Facilitated Transport via Carrier-Mediated Diffusion in Membranes

Part I. Mechanistic Aspects, Experimental Systems and Characteristic Regimes

Carrier-mediated transport in membranes as a globally nonreactive process is distinguished from film theory with chemical reaction and other facilitated diffusion phenomena. With the concept of stoichiometric and system invariants, an approach is developed for the analysis of carrier-mediated transport with multiple permeants involving multiple reactions in the membrane. Approximate solutions of the requisite differential equations according to the relative importance of diffusion and reaction rates are reviewed, as well as typical experimental studies. Criteria for evaluating whether a membrane is in the diffusion or equilibrium regime are given, and, in the latter case, the effects of some system parameters are given, for example, binding constants, competitive permeants.

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Advances in membrane technology have made it possible in recent years to manufacture membranes in diverse forms such as sheets, tubes, and hollow fibers. In most current applications to separations processes, the membrane functions as a physical diffusion barrier or simple (micro-) sieve. However, through recent studies on models of biological membranes, it has become evident that artificial membranes, often in the form of liquid films, can be made functionally very specific in their properties by incorporating mobile or partially mobile compounds within the membrane structure which selectively react with a restricted class of permeants, for example, in ion-specific electrodes. These compounds serve effectively as carriers which not only can render the membrane very specific in its transport properties but also can enhance the relative rate at which the preferred permeants diffuse across the barrier.

While various mechanistic models have been proposed to describe carrier-mediated transport in membranes, those models based on diffusion accompanied by chemical reaction have received the most theoretical and experimental study and are the main subject of this review. Recent studies of carrier-mediated membrane transport of this type has led to a basic and more precise understanding of the effect of the major parameters involved, including the reaction kinetics, equilibrium (binding) constant, membrane diffusivities, concentration gradients, membrane thickness, and solubilities of the permeants in the membrane phase.

Currently available numerical methods, together with various asymptotic and approximate analytic methods, based on the respective concepts of weak gradients or fast and slow reactions, allow one to estimate with a good deal of confidence the response of a particular carrier-mediated membrane to a variety of operational conditions. Apart from their potential for direct applications to processes such as drug transport into cells, the concepts and methods developed in these studies, relating to reaction boundary-layer analysis, global nonreactivity, and competitive interactions with carriers, suggest similar theoretical treatments in a diversity of related phenomena, such as facilitated heat transfer, ion-selective transport, and liquid-liquid ion exchange, where diffusion-coupled chemical reaction is of paramount importance.

The objective here is to review briefly some of the physico-chemical systems and conceptual models that have been studied as membrane systems; to provide a somewhat unified, theoretical framework for defining or characterizing certain invariant global aspects of carrier-mediated transport systems in general and the diffusion-reaction regimes of membranes in particular; and finally, to evaluate and extend some of the more powerful mathematical methods that are available for analyzing or predicting the detailed behavior of such carrier-mediated membranes.

CONCLUSIONS AND SIGNIFICANCE

The major emphasis of this review is on the homogeneous chemico-diffusion model for membrane transport. In this model the permeant species enter the membrane and react with other species which are confined to the membrane. The net flux of the permeant through the membrane is the result of its ordinary (Fickian) diffusion rate and the diffusion rate in combinations with other species (carriers).

To distinguish the augmentation (or hindrance) of permeant flux by this mechanism from other reaction-diffusion systems, we set the requirement that the membrane must be globally nonreactive under steady state (or cyclical) operating conditions, that is, from an external point of view the membrane acts as a passive medium of transport rather than a chemical reactor. The restriction to globally nonreactive systems excludes certain chemical reactions, (for example, irreversible reactions) and physical models (for example, film-theory models) from the class of membranes that are analyzed. However, for this restricted class of membranes one is able to derive certain generalizations which permit a systematic approach to the analysis and understanding of membrane behavior.

Specifically, for membranes in which there is at least one trapped (nonvolatile) species and where all reactions of permeants (volatiles) in the membrane involve one or more nonvolatiles, we obtain the result that for a system involving S chemical species there are system-composition invariants (linear combinations of species amounts), I' number which are related to the stoichiometry of the reaction system by $I' = F' - R = R' - F$, where F' is the number of nonvolatile species, R is the number of stoichiometrically independent chemical reactions, $R' = S - R$ the number of reaction invariants, and $F = S - F'$ the number of permeant or volatile species. It is indicated how systematic identification of the (R') reaction invariants and the associated (I') system invariants can lead to a reduction of the order of the differential diffusion-reaction equations for concentration fields and to the formulation of (I') integral constraints (necessary for uniqueness). These constraints are intimately related to the degrees of freedom in the chemical preparation of a carrier-mediated system.

