

# Facilitated Transport via Carrier—Mediated Diffusion in Membranes:

## Part II. Mathematical Aspects and Analyses

Part II of this review is concerned with the mathematical analysis of facilitated transport. An exposition is given of the most generally useful techniques for obtaining asymptotic or approximate solutions to one-dimensional carrier-mediated diffusion in membranes, involving multiple permeant and carrier species which undergo one or more chemical reactions. Primary emphasis is devoted to the limiting regimes of weakly-perturbed membranes (small driving forces) and slow or fast reactions (small or large Damkohler numbers). Many of the results appearing in the literature are unified and extended, and a systematic procedure for using these to estimate membrane performance is put forth. Finally, some areas for further work are identified.

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### SCOPE

In Part I\* of this review (Schultz et al., 1974) we have discussed mechanisms, experimental systems, and characteristic regimes of carrier-mediated diffusion through membranes. As pointed out there, the focus of our review is on membrane systems which are globally nonreactive in the steady state and in which the internal transport mechanism is postulated to consist solely of molecular diffusion accompanied by homogeneous reaction of permeant or volatile species with entrapped carriers or non-volatile species.

Then, with the assumption of constant diffusivities, the steady state behavior of these systems is governed by well-known field equations of the form

$$D \cdot \nabla^2 C = -r(C) \quad (I 4.1)$$

As defined in Part I, a carrier-mediated transport system has associated with it a rather characteristic boundary-value problem for (I 4.1), including zero-flux conditions on nonvolatiles and prescribed conditions on volatiles at the boundary of the system of interest, together with a set of stoichiometric restrictions on the kinetic function  $r(C)$  and an associated set of volume-integral constraints for system-composition invariants.

The purpose here in Part II is to provide a somewhat unified approach to the mathematical treatment of such problems.

After a brief discussion in Section 1 of the possible reductions of the problem based on stoichiometric considerations, a detailed review is given, together with extensions, of what the authors judge to be the most promising technique for attacking such problems, based on a combination of asymptotic and approximate solutions appropriate to the various regimes of membrane diffusion.

Section 2 provides a general solution for linearized kinetics, appropriate to weakly-perturbed systems or small driving forces, and the relation to linear-thermodynamic analyses is established. Permeant-flux computations are reduced here to the algebraic task of determining the relevant membrane resistance tensor or matrix.

Section 3 deals briefly with the regular-perturbation analysis appropriate to small Damköhler numbers or slow reactions and the near-diffusion regime. Then, an exposition is given of the asymptotic boundary-layer or singular-perturbation analysis for large Damköhler numbers or rapid reactions and the near equilibrium regime. A detailed discussion is devoted to a strong boundary-layer analysis applicable to the singular regime of rapid, nearly-irreversible reaction or carrier-dominated diffusion where shock-like reaction layers occur. At the same time, a general extension of a previous approximate technique for solution to this problem is presented since it has been found to give remarkably accurate and rapid predictions well into the nonequilibrium regime for several systems. The computation of permeant fluxes reduces, then, to one of solving a nonlinear equilibrium problem for concentration distributions in the core of the membrane, coupled with the computation of boundary-layer resistance tensors or matrices, for determining reaction-layer discontinuities at the membrane boundaries.

Together with a review of the above techniques, their most direct extensions are given, as new results, for application to complex problems involving multiple competing permeants and carriers with multiple reaction pathways.

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\* Errata for Part I appear on page 831.

## CONCLUSIONS AND SIGNIFICANCE

In the absence of convection and electric-field effects, it appears possible now to estimate mathematically, with some confidence, the steady state performance characteristics of highly complex carrier-mediated membranes, given the requisite kinetic, equilibrium, and diffusion constants. In many cases, predictions can be obtained by relatively straightforward and rapid analytical methods, based on asymptotic or approximate formulae.

The most useful and generally applicable results appear to be, roughly in the order of complexity and applicability,

1. The classical type of reaction-equilibrium approximation for investigating nonlinearities in the driving force or concentration gradients and the effects of transport parameters and binding constants,

2. The linearized-kinetic formulae for investigating reaction-rate limitations and nonequilibrium departures from 1, provided the linear approximation is valid in the equilibrium regime, that is, provided it gives reasonably accurate prediction of equilibrium fluxes under the im-

posed driving force, and, if not,

3. A strong boundary-layer analysis, based on extensions proposed here of an approximate method due to Kreuzer and Hoofd (1972) and Smith et al. (1973), to replace 2, together with

4. Near-diffusion or slow-reaction, perturbation formulae to determine the approximate lower limits of validity of 3.

At the very least, it appears that such formulae can provide useful information about the likely operational regimes and some valuable guidelines for the application of more difficult, numerical methods or the development of special approximate methods.

In the summary, suggestions are made for some further theoretical work, including extensions to other interesting geometric configurations and to unsteady operation, as well as to systems with electric-field and convection effects.

### 1. REDUCTION OF THE BASIC EQUATIONS AND APPLICATION TO ONE DIMENSION

Here, we wish to review and extend, in a formal way, the most important mathematical methods that have been used to analyze (steady state) carrier-mediated diffusion in membranes. As indicated in Part I,\* and here in Appendix 1, we shall assume for our discussion an elementary model of multicomponent diffusion in which diffusive coupling is admitted ( $D_s^m$  not necessarily zero for  $m \neq s$ , in Equation (I 3.45)), but where the diffusivities  $D_s^m$  are treated as constants and forced-diffusion or migration effects are not explicitly considered. These assumptions allow for some immediate reduction of the relevant field equations through direct application of the reaction-invariance established in Part I.

As a first step in this reduction and by way of establishing a connection between the general problem and the special case of linear kinetics to be discussed below, we employ the transformation of variables suggested by (I 3.32). Specifically we use the transformation to effect a change of basis by introducing a set of basis vectors  $E_i$ ,  $i = 1, 2, \dots, S$  with components  $E_i^s$  chosen as in (I 3.32), such that the first  $R'$  of these ( $i = 1, \dots, R'$ ) correspond to reaction invariants. Given any such basis, it is well known that there exists a reciprocal basis, say  $E^i$ ,  $i = 1, \dots, S$ , such that

$$E^i \cdot E_j \equiv (E^{-1})_s^i E_j^s = \delta_j^i, \text{ for } i, j = 1, \dots, S \quad (1.1)$$

where the components,  $(E^{-1})_s^i$ , of  $E^i$  define of course the inverse transformation (matrix) for (I 3.39). Since the last  $R$  vectors of the reciprocal basis,  $E^i$ ,  $i = R' + 1, \dots, S$  are orthogonal to the first  $R'$  stoichiometric invariants  $E_i$ ,  $i = 1, \dots, R'$ , in the original basis, their components  $(E^{-1})_s^i$  are seen by (I 3.24) to represent an admissible set of stoichiometric coefficients for the ( $R$ ) independent reactions.

In the notation of (I 3.30) and (I 3.31), the species concentration and diffusion flux are expressible then as

$$C = \xi_i E^i \quad \text{and} \quad \vec{J} = \vec{j}_i E^i \quad (1.2)$$

We can express the product  $D \cdot C$  as

$$D \cdot C = X_i E^i \quad (1.3)$$

such that

$$X_i = E_i^s D_s^m C_m \quad \text{and} \quad C_s = (D^{-1})_s^m (E^{-1})_m^i X_i$$

(which corresponds formally to the introduction of a yet another basis,  $D^{-1} \cdot E^i$ , *vide infra*).<sup>\*</sup> Equations (I 4.1) and (I 4.2), when expressed in terms of the components  $X_i$ , take on the simpler forms

$$\vec{j}_i = -\vec{\nabla} X_i \quad (1.4)$$

and

$$\nabla^2 X_i = -\omega_i \quad (1.5)$$

for  $i = 1, \dots, S$ . Since the first  $R'$  components of the reaction term vanish identically, in (1.5) as in (I 3.33), some reductions are immediately possible. In Appendix 2, this reduction is used to show that the specification of  $I'$  integrals invariants of the type (I 3.38) is necessary for unique solution to a general problem in three spatial dimensions. However, we are mainly interested here in the application to membranes where further simplifications are in order.

If we restrict our discussion to the usual steady state experiment on membranes, conditions are such that one-dimensional diffusion results, and the corresponding forms of the field equations (I 4.1) with  $\nabla^2 \equiv (d/dx)^2$  are applicable. Here,  $x$  measures normal distance through the membrane, from one of its interfaces  $x = 0$  to the other  $x = L$ , both of which then serve as system boundaries. In this situation, further integrations of the reaction-free equations in (1.5) are possible, and one obtains the following as the  $R'$  integrals:

$$X_i = -(j_i x + b_i), \text{ with } j_i, b_i \text{ constants for } 0 \leq x \leq L, \\ i = 1, \dots, R',$$

and

$$j_i \equiv 0, \text{ for } i = F + 1, \dots, R' \quad (1.6)$$

The constants  $j_i$  which vanish follow from the more general results established in Appendix 2, whereas the remain-

\* Part I of this review, Schultz et al., *AICHE J.*, 20, 417 (1947). Equations of Part I are cited herein with Roman Numeral I as prefix.

\* Appendices 1 and 3, especially.

ing nonzero  $j$ 's are given by

$$j_i \equiv E_i^s J_s(x), \quad \text{for } i = 1, \dots, F, \quad (1.7)$$

and are simply the constant diffusional fluxes of the reaction invariants or radicals associated with the volatile species.

Thus, the mathematical problem reduces to that of solving the  $R$  simultaneous second-order differential equations remaining in (1.5), the number  $R$  being equal to the number of stoichiometrically-independent reactions. The solution must satisfy the one-dimensional form of the boundary conditions (I 4.2) on the nonvolatile species and the conditions

$$C_v = \begin{cases} \bar{C}_v & \text{at } x = 0 \\ C_v & \text{at } x = L \end{cases} \quad \text{for } v = 1, \dots, F, \quad (1.8)$$

or some other appropriate conditions on the volatiles, at  $x = 0, L$ .

Because of (1.6), both sets of boundary conditions (I 4.2) and (1.8), as well as the nonzero reaction rate terms  $\omega_i$  in (1.5), will generally involve implicitly the constants of integration  $j_i$  and  $b_i$ . These constants are of course unknowns ultimately to be determined through the boundary conditions and the  $I'$  integral constraints of (I 3.38), which can be expressed as

$$C_{\text{tot}}\{E_i\} = \frac{1}{L} \int_0^L \xi_i dx \\ \equiv \frac{1}{L} E_i^m (D^{-1})_m^s (E^{-1})_s^j \int_0^L X_j dx \quad (1.9)$$

for  $i = F + 1, \dots, R'$ , where  $C_{\text{tot}}\{E_i\}$  is some prescribed, mean initial concentration of a composition invariant  $E_i$  in the system.

The determination of the  $j_i$ ,  $i = 1, \dots, F$ , is an essential part of the problem, since these constants determine the flux of the volatiles through the membrane. Thus, from the form of the transformation (I 3.32) and its inverse, one concludes immediately that the desired fluxes are given in terms of the  $j$ 's by

$$N_v \equiv J_v(0) \equiv J_v(L) = \sum_{i=1}^F (E^{-1})_v^i j_i \quad (1.10)$$

where, as before,  $v = 1, 2, \dots, F$ , refers to the volatiles.

By means of (I 3.31), the preceding relation for transmembrane flux can be put into the form

$$N_v = Z_v^m J_m(x), \\ Z_v^m = \sum_{i=1}^F (E^{-1})_v^i E_i^m, \quad m = 1, \dots, S, \quad (1.11)$$

where the  $Z_v^m$  are the transport numbers previously defined in (I 3.43). Hence, upon application of (1.8) and (I 3.44) with constant  $D_s^m$  the flux relation cited previously, (I 3.47), follows:

$$N_v = Z_v^m D_m^s [C_s(0) - C_s(L)]/L \quad (1.13)$$

The above reductions can be useful for theoretical purposes, for example, as used in Appendix 2, or for practical purposes, such as numerical solution of the differential equations. However, in the analysis to follow, it will not be necessary to make explicit use of such reduction because it is already implicit in the various (linear-algebraic) formulae involved.

Thus, unburdened by the explicit notational apparatus for invariants, the results of the analysis become easier both to state and to comprehend. Nevertheless, in Ap-

pendix 1 it is shown how the basic transport equations can be cast in terms of invariants and extents of reaction for purposes of relating the present treatment to other works on the subject, particularly the linearized thermodynamic analyses.

## 2. LINEAR KINETICS

### General Solutions for Steady Membrane Diffusion with Constant Diffusivity

In terms of a dimensionless distance coordinate  $x/L$ , which we shall also denote by  $x$ , Equation (I 4.1) reduces for constant  $D$  to

$$\frac{d^2 C}{dx^2} = \mathbf{\Gamma} \cdot C \quad (0 < x < 1) \quad (2.1)$$

with

$$\mathbf{\Gamma} = (L)^2 D^{-1} \cdot \mathbf{K}$$

It is possible to write down immediately the appropriate formal solution to (2.1) which, as a generalization of the equivalent scalar equation, is

$$C - \langle C \rangle = h \left( \mathbf{\Lambda}, \frac{1}{2} - x \right) \cdot \bar{\Delta} C \quad (2.2)$$

where

$$(\mathbf{\Lambda})^2 = \mathbf{\Lambda} \cdot \mathbf{\Lambda} = \mathbf{\Gamma} \quad (2.3)$$

and  $h(\mathbf{\Lambda}, Z)$  is the tensor\* (or matrix) generalization of the scalar function

$$h(\lambda, Z) = \frac{1}{2} \sinh(\lambda Z) / \sinh(\lambda/2) \quad (2.4)$$

defined on scalar variables (real or complex)  $\lambda$  and (real)  $Z$ . Also, the vectors

$$\langle C \rangle = (\bar{C} + C)/2 \quad (2.5)$$

$$\bar{\Delta} C = \bar{C} - C$$

appearing in (2.2), are related to the (mean and difference of), as yet unassigned boundary values for  $C$ , say

$$C = \bar{C} \quad \text{at } x = 0, \quad \text{and } C = C \quad \text{at } x = 1 \quad (2.6)$$

In this way, one obtains formally the transmembrane flux as

$$N = (J)_{x=0} = -D \cdot \left( \frac{dC}{dx} \right)_{x=0} = P \cdot \bar{\Delta} C \quad (2.7)$$

with

$$P \stackrel{\text{def}}{=} \frac{D}{L} \cdot \left[ \frac{\mathbf{\Lambda}}{2} \coth \left( \frac{\mathbf{\Lambda}}{2} \right) \right] \quad (2.8)$$

where, again, a generalized scalar function is implied.

Equation (2.7) gives the flux  $N$  in terms of the driving force  $\bar{\Delta} C$  and a (symmetric or self-adjoint) permeability tensor  $P$ , that is,

$$N_s = P_s^m \bar{\Delta} C_m \quad (2.9)$$

for  $s = 1, \dots, S$ . There are several standard matrix theoretic methods by which the tensor  $P$  can be made explicit as discussed below. First, however, one may put (2.7) into a form appropriate to carrier-mediated diffusion, where we have as prescribed conditions:

\* We have chosen to use the designation *tensor* (as opposed to *matrix*) for the various linear transformations discussed here. We feel this is justified by the invariance (under affine transformations) of the basic equations and the considerations of Appendix 1. In the present context no confusion with physical-space tensors is likely to occur.

$$N_n = 0; \text{ with } \bar{C}_v, \underline{C}_v \text{ and, hence, } \bar{\Delta}C_v = \bar{C}_v - \underline{C}_v \text{ given} \quad (2.10)$$

where, in the notation of Part I,  $v = 1, \dots, F$ , refers to volatiles and  $n = F + 1, \dots, S$ , to nonvolatiles.

Then one can verify that the partition referred to in Part I, Section 3, is realized explicitly in the linear analysis at hand. Here the problem is evidently similar to one involving two species in which the components in (2.10) are given while  $N_v, \bar{\Delta}C_n$  are regarded as unknowns. The formal solution is therefore obvious, when stated in terms of the corresponding partition (for the matrices) of the permeability tensor  $\mathbf{P}$  and its inverse, the resistance tensor  $\mathbf{\Omega}$ , say,

$$[\mathbf{P}] = \begin{pmatrix} P_t^v & P_t^p \\ \vdots & \vdots \\ P_n^v & P_n^p \end{pmatrix} \text{ and } [\mathbf{\Omega}] = \begin{pmatrix} \Omega_t^v & \Omega_t^p \\ \vdots & \vdots \\ \Omega_n^v & \Omega_n^p \end{pmatrix} \quad (2.11)$$

for  $v, t = 1, 2, \dots, F$ , and  $n, p = F + 1, \dots, S$ , where

$$\mathbf{\Omega} \stackrel{\text{def}}{=} \mathbf{P}^{-1} \quad (2.12)$$

The desired relation between the transmembrane flux of volatiles  $N_v$  and their driving force  $\bar{\Delta}C_v$  is readily found, then, by application of (2.7), (2.10) and (2.11) to be

$$\bar{\Delta}C_v = \Omega_v^t N_t$$

that is,

$$\bar{\Delta}C_s = \sum_{n=1}^F \Omega_s^m N_m, \text{ for } s = 1, \dots, F \quad (2.13)$$

where  $\Omega_s^m$  denotes, of course, the components of  $\mathbf{\Omega}$ . The inverse form of (2.13), giving flux in terms of driving force can, in principle, be obtained by matrix inversion.

At any rate, the problem of finding the flux of volatiles is reduced to the purely algebraic task of determining the relevant components of the resistance tensor, which, in turn, can be carried out formally by means of the eigenvalue problem for the tensor  $\mathbf{\Gamma}$  of (2.1). This problem has received numerous applications in related works (see Ulanowicz and Frazier, 1968) but most often it is used in treating the differential equations themselves. In some cases this tends to obscure the formal simplicity of the resultant solutions.

