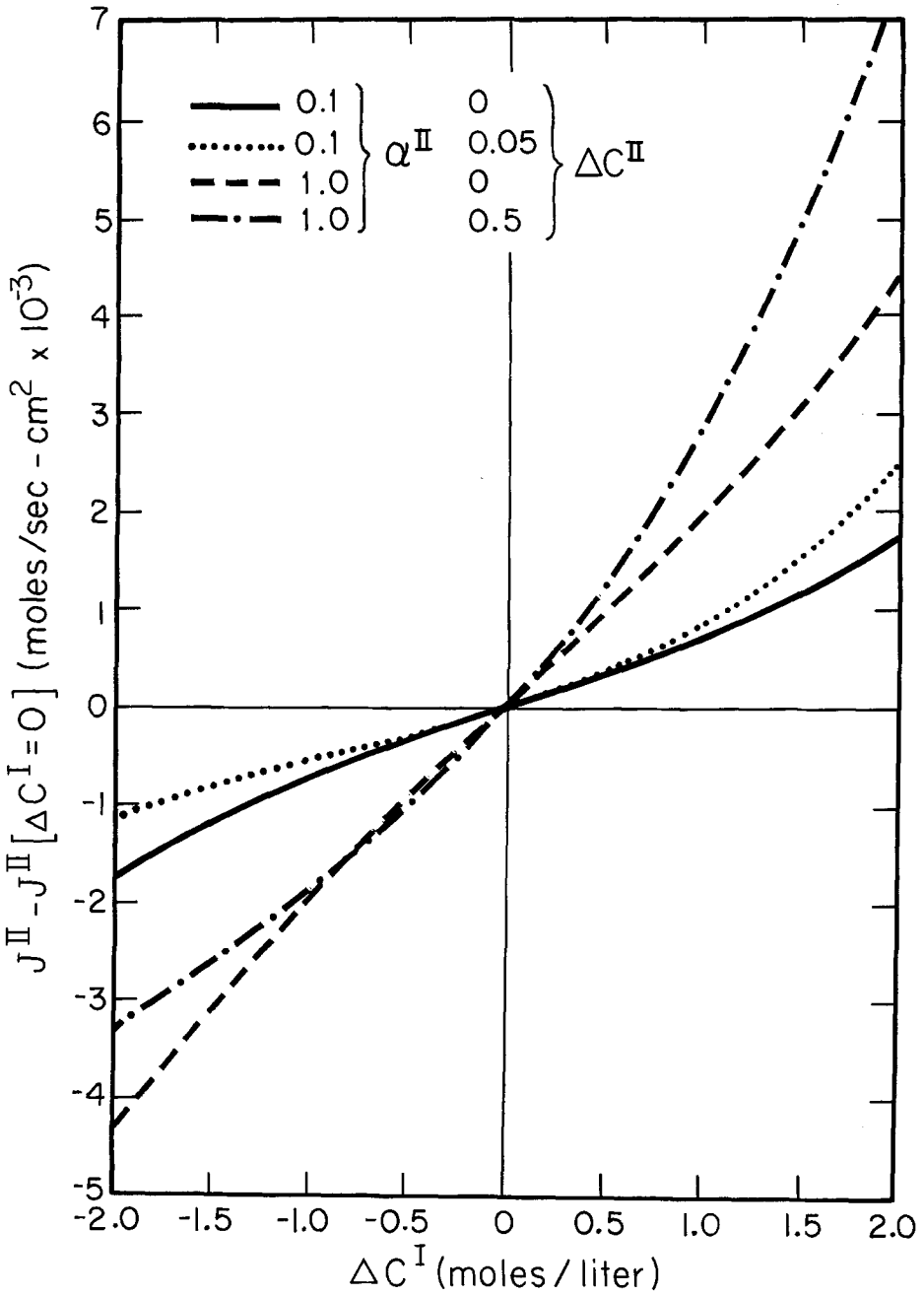

Fig. 2. Current coupling *vs.* Δc^I at various values of α^{II} and Δc^{II} using the nearest-neighbor form of the transition mechanism. Observe that $J^{II} - J^{II}(\Delta c^I = 0) = \mu^{II} \Delta c^I$ and μ_{NN} is given by the slope at $\Delta c^I = 0$. As α^{II} and Δc^{II} increase, the coupling appears to increase correspondingly. Zero slope means no current coupling