Because of the above properties, a knowledge of system stoichiometry alone allows one to derive in a general way some simple flux relations for membranes. Thus, in the case of constant diffusivities, the flux of any volatile species (v) through the membrane may be expressed by equations of the type

$$N_v = \frac{Z_v{}^m D_m{}^s}{L} [C_s(0) - C_s(L)]$$

where the $Z_v{}^m$ are transport numbers related to the invariants of the system, which play a role in diffusive transport of volatiles analogous to ionic charge in the transport of electrolytic current.

A more detailed analysis of membrane behavior requires knowledge of its kinetics and requires treatment of nonlinear boundary-value problems. However, there are two asymptotic regimes corresponding to small or large values of a characteristic Damkohler number (kL^2/D) wherein the equations can be solved directly to obtain the unknown boundary concentration in the above flux equation. For small Damkohler numbers, the near-diffusion or frozen regime, solutions proceed from a regular perturbation analysis. For large Damkohler numbers, the equilibrium regime, solutions are obtained assuming reaction equilibrium everywhere in the film. In the latter case many of the salient features of carrier-mediated transport are most directly deduced.

First of all, it is found that there is an optimum value of the binding (or equilibrium) constant K, which gives maximum equilibrium facilitation. In the simple example $A + B \rightleftarrows AB$, the optimum binding constant is given in terms of the respective boundary concentrations of permeant as $K = (\overline{C}_A \underline{C}_A)^{-1/2}$. For large K, facilitation is very sensitive to downstream concentrations and the membrane is easily switched off by back pressure.

When two permeants compete for the same carrier, conditions can be found such that one of the permeants can be transported against its overall concentration gradient (uphill transport) or can be accelerated in the usual direction of diffusion down the gradient.

In these systems, the use of tracers to determine the properties of the membranes may be misleading unless the membrane is in the equilibrium regime and the total concentration (labeled plus unlabeled forms) of each permeant is uniform throughout the membrane.

Finally, composite membranes that possess a carrier-mediated part will display asymmetric transport characteristics. These are the major conclusions of Part I. In Part II, a detailed discussion of the mathematical modeling and analysis of carrier-mediated membranes will be given.*

"Carriers and carrier processes in living systems are now commonly postulated whenever a membrane transport is unusually fast, selective, or specific beyond the expectation based on the classical criteria of lipoid solubility, molecular size, and electric charge. The obvious and currently much favored assumption is that transmembrane passage involves a temporary binding of the transported material to some component of the membrane, the carrier, and the passage of this complex across the membrane by diffusion (or convection)." ... Shean and Sollner (1966).

1. GENESIS AND NATURE OF CONCEPTS

The concept of a molecular carrier mechanism involving a reversible chemical combination between permeant and mobile species was pursued and developed by Osterhout and colleagues in the early 1930s. Although the principle had been enunciated much earlier by Pfeffer in 1890 and by Freundlich and Gann in 1915 (see Shean and Sollner, 1966), the model experiments of Osterhout (1940) using a weak organic acid, quiacol, as a carrier for sodium and potassium ions in the form of quiacolate salts across a nonaqueous bridge of quiacol, firmly established the concept in the biological literature.

The mechanistic and kinetic aspects of a carrier model were further developed by other researchers, primarily concerned with the experimental system of sugar transport into erythrocytes (Widdas, 1954).

Much of the recent chemical engineering interest in facilitated carrier-mediated transport has been stimulated by the discoveries of Scholander (1960) and Wittenberg (1966), which demonstrated that hemoglobin and myoglobin could accelerate the transfer of oxygen across water films. The fact that the composition of model membranes and imposed boundary conditions on O_2 concentrations can be experimentally controlled led to the accumu-

* Part II of this paper will appear in the July issue of the *AIChE Journal*.

lation of much data which could be used to evaluate theories concerning the mechanism of carrier-transport.