In the problem at hand, one has simply to choose the last  $R$ , otherwise arbitrary basis vectors  $\mathbf{E}_i, i = R' + 1, \dots, S$ , and the  $R$  elements of the reciprocal basis  $\mathbf{E}^i, i = R' + 1, \dots, S$ , to be related, respectively, to the  $R$ , presumably distinct eigenvectors of  $\mathbf{\Gamma}^T$  and  $\mathbf{\Gamma}$ , corresponding to nonzero eigenvalues, say  $\lambda_i^2 = (\lambda_i)^2$ , as follows:

$$\mathbf{E}_i = \mathbf{D}^{-1} \cdot \mathbf{u}_i, \text{ that is } \mathbf{E}_i^s = (D^{-1})_m^s \mathbf{u}_m^i \quad (2.14)$$

and

$$\mathbf{E}^i = \mathbf{D} \cdot \mathbf{u}^i, \text{ that is } (E^{-1})_s^i = D_s^m \mathbf{u}_m^i$$

where

$$\mathbf{\Gamma} \cdot \mathbf{u}^i = \lambda_i^2 \mathbf{u}^i, \text{ and } \mathbf{\Gamma}^T \cdot \mathbf{u}_i = \lambda_i^2 \mathbf{u}_i \text{ (no sum)} \quad (2.15)$$

and the  $\lambda_i^2$  are the nonzero roots of the characteristic equation

$$\det(\mathbf{\Gamma} - \lambda^2 \mathbf{1}) = 0 \quad (2.16)$$

In this way, one can identify the  $R'$  basis vectors corresponding to reaction invariants  $\mathbf{E}_i, i = 1, \dots, R'$ , and the elements of the reciprocal basis  $\mathbf{E}^i, i = 1, \dots, R'$ , with the respective eigenvectors of  $\mathbf{\Gamma}^T$  and  $\mathbf{\Gamma}$ , corresponding to  $R'$  zero eigenvalues, say  $\lambda_i^2 \equiv 0$ , for  $i = 1, 2, \dots, R'$ . (If we assume  $\mathbf{K}$  to be symmetric, then the  $\mathbf{E}_i$ , as defined in (2.14), are seen to be proportional to the eigenvectors of  $\mathbf{\Gamma}$ . This corresponds to the case of an orthogonal basis.)

If  $\mathbf{K}$  is also taken to be positive ( $\mathbf{u} \cdot \mathbf{K} \cdot \mathbf{u} \geq 0$ ), then the square root implied in (2.3) is well defined and the  $\lambda_i$  can be identified with (nonnegative, real) eigenvalues for  $\mathbf{\Lambda}$  (Appendix 3).

With this interpretation of the basis elements, one finds readily that the permeability tensor of (2.8) and its inverse take on (as sums of dyads; see Appendix 3) the forms

$$\mathbf{P} = \left\{ \sum_{i=1}^S \mathbf{E}^i \mathbf{E}_i / w_i \right\} \cdot \mathbf{D} / L,$$

and

$$\mathbf{\Omega} = L \mathbf{D}^{-1} \cdot \left\{ \sum_{i=1}^S w_i \mathbf{E}^i \mathbf{E}_i \right\} \quad (2.17)$$

so that the desired components of  $\mathbf{\Omega}$  in (2.13) are given explicitly by

$$\Omega_s^m = L (D^{-1})_s^t \sum_{i=1}^S w_i (E^{-1})_t^i E_i^m \quad (2.18)$$

where, in both (2.17) and (2.18),\*

$$w_i = w(\lambda_i) \text{ and } w(\lambda) = \frac{2}{\lambda} \tanh\left(\frac{\lambda}{2}\right) \quad (2.19)$$

Since  $\lambda_i \equiv 0$  for  $i = 1, \dots, R'$ , the corresponding  $R'$  terms in (2.18) have  $w \equiv 1$  (see Appendix 3).

The actual evaluation of (2.18) would require the computation of eigenvectors of  $\mathbf{\Gamma}$  or some alternative matrix algebraic manipulations, as discussed in Appendix 3, which is a more or less complex task depending on the complexity and number of reactions treated. Irrespective of the actual practical complexity of such computation, the expressions (2.17) and (2.18) provide, as they stand, some valuable theoretical insight into the problem. This is best appreciated by considering the reduced form of (2.17) for a single chemical reaction, a problem already treated by Friedlander and Keller (1965).

#### Single Reaction with Linear Kinetics

In the case where there is only one stoichiometrically independent reaction,  $R = 1$ , the rate constant  $\mathbf{K}$  in (2.1) takes on the dyad form

$$\mathbf{K} = -\alpha \mathbf{k} \text{ (or } K_s^m = -\alpha_s k^m) \quad (2.20)$$

where the vector  $\alpha$  represents the stoichiometric coefficients for the reaction, related to the (last element of the) basis introduced above,  $\mathbf{E}^S$ , by  $\alpha_s \equiv (E^{-1})_s^S, s = 1, \dots, S$ . Therefore, the tensor  $\mathbf{\Gamma}$  reduces also to a dyad

$$\mathbf{\Gamma} = -L^2 \mathbf{u} \mathbf{k}, \text{ with } \mathbf{u} = \mathbf{D}^{-1} \cdot \alpha \quad (2.21)$$

having eigenvector  $\mathbf{u}$ , for the nonzero eigenvalue

$$\lambda^2 \equiv (\lambda)^2 = -L^2 (\mathbf{u} \cdot \mathbf{k}) \equiv -L^2 [\alpha_s (D^{-1})_m^s k^m] \quad (2.22)$$

Thus, the corresponding reduced forms of (2.17) are

$$\mathbf{P} = \{(1 - \alpha\beta) + \alpha\beta/w\} \cdot \mathbf{D} / L$$

and

$$\mathbf{\Omega} = L \mathbf{D}^{-1} \cdot \{(1 - \alpha\beta) + w\alpha\beta\} \quad (2.23)$$

where  $w$  is given by (2.19), and

$$\beta \equiv \mathbf{E}_S = -L^2 (\mathbf{D}^{-1} \cdot \mathbf{k}) / \lambda^2 \quad (2.24)$$

is the eigenvector of  $\mathbf{\Gamma}^T$ , with eigenvalue  $\lambda^2$  given by (2.22), and normalized such that  $\beta \cdot \alpha = 1$  (that is, for-

\* The function  $w(\lambda)$  is a familiar one in diffusion-reaction theory and, as pointed out by Perelson and Katchalsky (1972),  $\lambda$  is analogous to the Thiele modulus of diffusion-limited catalytic reaction.

mally,  $\mathbf{E}^s \cdot \mathbf{E}_s = 1$ , no sum implied).

The forms of the permeability tensor and its inverse given in (2.23) have a somewhat transparent interpretation. The dyad  $\alpha\beta$  (with components  $\alpha_s\beta^m$ ) represents an oblique projection onto the reaction path defined by the vector of stoichiometric coefficients  $\alpha(\alpha_s)$ , whereas the term  $(1 - \alpha\beta)$  is a projection onto the linear space, or hyperplane, orthogonal to  $\alpha$ , which represents the space of reaction invariants. Hence, the interpretation of the corresponding forms in (2.17) appropriate to multiple reactions becomes more evident: The sum over terms  $i = 1, 2, \dots, R'$  (with  $w_i \equiv 1$ ) in (2.17) represents, again, a projection onto the space of reaction invariants, while the  $R$  remaining individual terms  $i = R' + 1, \dots, S$  represent projections onto special reaction paths, defining the normal or uncoupled modes of the diffusion-reaction system. Accordingly, one has generally a discrete spectrum of  $R$  finite relaxation lengths  $(L/\lambda_i)$ ,  $i = R' + 1, \dots, S$ , as pointed out by Ulanowicz and Frazier (1970) in a related context (see Appendix 3 here).

Returning to the case of a single reaction, we can rather easily derive explicit expressions for the flux of volatiles by means of the relations (2.13) and (2.23) even for the situation where there are several volatile species. In the simplest example, where no diffusive coupling exists between different species, that is, where (13.45) holds, the flux  $N_v$  of every volatile species through the membrane can be expressed in terms of a single number  $\rho$  as

$$N_v = (N_v)_0 + \alpha_v \rho \quad (v = 1, \dots, F) \quad (2.25)$$

where

$$\rho = \frac{1 - w}{1 + (w - 1)\beta^v \alpha_v} [\beta^v (N_v)_0]$$

with

$$\beta^v \alpha_v \equiv \sum_{s=1}^F \beta^s \alpha_s \quad (2.26)$$

and

$$\beta^v (N_v)_0 \equiv \sum_{s=1}^F \beta^s (N_s)_0$$

denoting sums over volatiles. In these relations,

$$(N_s)_0 = D_s \left[ \frac{\Delta C_s}{L} \right] = \left[ \frac{D_s}{L} \right] (C_s - C_s), \quad (\text{no sum}) \quad (2.27)$$

denotes the Fick's law or purely diffusive flux of species  $s$ , while the  $\alpha_s$  are stoichiometric coefficients. Also, the  $\beta^s$  are the components of the vector defined by (2.24), and  $w(\lambda)$  is the quantity defined by (2.19) and (2.22). In the present example, where there is no coupling of diffusion, the quantities  $\beta^s$  and  $\lambda$  take on the simple forms

$$\beta^s = - \left( \frac{L}{\lambda} \right)^2 \frac{k^s}{D_s}, \quad s = 1, 2, \dots, S \quad (\text{no sum})$$

and  $(2.28)$

$$\left( \frac{\lambda}{L} \right)^2 = - \sum_{s=1}^S \frac{k^s \alpha_s}{D_s}$$

which are seen to involve relaxation or reaction-layer lengths for the individual species,<sup>†</sup> say

$$\delta_s = \sqrt{D_s/k^s \alpha_s}, \quad (\text{no sum}) \quad (2.29)$$

The relation (2.25) then provides a generalization of a result first given by Friedlander and Keller<sup>9</sup> for the case

<sup>†</sup> Thus, the quantity  $\lambda/L$  as defined here is the reciprocal of the quantity denoted by the same symbol in Friedlander and Keller (1965) or Ulanowicz and Frazier (1968).

of a single volatile species.

It is interesting to consider the limiting form of (2.25) for the case of infinitely rapid reaction where formally  $\lambda \rightarrow \infty$  in (2.28). In this case, a state of complete reaction equilibrium obtains in the membrane, and the corresponding fluxes of (2.25) reduce to the equilibrium fluxes

$$(N_s)_{\text{eq}} = (N_s)_0 + \alpha_s \rho_{\text{eq}}, \quad s = 1, \dots, F \quad (2.30)$$

where

$$\rho_{\text{eq}} = \lim_{\lambda \rightarrow \infty} \rho = \frac{\beta^v (N_v)_0}{\beta^n \alpha_n} \quad (2.31)$$

with

$$\beta^n \alpha_n \equiv 1 - \beta^v \alpha_v \equiv \sum_{s=R'+1}^S \beta^s \alpha_s \quad (2.32)$$

denoting a sum over the nonvolatiles.

Then, for any finite  $\lambda$ , Equation (2.25) can be expressed in a form which gives the absolute mediation (or, when positive, the facilitation or enhancement) of flux  $N_s - (N_s)_0$  for any volatile species in terms of the equilibrium mediation  $[N_s - (N_s)_0]_{\text{eq}}$  for that species, as

$$N_s - (N_s)_0 = [N_s - (N_s)_0]_{\text{eq}} f, \quad (s = 1, \dots, F), \quad (2.33)$$

where

$$f \equiv \rho / \rho_{\text{eq}} = \frac{(1 - w) \beta^n \alpha_n}{1 + (w - 1) \beta^v \alpha_v} \equiv 1 - \frac{1}{\beta^n \alpha_n (1/w - 1) + 1} \quad (2.34)$$

is the fractional mediation relative to equilibrium which, accordingly, is seen to be the same for all volatile species.

In the case of several transferred species, the forms of Equations (2.25) or (2.33) suggest that they might be useful for testing consistency of experimentally measured volatile fluxes or permselectivity in the limit of small concentration differences across a membrane.

To summarize then, we have shown here how the linearized analysis for weakly perturbed or nearly uniform films can be extended to problems of arbitrary complexity, involving multiple permeants, coupled diffusion, and multiple chemical reactions. The evaluation of permeant fluxes requires the evaluation of the relevant permeability tensor from the various kinetic constants and diffusivities, and the partition of its inverse, the resistance tensor, by fairly standard linear algebraic methods (see Appendix 3).

### 3. ASYMPTOTIC AND APPROXIMATE ASYMPTOTIC SOLUTIONS

As indicated in Part I, we wish here to review and extend the analytical methods available for treating the asymptotic regimes of carrier-mediated diffusion in membranes corresponding to the limits (I4.11) of slow and fast reaction. In extending previous results to cover the case of multiple reactions, we shall consider the most elementary mathematical idealization of the asymptotic regimes, wherein all reaction rates are either rapid or slow compared to intrinsic diffusion rates.

To date, no one has apparently given any systematic theoretical treatment of multiple reactions with greatly different intrinsic rates in the presence of diffusion. Rather, it appears that in most instances one is forced to ignore diffusion and to fall back onto assumptions such as the classical quasi steady state approximation of chemical kinetics in order to eliminate certain presumably rapid reac-

tions, together with the associated reaction intermediates, from a complex kinetic scheme.\* It is, of course, not clear that this approximation would always be tenable whenever there are diffusion limitations on the intermediate species involved. Therefore, an analysis of such phenomena would be most valuable in this regard, both for theoretical understanding and for any practical guidance it might provide in the simplification of otherwise complex kinetic schemes. Lacking that, however, the following discussion is devoted to the highly idealized but nevertheless conceptually valuable case of uniformly rapid reactions.

#### Slow Reactions—the Near-diffusion Regime

If all quantities are rendered dimensionless by the respective characteristic magnitudes,  $r^*$ ,  $C^*$ ,  $D^*$ ,  $L$  as in (I 4.11), the dimensionless form of (I 4.1) becomes

$$D \cdot \frac{d^2C}{dx^2} = -\gamma r \quad (3.1)$$

where  $\gamma$  is a Damkohler number, as defined in (I 4.11).

For small  $\gamma$  it is appropriate to put (3.1) in the form of an implicit integral equation, obtained by a double integration:

$$D \cdot C(x) = -\gamma \int_0^x (x-y)r[C(y)] dy - J(0)x + D \cdot C(0) \quad (3.2)$$

Then, by means of the condition of global nonreactivity,

$$\int_0^1 r[C(x)] dx = 0 \quad (3.3)$$

Equation (3.2) gives the transmembrane flux (in dimensionless form) as

$$N = D \cdot \bar{\Delta}C + \gamma \int_0^1 x r[C(x)] dx \quad (3.4)$$

where  $\bar{\Delta}C$  is the dimensionless form of the quantity defined in (2.5). The boundary conditions of the type (2.10) apply here and, of course, the components of flux and concentration  $N_v$ ,  $C_n$ , for volatiles and nonvolatiles, respectively, are quantities to be determined.

An obvious perturbation series in the parameter  $\gamma$  for  $\gamma \approx 0$  is, then,

$$C(\gamma, x) = C_0(x) + \gamma C_1(x) + O(\gamma^2) \quad (3.5)$$

where

$$C_0(x) \equiv -D^{-1} \cdot N_0 x + C_0(0) \quad (3.6)$$

the zeroth perturbation or the pure-diffusion limit, must satisfy the exact boundary conditions, while  $C_1(x)$ , the first perturbation due to reaction, is to satisfy homogeneous boundary conditions on  $N_n$ ,  $C_v$ .

Substitution of (3.5) together with a similar series for the diffusion flux  $J(0)$  into (3.2) provides a recursive scheme for calculation of higher-order terms. However, to terms  $O(\gamma)$  the transmembrane flux can be obtained from (3.4) as

$$N = J(0) = D \cdot \bar{\Delta}C_0 + \gamma \int_0^1 x r[C_0(x)] dx + O(\gamma^2) \quad (3.7)$$

once  $C_0(x)$  is known.

In order to determine  $C_0(x)$  one must, in general, employ the appropriate ( $I$ ) integral constraints, Equation (I 3.38), on system invariants plus ( $R$ ) conditions of global nonreactivity of the form (3.3). In this respect, the

effect of chemical reaction enters the picture even in the zeroth perturbation. The said relations together with (3.6) and the boundary conditions, then suffice to specify completely the unperturbed (linear) concentration fields of volatiles and nonvolatiles.

As mentioned earlier, Smith et al. (1973), as well as Suchdeo and Schultz (1974) have carried out such perturbation analyses to higher-order terms in  $\gamma$ ; in the latter case for the reaction system



with kinetics

$$r_A = -k(C_B, C_C) [C_A C_B^n - C_C^m / K] \quad (3.8)$$

The main conclusion to be drawn from their work is that such perturbation series have a very limited range of utility in the parameter  $\gamma$ .

Moreover, it might be noted here that even were one so fortunate as to be able to generate as many terms as desired, the unqualified convergence of such a series would not be guaranteed even though the concentration field  $C(\gamma, x)$  may be analytic in  $\gamma$  for some range of parameter values  $\gamma > 0$ . (This can most simply be illustrated by considering the case of linear kinetics, where it is not too difficult to show that the expression of (2.8) has a sequence of simple-pole singularities at imaginary points in the complex plane, the first of which limits the radius of convergence of any Taylor series in  $\gamma$ .)

Finally, since the main interest here is in reaction enhancement or facilitation of diffusion, the case of slow reaction, or near-diffusion systems, is inherently of less interest than the other limit, systems near-reaction-equilibrium,\* where in general one expects to achieve the extremes of flux.

#### Multiple Reactions—The Equilibrium Approximation

In the general case of multiple, equally rapid reactions, one has to consider the asymptotic solutions of (3.1) for  $\gamma \rightarrow \infty$ . It is somewhat more convenient in this case to employ the related, small parameter

$$\epsilon = \frac{1}{\sqrt{\gamma}} \equiv \delta^*/L \quad (3.9)$$

where  $\delta^*/L$  is defined in (I 4.11). Then, (3.1) assumes the form

$$\epsilon^2 \frac{d^2C}{dx^2} = -D^{-1} \cdot r \quad (3.10)$$

and the physical limit of infinitely fast reaction corresponds formally then to the mathematical limit  $\epsilon \rightarrow 0$ . On neglecting the term in  $\epsilon^2$  from (3.10) one obtains, as an approximation to the concentration field  $C(x)$  for  $\epsilon \ll 1$ , a function  $\hat{C}(x)$ , say, which must satisfy the equilibrium condition

$$r\{\hat{C}\} = 0, \quad \text{for } 0 < x < 1 \quad (3.11)$$

everywhere in the interior of the membrane.† Since Equa-

\* The term *near-equilibrium* has been used (in particular by the present authors) to refer to this limit of rapid, reversible reactions, for which a condition of reaction equilibrium is achieved almost everywhere on the concentration fields. In view of the possibilities for confusion, it would perhaps have been preferable to reserve the term *near-equilibrium* for systems near thermodynamic equilibrium, as discussed in Section 2 above, where all driving forces (affinities) and affinity gradients are small (Goddard et al., 1970).