values, all in the units of moles per second:

$$\alpha^I = 1.000, \quad \beta = 0.7900, \quad \text{and} \quad k = 0.4200.$$

There is also the proportionality constant g (*see* Section II*A*) at our disposal. We have chosen $g = 1$ liter/sec cm^2, so that J and Δc appear in the familiar dimensions of moles/sec cm^2 and moles per liter, respectively. It must be noted that owing to our arbitrary choice for the physical parameters used in these numerical examples, only the relative, but not the absolute, values have any significance.

In Fig. 1, the solutions are set at $\Delta c^{II} = 0$ and the current j^I is examined for the dependence on Δc^I at three values of α^{II}. Evidently the flow of one component is reduced as the concentration of the other component rises. The range of the linear regime appears larger than expected. In Fig. 2, the effect of the current coupling is demonstrated, i.e., $j^{II} - j^{II}(\Delta c^I = 0) = \mu^{II} \Delta c^I$. If there were no coupling, the current j^{II} would be independent of Δc^I. What is shown here is a case of strong coupling. We may note that as the mean concentration of the second component approaches the value of the first component ($\alpha^{II} \to \alpha^I$), there appears a significant change in the j vs. Δc relationship.

C. Next Nearest-Neighbor Description and Modified Channeled Flows

If the *n.n.* form of the transition mechanism is relaxed to include more distant neighbors (e.g., next *n.n.*'s), the resulting flows are no longer one dimensional but assume the appearance of multiple crossed channels. Consider the following form which is the simplest extension of the *n.n.* form:

$$k(l\mathbf{r}, l'\mathbf{r}') = k_o \delta_{\mathbf{r}\mathbf{r}'} + k_1 \delta_{\mathbf{r},\mathbf{r}'-\mathbf{R}} \tag{18}$$

where k_o and k_1 are, respectively, the magnitudes of *n.n.* and next *n.n.* transition coefficients and R is the next *n.n.* distance. It is a simple matter to generalize the above to include more distant neighbors. If $z \ll 1$, where $z = k_1/k_o$, the flows are still dominantly channeled.

The current for the above form of the transition mechanism can best be obtained numerically. In Fig. 3, the current coupling is shown as a function of the concentration gradient at a few values of z. For computational simplicity, we allow one *n.n.* and also one next *n.n.* only and set $\Delta c^{II} = 0.0500$ moles per liter. The rate coefficients are (in the units of moles per second) $\alpha^I = 1.0000$, $\alpha^{II} = 0.1000$, $\beta = 0.7900$, and $k = 0.4200$. Our