Although other model transport systems of the same nature, for example, gas transport through liquid membranes, have been suggested and studied (Ward and Robb, 1967; Bassett and Schultz, 1970; Otto and Quinn, 1971), more sustained interest has been accorded to hemoglobin and myoglobin as carriers, owing in large part no doubt to their physiological significance.

Another more recent discovery that has led to an even greater level of research activity is the demonstration that certain polypeptides (for example, valinomycin), cyclic polyethers, and polyether carboxylic acids (for example, monesin), could increase the transport of ions across lipid bilayer membranes by many orders of magnitude (Andreoli et al., 1967; Shemyakin et al., 1969). Thus, potassium flux augmentation on the order of 10^5, as measured by conductivity, can be produced by as little as 10^{-6} M valinomycin in the membrane phase (Stark and Benz, 1971). Also the availability of many compounds with different structural features and widely different selectivities for different cations makes this type of system a fertile field for testing theories of carrier transport (Pedersen, 1968; Pressman, 1968).

For the most part, the research on carrier-mediated transport has been directed towards biological problems reported in primarily biological journals and, for this reason, may have escaped the attention of those interested in other applications, for example, in chemical engineering. However, these phenomena have importance not only in their own right and for the understanding of biological transport but also for the potential they hold for devising new and highly-selective separation methods.

Mechanistic Considerations

In a crude sense, transport phenomena in biological membranes can be grouped according to complexity into three categories: (1) molecular diffusion, where the transport rate is proportional to the solubility and diffusivity of the permeant in the membrane phase (Stein, 1967; Rogers et al., 1972; Lieb and Stein, 1971); (2) passive carrier transport, where transport rates show saturation phenomena, a high degree of specificity depending on the structure of the permeant, and competitive effects between permeants of similar chemical structure (Wilbrandt and Rosenberg, 1961); and (3) active carrier transport where, in addition to the above characteristics, net chemical reactive processes are involved which promote the transport of a permeant even if all substances are maintained at the same chemical potential on both sides of the membrane (Schultz and Curran, 1970).

In addition to above mechanisms of transport, there is another distinction, helpful in the discussion of membranes, as to whether the membrane behaves as a one- or two-dimensional structure. Electron microscope studies (Branton and Park, 1967), X-ray diffraction studies on artificial films (Luzzati, 1968) indicate (Nystrom, 1973) that the influence of mosaic or heterogeneous membrane structure on transport must be given due attention. Recently studies of model reaction systems which form dynamic two-dimensional structures suggest that dissipative reactions may account for the structural heterogeneity in membranes (DeSimone et al., 1973).

While recognizing the potential importance of a two-dimensional structure in membranes, our mathematical development on flux calculations will be restricted here to uniform or one-dimensional films.

Numerous molecular mechanisms have been proposed to explain the saturatable transport characteristics of biological membranes, but, at present, their validity is open to question. The relatively simple model that will be the focus of our attention here may be termed a homogeneous chemico-diffusion model (Figure 1a). In this model, permeant(s) A enters directly into the membrane phase and reversibly reacts throughout the membrane with a freely mobile membrane component(s) B to form a mobile complex(es) A-B. The solid curves in Figure 1a give the qualitative trends in the concentration profiles of the three (kinds of) species A, B, A-B, and the arrows indicate the direction of net movement of these species. Note that A moves across the membrane as a free species as well as in the complexed form. The dashed lines indicate the homogeneous chemical reactions occurring throughout the membrane, and the arrows on these lines signify a net rate of formation of A-B at $x = 0$; roughly equal rates of formation and decomposition of A-B in the center or core of the membrane; and a net rate of dissociation of the complex at the right boundary, where some A leaves the membrane phase.

Salient differences between this model and other current concepts are shown in the other panels of the figure. In the heterogeneous surface reaction model, Figure 1b,