† There is, in the older literature, a frequent recurrence of logical fallacy in conjunction with the assumption of reaction equilibrium, where several authors set  $r = 0$  and then proceed to obtain the solution to the resultant diffusion equation in (3.10) (See Enns 1964).

\* This has, in effect, been done for the rather complex system for bicarbonate facilitation of  $\text{CO}_2$  transport (Part I, Example 6, Table I) by Otto and Quinn (1971) and Suchdeo and Schultz (1974).

tion (3.11) will generally admit a family of solutions, some further restrictions on the concentration field are necessary.

As the primary restrictions,  $\hat{C}$  must satisfy the flux conditions and integral constraints on radicals and system invariants which, it will be recalled, from (1.7) to (1.9) are

$$J\{E_i\} = E_i \cdot J = -E_i \cdot D \cdot \frac{dC}{dx} = j_i \quad (3.12)$$

with  $j_i$  constant, independent of  $x$  for  $i = 1, \dots, R'$ , and with

$$j_i \equiv 0, \text{ and } \int_0^1 E_i \cdot C(x) dx = C_{\text{tot}}\{E_i\}, \text{ given } (3.13)$$

for (the  $I'$  values)  $i = F + 1, \dots, R'$ .

We note then that within the accuracy of any such equilibrium approximation  $\hat{C}$ , the corresponding (dimensionless) flux of volatiles through the membrane,  $N_v$ , say, is given by

$$N_v = \frac{L}{D \cdot C^*} \hat{J}_v(0) = Z_v^m D_m^s [\hat{C}_s(0) - \hat{C}_s(1)] \quad (3.14)$$

Then, Equations (3.11) to (3.14) are merely generalizations of equations which have often been used to describe carrier-mediated diffusion for a single reaction, in the limit of reaction equilibrium.

By inspection of these equations, one surmises that they are still not complete and that, in general, a number  $2F$  of additional conditions will be necessary to determine a unique equilibrium concentration field  $\hat{C}$ , and, hence to permit specification of the boundary concentrations  $\hat{C}(0)$ ,  $\hat{C}(1)$  in the expression of (3.14) for the desired fluxes. At the same time, it becomes evident that, with only  $2F$  conditions at our disposal, it will not be possible, in general, to satisfy simultaneously the  $2F'$  flux conditions of (2.10) on the nonvolatiles, together with a set of  $2F$  boundary conditions on the volatiles.

This situation of indeterminacy can be attributed to the neglect of the  $x$ -derivatives from the differential Equation (3.10) to obtain an essentially algebraic equation, (3.11), which results in an approximation of the so-called "singular-perturbation" variety.

The consequences of this approximation in the present realm have been emphasized recently by Goddard, Schultz, and Basset (1970) in a fairly general discussion of the case of a single reaction and also by Murray (1971) for some special applications.

As indicated in these works, a solution to the equilibrium equation of (3.11) will, in general, provide a valid approximation  $\hat{C}(x)$  to the actual concentration distribution for  $0 \leq x \leq 1$  only in some central interior region or core of the membrane; but, for any  $\epsilon \rightarrow 0$ , however small, the approximation will fail in boundary-layer regions of width  $O(\epsilon)$  near  $x = 0, 1$ . This boundary layer structure, common to other physical problems, can in the present context be associated with the physical occurrence of reaction layers or transition zones of intense chemical reaction near the membrane boundaries which are necessary to the establishment of the state of reaction equilibrium in the core.

While the asymptotic flux for  $\epsilon \rightarrow 0$  can in principle be calculated by (3.11) to (3.13), once the correct set of  $2F$  boundary conditions are specified on the equilibrium approximation  $\hat{C}(x)$ , for  $x \rightarrow 0+$  or  $1-$ , these conditions can be obtained rigorously only by a detailed consideration

of the boundary-layer structure, which is the principal theme of the works cited immediately above.

However, in the usual less rigorous mathematical treatments of carrier-mediated diffusion, one customarily obtains the necessary boundary conditions on the equilibrium

concentration field  $\hat{C}(x)$  by requiring that it match exactly with the (usually prescribed) interfacial concentration of volatiles at the membrane boundaries. On the other hand,

one does not usually require that  $\hat{C}(x)$  satisfy the zero-flux conditions on nonvolatiles at  $x = 0, 1$ , which is justified, at least intuitively, by the implicit presupposition of reaction zones at the boundaries.

The latter, intuitive approach is reinforced by previous theoretical studies of diffusion with rapid chemical reaction, such as the work of Olander (1960); and, thus guided by a combination of physical insight and mathematical reasoning, one arrives at what appears to be an altogether reasonable requirement of mathematical continuity of concentration fields at the membrane boundary, while at the same time admitting the possibility of discontinuities in the associated fluxes.

The validity of these notions is to some extent borne out by a detailed singular perturbation analysis for small  $\epsilon$  based on the method of matched asymptotic expansions (Goddard, Schultz, and Basset, 1970). This analysis is also used to formulate a power series of correction terms in  $\epsilon$  for the equilibrium concentration field of (3.11) and for the corresponding fluxes in (3.14) as well.

Although the above perturbation analysis is restricted to the case of a single reaction, an important inference can be drawn from it, based on a number of example reactions. In particular, one is led to the tentative conclusion that the first-order correction term, accounting for departure from reaction equilibrium, will tend to be large whenever the computed equilibrium fluxes are large relative to those obtained for pure diffusion.

Otherwise stated, the chemical reactions must then be exceedingly rapid, hence the parameter  $\epsilon$  extremely small, to achieve the asymptotic state of complete reaction equilibrium. From a practical point of view this means, roughly speaking, that any prediction of large flux based on the assumption of complete reaction equilibrium is all the more likely to be inaccurate. This important point has apparently not been adequately appreciated or, if so, has not been sufficiently emphasized in much of the literature on carrier-mediated diffusion, where the assumption of reaction equilibrium often has been routinely invoked. A further implication is that perturbation analyses of the type referred to above will mainly be useful for estimating nearness to equilibrium, as illustrated in Part I, Section 4, but they will be of little value in actual computations when the equilibrium flux is large, a point already suggested by Goddard et al. (1970).

#### Failure of the Equilibrium Approximation—Carrier-Dominated Diffusion and Boundary-Layer Shocks

Some insight as to the nature of the singular limit, characterized by rapid reaction with large equilibrium flux, can be gained by a consideration of the simple example of a single reaction with linear kinetics,



$$r_A = -k(C_A - 1/K C_B)$$

and with simple diffusivities  $D_A, D_B$ , for the case of no diffusive coupling. The exact solution to this problem can be derived directly or by use of the general results given in Section 2. Thus, if the characteristic Damköhler number

is chosen to be

$$\gamma = kL^2/D_A \equiv 1/\epsilon^2 \quad (3.16)$$

where  $k$  is the forward-rate constant in (3.15), the results (2.26) and (2.30) can be expressed in terms of the facilitation  $\Phi$  and its equilibrium limit  $\Phi_{eq}$  for  $\epsilon = 0$  as

$$\Phi \stackrel{\text{def}}{=} \frac{N_A - (N_A)_0}{(N_A)_0} = \frac{\Phi_{eq} (1 - w)}{1 + \Phi_{eq} w} \quad (3.17)$$

where, it will be recalled,  $w(\lambda)$  is defined by (2.19), and where

$$\lambda^2 = \frac{1}{\epsilon^2} \left[ \frac{\Phi_{eq}}{\Phi_{eq} + 1} \right]^{-1} \quad \text{and} \quad \Phi_{eq} = \frac{KD_B}{D_A} \quad (3.18)$$

in which  $K$  is the equilibrium or binding constant of (3.15).

Then, in the limit of interest, where  $\epsilon \ll 1$  and the hyperbolic tangent in (2.19) becomes essentially unity, we have

$$\Phi \simeq \frac{\Phi_{eq}}{1 + 2\epsilon [(\Phi_{eq} - 1)^2/\Phi_{eq} + 1]^{1/2}} \quad (3.19)$$

It becomes evident from (3.19) that, when regarded as a function of  $\Phi_{eq}$  and  $\epsilon$ , the facilitation  $\Phi$  exhibits singular behavior in the double limit  $\epsilon \rightarrow 0$  and  $\Phi_{eq} \rightarrow \infty$ . In particular, the asymptotic forms in the respective limits are evidently given by

$$\Phi \simeq \Phi_{eq}, \quad \text{for } \epsilon \rightarrow 0 \quad (\text{with } \Phi_{eq} \text{ fixed}) \quad (3.20)$$

and

$$\Phi \simeq \frac{1}{2\epsilon}, \quad \text{for } \Phi_{eq} \rightarrow \infty \quad (\text{with } \epsilon \text{ fixed}) \quad (3.21)$$

That is to say, the limits are not formally interchangeable and, moreover, it is evident from (3.19) that for  $\epsilon \ll 1$ ,  $\Phi$  can be well approximated by its equilibrium limit  $\Phi_{eq}$  for  $\epsilon = 0$ , only if the product  $\epsilon\Phi_{eq} \ll 1$ . One sees, by means of the expression for  $\Phi_{eq}$  in (3.18), that this is equivalent to the requirement

$$\left[ \frac{KD_B}{D_A} \right] \epsilon \ll 1 \quad (3.22)$$

which, roughly speaking, will fail to be satisfied whenever either the carrier-permeant diffusivity ratio  $D_B/D_A$  or the binding constant  $K$  are excessively large, the latter situation being more often pertinent to the usual physical examples.

At first glance, (3.22) might seem to indicate that the failure of the equilibrium approximation (3.20) could be attributed to a small Damköhler number for the reverse reaction in (3.15), say

$$\gamma' = \frac{kL^2}{KD_A} \equiv \frac{1}{\epsilon^2 K} \quad (3.23)$$

which, if small, could imply a breakdown of the rapid-reaction approximation for the reverse step in (3.15). However, it is evident that (3.20) and (3.22) can fail to apply even if  $\gamma' \gg 1$  (for example, for  $\epsilon \rightarrow 0$  with  $K\epsilon$  fixed). The singularity appears, then, to be of a more subtle, if related variety, and it can perhaps be best understood by consideration of the membrane concentration profiles for the example system under consideration.

Thus, from the appropriate form of the general result (2.2), one finds that the concentration fields  $C_A(x)$  and  $C_B(x)$  take on radically different forms for  $\epsilon \rightarrow 0$ , depending on whether  $D_B K \epsilon / D_A \ll 1$  or  $D_B K \epsilon / D_A = 0(1)$ . Specifically, for  $\epsilon \rightarrow 0$ , one has in the core of the membrane

$$\left. \begin{aligned} C_A &\simeq \langle C_A \rangle + \bar{\Delta} C_A (1/2 - x) + 0(\epsilon) \\ \frac{C_B}{K} &\simeq C_A + 0(\epsilon) \end{aligned} \right\} \quad \text{for } 0 < x < 1 \quad (3.24)$$

if  $D_B K \epsilon / D_A \ll 1$ , where the notation is the same as in (2.5), and both  $\langle C_A \rangle$  and  $\langle C_B \rangle = K \langle C_A \rangle$  are constants. On the other hand, for  $D_B K \epsilon / D_A = 0(1)$  or greater,

$$C_A \simeq \langle C_A \rangle + 0(e^{-1/\epsilon}) \quad (3.25)$$

$$\frac{C_B}{K} \simeq \langle C_A \rangle - \frac{D_A}{D_B K \epsilon} \frac{\bar{\Delta} C_A}{2} (x - 1/2) + 0(e^{-1/\epsilon}), \quad \text{for } 0 < x < 1$$

Of course, in the neighborhoods of either membrane boundary there exist boundary-layer correction terms to (3.24) and (3.25) which involve exponentials of the type  $e^{-\lambda x}$ , near  $x = 0$ , or  $e^{-\lambda(1-x)}$  near  $x = 1$  (Figure 1).

The important points to be made here, however, are as follows: while the equilibrium core profile of  $C_A(x)$  in (3.24) satisfies the imposed boundary conditions on  $C_A(x)$ , the profile in (3.25) does not. Furthermore, it can be seen that the linear term in the core profile (3.25) for the carrier  $B$  accounts for effectively all the transmembrane flux of the volatile  $A$  and, hence, for the limiting form of the facilitation  $\Phi$  in (3.21). This limiting flux, incidentally, is also derivable from the asymptotic form of the boundary-layer concentration profile  $C_A$  near  $x = 0$ , namely

$$C_A \simeq \langle C_A \rangle + \frac{\bar{\Delta} C_A}{2} e^{-x/\epsilon} \quad (3.26)$$

for  $x/\epsilon = 0(1)$ .

Thus, it is seen that (3.25) reflects a situation which might generally be termed *carrier-dominated* equilibrium transport. In this regime, a type of strong boundary-layer structure emerges in the limit of fast reaction,  $\epsilon \rightarrow 0$ , in which there is a virtual discontinuity in the concentration field of the permeant species  $A$  between core and boundary. The boundary layer can be interpreted then as a shock-like transition zone of exceedingly intense reaction arising from either a large carrier/permeant diffusivity ratio or a nearly irreversible reaction wherein the permeant and carrier undergo virtually complete interconversion over a distance  $0(\epsilon)$ . In this case, the asymptotic form of the facilitation  $\Phi$  in (3.21) suggests that one may consider the volatile flux to be controlled solely by diffusion of the volatile  $A$  across boundary layers of thickness

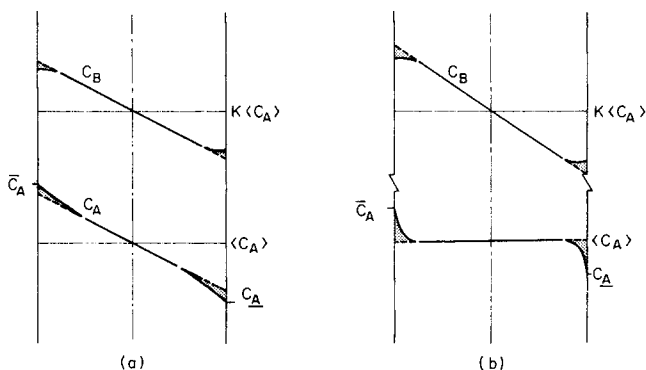


Fig. 1. Qualitative sketch of concentration profiles in the reaction of (3.15) for  $\epsilon \rightarrow 0$ , with (a) moderate  $K$ , and (b) the carrier dominated regime of large  $K$ ,  $K\epsilon = 0(1)$ . The boundary-layer regions are shaded.



$$\delta_A = \sqrt{\frac{D_A}{k}} \equiv \epsilon L \quad (3.27)$$

which is a special case of the relaxation layer thickness in (2.29) for species A.

For the more general case of a (hypothetical) single reaction with linear kinetics, but with an arbitrary number of volatiles and nonvolatiles, the same type of singular phenomenon is evident. Indeed, one sees that the fractional mediation  $f$  defined in (2.34) exhibits the behavior

$$f \simeq \frac{1}{1 + 2\epsilon \frac{\sigma^3}{\sqrt{1 + \sigma^2}}} \quad \text{for } \epsilon \rightarrow 0 \quad (3.28)$$

where now  $\epsilon$  is defined in terms of the relaxation lengths of all the volatile species by

$$\frac{1}{\epsilon^2} = \sum_{s=1}^F (L/\delta_s)^2 \equiv -L^2 \sum_{s=1}^F \left[ \frac{k^s \alpha_s}{D_s} \right] \quad (3.29)$$

and  $\sigma^2$  is the ratio of such quantities, for volatiles relative to nonvolatiles:

$$\sigma^2 = (\sigma)^2 = \frac{\beta^v \alpha_v}{\beta^n \alpha_n} \equiv \sum_{s=1}^F (1/\delta_s)^2 \left[ \sum_{s=F+1}^S (1/\delta_s)^2 \right]^{-1} \quad (3.30)$$

The singular, carrier-dominated limit arises whenever  $\sigma^2 \epsilon \equiv 0(1)$  for  $\epsilon \rightarrow 0$ , and the transmembrane flux of volatiles again governed by boundary-layers of thickness  $\epsilon$ , given by (3.29) and therefore determined solely by relaxation lengths associated with the volatiles.

In the case of several reactions, one might anticipate this same type of singularity although the kinetic constants would have to be attributed to the various normal reaction modes. This point will not be pursued further in the present context since, apart from its conceptual value in helping to understand the nature of the carrier-dominated singularity for rapid reactions, the strictly linear kinetic model has limited applicability to real systems.

The limitations of the linear model notwithstanding, one is led to expect, from the examples just considered, that generally even though a boundary layer structure may evolve for  $\epsilon \ll 1$  consisting of type of equilibrium-core region bounded by thin reaction layers of thickness  $0(\epsilon)$ , the core concentration profiles do not necessarily take on the exact or true boundary values at  $x = 0, 1$ . Furthermore, one sees by (3.21) or (3.28) that when (3.22) fails, the facilitation or mediation can exhibit a simple-pole type of singularity in  $\epsilon$ , with singular point very near to  $\epsilon = 0$ . One would therefore not expect the kind of weak-boundary-layer analysis given by Goddard et al. (1970),\* which proceeds by a perturbation expansion about the state of complete reaction equilibrium,  $\epsilon = 0$ , to be uniformly valid in the parametric limit of carrier-dominated equilibrium discussed above.

For this carrier-dominated limit, another approach is desirable, and such a method was originally suggested by Kreuzer and Hoofd (1970) for the approximate treatment of a specific reaction of the type (3.8), with  $n = m = 1$ ,  $k$  const. This approach, which in light of the above remarks may be termed a *shock-layer* or *strong-boundary-layer* analysis, was further improved upon by Kreuzer and Hoofd (1972) and by Smith et al. (1973). More recently, the same type of method has been applied by Suchdeo

and Schultz (1974b) to analyze a single-reaction model for the bicarbonate-facilitated transport of carbon dioxide, in which the assumed kinetics are somewhat more complicated than those in (3.8).