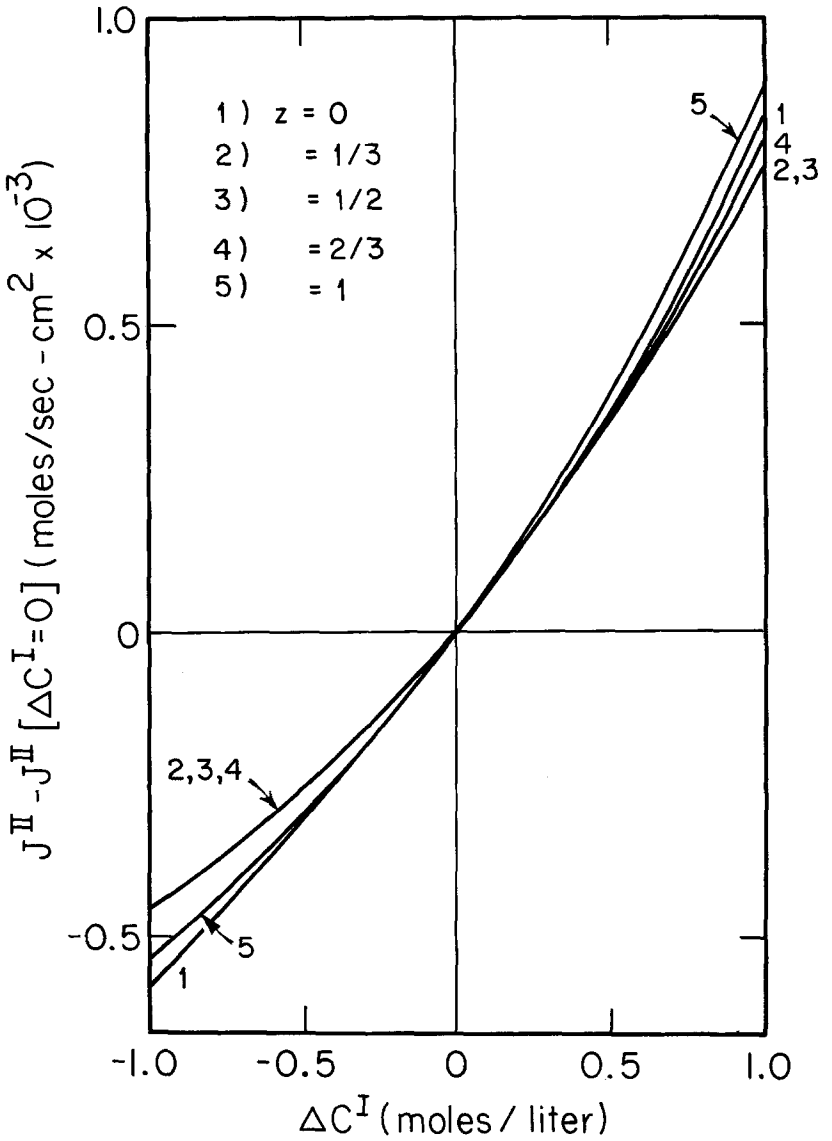

Fig. 3. Current coupling *vs.* Δc^I at various values of z (relative strengths of the nearest- and next-nearest neighbor transition rates as defined in the text). The addition of next nearest-neighbors does not appear to give any significant change in the current coupling.

results all exhibit current coupling as expected, but the coupling itself appears to depend little on z. For our choice of values of the parameters, the addition of next *n.n.*'s produces only small change in the current coupling. This result suggests that the *n.n.* form of the transition mechanism is sufficiently adequate for probing current coupling in channeled flows.

III. Cooperative Flows

Suppose that the structural units in the membrane, which act as binding sites for the solute molecules, change conformation upon being occupied. Then flows of molecules can be affected and controlled by the type of conformation that the system favors [3]. If sites in the same layer favor, for example, like-conformation (i.e., occupancy of one site enhances the likelihood of occupancy of other sites), then transport of molecules can be retarded. In this case, the processes of transport must first break the stabilizing conformation which usually raises the energetic requirement. In the allosteric cooperative phenomena, one may indeed encounter such a mechanism for flows of molecules which are fundamentally different from the mechanism governing noncooperative flows [19].

The cooperative current may be obtained form the simple binary current (Eq. (6)) by a suitable modification,

$$J^{\nu}(\sigma)=\sum_{\mathbf{r}\mathbf{r}'} k(l\mathbf{r},l'\mathbf{r}')[x^{\nu}_{l\mathbf{r}}\bar{x}_{l'\mathbf{r}'}S_{\sigma}(l\mathbf{r},l'\mathbf{r}') - \bar{x}_{l\mathbf{r}}x^{\nu}_{l'\mathbf{r}'}S_{\sigma}(l'\mathbf{r}',l\mathbf{r})]. \tag{19}$$