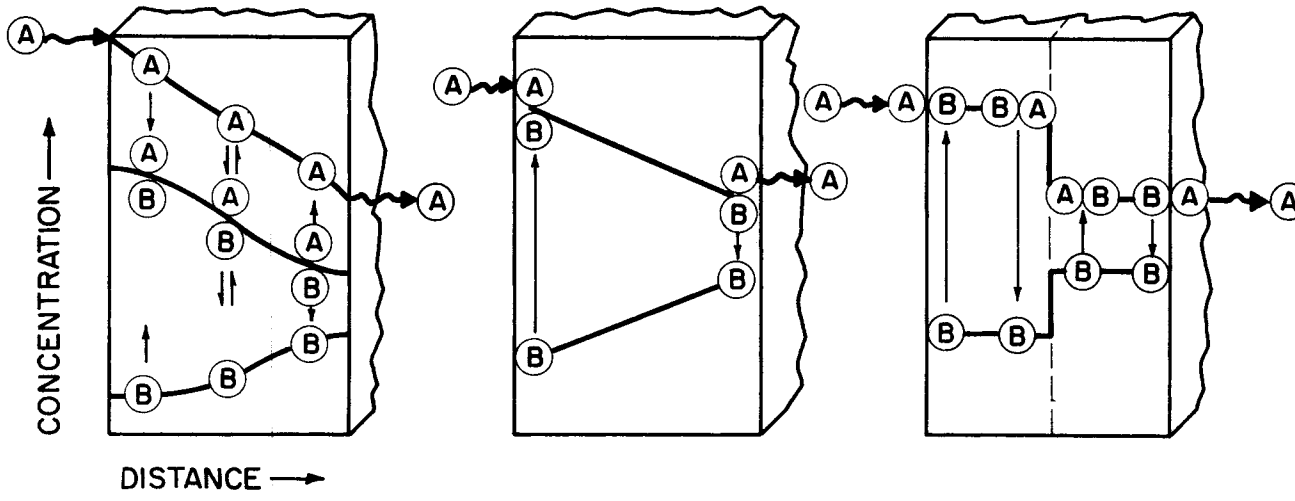


Fig. 1. Conceptual models for the mechanism of transport in membranes: a. Homogeneous chemico-diffusion model; b. Heterogeneous surface reaction model; c. Two-compartment heterogeneous model.

the permeant(s) A does not enter the membrane in the free form, but only through the mobile A-B complex(es) formed by a heterogeneous reaction at the interfaces. The concentration profiles within the membrane are necessarily straight lines (for the simplest type of diffusion) since no species generation due to reaction occurs in the core of the membrane. This is a common model for ion transport in bilayers, where the possibility of exchange reactions in the central region is also admitted (Ciani et al., 1969).

Finally, a two-compartment heterogeneous model is shown in Figure 1c. Again the permeant is not soluble in the membrane itself but reacts at the interfaces with the membrane component(s) B. Moreover, the B species may be restricted in their movement to remain on one or the other surfaces of the membrane. Some sort of activation-energy barrier is presumed to exist between the two compartments of the membrane, which results in a binary distribution of the carrier(s) and carrier-permeant complex(es) between the compartments. Within the individual compartments, no concentration gradients are presumed to exist. In the earliest such theories (Widdas, 1954), the total concentration of carrier molecules in both compartments were assumed to be equal: whereas, in later theories (Regen and Mogan, 1964; Jacquez, 1964) the concentration levels of carrier molecules of all forms are allowed to vary between the compartments, by permitting the translocation rates of the various carrier species to differ.

Hill and Kedem (1966) have treated 26 of the many possible two-compartment models with the restriction that all rates are linear or first order in concentrations. In a recent variation of the two-compartment model (Lieb and Stein, 1972) the carrier is assumed to be immobile, and the permeant moves within the membrane by an exchange reaction mechanism.

For purposes of this review, it might be useful to discriminate, by the nomenclature for facilitated transport, according to the carrier function. Thus, models 1b and 1c could be called *(strict) carrier transport* since the carrier is responsible for all the transport through the membrane. In contrast, Model 1a might be called *carrier-mediated transport* since the carrier aids the transport of permeant, while the permeant can also pass independently through the membrane. We will use the term *facilitated transport* in the latter sense as well.

The subtle differences in these models lead to fundamentally different mathematical formulations of the field or transport equations for the interior of the membrane. In the carrier mediated transport model, Figure 1a, a system of second-order nonlinear differential equations usually are needed to describe the concentration field within the membrane. Explicit solutions to these equations are generally not available and various approximate or numerical methods are required. Our major emphasis here will be on providing a framework for the procedures and insights that have recently been developed to handle the equations for reaction-coupled diffusion through homogeneous films.