Most of the applications reported to date have dealt with the case of a single reaction, involving a single volatile species, uncoupled diffusion, and equal diffusivities of nonvolatiles. Since the method appears to give excellent agreement with existing numerical finite-difference solutions, Smith et al. (1973), Suchdeo et al. (1973), Goddard et al. (1974), well into the near-diffusion range,  $\epsilon \gg 1$ , it appears worthy of generalization as an analytical method, for potential application to carrier-mediated systems with multiple reactions and several volatile species, or, to related problems, involving ionic transport or heat transport in chemically reacting media.

### Boundary-Layer Analysis and Solution

In the spirit of the boundary-layer analysis based on matched asymptotic expansions in Goddard et al. (1970), the solution to (3.10) for  $\epsilon \rightarrow 0$  is represented by an equilibrium-core approximation of the form

$$\mathbf{C}(\epsilon, x) = \hat{\mathbf{C}}(\epsilon, x) + o(\epsilon), \quad \text{for } 0 < x < 1 \quad (3.31)$$

where  $\hat{\mathbf{C}}$  satisfies (3.11), (3.12) and (3.13) and where  $o(\epsilon)$  is the standard notation for quantities of order less than one in  $\epsilon$ , that is  $o(\epsilon)/\epsilon \rightarrow 0$  for  $\epsilon \rightarrow 0$ . On the other hand, in the neighborhood of the membrane boundaries,  $x = 0, 1$ , the concentration field  $\mathbf{C}(\epsilon, x)$  is represented, respectively, by

$$\mathbf{C}(\epsilon, x) = \bar{\mathbf{C}}(\epsilon, \bar{x}) + o(\epsilon) \quad (3.32)$$

near the left-hand boundary, where, in terms of a stretched coordinate,

$$\bar{x} \equiv x/\epsilon = 0(1) \quad (3.33)$$

and by

$$\mathbf{C}(\epsilon, x) = \underline{\mathbf{C}}(\epsilon, \underline{x}) + o(\epsilon) \quad (3.34)$$

near the right-hand boundary, where

$$\underline{x} \equiv (1 - x)/\epsilon = 0(1) \quad (3.35)$$

The (left-hand) boundary-layer function  $\bar{\mathbf{C}}(\epsilon, \bar{x})$  in (3.32) must be chosen, then, to satisfy the stretched coordinate form of (3.10),

$$\frac{d^2 \bar{\mathbf{C}}}{d\bar{x}^2} = -\mathbf{D}^{-1} \cdot \mathbf{r}(\bar{\mathbf{C}}) \quad (3.36)$$

on the semi-infinite interval  $0 \leq \bar{x} < \infty$  and subject to the exact boundary conditions at  $x = 0$  on both volatiles and nonvolatiles. Furthermore, the limiting form of this function is to match asymptotically with the limiting form of the core approximation of (3.11) for  $x \rightarrow 0$ , to terms  $o(\epsilon)$ . This requires that

$$\bar{\mathbf{C}}(\epsilon, \bar{x}) \rightarrow \hat{\mathbf{C}}(\epsilon, 0) + \epsilon \bar{x} \frac{d\hat{\mathbf{C}}}{dx}(\epsilon, 0) + o(\epsilon), \quad \text{for } \bar{x} \rightarrow \infty \quad (3.37)$$

A similar set of relations also holds at the right-hand boundary.

The relations (3.36) *et seq.* define a complete boundary-layer problem, to which it is presumably possible to obtain solutions satisfying the requisite boundary conditions at  $\bar{x} = 0$  and exhibiting the linear behavior for  $\bar{x} \rightarrow \infty$  implied by (3.37). These requirements, together with similar relations for the right-hand boundary, should in turn serve

\* This kind of parametric nonuniformity, as opposed to the usual spatial nonuniformity associated with singular perturbations, was anticipated in the article cited but no explanations of its origins, nor remedies for it, were evident at the time.

to determine the correct forms of boundary conditions on the core approximation  $\hat{C}$  at  $x = 0, 1$  and, thereby, to provide for the calculation of permeant flux with an accuracy  $O(\epsilon)$ . In its present general form the complete problem is clearly not tractable by analytical methods, and, while a solution might be effected by numerical methods, it is not fully obvious how one would proceed.

Fortunately, however, one has recourse to the above-mentioned approximation technique suggested by the previous work of Kreuzer and Hoofd.\* In particular, one assumes that the boundary-layer function can be expressed as

$$\bar{C}(\epsilon, x) = \hat{C}(\epsilon, 0) + \bar{\epsilon} \frac{d\hat{C}}{dx}(\epsilon, 0) + \epsilon \bar{C}^{(1)}(\epsilon, \bar{x}) + o(\epsilon) \quad (3.38)$$

where  $\bar{C}^{(1)}(\epsilon, \bar{x})$  is  $O(1)$  and where, because of (3.37),

$$\bar{C}^{(1)}(\epsilon, \bar{x}) \rightarrow 0 \text{ for } \bar{x} \rightarrow \infty \quad (3.39)$$

Next, the rate term  $r(\bar{C})$  in (3.36) is formally linearized, in the explicit first-order terms in  $\epsilon$ , about the zeroth-order term  $\hat{C}(\epsilon, 0)$ . Then, because of the equilibrium condition (3.11) on  $\hat{C}(\epsilon, x)$ , one obtains the following (set of) linear differential equations with constant coefficients for  $\bar{C}^{(1)}$ :

$$\frac{d^2 \bar{C}^{(1)}}{d\bar{x}^2} = \bar{\mathbf{F}} \cdot \bar{C}^{(1)} \quad (3.40)$$

where

$$\bar{\mathbf{F}} = \mathbf{D}^{-1} \cdot \bar{\mathbf{K}}, \text{ and } \bar{\mathbf{K}} = -[\partial r / \partial \mathbf{C}]_{\mathbf{C}=\hat{C}(\epsilon, 0)} \quad (3.41)$$

and of course another such equation is involved at the right-hand boundary involving a matrix  $\bar{\mathbf{F}}$ , say.

The differential equation (3.40) will be recognized as the formal equivalent of (2.1), corresponding to linear kinetics, but in the case at hand there are two distinct equations which apply to the respective boundary-layer functions (at  $x = 0, 1$ ), and their domain of application is the semi-infinite intervals of the stretched coordinates  $\bar{x}$  and  $x$ . Accordingly, the appropriate formal solution to (3.40) is†

$$\bar{C}^{(1)}(\bar{x}) = \exp(-\bar{\mathbf{A}} \bar{x}) \cdot \bar{C}^{(1)}(0) \quad (3.42)$$

where  $\bar{\mathbf{A}}$  is formally to be determined from the analogue of (2.3):

$$(\bar{\mathbf{A}})^2 = \bar{\mathbf{F}} \quad (3.43)$$

and where the vector  $\bar{C}^{(1)}(0)$  in (3.42) in the (as yet unspecified) boundary value of  $\bar{C}^{(1)}$  at  $\bar{x} = 0$ .

For later reference, we note that (3.39) and (3.42) imply that  $\bar{C}^{(1)}(0)$  is contained in the range of  $\bar{\mathbf{F}}$ , regarded as a linear transformation on  $\bar{C}^{(1)}$ . Since, however, the set of vectors  $\mathbf{D} \cdot \mathbf{E}_i$  found from the  $R'$  reaction invariants  $\mathbf{E}_i$  of (1.1) must lie in the null space of  $\bar{\mathbf{F}}^T$ , that is

$$(\mathbf{D} \cdot \mathbf{E}_i) \cdot \bar{\mathbf{F}} = (\bar{\mathbf{F}})^T \cdot (\mathbf{D} \cdot \mathbf{E}_i) = 0, \text{ for } i = 1, \dots, R' \quad (3.44)$$

it follows that

$$\mathbf{E}_i \cdot [\mathbf{D} \cdot \bar{C}^{(1)}(0)] = 0, \text{ for } i = 1, \dots, R' \quad (3.45)$$

and, hence that the projection (see Section 2) of  $\mathbf{D} \cdot \bar{C}^{(1)}(0)$  onto the space of reaction invariants must vanish:

$$\left[ \sum_{i=1}^{R'} \mathbf{E}_i \mathbf{E}_i \right] \cdot [\mathbf{D} \cdot \bar{C}^{(1)}(0)] = 0 \quad (3.46)$$

Now, we derive the result of primary interest here. By application of Equation (3.38) at  $\bar{x} = 0$  and its  $x$ -derivative for  $\bar{x} \rightarrow \infty$ , one obtains a single relation connecting  $\hat{C}(0)$ , the boundary value of the core function  $\hat{C}(x)$ , and the boundary diffusion flux derived from  $\hat{C}(x)$ , say

$$\hat{\mathbf{J}}(0) = -\mathbf{D} \cdot \left( \frac{d\hat{C}}{dx} \right)_{x=0} \quad (3.47)$$

with the actual concentration  $\bar{C}$  and flux  $\mathbf{J}(0)$  at  $x = 0$ . This relation, which is the desired result, can be cast into the form

$$\mathbf{N} \equiv \mathbf{J}(0) = \hat{\mathbf{J}}(0) + \bar{\mathbf{P}} \cdot [\bar{C} - \hat{C}(0)] + o(\epsilon) \quad (3.48)$$

where, in analogy with the (dimensionless) limiting form of the permeability tensor in (2.8) and (2.17), for rapid reaction or large  $\mathbf{A}$ , the tensor  $\bar{\mathbf{P}}$  is a boundary-layer permeability defined by

$$\bar{\mathbf{P}} = \mathbf{D} \cdot \bar{\mathbf{A}} / \epsilon \quad (3.49)$$

As a further result of the relations (3.38), (3.44), and (3.47), one finds that

$$\sum_{i=1}^{R'} \mathbf{E}_i \mathbf{E}_i \cdot [\mathbf{J}(0) - \hat{\mathbf{J}}(0)] = 0 \quad (3.50)$$

This merely indicates that the actual flux of reaction invariants is equal to their boundary flux derived from the core profile  $\hat{C}$ , which is in accordance with the condition that this flux be spatially constant and locally unaltered by chemical reaction.\* It is therefore apparent that (3.48) involves, so to speak, only the reactive components, that is, the projections onto the space of chemical reactions, of the species fluxes and concentrations (see Appendix 3).

A relation similar to (3.48) is also found to apply at the right-hand boundary  $x = 1$ , namely

$$\mathbf{N} \equiv \mathbf{J}(1) = \hat{\mathbf{J}}(1) - \underline{\mathbf{P}} \cdot [\underline{\mathbf{C}} - \hat{C}(1)] + o(\epsilon) \quad (3.51)$$

where  $\underline{\mathbf{C}}$  represents the actual boundary value of the concentration field at  $x = 1$ , and  $\underline{\mathbf{P}}$  is defined by the analogue of (3.48) for the right-hand boundary. In both (3.48) and (3.51), the vector  $\mathbf{N}$  denotes the net transmembrane flux, which, of course, must be identical with the respective boundary flux because the nonvolatile flux components vanish and the volatile flux components are the same at  $x = 0$  as at  $x = 1$ .

By a formal inversion of (3.48) and (3.51), one obtains a type of boundary-layer resistance formula which gives the discontinuity of concentration, between the core and membrane boundaries, in terms of the transmembrane flux.

\* In essence, this is the only type of continuity that one can rigorously demand, a fact which elucidates the shortcomings of the equilibrium approximation discussed above.

\* In the works of Kreuzer and Hoofd (1972) and the related work of Smith et al. (1973) a somewhat different approach is used for only a single reaction. The general version given here is thought to be a succinct statement of the underlying logic, which accounts for the order in  $\epsilon$  of the terms involved, allows for extension to multiple reactions, and leads basically to the same results for a single reaction.

† The dependence on  $\epsilon$  of the quantities involved is not indicated explicitly in (3.41) or in the relations following.

In fact, the core-flux terms  $\hat{J}(0)$  and  $\hat{J}(1)$  effectively do not enter into the relations (3.48) and (3.51) as can be seen by the equilibrium condition in (3.11) which requires that, for  $0 < x < 1$ ,

$$0 = \partial r(\hat{C})/\partial x \equiv \mathbf{D} \cdot \hat{\mathbf{r}} \cdot \mathbf{D}^{-1} \cdot \hat{\mathbf{J}}(x) \quad (3.52)$$

where

$$-\hat{\mathbf{r}} = \mathbf{D}^{-1} \cdot [\partial r(\mathbf{C})/\partial \mathbf{C}]_{\mathbf{C}=\hat{\mathbf{C}}(x)}$$

Therefore, for the limiting value  $x = 0$ , one has

$$\bar{\mathbf{r}} \cdot \mathbf{D}^{-1} \cdot \hat{\mathbf{J}}(0) = 0 \quad (3.53)$$

together with a similar relation at  $x = 1$ . That is to say, the vector  $\mathbf{D}^{-1} \cdot \hat{\mathbf{J}}(0)$  lies in the null space of  $\bar{\mathbf{r}}$  and, presumably, also in the null space of  $\bar{\mathbf{A}}$ , as formally defined in (3.43).

As a consequence, the inverse relations for (3.48) and (3.51) can be expressed formally, as

$$\bar{\mathbf{C}} - \hat{\mathbf{C}}(0) = \bar{\mathbf{P}}^{-1} \cdot [\mathbf{N} - \hat{\mathbf{J}}(0)] \equiv \epsilon \bar{\mathbf{\Omega}} \cdot \mathbf{N} + o(\epsilon) \quad (3.54)$$

$$\underline{\mathbf{C}} - \hat{\mathbf{C}}(1) = -\mathbf{P}^{-1} \cdot [\mathbf{N} - \hat{\mathbf{J}}(1)] \equiv -\epsilon \underline{\mathbf{\Omega}} \cdot \mathbf{N} + o(\epsilon)$$

where  $\bar{\mathbf{\Omega}}$ , a (left-hand) boundary-layer resistance tensor, is the *inverse*<sup>\*</sup> of  $\mathbf{D} \cdot \bar{\mathbf{A}}$  regarded as a linear transformation restricted to the range of  $\bar{\mathbf{A}}$  (or of  $\bar{\mathbf{r}}$ ); and,  $\underline{\mathbf{\Omega}}$  is defined similarly in terms of  $\underline{\mathbf{A}}$  (or  $\underline{\mathbf{r}}$ ). In this regard, it will be noted that the relations (3.54) are analogous to Equation (2.13) obtained for strictly linear kinetics.

Apart from the linear-algebraic task of rendering (3.54) explicit, which will be discussed in Appendix 3, one is now in a position to determine the transmembrane flux  $\mathbf{N}$ , up to terms  $o(\epsilon)$ . In particular, one has in addition to the relations (3.54), equations of the type (I 3.47) relating flux to overall concentration differences across the membrane. However, by (3.54) these differences can be expressed as

$$\bar{\Delta \mathbf{C}} = \bar{\Delta \hat{\mathbf{C}}} - 2\epsilon \langle \bar{\mathbf{\Omega}} \rangle \cdot \mathbf{N} + o(\epsilon) \quad (3.55)$$

Here,  $\bar{\Delta \mathbf{C}}$ , is the actual difference in the (appropriately dimensionless) boundary concentrations, as defined in (2.5),

$$\bar{\Delta \hat{\mathbf{C}}} \equiv \hat{\mathbf{C}}(0) - \hat{\mathbf{C}}(1) \quad (3.56)$$

is the corresponding difference in core concentrations, and

$$\langle \bar{\mathbf{\Omega}} \rangle \equiv 1/2 (\bar{\mathbf{\Omega}} + \underline{\mathbf{\Omega}}) \quad (3.57)$$

is the arithmetic mean of the boundary-layer resistance tensors occurring in (3.54).

For the boundary-value problem of main interest here, defined by (2.10), one is now able in principle to determine the transmembrane flux  $N_v$  up to terms  $o(\epsilon)$ . By means of (I 3.47) and (3.55), together with relations of the form (3.44), the flux can be expressed in a number of alternate forms:

$$\begin{aligned} N_v &= Z_v^m D_m^s \bar{\Delta C}_s \equiv (N_v)_0 + Z_v^m D_m^s \bar{\Delta C}_n \\ &= Z_v^m \hat{J}_m(0) + o(\epsilon) = Z_v^m \hat{J}_m(1) + o(\epsilon) \\ &= Z_v^m D_m^s \bar{\Delta \hat{C}}_s + o(\epsilon) \end{aligned} \quad (3.58)$$

These relations involve the driving forces derived from the actual boundary values on all species [from which the

contribution of the volatiles could be expressed, as shown, in terms of the (known) purely diffusive flux of volatiles  $(N_v)_0$ , or else they involve quantities that can be derived directly from the boundary values for the core distribution  $\hat{\mathbf{C}}(x)$ .

No matter which expression for  $N_v$  in (3.58) is chosen, the quantities appearing there can in principle be determined with an accuracy  $o(\epsilon)$  from a knowledge of the core-concentration field  $\hat{\mathbf{C}}(x)$ . The latter, we recall, is governed by Equations (3.11) to (3.13), together with boundary conditions (on the volatiles), given by (2.10) and (3.54) as

$$\hat{C}_v(0) = \bar{C}_v - \bar{\Omega}_v^t N_t + o(\epsilon)$$

and

$$\hat{C}_v(1) = \underline{C}_v + \underline{\Omega}_v^t N_t + o(\epsilon), \quad \text{for } v = 1, 2, \dots, F \quad (3.59)$$

In addition to the boundary values  $\bar{C}_v, \underline{C}_v$  on the volatiles,

the preceding boundary conditions on  $\hat{C}_v(x)$  involve contributions from what may be regarded as flux-induced discontinuities at the boundaries. Since the latter are seen to depend on the volatile fluxes  $N_v$ , and on certain components of the resistance tensors which involve quantities defined in equations of the form (3.41) and (3.43), the set of Equations (3.11) to (3.13) plus (3.58) to (3.59) is obviously of the implicit variety.