The transitions now depend on the cooperative factor S_{σ} which is defined as

$$S_{\sigma}(l\mathbf{r},l'\mathbf{r}')=1-\frac{1}{N}\sum_{\rho}\sigma_{r\rho}(1-2\bar{x}_{l\rho}) + \frac{1}{N}\sum_{\rho'}\sigma_{r'\rho'}(1-2\bar{x}_{l'\rho'}) \tag{20}$$

where σ_{ij} represents the dimensionless cooperative coupling strength between two sites i and j belonging to the same layer (i.e., intralayer sites) and N is the total number of intralayer sites. To exclude self-cooperative terms we shall define $\sigma_{ii}=0$. Sites belonging to different layers (i.e., interlayer sites) are considered to be cooperatively inactive in this treatment. The situation $\sigma_{ij}>0$ indicates that the like-conformation of intralayer sites i and j is favored and $\sigma_{ij}<0$ indicates that the unlike-conformation of intralayer sites i and j is favored. We will also require that the cooperative factor S_{σ} be nonnegative (i.e., $S_{\sigma}\geqq 0$) so that the cooperativity here can only either enhance or retard the transitions but not reverse the directions of the transitions. This generally imposes a maximum value on the cooperative coupling strengths σ.

Observe that as all $\sigma \to 0$, the cooperative current (Eq. (19)) reduces to the simple binary current previously obtained (Eq. (6)). It will thus be useful to develop the cooperative current perturbatively in terms of σ. The cooperative factor S_σ given by Eq. (20) is the simplest form which still can take into account adequately the full effect of two types of conformation. The first summed term of Eq. (20), for example, can be decomposed into two parts: $-\Sigma\sigma_{\mathbf{r}\rho}(1-2\bar{x}_{l\rho}) = -\Sigma\sigma_{\mathbf{r}\rho}(1-\bar{x}_{l\rho}) + \Sigma\sigma_{\mathbf{r}\rho}\bar{x}_{l\rho}$. These terms are related, respectively, to the fractions of sites in the l-layer being occupied and unoccupied. Thus, we have introduced through the cooperative factor S_σ the condition that a molecule, in making a transition from site $(l\mathbf{r})$ to site $(l',\mathbf{r}')$, is dependent also on the configurations of the initial and final layers. In a noncooperative flow (i.e., $S_\sigma = 1$ or all $\sigma = 0$), the transitions are functions only of occupied and unoccupied interlayer sites. The transitions are otherwise wholly unaffected by the configurations of the two adjacent layers.

The cooperativity of the form Eq. (20) is a special case of cooperativity generally found in statistical physics. The case of $\sigma > 0$ corresponds, notably, to the spins in the ferromagnetic ordering. Since to overturn a spin in this environment would require an expenditure of energy, the ground state of the system is ferromagnetically stabilized. Similarly, in a like-conformationally stabilized configuration, the transport requires an expenditure of energy and the dynamic processes are thus retarded. There exists a close formal analogy between the molecular conformation and spin ordering [17].

Our relatively simple form of S_σ can provide a considerable range of cooperative control via intersite coupling σ_{ij}. In the following section, we shall consider the current (Eq. (19)) when the cooperative coupling describes two special limits.

A. Long-Range Cooperative Mean-Field Current

Consider that for a given occupied site at i,

$$\sigma_{ij} = \sigma \tag{21}$$

for all other intralayer sites j. Since the given occupied ith site is uniformly influenced by the configurations at all other intralayer sites, this limit represents a form of long-range cooperativity.

With the above limit (Eq. (21)) and a mean-field description for the transition mechanism, one can obtain a closed form solution for the

steady-state current (Eq. (19)) [1]. Our result for $|\sigma| \ll 1$ is,

$$j^I_{MF}(\sigma) = \Omega^I_{MF}(\sigma)\,\Delta c^I + \mu^I_{MF}(\sigma)\,\Delta c^{II} \tag{22}$$

where

$$\Omega^I_{MF}(\sigma) = \Omega_{MF}[1 + \Lambda\sigma + O(\sigma^2)] \tag{23}$$

$$\Lambda = \frac{\alpha-\beta}{(\alpha+\beta)^2}\left(-3\alpha+\beta+\frac{(\alpha+\beta)^2+4\alpha k}{\alpha+\beta+2k}\right) \tag{23a}$$

and

$$\mu^I_{MF}(\sigma) = \frac{4\Omega^2_{MF}\alpha^I(\alpha-\beta)^2}{k(\alpha+\beta)^2}\sigma^3 + O(\sigma^4). \tag{24}$$

In these expressions, Ω_{MF} denotes the permeability in the absence of the cooperativity (*see* Eq. (10)).