In the other two (strict) carrier transport models, the transport equations tend to be primarily algebraic in nature because, in 1b, no net reaction is occurring within the membrane and, in 1c, the primary resistance to transport, whether reactive or diffusive, occurs at a few specific positions within the membrane. Most models of membrane behavior that appear in the biological literature (Wilbrandt and Rosenberg, 1961; Britton, 1965; Haydon and Hladky, 1972) are of the latter type and will not be treated further here.

However, independent of the precise mechanism of translocation there are certain aspects of the analysis of membrane transport relating to stoichiometric and material balance constraints that are common to all of the models. These general features, present in essentially all models of membrane transport, are treated in the first part of this review.

At any rate it appears that model 1a can be considered applicable to several experimental observations on microscopic artificial membranes thicker than about 2μ with carrier transport (Ward and Robb, 1967; Bassett and Schultz, 1970; Otto and Quinn, 1971). The transport mechanism in artificial bilayer membranes ($\sim$100Å thick) has not been delineated as yet, but there are indications that a two-compartment model (1b) with both heterogeneous and homogeneous reactions may have some validity (Stark and Benz, 1971).

It is somewhat unfortunate that most of the experimental and theoretical developments on biological transport have been restricted to evaluating model 1(c), in one or more of its forms, with very little attention (with some notable exceptions, Blumenthal and Katchalsky, 1969; Katchalsky and Oster, 1969) paid to the coupled chemico-diffusion model. The relevance of studies on artificial model membranes to natural biological membranes will not be fully evident until the physical chemistry of natural membranes has been more fully elucidated. Although there is a vigorous research activity to isolate and identify natural membrane carriers, (Pardee, 1968; Maddy, 1969), a fully active natural membrane at present has not been formed from component parts.

2. EXAMPLES OF CARRIER-MEDIATED TRANSPORT SYSTEMS MODELING

Simple Membrane Systems

As a point of departure and basis for discussion, we will primarily consider the properties of simple membranes. By a simple membrane we mean essentially a planar geometry of uniform thickness and composition (in a rest state), with distinct interfaces which separate it from the surroundings. The major parameters which are expected to determine the characteristics of such membranes are the physical dimensions, chemical composition, mobilities of all the substances present, the kinetics of all reactions, and the distribution of fixed charges within the membrane. Because of the complexity, experimentalists have had to cope with an incomplete knowledge of the physical chemistry of the membranes.

The usual physical configuration for investigating membrane transport involves the membrane material, in the form of a sheet, placed between two chambers which contain the permeant species at known concentrations. One favorite experimental maneuver is to make an immobile membrane phase, by wetting a sheet of filter paper with a liquid solution, the wetted filter serving then as a model membrane.

The interfaces of a simple membrane are presumed to be impermeable to some of the species which chemically react with the permeant species. The gradients of these trapped nonpermeant compounds at the interfaces are therefore known to be zero (at least for uncoupled diffusion). In this system the boundary concentrations of the permeant species alone are under experimental control, and the boundary concentrations of the nonpermeant species must be inferred from calculations. However, Ward (1970a) and Bdzil et al. (1973) have suggested that for electroactive species, the concentration ratio of nonpermeants across the membrane may be obtained by electrical potential measurements. Of course, since simple

membranes are assumed to be homogeneous, transport through them is inherently symmetrical with respect to the driving force.

The pseudo steady state flux of the permeant species, measured usually by isotopic tracers, gas analysis, or conductivity, is the primary type of information extracted from these diffusion experiments. In this manner, the flux is determined as a function of driving force based on interfacial concentrations of permeant in the external phases.

Typical data for oxygen transport through hemoglobin solutions obtained by this technique are illustrated schematically in Figure 2. Two major characteristics of carrier-type transport can be discerned from these figures.

In Figure 2a, the flux of the permeant or volatile, species is not linear with concentration but exhibits a saturation behavior. The facilitation effect is represented by the heavy arrow in Figure 2a, where the dashed line represents the flux expected when no carrier is present. Often the physical conditions are such that even this line cannot be measured directly but must be inferred from other data. And, in Figure 2b, when the lower or downstream interfacial concentration is increased above zero, the flux diminishes drastically, even when the concentration difference across the membrane is maintained constant, owing to saturation of the carrier throughout the membrane.