This implicitness is characteristic of the technique of Kreuzer and Hoofd (1972) and Smith et al. (1973), and in practice it necessitates some type of iterative computation.<sup>\*</sup>

#### Application to a Single Reaction and Relation to Other Perturbation Analyses

The structure of Equations (3.58) to (3.59) is perhaps best illustrated by considering the special case of a single reaction with an arbitrary number of volatiles. Here, the reaction rate is expressible in terms of the stoichiometric coefficient (vector)  $\alpha$  and a (scalar) rate function  $r$  as  $\mathbf{r} = \alpha r(\mathbf{C})$ . Thus, the resistance tensors of (3.58) and (3.59) take on dimensionless forms that can be deduced directly from the formula (2.20) to (2.24) derived for the case of linear kinetics:

$$\bar{\mathbf{\Omega}} = \frac{1}{\lambda} \mathbf{u} \bar{\mathbf{\beta}} \equiv \frac{1}{\lambda^3} \mathbf{u} (\mathbf{D}^{-1} \cdot \bar{\mathbf{k}}) \quad (3.60)$$

where (again in terms of dimensionless quantities)

$$\bar{\mathbf{k}} = [\partial r/\partial \mathbf{C}]_{\mathbf{C}=\hat{\mathbf{C}}(0)} \quad (3.61)$$

and

$$\bar{\lambda}^2 = -\bar{\mathbf{k}} \cdot \mathbf{u}$$

with similar equations for  $\underline{\mathbf{\Omega}}$  at the right-hand boundary. The vector  $\bar{\mathbf{k}}$  (or  $\underline{\mathbf{k}}$ ) represents, of course, the linear-response coefficients of reaction rate or pseudo first-order

<sup>\*</sup> For example, given any initial estimate of the boundary values on the core concentration field for volatiles  $\hat{C}_v(0), \hat{C}_v(1)$ , one obtains an approximation for the core concentration field and its boundary values (for nonvolatiles) from (3.11) to (3.13), thence, for the volatile flux, from the last expression in (3.58), and, finally, for the relevant components of the resistance tensors. Then, Equations (3.59) provide a second approximation for  $\hat{C}_v(0), \hat{C}_v(1)$ , and so forth. It might be noted that other computational schemes can be envisioned, based on alternate expressions for  $N_v$  in (3.58). For example, the term  $\bar{\Delta C}_n$  in the second expression of (3.58) can be related to core quantities and volatile flux by means of (3.55).

<sup>\*</sup> Sometimes referred to as a *pseudo-inverse*. See Appendix 3.

rate constants evaluated at the equilibrium state  $\hat{C}(0)$  [or  $\hat{C}(1)$ ].

The form of (3.58) can also be appropriately simplified, and, in particular, one has, in terms of core fluxes and stoichiometric coefficients, and with an error  $o(\epsilon)$ , that

$$N_v = \hat{J}_v(0) - \alpha_v \hat{\rho}(0) = \hat{J}_v(1) - \alpha_v \hat{\rho}(1) \quad (3.62)$$

with

$$\hat{J}_n(0) = \alpha_n \hat{\rho}(0), \quad \text{and} \quad \hat{J}_n(1) = \alpha_n \hat{\rho}(1)$$

Here, the quantities  $\hat{\rho}(0)$  and  $\hat{\rho}(1)$  represent reaction-layer contributions to flux, and, in this respect, are the boundary-layer analogues of (2.25).

From the correspondingly simple forms of (3.59) one obtains, then, the following set of equations:

$$\hat{\rho}(0) = N_v \bar{\beta}^v \equiv (\hat{J}_v(0) \bar{\beta}^v) / (\alpha_n \bar{\beta}^n) \quad (3.63)$$

$$\hat{\rho}(1) = N_v \underline{\beta}^v \equiv (\hat{J}_v(1) \underline{\beta}^v) / (\alpha_n \underline{\beta}^n)$$

and

$$\hat{C}_v(0) = \bar{C}_v - \frac{\epsilon}{\lambda} u_{v\rho} \hat{\rho}(0) \quad (3.64)$$

$$\hat{C}_v(1) = \underline{C}_v + \frac{\epsilon}{\lambda} u_{v\rho} \hat{\rho}(1)$$

for the boundary conditions on the equilibrium-core field. It is evident, then, that (3.63) and (3.64) serve as implicit relations for the boundary-values on the core field, which, once determined, provide the desired volatile flux, as would be given by (3.62).

From the form of (3.63), which is seen to be the analogue of (2.31), it is moreover apparent that in the carrier dominated limit, where

$$\alpha_n \bar{\beta}^n \rightarrow 0, \quad \text{and/or} \quad \alpha_n \underline{\beta}^n \rightarrow 0,$$

one or more components of the volatile flux  $N_v$ , as well as the boundary discontinuity in concentration defined by (3.64), can become relatively large quantities. That is, of course, precisely where the weak boundary-layer analysis referred to above becomes invalid.

As a final consideration here, the relation of the weak boundary-layer perturbation scheme to the strong boundary-layer analysis can now be exhibited in a fairly lucid and general way. In particular, for a state of complete equilibrium,  $\epsilon \equiv 0$ , one has by (3.64) that

$$\hat{C}_v(0) = [C_v(0)]_{\text{eq}} \equiv \bar{C}_v, \quad (3.65)$$

$$\hat{C}_v(1) = [C_v(1)]_{\text{eq}} \equiv \underline{C}_v,$$

that is, the core distribution takes on the true boundary values of  $C_v$ , and the corresponding equilibrium flux of volatile,  $(N_v)_{\text{eq}}$  say, is then determined by (3.62). However, for any small  $\epsilon > 0$  we may write formally

$$N_v = (N_v)_{\text{eq}} + \left[ \frac{\partial N_v}{\partial \hat{C}_t(0)} \right]_{\text{eq}} [\hat{C}_t(0) - \bar{C}_t] + \left[ \frac{\partial N_v}{\partial \hat{C}_t(1)} \right]_{\text{eq}} [\hat{C}_t(1) - \underline{C}_t] + \dots \quad (3.66)$$

where the derivatives  $[\partial N_v / \partial \hat{C}_t]_{\text{eq}}$  represent the response of flux to the core-distribution boundary values (for volatiles) at  $\epsilon = 0$ . By regarding these quantities and the con-

centration differences in (3.66) as functions of  $\epsilon$ , the latter being given generally by (3.59), we have that

$$\left[ \frac{\partial N_v}{\partial \hat{C}_t(0)} \right]_{\text{eq}} = \left[ \frac{\partial N_v}{\partial \bar{C}_t} \right]_{\text{eq}} \equiv \frac{\partial (N_v)_{\text{eq}}}{\partial \bar{C}_t}, \quad (t, v = 1, 2, \dots, F) \quad (3.67)$$

together with a similar result for the remaining derivative in (3.66). As a consequence, Equation (3.66) can be expressed in a linear form for  $N_v$ :

$$N_v = (N_v)_{\text{eq}} - 2\epsilon \langle G_v^t \rangle_{\text{eq}} N_t + \dots \quad (3.68)$$

where, of course, the repeated index ( $t$ ) denotes a sum over volatiles, and where

$$\langle G_v^s \rangle_{\text{eq}} \equiv \frac{1}{2} \left[ \frac{\partial N_v}{\partial \bar{C}_t} \bar{\Omega}_t^s - \frac{\partial N_v}{\partial \underline{C}_t} \Omega_t^s \right]_{\text{eq}}, \quad \text{for } s = 1, \dots, F \quad (3.69)$$

In (3.69), the quantities in the square brackets are all to be evaluated at  $\epsilon = 0$ , in which case Equation (3.65) is also applicable. Thus, for small  $\epsilon$ , Equation (3.68) provides a first approximation to  $N_v$ , involving quantities that are derivable from the limiting core solution for complete equilibrium,  $\epsilon \equiv 0$ . It is obvious, then, that the magnitudes of the derivatives appearing (3.69) will play a crucial role in determining the nature of this approximation for  $N_v$ .

Specifically, if it is assumed\* that the (components of the) resistance tensors  $\Omega_v^s$  in (3.59) are  $o(1)$  for  $\epsilon \rightarrow 0$ , then two different types of approximation for  $N_v$  arise, depending on whether the products

$$\epsilon \left[ \frac{\partial N_v}{\partial \bar{C}_t} \right]_{\text{eq}} \quad \text{and} \quad \epsilon \left[ \frac{\partial N_v}{\partial \underline{C}_t} \right]_{\text{eq}} \quad (3.70)$$

are small or large in some sense. If they are both small, that is,  $o(\epsilon)$ , then it is appropriate to replace  $N_v$  on the right-hand side of (3.68) by  $(N_v)_{\text{eq}}$ , which yields the explicit expression for  $N_v$ :

$$N_v = (N_v)_{\text{eq}} - 2\epsilon \langle G_v^t \rangle_{\text{eq}} (N_t)_{\text{eq}} + o(\epsilon) \quad (3.71)$$

This expression is, in fact, *identical* with the first-order approximation (in  $\epsilon$ ) that one would obtain by a weak boundary-layer analysis of the type proposed by Goddard et al. (1970) for a single reaction.†

On the other hand, if at least one of the quantities (3.70) is large, that is,  $o(1)$  or larger for  $\epsilon \rightarrow 0$ , then the expression in (3.71) will no longer provide a valid approximation to  $N_v$ . In this case, which corresponds essentially to the carrier-dominated equilibrium regime discussed above, the correct approximation for  $N_v$  should instead be obtained by inversion of the linear equation implied in (3.68), that is, formally by

$$N_v = [\delta_v^t + 2\epsilon \langle G_v^t \rangle_{\text{eq}}]^{-1} (N_t)_{\text{eq}} + \dots \quad (3.72)$$

where  $\delta_v^t$  is the Kronecker delta. Then, whenever the term  $\epsilon \langle G_v^t \rangle_{\text{eq}}$  is small compared to unity, the expression in (3.72) can be well approximated by (3.71). Otherwise, (3.72) provides only a rough first approximation for flux of volatiles, an approximation which may involve errors larger than  $o(\epsilon)$  for  $\epsilon \rightarrow 0$ , because of the approximate nature of (3.66).

Again, for purposes of illustration, we consider the case

\* This assumption can always be realized through the appropriate choice of the somewhat arbitrary parameter  $\epsilon$ .

† Equation (3.72) is thought to represent a significant generalization of the results provided by Smith et al. (1973) and, at the same time, is strikingly simple to interpret in its general form.

of a single reaction, where Equation (3.72) can be solved explicitly to give

$$N_v = (N_v)_{\text{eq}} - \frac{\epsilon}{B} (\overline{H} \overline{d}_v + \underline{H} \underline{d}_v) + \dots \quad (3.73)$$

$$B = (1 + \epsilon \overline{a})(1 + \epsilon \underline{a}) - \epsilon^2 \overline{b} \underline{b}$$

$$\overline{H} = 1 + \epsilon (\overline{a} \overline{N} - \overline{b} \underline{N})$$

$$\overline{N} = \overline{\beta}^v (N_v)_{\text{eq}}, \quad \overline{a} = \overline{\beta}^v \overline{d}_v, \quad \overline{b} = \overline{\beta}^v \overline{d}_v,$$

with overbars and underbars interchanged in the corresponding definition of  $\underline{H}$ ,  $\underline{N}$ ,  $\underline{a}$ , and  $\underline{b}$ , and with

$$\overline{d}_v = \frac{u_t}{\lambda} \left[ \frac{\partial N_v}{\partial \overline{C}_t} \right]_{\text{eq}}, \quad \underline{d}_v = -\frac{u_t}{\lambda} \left[ \frac{\partial N_v}{\partial \underline{C}_t} \right]_{\text{eq}}$$

Here, in accordance with our previous convention, the repeated index ( $t$ ) denotes a summation over volatiles.

In the practically important case where there is only one volatile species, the above relation can be further simplified to give

$$N_v = (N_v)_{\text{eq}} - \left( \frac{2\epsilon}{B} \right) \langle d_v \beta^t \rangle (N_t)_{\text{eq}} + \dots \quad (3.74)$$

$$\equiv (N_v)_{\text{eq}}/B$$

where now

$$B = 1 + 2\epsilon \langle d_t \beta^t \rangle \quad (3.75)$$

$$\langle d_v \beta^t \rangle = \frac{1}{2} (\overline{d}_v \overline{\beta}^t + \underline{d}_v \underline{\beta}^t)$$

Here, the free index  $v$  and the summation index  $t$  have essentially only one value, say  $t = v = 1$ , whence follows the second equality in (3.74). Nevertheless, the quantity immediately following the first equality in (3.74) has been left in a general form since it suggests a useful approximation to be employed in lieu of the correct but more complex form (3.72) for situations involving more than a single volatile species.

Equation (3.74) is a general form of the so-called "first-order approximation" proposed by Smith et al., for  $n = m = 1$ ,  $k = \text{constant}$ , in the reaction model of (3.8). In the special case which they treat, involving uncoupled diffusion and equal diffusivities ( $D_B \equiv D_C$ ) of the carrier species  $B$  and  $C$ , the equilibrium core solution can be obtained by straightforward algebraic methods and, consequently, Equation (3.74) can be reduced to the following explicit expression for the facilitation  $\Phi$ :

$$1 + \Phi = \frac{(1 + \Phi)_{\text{eq}}}{1 + [\overline{Z}^2 \delta(\overline{Z}) + \underline{Z}^2 \delta(\underline{Z})]} \quad (3.76)$$

where

$$\delta(Z) = \frac{\epsilon}{\lambda(Z)} = \epsilon \left[ \frac{\sigma Z}{1 + Z^2} \right]^{1/2},$$

$$\epsilon = [D_A/L^2 k C_{\text{tot}} \{B\}]^{1/2}, \quad \overline{Z} = \frac{\sigma}{1 + K\overline{C}_A},$$

$$\underline{Z} = \frac{\sigma}{1 + K\underline{C}_A}, \quad \sigma = \left[ \frac{KC_{\text{tot}} \{B\} D_B}{D_A} \right]^{1/2}$$

and

$$\Phi_{\text{eq}} = \overline{Z} \underline{Z}. \quad (3.77)$$

The notation for the quantities  $\delta(\overline{Z})$ ,  $\delta(\underline{Z})$  is intended to suggest a boundary-layer thickness or equivalently, a mass transfer resistance. Accordingly, (3.76) can be rearranged into an inverse form, suggestive of a sum of mass transfer resistances arising from the core and boundary layers.

As pointed out by Smith et al. (1972), the expression for  $\Phi$  in (3.76) becomes identical with that of (3.71), for  $\epsilon \rightarrow 0$ , namely

$$(1 + \Phi) = (1 + \Phi_{\text{eq}}) \{1 - [\overline{Z}^2 \delta(\overline{Z}) + \underline{Z}^2 \delta(\underline{Z})] + O(\epsilon^2)\} \quad (3.78)$$

which, in different notation, is the perturbation formula given previously by Goddard et al. (1970), as a first-order correction in  $\epsilon$  to account for departure from reaction equilibrium. As indicated by the latter work, and in line with the remarks made earlier in the present review, this formula is generally useful only if the equilibrium facilitation  $\Phi_{\text{eq}}$  is small relative to unity. Otherwise, the first-order correction term in (3.78) is large for all but exceedingly small  $\epsilon$ .

For large  $\Phi_{\text{eq}}$ , even the relatively more accurate formula (3.76) provides only a rough first approximation to flux, and to obtain a better approximation to  $\Phi$  one should employ the implicit relations derived from (3.64). For the present example, these can be reduced to

$$\hat{C}_A(0) = \overline{C}_A - H(\overline{Z}) (\overline{C}_A - \underline{C}_A) + o(\epsilon) \quad (3.79)$$

$$\hat{C}_A(1) = \underline{C}_A + H(\underline{Z}) (\overline{C}_A - \underline{C}_A) + o(\epsilon)$$

and

$$1 + \Phi = \frac{1 + \overline{Z} \underline{Z}}{B} + o(\epsilon)$$

with

$$H(Z) = \left[ \frac{1 + \overline{Z} \underline{Z}}{1 + Z^2} \right] Z^2 \delta(Z) \quad (3.80)$$

and

$$B = 1 + H(\overline{Z}) + H(\underline{Z})$$

Here the function  $\delta(Z)$  is defined as in (3.77) but, in contrast to (3.77), the arguments  $\overline{Z}$ ,  $\underline{Z}$  are now to be based on boundary values associated with the core distribution:

$$\overline{Z} = \frac{\sigma}{1 + K\overline{C}_A(0)}, \quad \underline{Z} = \frac{\sigma}{1 + K\underline{C}_A(1)} \quad (3.81)$$

Thus, Equations (3.79) to (3.81) provide an implicit or iterative scheme for determination of  $\hat{C}_A(0)$ ,  $\hat{C}_A(1)$ , and the facilitation  $\Phi$ , to terms  $o(\epsilon)$ . We recall that such a calculation has been applied in a somewhat different form by Kreuzer (1972) as a model for hemoglobin- and myoglobin-facilitated diffusion of oxygen. Also, Smith et al. (1973) have made similar computations for the same model and give detailed comparisons with numerical and other solutions. More recently, Suchdeo and Schultz (1974) have applied this method, but with a different reaction model, to the bicarbonate-facilitated diffusion of carbon dioxide (see Figure 9 of Part I).

In closing here, we should perhaps re-emphasize that, whenever conditions are such as to necessitate the strong boundary-layer analysis elaborated on here, the formal linearization used in arriving at (3.38) and, hence, the results of (3.54) appear to give only an approximate solution to a nonlinear boundary-layer problem [see the remarks preceding (3.38) and those of Kreuzer and Hoofd (1970, 1972)]. This approximation has the virtues of removing the singularity associated with the carrier-dominated limit, of being exact for strictly linear kinetics, and, finally, of being accurate to terms  $O(\epsilon)$  for  $\epsilon \rightarrow 0$  (as of course is the weak boundary-layer analysis).

Although Smith et al. (1973) have proposed a method

of deriving higher-order correction terms, these appear to constitute nothing more than the type of formal series development in integral powers of  $\epsilon$  (or, as they put it, powers of  $1/L$ ) employed in the weak boundary-layer analysis. That such series expansions can fail, owing to nonlinear kinetics, has already been illustrated by the example of second-order boundary layers discussed by Goddard et al. (1970) where the correct expansion is shown to proceed in powers of  $\epsilon^{1/3}$  (that is,  $L^{-1/3}$ ).