Observe that in the limit $\sigma \to 0$, $\Omega^I_{MF}(\sigma)$ reduces to Ω_{MF} and μ^I_{MF} vanishes. To *first* order in σ, the permeability coefficient is still uniquely defined and there is no current coupling, i.e., the current is ideal. At higher orders of σ (i.e., $O(\sigma^3)$ and higher), both $\Omega^I_{MF}(\sigma)$ and $\mu^I_{MF}(\sigma)$ are present and the current is no longer ideal. These higher-order contributions, however, are insignificant when the cooperative strengths are weak, i.e., $|\sigma| \ll 1$.

For $\sigma \to 0$, it appears thus that the effect of cooperativity can be adequately described by a perturbative approach. Here, the cooperativity, in a sense, acts to perturb the mean-field description and brings out certain features which were previously glossed over. For finite σ (i.e., $|\sigma| \sim 1$) this approach may be inadequate. Numerical evidence (*see* Fig. 4 and next section) suggests that permeability and current-coupling behave discontinuously at some value of σ. This sort of information forecasts a breakdown of the perturbative approach and a possible existence of phase transitions.

B. Short-Range Cooperative Mean-Field Current

Next consider that for a given occupied site at i,

$$\sigma_{ij} = N\sigma \tag{25a}$$

if j are nearest-neighbor intralayer sites; and

$$\sigma_{ij} = 0 \tag{25b}$$

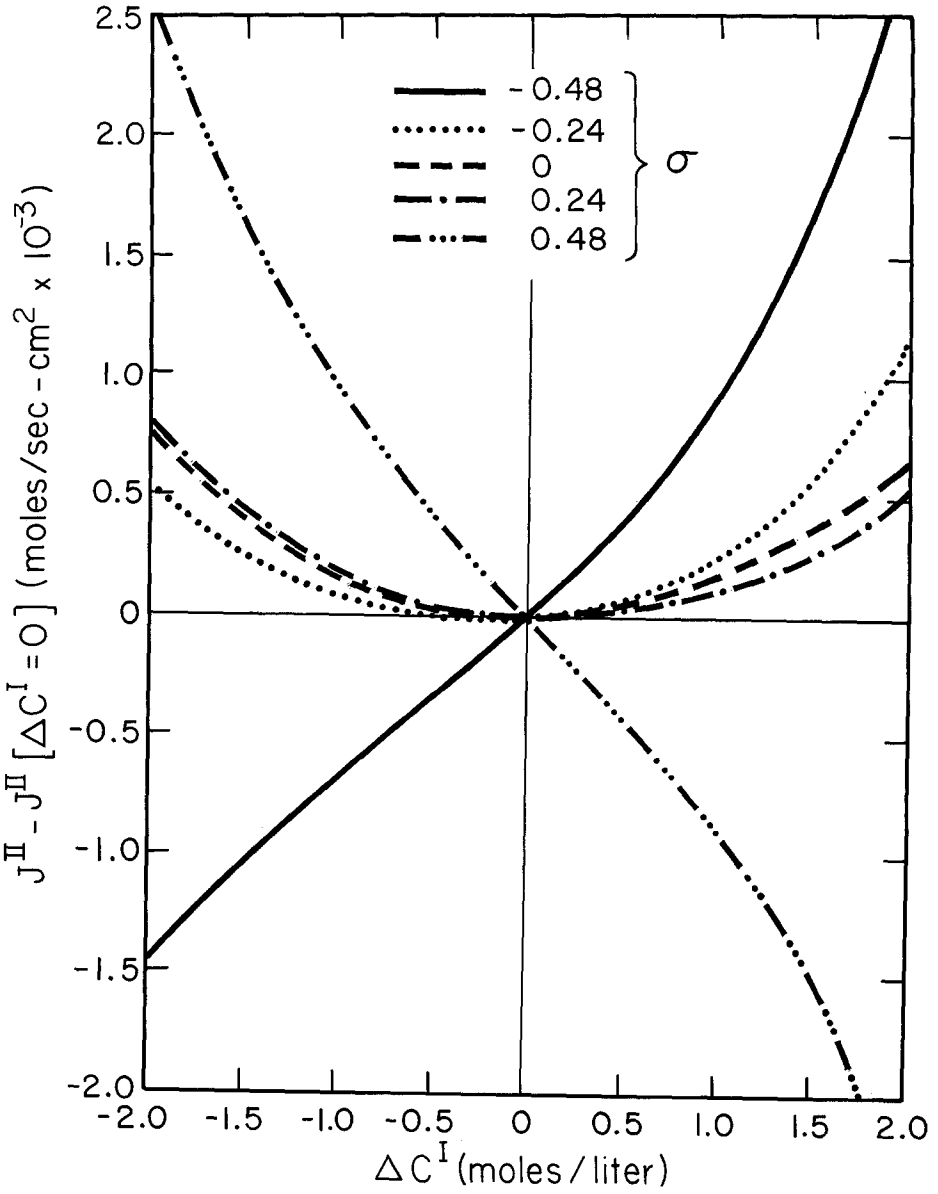

Fig. 4. Current coupling *vs.* Δc^I at various values of the cooperative strength σ. There is a marked dependence on the sign and magnitude of σ. Below a certain critical strength $|\sigma| = \sigma_c \approx 0.3$, the slope at Δc^I vanishes indicating the absence of coupling.

if otherwise. Since the given occupied *i*th site is influenced by the configurations at only nearest-neighbor intralayer sites, this limit represents a form of short-range cooperativity.

With the short-range limit (25a, b) and a mean-field description for

the transition mechanism (Eq. (8)), we have obtained a solution for the current numerically. We have numerically studied the case where there is only *one* nearest-neighbor intralayer site. Some of our results are displayed in Fig. 4.