In studies of this type, the membrane thicknesses are on the order of 25 to 500 microns, or even as small as 100Å for the lipid bilayers, dimensions which generally preclude the measurement of concentration profiles within the membrane matrix by ordinary analytical techniques. Therefore, a practical but nonetheless important limitation of most experimental studies is that rarely, by experiment alone, is one able to verify directly any theoretical predictions of the internal distribution of substances within a membrane. On the other hand, the variation of flux rate with permeant boundary concentration is usually under direct experimental control, effected by changing the composition of the phases external to the membrane. However, there may be some uncertainties in this respect as well. As pointed out by Wittenberg (1970) and Murray (1971), and, more analytically, by Kreuzer (1970), and Jacquez et al. (1972), it may be difficult to define the permeant concentrations at the membrane interfaces because of stirring problems within the bulk phases or absorbed layers at the membrane interface. A precise knowledge of downstream interfacial concentration of permeant is particularly important because the net flux is often very sensitive to this variable as shown in Figure 2b (Kreuzer and Hoofd, 1972; Jacquez et al., 1972).

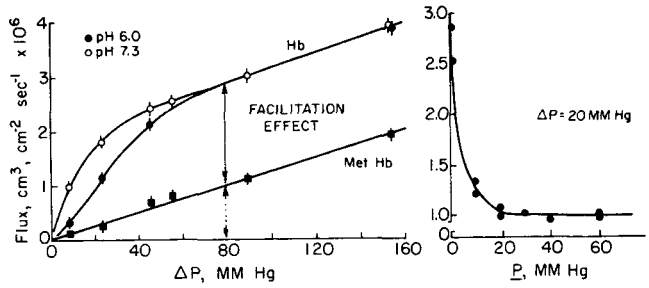


Fig. 2. Typical nonlinear flux patterns for carrier-mediated facilitated diffusion: a. Oxygen diffusion through hemoglobin solution, measured by O_2[18] (Hemmingsen, 1962); b. Effect of back pressure on facilitated flux through hemoglobin solutions (Hemmingsen and Scholander, 1960).

Other Geometric Configurations for Studying Carrier-Mediated Transport

In Figure 3, we distinguish between the simple membrane configuration (Figure 3a) defined above and other types of geometric arrangements that have been studied with regard to their facilitated-diffusion characteristics. For example, in Keller and Friedlander's (1966) study of oxygen diffusion through hemoglobin solutions, one interface of the liquid membrane was in contact with a plastic membrane, and the other in contact with an O_2-containing gas mixture. In Ward's (1970a) study of electrically induced transport of NO, a liquid layer of $FeCl_2$ in formamide was held between two permeable silicone rubber films as shown in Figure 3b. A similar technique was used in Otto and Quinn's (1971) study of CO_2 transport. In this situation, the permeant concentration at the membrane interface is not under direct experimental control, but must be inferred by calibration techniques. Also, this arrangement has the potential to show asymmetric characteristics for flux if the plastic membranes are not identical (Schultz, 1971).

The hydrodynamic boundary layer or hypothetical unstirred film (Figure 3c) has been the subject of much analysis in the diffusion literature (Olander, 1960; Dankwerts, 1970). Ulanowicz and Frazier (1970) have used this model to arrive at theoretical deductions with respect to facilitated diffusion with multiple reactions. In this model all the species are assumed to be in chemical equilibrium at the bulk-film interface but not necessarily so at the other interface. This renders the film model inherently asymmetric. Also, the assumption of equilibrium at the bulk-film interface may not be tenable if the reaction boundary layer, to be discussed in Part II, exceeds the hydrodynamic film in thickness.

The idealized double-film boundary layer, Figure 3d, between immiscible phases has also been analyzed by Ulanowicz and Frazier (1968). As an analogy to membrane transport it has some of the same deficiencies mentioned above, but it is nevertheless interesting because this model represents half of the transport path in the Schulman cell shown in Figure 3f.

The study of diffusion through lipid bilayers interposed between aqueous solutions basically conforms to a three-phase system as shown in Figure 3e. Here, carrier transport is limited to the central layer, thus, and the hydrodynamic boundary layers external to the lipid film represent only a simple resistance to diffusion (Andeoli and Troutman, 1971). The whole system may exhibit simple facilitated diffusion if the aqueous boundary-layer resistance to diffusion is small. On the other hand, several authors have considered the carrier reaction to occur in the external films, with the central core membrane serving as an unreactive semipermeable medium. Stehle and Higuchi (1967) used this as a model for drug transport across tissues. Finkelstein and Cass (1968) and Gutknecht et al. (1972) have also used this same model to express the high flux of halogens across bilayer and natural membranes.