#### 4. SUMMARY

In this review we have focused our attention on carrier-mediated transport in simple membranes and, to some extent, feel we have merely scratched the surface of the variety of phenomena that may occur, even in globally nonreactive systems. Our emphasis has been on presenting a general basis for the understanding of these problems and, also, in suggesting some approaches for obtaining analytical-type solutions valid for limiting or otherwise restricted conditions (as, for example, our assumption of uniformly rapid reactions).

One might expect that exact solutions are always possible through the use of numerical methods. However, in these 2-point boundary problems, numerical methods have also met with limitations. For example, Kutchai et al. (1970) showed that the technique of quasilinearization can be used successfully to calculate concentration profiles and fluxes for various cases. However, it has been our experience (Suchdeo and Schultz, 1971) that this method becomes awkward, that is, it requires extremely small step sizes, as the Damköhler number increases and the system approaches the equilibrium regime. Bassett and Schultz (1970) used a Runge-Kutta technique but found that convergence was difficult to realize even in the near-diffusion, nonequilibrium regime. Ward (1970) and Smith et al. (1973) have presented numerical solutions, but their algorithms were not given in detail. Recently Yung and Probst (1973) have suggested a method of formulating the differential equations for the particular case  $A \uparrow + B = C$  in dimensionless form so as to make convergence of the numerical solution somewhat more direct.

The availability of analytical solutions is even more restrictive than that of numerical solutions. As shown in several places in this review, exact analytical solutions for simple membranes have been derived only for reactions with linear kinetics. Another approach that has been taken is to obtain an analytical solution for a particular set of restrictive conditions and then attempt to extend the range of validity by incorporating an interpolation factor.

Thus, Brian and Bodman (1964) showed that a linearized solution for facilitated heat transfer could be extended over a wide parametric range by incorporating a factor to make the solution correct in the extremes of equilibrium and frozen conditions.

A similar device was used by Yung and Probst (1973) for the example cited above, with the restrictions of equal carrier diffusivity ( $D_B = D_C$ ) and zero downstream concentration for the permeant species A. An analytical solution was obtained for the limit of small upstream concentrations of A,  $\bar{C}_A K \rightarrow 0$ , and then extended to finite upstream concentration of A by an interpolation formula, to give the following:

$$\Phi = \frac{2 \frac{D_B}{D_A} \frac{C_{\text{tot}}\{B\}}{C_A} \left( \frac{C_B(1)}{C_B(0)} - 1 \right)}{1 + \frac{C_B(1)}{C_B(0)} + K C_A} \quad (4.1)$$

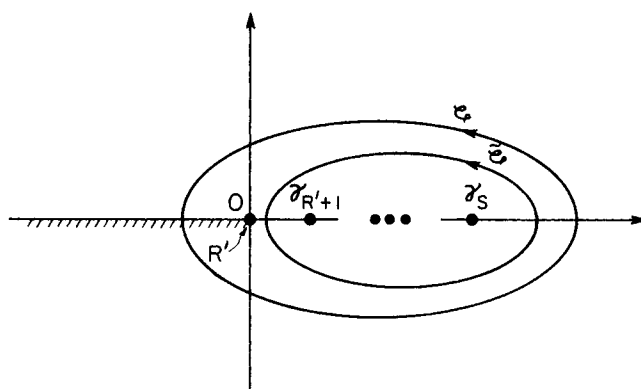


Fig. 2. Representation of the eigenvalues or spectrum of  $\mathbf{M}$  in the complex plane, the contours  $G$  and  $\tilde{G}$ , and the branch cut associated with  $z^{1/2}$  at  $z = 0$ .

and

$$\left( \frac{C_B(1)}{C_B(0)} - 1 \right) = \frac{(1 - 2\sqrt{\tau} \tanh(2\sqrt{\tau})^{-1}) K \bar{C}_A}{1 + \frac{D_B}{D_A} K C_{\text{tot}}\{B\} 2\sqrt{\tau} \tanh(2\sqrt{\tau})^{-1}} \quad (4.2)$$

where

$$\tau = \frac{D_B}{k_2 L^2} \left[ \frac{1}{1 + \frac{D_B}{D_A} K C_{\text{tot}}\{B\}} \right] \quad (4.3)$$

This solution works well for moderate values of the parameters  $\bar{C}_A K$  and  $D_B/D_A K C_{\text{tot}}\{B\}$ .

In view of the fact that only a very few of the many possible types of carrier-mediated transport systems have been studied in detail, we have thought it useful to suggest a systematic approach for analyzing new systems of interest, as follows:

Based on the results already obtained for various systems and reported in the literature, it appears that if the facilitation factors calculated for linear kinetics are approximately equal to those calculated assuming complete chemical reaction equilibrium, then the linearized equations provide the easiest and most direct path to an overall description of the system. In terms of the development outlined here, one first estimates the expected fluxes for the specific physical conditions but assuming reaction equilibrium as outlined in Section 3, Equations (3.11) to (3.14). Then, similar calculations are made by linearizing the kinetic expression as outlined in Part I, Section 4, and Part II, Section 2, Equations (2.14) to (2.19). If the facilitation factors  $\Phi$  estimated by these two techniques are similar in the reaction equilibrium regime, then the facilitation estimated by the linearized technique would be expected to be valid over the entire range of Damköhler numbers, all the way from the near-diffusion to the near-equilibrium regime.

If, on the contrary, the results of the linear analysis are not valid in the near equilibrium regime, then one can use the strong boundary-layer analysis as outlined in Section 3. Although one is not completely sure of the range of validity of these approximate equations in terms of Damköhler numbers one can augment this calculation with the near-diffusion, regular perturbation scheme as discussed in Equations (3.4) to (3.7).

If these approximate analytical techniques do not pro-

vide reasonably consistent estimates of fluxes, then one may be forced to explore direct numerical solutions of the differential equations.

While not stated above in explicit mathematical terms, we should point out in concluding here that our assumption of prescribed concentration on permeant species at the membrane interfaces does not preclude treatment of other situations such as heterogeneous reactions at the interfaces or hydrodynamic (unstirred layer) resistances external to the membrane phase. With such effects (as with the Donnan effects mentioned in Part I, Section 4) one has simply to couple the membrane equations with the other relevant governing equations (which in some cases might even involve the boundary concentrations of nonvolatile species). In this case, equations identical in form with (2.13) and (3.59) also apply to nonvolatiles with  $v$  replaced by  $n$ . For example, in the relatively simple case of (linear) external resistances these may be added, a priori, to the membrane resistance of (2.13) or the boundary-layer resistances of (2.13) and (3.59).

#### Areas Which Deserve Further Attention

In the course of writing this review, several areas have emerged which, in our view, are not well understood and merit attention. We list them here, with some brief commentary, in the hope of kindling interest in the questions:

1. *Rational Correction to Linear Theory.* We have derived some general results for linearized kinetics in Section 2. However, these results suffer, as do those of irreversible thermodynamics, from the fact that no criteria for the range of validity of the solutions are available. There is a need for the development of rational correction terms to indicate the range of validity of the results.

2. *Exact Treatment of the Boundary-Layer Problem and Derivation of Rational, Higher Order Correction Terms.* As pointed out in the concluding remarks of Section 3, the boundary-layer method discussed there must be regarded as approximate since it involves linearization in terms that, while nominally  $O(\epsilon)$ , may actually be  $O(1)$  for  $\epsilon \rightarrow 0$  in the carrier-dominated regime. Until the nature of this approximation is further elucidated, there is some doubt as to the meaning of the type of higher-order expansion proposed for a special case by Smith et al. (1973).

While the method as it stands appears to give excellent results in several applications, even without higher-order corrections, we feel it would be desirable to study the initial, linear approximation further in order to derive correction term in a rational way.

3. *Other Geometries.* Almost all the results given here are for simple planar geometries. Yet, in the application of carrier-mediated transport, it is quite likely that spherical shapes (for example, cells) and cylindrical forms (for example, tubular membranes), as well as heterogeneous media, will often be of more interest. Stroeve et al. (1972) have attacked this kind of problem within the framework of the linearized analysis, and extensions to the nonlinear regime would be of interest. Not the least problem in this regard is the development of a general method for calculating reaction-equilibrium fluxes in these systems.

4. *Multiple Reactions with Vastly Different Reaction Rates.* In all but the linear analyses, we have restricted ourselves to reactions which can all be assumed slow or fast relative to diffusion. Clearly, in many situations some reactions will be virtually instantaneous in comparison with other coexistent steps. The transport of  $\text{CO}_2$  through bicarbonate solutions is a case in point. The analysis is simplified enormously if some of the reactions can be assumed to be at equilibrium; however, there is no method available now to make this assessment objectively.

5. *Unsteady and Cyclic Operation.* We have restricted ourselves here mainly to steady state operation, but it is clear that rather different behavior would be expected in the unsteady state. There has been virtually no analysis of these effects, apart from some numerical studies for oxygen diffusion into hemoglobin solutions of finite thickness, see Spaan (1973).

6. *Electrical Field and Charge Effects.* As mentioned in Part I, most of the theoretical work on electrical field and charge effects has been directed toward the study of lipid-bilayer membranes. In these studies, homogeneous chemical reaction rates are usually assumed to be instantaneous. However, it is precisely in the case of extremely thin films, with low Damköhler numbers, that reaction-rate limitations may severely decrease the carried-mediated flux.

7. *Forced, Natural Convection, and Marangoni Effects.* One can expect increased transport rates when bulk flows occur to supplement the rates of diffusion of carriers and other species. Such convection, due to coupling, might even occur in natural membranes, owing to the mobility of surface layers.

8. *Thermodynamics and Efficiency of Membrane Separations.* One of the important questions in biological membrane transport relates to the energetic requirements for solute transport since a large part of the metabolic load on a cell may be attributed to the work of transport. Here not only must one consider the coupling of passive mechanisms but also, and perhaps more importantly, the coupling of irreversible reactions with carrier-mediated transport. As a prelude to such questions there is a brief discussion of energetics in Appendix 4.

#### ACKNOWLEDGMENT

This work was supported in part by Grant GM15152 from the Public Health Service and a Research Career Development Award IKOGMO8271 to J. S. Schultz. The authors wish to express their appreciation to Dr. Shyam Suchdeo, coauthor of Part I, for his numerous contributions to this endeavor, and to Mrs. Alvalea May for her efforts in the preparation of both parts of this manuscript.

#### NOTATION

$a$	= Helmholtz free energy/vol. of mixture (Appendix 1)
$a^{ij}$	= metric tensor, derived from $a$ at an equilibrium state
$A_i^s$	= coefficients of transformation
$b_i$	= constants of integration, (1.6) and (A2.1)
$C\{\}$	= concentration of a species, mole/cm <sup>3</sup>
$C, (C_s)$	= vector of concentrations (and components), mole/cm <sup>3</sup>
$D, (D_m^s, D_s)$	= diffusivity, tensor (and components), cm <sup>2</sup> /s
$D_{\text{eff}}$	= effective or apparent diffusivity, cm <sup>2</sup> /s
$E, E_i (E^s, E_i^s)$	= reaction invariants (and components) or basis vectors
$\mathcal{E}$	= chemical species
$f$	= fractional mediation, relative to equilibrium, (2.33)
$\vec{f}^k$	= diffusion plus migration force, (A1.4)
$f(z)$	= function of a complex variable (Appendix 3)
$F$	= number of free or permeant species
$F'$	= number of nonvolatile or trapped species
$\vec{g}^k$	= migration force, (A1.5)
$\langle G_v^t \rangle_{\text{eq}}$	= matrix in (3.69)
$I^s, I_i^s$	= components of composition invariants

$I'$  = number of fixed stoichiometric invariants  
 $I_s$  = system composition invariant  
 $\vec{j}_i, j_i$  = general diffusion-flux, moles  $i/\text{cm}^2\text{-s}$   
 $\vec{J}, (\vec{J}_s)$  = diffusion flux vector (and components), mole/  
 $\text{cm}^2\text{-s}$   
 $\mathbf{k}, (k^s)$  = vector of reaction rate constants (and compo-  
nents)  
 $\mathbf{K}, (k_s^m)$  = tensor of kinetic constants (and components)  
 $K$  = equilibrium constant  
 $L$  = membrane thickness, cm  
 $L_{ij}$  = Onsager coefficients for diffusion (Appendix 1)  
 $\vec{n}$  = surface normal  
 $\vec{N}, (\vec{N}_s)$  = flux vector (and components), mole/ $\text{cm}^2\text{-s}$   
 $N\{\}, N_v$  = total molar flux or transmembrane flux of a  
species, mole/ $\text{cm}^2\text{-s}$   
 $n\{\}$  = amount (species, or entity), moles  
 $\mathbf{P}, (P_m^s)$  = permeability tensor (and components)  
 $R$  = number of independent chemical reactions  
 $R'$  = number of reaction invariants or radicals  
 $\mathbf{r}, (r_s)$  = vector of species reaction rates (and compo-  
nents)  
 $S$  = number of chemical species  
 $\mathcal{S}$  = linear space of chemical species  
 $T$  = absolute temperature  
 $t$  = time, s  
 $\mathbf{u}^i, \mathbf{u}_i$  = right and left eigenvectors of  $\mathbf{\Gamma}$  (Appendix 3)  
 $V$  = volume,  $\text{cm}^3$ , or region in space;  $\partial V$  = boundary  
of  $V$   
 $\vec{v}$  = molar average velocity, Equation (A1.3),  $\text{cm/s}$   
 $\omega(\lambda)$  = function defined by Equation (2.19)  
 $x$  = distance, cm  
 $X_i$  = components of concentration on basis of Equation  
(1.4)  
 $Z$  = parameters defined in Equation (3.77) or Equa-  
tion (3.81)  
 $Z_s^m$  = transport numbers  
 $z$  = (complex) variable (Appendix 3)

### Greek Letters

$\alpha, (\alpha_s)$  = vector of stoichiometric coefficients (and compo-  
nents)  
 $\beta, (\beta_s)$  = vector [and components of Equations (2.24)  
and (3.60)]  
 $\gamma$  = a Damköhler number defined by Equation (I 4.11)  
 $\gamma_i$  = eigenvalues of  $\mathbf{\Gamma}$  (Appendix 3) Damköhler num-  
bers for reaction modes  
 $\mathbf{\Gamma}$  = diffusion-reaction tensors of Equations (2.1) and  
(3.41)  
 $\delta(Z)$  = reaction-layer dimension defined by Equations  
(3.77)  
 $\delta_j^i$  = Kronecker delta  
 $\delta_s$  = reaction-layer thickness for species  $s$ , Equation  
(2.29)  
 $\bar{\Delta}\{\}$  =  $\{\} - \{\}$ , decrement across membrane, Equation  
(2.5)  
 $\epsilon$  =  $\gamma^{-1/2}$ , perturbation parameter for rapid reactions  
 $\kappa_j^i, \kappa_{ij}$  = Onsager coefficients for reaction (Appendix 1)  
 $\mathbf{\Lambda}$  = positive square root of  $\mathbf{\Gamma}$ , Equations (2.3) and  
(3.43)  
 $\lambda$  = inverse reaction-layer thickness  
 $\lambda_i$  =  $\sqrt{\gamma_i}$ , eigenvalues of  $\mathbf{\Lambda}$   
 $\xi_i$  = composition coordinate  
 $\rho$  = reaction contribution to flux, Equations (2.25),  
(3.62)  
 $\Phi$  = facilitation factor

$\mu^i$  = chemical potential, Equation (A1.6)  
 $\vec{v}_i$  = general flux vector  
 $\mathbf{\Pi}^{(i)}$  = oblique projections onto the respective eigen-  
spaces of  $\mathbf{\Gamma}$   
 $\sigma$  = parameter, Equations (3.30) and (3.76)  
 $\omega_i$  = general reaction rate coordinate  
 $\mathbf{\Omega}, (\Omega_m^s)$  = resistance tensors (and components), Equa-  
tions (2.12), (3.54), and (A3.19)

### Superscripts

$i, j, k$  = co-variant components (contrary to the usual ten-  
sor convention), or enumerative indices, for reac-  
tion invariants or reaction paths  
 $n, p$  = nonvolatile or permanent species  
 $s, l, m$  = species  
 $v, t$  = volatile species  
 $\circ$  = typical or equilibrium value  
 $-1$  = inverse of tensors (or matrices); for example,  
 $(E^{-1})_m^i$  are the components of the inverse for  
 $E_i^s$ ;  $\mathbf{D}^{-1}$  is the inverse of  $\mathbf{D}$ , etc.

### Subscripts

$A, B, C$  = value for species  $A, B, C \dots$   
eq = value evaluated at chemical-reaction equilibrium  
0 = value in the absence of chemical reactions  
 $i, j, k$  = contravariant components (*vide supra*, under  
Superscripts), or enumerative indices, for reac-  
tion invariants or reaction paths  
 $n, p$  = nonvolatile or "permanent" species  
 $s, l, m$  = chemical species  
 $v, t$  = volatile species  
tot = initial amount added to membrane

Overbar indicates value evaluated at left boundary (or  
on the boundary  $\partial V$  of a three dimension region) and  
underbar indicates value evaluated at right boundary. Carets  
denote equilibrium-core values. Brackets  $\langle \rangle$  denote arith-  
metic average of boundary values. For "direct" vector and  
tensor notational convention, see Part I, Notation, and Ap-  
pendix 1 here.\*

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\* Only that notation from Part I (Schultz et al., 1974) which is  
most directly relevant to Part II, is included here. Some of the mathe-  
matical symbols of Part II, defined only in isolated contexts, are not  
listed here. No notational distinction is generally made between dimen-  
sional quantities  $x, D, k, \dots$  and their dimensionless counterparts  $x/L,$   
 $D/D^0, kc^0/r^0, \dots$ . Dimensional consistency or textual commentary  
will generally serve to distinguish these.