In Fig. 4, current coupling for j^{II} is illustrated as a function of Δc^I for the range of $|\sigma| \leqq 0.48$ with $\Delta c^{II} = 0.0500$ and using only one *n.n.* intralayer site. For computational convenience, the rate coefficients are (in the units of moles per second) $\alpha^I = 1.000$, $\alpha^{II} = 0.1000$, $\beta = 0.7900$, and $k = 0.8400$. Observe that for $|\sigma| \leqq 0.24$, there is only minimal current coupling for a considerable range of Δc^I and it is almost symmetric about $\Delta c^I = 0$. At the extreme values $\sigma = \pm 0.48$, there is a large linear regime for the current coupling. The coupling is also almost antisymmetric about $\Delta c^I = 0$. In the two cases, the magnitudes of coupling are nearly the same, but the directions are reversed. Thus, unlike in the case of channel flow, current coupling here may be either positive or negative, depending on the strength and nature of cooperative coupling. For further numerical details, *see* our ref. 1.

IV. Discussion

We have constructed a classical lattice model of sites in which the flows, driven by concentration gradients, are obtained as a first approximation to passive transport processes observed in real membranes. In obtaining the flows of mixed molecular species, two types of transition mechanism are considered: the mean-field and *n.n.* descriptions, with the former giving an ideal form of the current equation and the latter a nonideal form. In some transport processes, cooperativity is believed to play a role. To account for such cooperative flows, we have introduced an additional control into the transition mechanism via a conformational cooperativity between neighboring sites.

The physical picture we have envisioned is that molecules, upon being adsorbed at a surface, undergo a series of discrete transitions and finally become desorbed at the other surface. In doing so, these molecules overcome a potential barrier. On the molecular scale, the potential across the width of the membrane cannot be uniform and must contain a number of attractive regions. To be bound or captured at these regions, the permeating molecules must possess energies E in some range

$E_1 < E < E_2$, where E_1 is a threshold energy needed to be adsorbed initially at the surface and E_2 is a barrier height. To go over into neighboring regions, the molecules must gain energy beyond E_2 through scattering with other molecules directly or indirectly mediated by the membrane. By such a sequence of transitions, the molecules ultimately reach the second surface. The permeability of a membrane, thus, must reflect these multiple scattering steps that the molecules undergo.