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## APPENDIX 1. A NOTE ON RATE EQUATIONS

Apart from the somewhat speculative considerations of unusual transport mechanisms discussed above in Part I, most of the past mathematical treatments of carrier-mediated transport have proceeded from the suppositions that the relative mobility of each chemical species can be attributed solely to molecular (or else, Brownian) diffusion and that the classical linear laws of diffusion in a mixture are adequate to describe this phenomenon. The relevant theory of diffusion is well established and discussed in several textbooks (for example, DeGroot and Mazur, 1962; Bird, Stewart, and Lightfoot, 1960; Katchalsky and Curran, 1967; Lightfoot, 1974). Here, we wish merely to summarize a few key relationships that establish the connection between the form of the rate laws for diffusion and reaction adopted here and those employed elsewhere, especially in the treatments based on linear nonequilibrium thermodynamics (Friedlander and Keller, 1965; Blumenthal and Katchalsky, 1969; Katchalsky and Curran, 1967).

In terms of general composition coordinates related to actual (molar) concentration and flux fields by a (constant) transformation of the form (I 3.31), we may define a general diffusional flux (with units of  $A_i$  per unit area per unit time) by

$$\vec{j}_i = \vec{J}\{A_i\} = A_i^s \vec{J}_s \quad (\text{A1.1})$$

Here,  $\vec{J}_s$  is the diffusional (plus migrational) species flux relative to the mixture, as defined by

$$\vec{J}_s = \vec{N}_s - C_s \vec{v}, \quad S = 1, \dots, S \quad (\text{A1.2})$$

where  $\vec{v}$  is the (molar average) mixture velocity

$$\vec{v} \equiv \left[ \sum_{s=1}^S \vec{N}_s \right] / \left[ \sum_{s=1}^S C_s \right] \quad (\text{A1.3})$$

Then, the general (isothermal) form of the linear diffusion law is taken to be

$$\vec{j}_i = L_{ik} \vec{f}^k \quad (\text{A1.4})$$

where  $L_{ik}$  is an Onsager coefficient and  $\vec{f}^k$  is the diffusional plus migrational force (per unit  $A_k$ ). The force is understood here to be

$$\vec{f}^i = -\vec{\nabla} \mu^i + \vec{g}^i \quad (\text{A1.5})$$

the first term of which represents the chemico-diffusional force, as derived from the chemical potential; that is, in terms of the variables adopted here, the partial derivatives (at constant temperature)

$$\mu^i = \left( \frac{\partial a}{\partial \xi_i} \right)_{T, \xi_k} \quad k \neq i \quad (\text{A1.6})$$

where  $a$  represents the local Helmholtz free energy per unit volume of mixture. (In the case where the variables  $\xi_i$  correspond to actual species concentrations  $C_s$ , the corresponding derivatives  $\mu^s$  can of course be equated to the partial molar Gibbs free energy.) The second term of (A1.5) represents, then, the migrational force due to all other force fields. (Any physical units for  $\xi_i$  allowed by a transformation of the type (I 3.31) are permissible. The units of other quantities follow then from the requirements that Equations (A1.4) and (A1.5) be term-wise dimensionally consistent and that  $\vec{f}^i \cdot \vec{j}_i$  represent a dissipation rate with dimensions energy/volume/time.)

As in most of the existing treatments of carrier-mediated transport, we have restricted our attention to systems that are presumably uniform in temperature (and pressure) and therefore we have excluded the type of terms from (A1.1) that are often used to describe effects such as thermo- (and pressure) diffusion. Moreover, we have adopted a form of (A1.1) that is, strictly speaking, appropriate only to isotropic media, an assumption which appears to be typical of most analyses on the present subject. Even though some biological and artificial media may not possess this character, manifestations to the contrary would often be concealed especially in the usual experiments on membranes where only unidirectional gradients and fluxes come into play.\*

On the other hand through the term  $\vec{g}^i$  in (A1.5) such effects as forced migration, most importantly electro-migration may be considered. These arise generally in connection with the presence of charged or ionic species. However, in the mathematical analysis of this review no explicit account is made of electro-diffusion effects or of other force fields, nor is convection in the medium considered, so that in effect we have set  $\vec{v} \equiv 0$  and  $\vec{g}^i \equiv 0$  in (A1.5).

As is done in thermodynamic treatments of multicomponent diffusion, we have adopted here the chemical potential as the progenitor of the compositional driving force for diffusion. For the purposes of establishing a complete correspondence with linear-thermodynamic treatments, it is convenient to pursue this formalism further. In particular, we may now set down a formal transformation rule, based on the use of general tensor notation, which allows for a rather direct connection with the linear-irreversible thermodynamic approaches that have been exploited in several instances to treat reaction-coupled transport. In particular, we have anticipated the desirability of distinguishing between contravariant and covariant quantities (superscripted and subscripted) respectively, for the present purposes, to be related through a suitable metric tensor  $a^{ij}$ , say, with metric having dimensions of energy density. Whatever the (positive-definite, nonsingular) metric tensor adopted, we stipulate that it reduce in the near-equilibrium limit to\*\*

$$a^{ij} = \frac{\partial \mu^i}{\partial \xi^j} \equiv \frac{\partial^2 a}{\partial \xi_i \partial \xi_j} \quad (\text{A1.10})$$

In this case, the requirement of positive-definiteness will be recognized as the restriction on the convexity of  $a$ , that is, the restriction on the Hessian form (with units of energy per unit volume),

$$\delta^2 a = \left( \frac{\partial^2 a}{\partial \xi_i \partial \xi_j} \right)_{\text{eq}} \delta \xi_i \delta \xi_j \geq 0 \quad (\text{A1.11})$$

imposed by the classical condition of stability of an (isothermal) equilibrium state where

$$\delta a = \mu^i \delta \xi_i \equiv \left( \frac{\partial a}{\partial \xi_i} \right) \delta \xi_i = 0 \quad (\text{A1.12})^\dagger$$

Then, we may raise and lower indices in accordance with the

\* As discussed in Part I, it would appear that the character of an asymmetric membrane, with apparent directional anisotropy in the normal direction to its plane, could often be more plausibly explained as a gross manifestation of a corresponding directional nonhomogeneity, arising from structural gradients, as in stratified membranes, or from property gradients, owing possibly to gradients in temperature or activity (such as might be induced by pH in the latter case). Some workers have at least broached the theoretical question, for example, Katchalsky and Oster (1968), who point out that anisotropy introduces the possibility (or perhaps one should say "raises the specter") of such complex phenomena as linear coupling between reaction kinetics and diffusion.

\*\* The introduction of a metric is implicit in the thermodynamic treatment presented in other works, for example, DeGroot and Mazur (1962). Under large departures from local thermodynamic equilibrium, the formal adherence to a metric derived from the chemical potential must be regarded as a tenuous procedure. In this case, the metric must be regarded as somewhat arbitrary although it might be made to correspond to the notion of a pseudo-free-energy discussed by Feinberg (1972).

† Thus, with our previous interpretation of certain of the  $\xi_i$  as extents of reaction, Equation (A1.12) will be recognized as the usual condition for chemical equilibrium in terms of these coordinates, which express the degrees of freedom in a closed system, subject to the constancy of the reaction invariants.

usual tensor formalism. For example, if the variables  $\xi_i$  are taken to be the actual molar concentrations  $C_s$ , we denote  $L_{ij}$  by  $L_{sm}$ , and, to relate those to a set of multicomponent diffusivities often used in the literature on diffusion (see Bird et al., 1960, Lightfoot, 1974) we take

$$D_s^m = L_{st} a^{tm}, \quad \text{with} \quad a^{tm} = \left( \frac{\partial \mu^t}{\partial C_m} \right) \quad (\text{A1.13})$$

In terms of these quantities, then, the molar diffusion fluxes,  $\vec{J}_s$  (moles/area-time) are derived from the concentration fields (moles/volume) by

$$\vec{J}_s = -D_s^m \vec{\nabla} C_m \quad (\text{A1.14})$$

With the notational convention adopted above, we can express the various balance and rate equations used here in an unambiguous *direct* notation. Thus we have, for total flux:

$$\vec{N} = \vec{J} + C \vec{v}$$

and for the diffusion plus migration flux:

$$\vec{J} = \mathbf{D} \cdot (-\vec{\nabla} C + \vec{g}) \quad (\text{A1.15})$$

and species balance:

$$\vec{\nabla} \cdot \vec{N} = r - \frac{\partial C}{\partial t}$$

where any set of independent coordinates of the type (1.2) may be used to express the components involved.

One is now in a position to establish a direct connection with the linearized thermodynamic analyses of previous works. Thus, in terms of general composition coordinates, the linearized rate expression (I 4.3) becomes

$$\omega_i = -\kappa_i^j (\xi_j - \xi_j^0) \quad (\text{A1.16})$$

For the special choice of coordinates in (I 3.32) and (I 3.39), the only nonzero reaction rates  $\omega_i$  are those corresponding to the  $R$  extents of reaction  $\xi_i$ ,  $i = R' + 1, \dots, S$ ; and, therefore, the chemical potential  $\mu^i$  is the affinity for the associated  $\xi_i$ . Thus, at equilibrium where  $\xi_i = \xi_i^0$ ,

$$(\mu^i)_{\text{eq}} = 0; \quad (\text{A1.17})$$

whereas, in a state near to equilibrium, Equation (A1.16) is equivalent to

$$\omega_i = -\kappa_{ij} \delta \mu^j \quad (\text{A1.18})$$

with

$$\delta \mu^j \equiv \mu^j - (\mu^j)_{\text{eq}} \equiv \mu^j = a^{ij} \delta \xi_i \equiv a^{ij} (\xi_i - \xi_i^0)$$

and with

$$\kappa_i^j = a^{jk} \kappa_{ki}$$

Having established the above formal correspondence with near-equilibrium thermodynamic theories, we shall also adopt certain of the (constitutive) restrictions on the various kinetic coefficients which are usually imposed in these theories (DeGroot and Mazur, 1962; Katchalsky and Curran, 1967). In particular, we shall adopt the usual symmetry requirement for the Onsager coefficients:

$$L_{ij} = L_{ji}, \quad \kappa_{ij} = \kappa_{ji} \quad (\text{A1.19})$$

$i, j = 1, \dots, S$ , and assume the positive-definiteness (and, hence, invertibility) of  $L_{ij}$ :

$$L_{ij} b^i b^j > 0 \quad (\text{A1.20})$$

for (real)  $b^i \neq 0$ ,  $i = 1, \dots, S$ .

In general terms, this implies that the tensors (matrices)  $\mathbf{D}$  and  $\mathbf{K}$  are real and self-adjoint (that is, similar to symmetric matrices) and that  $\mathbf{D}$  is positive definite (and nonsingular). Similarly, if one rules out near-equilibrium kinetics of the unstable (in time) type, one has the further requirement that  $\mathbf{K}$  be nonnegative (Higgins, 1967):

$$\mathbf{b} \cdot \mathbf{K} \cdot \mathbf{b} \geq 0 \quad (\text{A1.21})$$

for real  $\mathbf{b} \neq 0$ . This assumption appears to be crucial to the

boundary-layer analysis of Section 3, since it ensures an exponential spatial decay to equilibrium (see Goddard et al., 1970).

As a final note here, we should, of course, acknowledge that the assumption of constant diffusivity  $D$ , used as a simplification in most of the analysis of this review, cannot generally be correct. As usual in diffusion problems, a correct accounting for the variation of  $D$  with concentration (were one so fortunate as to know it!), would lead to greater mathematical complexity (nonlinearity) without substantially altering, it is felt, the most important conclusions of the analysis.

At any rate, it is possible to account for variable  $D$  within the framework of the boundary-layer treatment given in Section 3 above (and to the order  $O(\epsilon)$  of terms retained), by simply employing values appropriate to the local equilibrium concentration  $\hat{C}$ . This has also been discussed for a related heat transfer problem (Goddard et al., 1974).

## APPENDIX 2. NECESSITY OF INTEGRAL CONSTRAINTS

Here we wish to show briefly that the specification of integral constraints or system invariants is necessary for uniqueness of solutions to the steady state diffusion-reaction problem governed by (1.5), in some bounded three-dimensional region  $V$  and subject to  $F'$  no-flux conditions on nonvolatiles together with an appropriate set of  $F$  conditions on the volatile species, on the boundary  $\partial V$  of  $V$ .

We have recourse to the general integral anticipated in (I 3.40), with  $\vec{j}_i \equiv \vec{\nu}_i$ , to which there corresponds the  $I'$  integrals for (1.4):

$$X_i = b_i \text{ (a constant in } V) \text{ for } i = F + 1, \dots, R' \quad (\text{A2.1})$$

Thus, we are left with the  $I'$  constants of integration  $b_i$  and a number  $S - I' = F + R$  of equations in (1.5),  $F$  of which are of the harmonic type ( $\omega = 0$ ), and  $R$  of which, having nonvanishing reaction terms, will generally involve the above constants  $b_i$  through the kinetic dependence of  $\omega_i$ . The solution of these remaining equations must satisfy the  $F'$  flux conditions

$$\sum_{i=1}^S (E^{-1})_s^i \frac{\partial X_i}{\partial n} = 0, \text{ on } \partial V, \text{ for } s = F + 1, \dots, S \quad (\text{A2.2})$$

where  $I'$  terms,  $i = F + 1, \dots, R'$ , corresponding to the constants  $b_i$  of (A2.1) vanish from the sum in (A2.2). However, at most  $R$  of the  $F'$  relations in (A2.2) are linearly independent, because the linear transformation, represented there by an  $F' \times I'$  matrix, is of rank  $R$  at most. This follows directly from the fact that the matrix  $(E^{-1})_s^i$  must have a form identical with that of its inverse  $E_i^s$ , displayed in (I 3.39)\* so that the non-zero elements of the above  $F' \times I'$  submatrix  $(E^{-1})_s^i$ ,  $s = F + 1, \dots, S$ ,  $i = 1, \dots, F, R' + 1, \dots, S$  are seen to consist simply of an  $F' \times R'$  matrix. The latter is of maximal rank  $R$ , since here  $F' - R \equiv I' \geq 0$ .

Then, given any set of  $F$  independent boundary conditions imposed on volatiles, for example, prescribed interfacial concentrations:

$$C_s = (D^{-1})_s^m E_m^i X_i = \bar{C}_s, \text{ on } \partial V \quad (\text{A2.3})$$

where the  $\bar{C}_s$  are given functions on the points of  $\partial V$ , for  $s = 1, \dots, F$ , we shall have  $F + R$  equations of the type (1.5), together with a total of  $F + R$  boundary conditions in (A2.2) and (A2.3) and with  $I'$ , as yet arbitrary constants that are generally involved in both (1.5) and (A2.3).

Therefore, in general, it appears that  $I'$  further conditions are necessary to eliminate the arbitrary constants and, thereby, to allow for a unique solution of the problem at hand. The physically obvious choice lies in the specification of volume integrals of the type (I 3.38), which in turn are seen to be intimately

connected with the general flux integrals of (I 3.40) and their consequents, (A2.1), for problems involving only diffusive transport.

## APPENDIX 3. REPRESENTATIONS FOR MEMBRANE AND BOUNDARY-LAYER RESISTANCES

We present here some formulae that are valuable for the representation and calculation of the various resistance tensors discussed in Sections 2 and 3 above.

We make use of some results from the spectral theory of linear operators on finite-dimensional linear vector spaces (see Friedman, 1956) or, equivalently, the theory of matrices (see Amundson, 1966; or Lancaster, 1969). In the present case, we are of course interested in the tensor  $\mathbf{\Gamma}$  defined by (2.1), in a space of  $S$  dimensions.\* In particular, given a linear transformation  $\mathbf{\Gamma}$  or its matrix representation together with a function  $f(z)$  defined on complex variables  $z$ , the linear operator or matrix function  $f(\mathbf{\Gamma})$ , analytic on the spectrum of  $\mathbf{\Gamma}$ , is defined by the Cauchy integral:

$$f(\mathbf{\Gamma}) = \frac{1}{2\pi i} \oint_{\mathcal{G}} f(z) (z\mathbf{1} - \mathbf{\Gamma})^{-1} dz, \quad (\iota = \sqrt{-1}) \quad (\text{A3.1})$$

where  $\mathcal{G}$  is a contour in the complex  $z$ -plane enclosing the spectrum (eigenvalues) of  $\mathbf{\Gamma}$ , and  $f(z)$  is any (scalar) function analytic on the closed region bounded by  $\mathcal{G}$  (Friedman, 1956; Lancaster, 1969). The spectrum of  $\mathbf{\Gamma}$  is of course determined by the roots  $\gamma_1, \gamma_2, \dots, \gamma_s$  of the characteristic equation

$$\det(\mathbf{\Gamma} - \gamma\mathbf{1}) = p(\gamma) = \gamma^s + p_{s-1}\gamma^{s-1} + p_{s-2}\gamma^{s-2} + \dots + p_0 = 0 \quad (\text{A3.2})$$

whose coefficients  $p_k$  can be computed directly from traces of the matrices for  $\mathbf{\Gamma}^k$ ,  $k = 1, 2, \dots, S$  (see Amundson, 1966). In the case of a discrete (or nondegenerate) spectrum of distinct eigenvalues, ( $\gamma_s \neq \gamma_m$  for  $s \neq m$ ) Equation (A3.1) leads, by means of the residue theorem, to the usual form of Sylvester's Theorem:

$$f(\mathbf{\Gamma}) = \sum_{i=1}^S f(\gamma_i) \mathbf{\Pi}^{(i)} \quad (\text{A3.3})$$

(Amundson, 1966), for  $i = 1, 2, \dots, S$ . Here,

$$\mathbf{\Pi}^{(i)} = \prod_{j=1}^{S(i)} \frac{(\mathbf{\Gamma} - \gamma_j\mathbf{1})}{(\gamma_i - \gamma_j)} \quad (\text{A3.4})$$

with parentheses  $(i)$  denoting exclusion from the product of the indicial value  $j = i$ . The products  $\mathbf{\Pi}^{(i)}$  represent oblique projections onto the invariant subspaces associated with the eigenvalues  $\gamma_i$  [and are called components in other contexts (Lancaster, 1969)]. Alternatively, and in terms of the corresponding, appropriately normalized right- and left-eigenvectors, say  $\mathbf{u}^i$  and  $\mathbf{u}_i$ , respectively, the projection  $\mathbf{\Pi}^{(i)}$  can be represented as the dyad

$$\mathbf{\Pi}^{(i)} = \mathbf{u}^i \mathbf{u}_i \text{ (no sum)} \quad (\text{A3.5})$$

where  $\mathbf{u}^i$  and  $\mathbf{u}_i$  satisfy equations of the type (2.15), and

$$\mathbf{u}^i \cdot \mathbf{u}_j = \delta_j^i \quad (\text{A3.6})$$

for  $i, j = 1, 2, \dots, S$ . Also one has the further relations

$$\mathbf{\Gamma} \cdot \mathbf{\Pi}^{(i)} = \gamma_i \mathbf{\Pi}^{(i)} \text{ (no sum)} \quad (\text{A3.7})$$

$$\mathbf{\Pi}^{(i)} \cdot \mathbf{\Pi}^{(j)} = \begin{cases} \mathbf{\Pi}^{(i)}, & i = j \\ 0, & i \neq j \end{cases}$$

for  $i, j = 1, 2, \dots, S$  (Lancaster, 1969).

In the present context, the  $\mathbf{u}_i$  represent reaction rate constants (vectors) associated with the individual reaction modes, whose

\* As Table 6, Part I.

\* Moreover,  $\Gamma$  can be assumed simple (Lancaster, 1969) because of the restrictions of Appendix I.

respective stoichiometric coefficients are given by  $\mathbf{D}^{-1} \cdot \mathbf{E}^t$  in (2.14).

However, in practice it is not expeditious to actually determine eigenvectors. Furthermore, because of stoichiometric dependence amongst reactions, the null space of  $\mathbf{\Gamma}$  can have dimension  $S - R = R' > 1$ , corresponding to a number of repeated null roots,  $\gamma = 0$ , of (A3.2) and to a range of  $\mathbf{\Gamma}$  having dimension  $R < S - 1$ , with nonzero (real, positive) eigenvalues,\* say,  $0 \leq \gamma_{R+1} \leq \dots \leq \gamma_S$ , as depicted in Figure 2. Thus, for the purposes of the actual computations required in Sections 2 and 3 above, some qualification and modification of the result (A3.3) is necessary.

#### Membrane Resistance for Linearized Kinetics

In the case of the resistance tensor  $\mathbf{\Omega}$  of (2.12), the function of interest:

$$f(z) \equiv w(z^{1/2}) = \left(\frac{2}{z^{1/2}}\right) \tanh\left(\frac{z^{1/2}}{2}\right) \quad (\text{A3.8})$$

implied formally by (2.8) and (2.12), that is,

$$\mathbf{\Omega} = \left[\frac{\mathbf{\Gamma}^{1/2}}{2} \coth\frac{\mathbf{\Gamma}^{1/2}}{2}\right]^{-1} \cdot \mathbf{D}^{-1}, \quad (\text{A3.9})$$

is indeed analytic on the spectrum of  $\mathbf{\Gamma}$  and, in particular, at  $z = 0$ , even though  $z^{1/2}$  is not. As a consequence, the contour integral of (A3.1) can be reduced, as already anticipated in (2.17), to the form:

$$f(\mathbf{\Gamma}) \equiv \left[\frac{\mathbf{\Gamma}^{1/2}}{2} \coth\frac{\mathbf{\Gamma}^{1/2}}{2}\right]^{-1} = \tilde{\mathbf{O}} + \sum_i^R w(\sqrt{\gamma_i}) \mathbf{\Pi}^{(i)} \quad (\text{A3.10})$$

where

$$\tilde{\mathbf{I}} = \sum_i^R \mathbf{\Pi}^{(i)}, \quad \tilde{\mathbf{O}} = \mathbf{I} - \tilde{\mathbf{I}} \quad (\text{A3.11})$$

and

$$\mathbf{\Pi}^{(i)} = \left[\frac{\mathbf{\Gamma}}{\gamma_i}\right]^{R'} \left\{ \prod_j^{R(i)} \left[\frac{\mathbf{\Gamma} - \gamma_j \tilde{\mathbf{I}}}{\gamma_i - \gamma_j}\right] \right\} \quad (\text{A3.12})$$

with  $\sum_i^R$  representing the sum over the  $R$ , presumably discrete, nonzero eigenvalues  $\gamma_i$  and  $\prod_j^{R(i)}$  denoting a product with

the factor for  $j = i$  excluded. (The present discussion is limited to the case where the nonzero  $\gamma_i$  are distinct:  $\gamma_i \neq \gamma_j$  for  $i \neq j$  and  $i, j = R' + 1, \dots, S$ , vide infra.) The projections  $\mathbf{\Pi}^{(i)}$

have the same interpretation as above, and  $\tilde{\mathbf{I}}$  represents the projection onto the range of  $\mathbf{\Gamma}$  (hence,  $\tilde{\mathbf{O}}$  the projection onto the null space of  $\mathbf{\Gamma}$ , which can be represented, as in (2.17), by any suitable orthonormal basis).

For purposes of computation, (A3.12) and, hence (A3.10), can be further simplified by means of the decomposition of the characteristic equation for  $\mathbf{\Gamma}$ :

$$(\mathbf{\Gamma})^{R'} \cdot \tilde{p}(\mathbf{\Gamma}) \equiv p(\mathbf{\Gamma}) \equiv \mathbf{O}, \quad (\text{A3.13})$$

where

$$\begin{aligned} \tilde{p}(\mathbf{\Gamma}) &= \prod_{j=R'+1}^S (\mathbf{\Gamma} - \gamma_j \tilde{\mathbf{I}}) = \mathbf{\Gamma}^R \\ &+ \tilde{p}_{R-1} \mathbf{\Gamma}^{R-1} + \tilde{p}_{R-2} \mathbf{\Gamma}^{R-2} + \dots + \tilde{p}_0 \tilde{\mathbf{I}} \equiv \mathbf{O} \end{aligned} \quad (\text{A3.14})$$

is the characteristic equation of  $\mathbf{\Gamma}$  restricted to the range of

\* For brevity in other formulae, we have written  $\lambda_i$  for  $\sqrt{\gamma_i}$  in the text. Also, we assume there is no null eigenvalue associated with a reaction-equilibrium point. Otherwise,  $R + 1$  would have to be interpreted as the actual number of stoichiometrically independent reactions.

$\mathbf{\Gamma}$ , the latter equation serving as well as (A3.11) to define  $\tilde{\mathbf{I}}$ . Then, the product appearing in (A3.12) becomes, by (A3.11) and (A3.14),

$$\begin{aligned} \mathbf{\Pi}^{(i)} &= \left[\frac{\mathbf{\Gamma}}{\gamma_i}\right]^{R'} \prod_j^{R(i)} \left[\frac{\mathbf{\Gamma} - \gamma_j \tilde{\mathbf{I}} - \gamma_j \tilde{\mathbf{O}}}{\gamma_i - \gamma_j}\right] \\ &= \left[\frac{\mathbf{\Gamma}}{\gamma_i}\right]^{R'} \left\{ \prod_j^{R(i)} \left[\frac{\mathbf{\Gamma} - \gamma_j \tilde{\mathbf{I}}}{\gamma_i - \gamma_j}\right] + \prod_j^{R(i)} \left[\frac{-\gamma_j}{\gamma_i - \gamma_j}\right] \tilde{\mathbf{O}} \right\} \end{aligned}$$

However, since  $\mathbf{\Gamma} \cdot \tilde{\mathbf{O}} = \mathbf{O}$  and because of (A3.7), it follows that

$$\mathbf{\Pi}^{(i)} = \prod_j^{R(i)} \left[\frac{\mathbf{\Gamma} - \gamma_j \tilde{\mathbf{I}}}{\gamma_i - \gamma_j}\right] \quad (\text{A3.15})$$

This relation, together with (A3.14), as a defining equation for  $\tilde{\mathbf{I}}$ , leads directly to the polynomial in  $\mathbf{\Gamma}$  of degree  $R$  for  $\mathbf{\Pi}^{(i)}$ :

$$\mathbf{\Pi}^{(i)} = \sum_{j=1}^R \Pi_j^{(i)} \mathbf{\Gamma}^j \equiv \Pi_1^{(i)} \mathbf{\Gamma} + \Pi_2^{(i)} \mathbf{\Gamma}^2 + \dots + \Pi_R^{(i)} \mathbf{\Gamma}^R \quad (\text{A3.16})$$

$$\Pi_R^{(i)} = \frac{1}{\gamma_i} \prod_j^{R(i)} \left(\frac{1}{\gamma_i - \gamma_j}\right) \equiv \left[z \frac{d\tilde{p}}{dz}(z)\right]_{z=\gamma_i}^{-1} \quad (\text{A3.17})$$

and

$$\begin{aligned} \Pi_j^{(i)} &= \Pi_R^{(i)} \sum_{k=j}^R \tilde{p}_k (\gamma_i)^{k-j} \\ &= \Pi_R^{(i)} [\tilde{p}_j + \tilde{p}_{j+1} \gamma_i + \dots + (\gamma_i)^{R-j}] \end{aligned} \quad (\text{A3.18})$$

for  $j = 1, \dots, R - 1, i = R' + 1, \dots, S$ . Here,  $\tilde{p}(z)$  represents the reduced polynomial in (A3.14), and  $\tilde{p}_k$  ( $\tilde{p}_R \equiv 1$ ) its coefficients. Equations (A3.10), (A3.11) for  $\tilde{\mathbf{O}}$ , and (A3.16) can obviously be combined, then, to give a polynomial of maximal degree  $\tilde{R} \leq S - 1$  for  $f(\mathbf{\Gamma})$ .

#### Boundary-Layer Resistances

In the case of the boundary-layer resistance tensors  $\overline{\mathbf{\Omega}}$  and  $\underline{\mathbf{\Omega}}$  of Section 3, we are confronted with formal operations of the type

$$\mathbf{\Omega} = (\mathbf{D}\mathbf{\Lambda})^{-1} \quad (\text{A3.19})$$

where, formally,

$$\mathbf{\Lambda} = \sqrt{\mathbf{\Gamma}}$$

(the positive square root) which, together with the inverse  $\mathbf{\Lambda}^{-1}$  implied in (A3.19), are restricted to the range of  $\mathbf{\Gamma}$ . Here, as in the following, we drop overbars and underbars to distinguish right- and left-hand boundaries.

In terms of a contour integral, the operation in question can simply be defined by substituting for the contour  $\tilde{\mathcal{G}}$  in (A3.1)

a contour  $\tilde{\mathcal{G}}$ , illustrated in Figure 2, which excludes the singular point  $z = 0$  of the function  $f(z) = z^{-1/2}$  and encloses only the positive spectrum of  $\mathbf{\Gamma}$ . Then, with a suitably chosen branch cut, say the negative real axis, as shown in Figure 2, the functions  $z^{1/2}$  and  $z^{-1/2}$  can be rendered analytic in the region bounded by  $\tilde{\mathcal{G}}$ . Therefore, for the case of a nondegenerate positive spectrum ( $\gamma_i \neq \gamma_j$  for  $i \neq j$  and  $i, j = R' + 1, \dots, S$ ), one has

$$\mathbf{\Lambda}^{-1} \equiv \tilde{\mathbf{\Gamma}}^{-1/2} = \sum_i^R \frac{1}{\sqrt{\gamma_i}} \mathbf{\Pi}^{(i)} \quad (\text{A3.20})$$

Again, a polynomial in  $\mathbf{\Gamma}$  can be obtained from (A3.16) and (A3.20).\*

\* Furthermore, the polynomial now has  $\Gamma$  as lowest-order term and is therefore factorizable.

Such polynomial forms are especially convenient for the computation involved in Section 2 and 3 and, indeed, have received application to the case of two independent reactions ( $R = 2$ ,  $S = 4$ ) by Suchdeo et al. (1973).

The exceptional case of degenerate eigenvalues, that is, repeated positive roots of (A3.2), can also be treated by contour integrals (involving multipole singularities), or equivalent devices (Friedman, 1956). However, we shall not attempt here to explicitly set down any of the details. [Because  $\mathbf{\Gamma}$  is assumed to be simple, the relevant polynomial forms for (A3.10) and (A3.20) can in principle always be derived from the minimal polynomial for  $\mathbf{\Gamma}$ , as, incidentally and alternatively, could the expressions proposed here for distinct nonzero roots. (See Lancaster, 1969.)]

#### APPENDIX 4. ENERGETIC ASPECTS OF CARRIER-MEDIATED TRANSPORT: PASSIVE VS. ACTIVE PROCESSES

In much of the literature on membrane transport processes, it has become the custom to categorize these as either passive or active, depending on the apparent energetics of the processes involved, and there have been various attempts to give precise definitions to these notions (see Katchalsky and Curran, 1967). Roughly speaking, one may say that passive transport is characterized by a net loss or dissipation of chemical potential engendered by the flux of volatile or itinerant species through the system, whereas an active transport process can exhibit an apparent dissipation rate of zero or even a net gain in chemical potential of the transported species, at least if attention is focused on some experimentally observed or otherwise select set of such species. In this context, the words *apparent* and *select* are crucial since it is imminently plausible that in all nominally active transport systems the necessary chemical or electrochemical energy supply can be attributed to chemical species which are inherent to, or transported into, a system and not accounted for.

It is beyond the scope of this review to dwell at length on such speculations and their implications for biological or artificial transport systems. Nevertheless, some further brief remarks are perhaps warranted in view of the numerous literature references to the role of carrier-mediation in nominally active processes (Schultz and Curran, 1970) and the frequent attributions of active character to carrier-mediated systems (Cussler, 1971).

In order to provide some rational basis for categorizing carrier-mediated transport according to energetics, a definition of passive (and, by exclusion, active) transport is offered here. For this purpose it is necessary to identify some select set of chemical species. In addition, attention will be restricted to systems which are in a steady state, or an apparent steady state with respect to the concentration fields of these selected substances.

As before, we suppose then, that, of the select set of species in question, some of them, the volatile or itinerant species,  $s = 1, \dots, F$ , may be transported across the system boundary, and that the respective chemical (or electrochemical) potentials of the volatiles  $\mu^s$ , say, are controllable, that is, may be adjusted or specified at will\* on the boundary  $\partial V$ . Then, we define the system as chemically passive if in the steady state, with respect to the select set of species (and possibly, in some restricted domain of variation of the  $\mu^s$ ,  $s = 1, \dots, F$ ), the following inequality holds for all distributions of  $\mu^s$  (in the domain of variation) on the boundary  $\partial V$ :

$$-\int_{\partial V} \frac{(\mu^v \vec{N}_v) \cdot \vec{n}}{T} dA \geq 0 \quad (\text{A4.1})$$

where  $T$  is the (presumably assignable) absolute temperature on the boundary and where  $\mu^v \vec{N}_v = \sum_{s=1}^F \mu^s \vec{N}_s$ . Otherwise, the system might be interpreted to be active with respect to the given set of chemical species.

For a steady state system the integral in (A4.1) is seen to represent the chemical (or electrochemical) dissipation rate associated with a given set of volatile species, as reckoned by the effect on the immediately adjacent surroundings. By contrast, the total dissipation rate would have to involve additional entropy-flux terms associated with supply to the system of heat, or entropy in all forms other than that accounted for in (A4.1). Hence, in a system which is thermally, electrically and mechanically at steady state, and in the absence of heating and mechanical or electrical work by the surroundings, the necessary positivity of total dissipation requires that some chemical entities, other than those accounted for explicitly, be exchanged with the surroundings or undergo accumulation (and/or depletion) in the interior of the system.

While again the intent here is not to explore the ramifications in great detail, it is worth noting that, if all chemical species were accounted for, the carrier-mediated transport system, as defined in Part I, would probably not qualify as producing an active transport process of the steady state\* variety, as just defined here. Without pursuing a fully rigorous demonstration of this postulate, we merely recall that the carrier-mediated transport systems under discussion here are globally nonreactive in the steady state. Hence, the gradual (as opposed to total) depletion of certain species and the accumulation of others due to irreversible chemical reaction is effectively ruled out.

Also, if all volatile or itinerant species (as opposed to a specially selected set) are to be included in (A4.1), then that the validity of (A4.1) would be ensured by the usual thermodynamic restrictions on chemical reactions and transport processes so that all membranes would have to be considered passive.

In the case of isothermal, unidirectional membrane transport, (A4.1) reduces to the elementary form

$$N_v \bar{\Delta} \mu^v \equiv \sum_{s=1}^F N_s \bar{\Delta} \mu^s \geq 0 \quad (\text{A4.2})$$

where  $N_v$  is the transmembrane flux, in a given direction, of volatile species  $v$  and  $\bar{\Delta} \mu^v$  is its transmembrane decrement of chemical potential, in the same direction.

Now, the operation and conceptual value of the above general definition becomes simpler. To evaluate the summation in (A4.2), a knowledge of the transport rates (fluxes) and chemical potentials of each member of the select set of volatile species must be known at both membrane surfaces. Whereas in the study of transport across the biological membranes, one is often not in a position to determine all these parameters but, rather, only has ready access to one side of the membrane. Under these circumstances one cannot correctly characterize the membrane as passive or otherwise.

Also, it is all the more evident from (A4.2) that an arbitrarily selected subset of the volatile species may fail to satisfy the dissipation inequality, as, for example, in the uphill transport of a single species, provided there is a sufficient compensating or pumping effect caused by the downhill transport of other volatile species not included in the summation.

Realistically speaking, our definition of passive transport has value primarily in a negative sense. That is, if for the select set of species the inequality (A4.2) is not satisfied, then one is assured that all the pertinent species transfers and/or other energetic processes involved in the transport have not been identified. On the other hand, a nonnegative value for the summation indicates passive transport but not necessarily the condition of global nonreactivity that is associated with our particular definition of carrier transport. For example, consider the simple reaction  $A \uparrow + B \uparrow \rightleftharpoons C \uparrow$ , which may occur in a membrane. Although the flux of species  $A$  into the membrane will be accelerated by the presence of  $B$  on the other side of the film and, also, the inequality (A4.2) would necessarily be satisfied, one would probably not characterize this system as being one of passive carrier transport; the point being that the system is globally reactive.

\* More generally, one could allow for the specification of joint conditions on the boundary flux and potential of the volatiles.

\* An extension of (A4.1) to periodic processes in time would doubtless exclude active transport of a cyclic variety as well.