Now in constructing our lattice model, we assume that the attractive regions are localized sites and that the arrays of these sites are uniformly distributed throughout the membrane forming a regular lattice. The lattice model and the attendant discrete nature of molecular motions may seem highly idealized. In statistical physics, however, analogous cell models for liquids, for example, are commonly used and they are known to give a very satisfactory account for a variety of observed liquid properties [9]. Hence, it seems reasonable to us to study the molecular movement on the basis of this model, on which refinements can later be built.

More seriously, classical treatments of the lattice model including this work suffer from some fundamental defects. Although these treatments purport to describe the flows in a membrane at the molecular level, their descriptions are a grossly averaged picture of molecular processes. The assumption that transitions are linear functions of the fractions of vacant sites can be valid only as a long-time average. The classical current equations depend on kinetic parameters which must be *a priori* given (and they are often not readily measurable). Perhaps the most serious defect is that molecular transitions are a dynamic manifestation of the system, i.e., cooperative. The classical treatments of this kind, being static in nature, cannot adequately describe the dynamic processes. One must overlook the fluctuations in the states of sites x, the time evolution $x(t)$, etc.; and, instead, one must be satisfied with the time behavior, for example, given only asymptotically in a steady-state limit. Within these limitations, we can nevertheless use the classical treatments to interpret appropriate experimental results, thereby gaining some insight into the molecular processes of transport.

In recent years considerable effort has been directed at elucidating the structure and function of biological membranes. With respect to permeation, membranes are shown to be susceptible to external conditions and selective in types of ions being transported. There are

indications that membranes exhibit a special kind of cooperativity as well. This sort of evidence suggests that the membrane has a dynamic structure and is more than a static potential barrier. That is, the membrane potential itself is time-dependent and, as a result, the attractive potential regions may be nonstationary.

It is, of course, important to inquire as to the relevance of our idealized theoretical treatment for mechanics of transport in biological membranes. It might seem that transport by way of regular lattice structures is inconsistent with the generally accepted asymmetric fluid mosaic model of Singer and Nicolson [16]. As pointed out by Oldfield, however, although some membrane lipid must be in a fluid condition, the "techniques of differential scanning calorimetry, X-ray diffraction, nuclear magnetic resonance (NMR), electron spin resonance (ESR), and monolayer studies have yielded evidence that ... large quantities of lipid may be quite rigid or crystalline" [12]. In response, Singer stated, "If part of the lipid is crystalline and the remainder is fluid ... there is no conflict with our fluid mosaic model of membrane structure" [15].

The concept that a biological transport system may resemble a linear lattice is long-standing, following Hodgkins and Keynes's demonstration that the interaction between potassium ions in the squid axon is of the kind expected if ions move through the membrane in a single file [6]. Morphological evidence suggests that multiple-subunit proteins might possibly account for this effect, although the evidence is as yet incomplete. As noted by Singer [14], "Subunit pores ... often contain narrow water-filled channels ... and similar membrane proteins could thereby provide specific pores across a membrane." Examples include the water-filled channel in the center of the tetrameric hemoglobin molecule [13], and the allosteric enzyme, glutamine synthetase of *E. coli*, which exists in solution as an aggregate of 12 identical subunits arranged in two hexagonal rings with a hole running down the central axis [21].

Several workers have invoked more extensive regions of symmetry in the interpretation of apparent membrane cooperativity. Thus, in an extension of the theory of regulatory enzymes, it is attempted to correlate membrane cooperativity with the organization of constitutive liproteic elements into highly ordered, symmetric oligomeric or infinite lattice structures, depending on the size of the cooperative assembly [2, 3].

Recent advances in microscopy indicate that structural evidence for periodicity is not artefactual, as was considered earlier. To quote Wallach [22], "More and more micromorphologic evidence, particularly from freeze-etching experiments, indicates that large membrane areas

consist of a periodic array of discrete morphological units (*i.e., lattices*). This is particularly prominent in the so-called "nexuses" between cells, which might be sites for ionic and other intercellular communications" [11].

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