The Schulman apparatus (Shean and Sollner, 1966) shown in Figure 3f reflects an attempt to generate a macroscopic membrane obviating the difficulty of forming stable thin films with organic liquids (Moore and Schechter, 1973). The boundary layer resistances, at each interface, usually of undetermined magnitude, complicate the analysis of the interfacial transport rates (Reusch and Cussler, 1973).

In another experimental variant, Wise and Houghton (1969) attempted to use the pseudo steady state con-

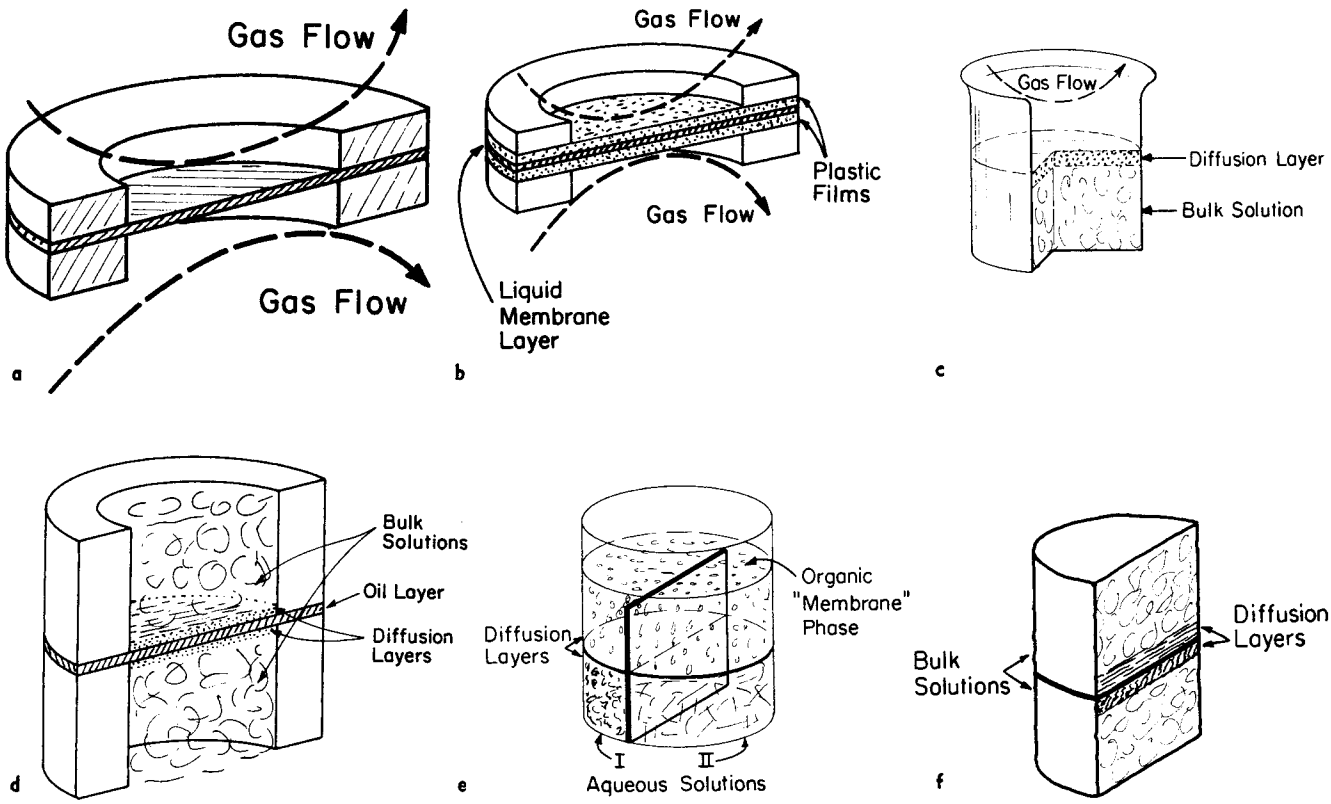


Fig. 3. Geometrical configurations that have been used in the study of carrier-mediated transport: (a) Simple membrane; (b) Membrane phase supported on each side by permeable plastic films; (c) Film theory boundary-layer of gas-liquid interface; (d) Two diffusion film boundary layers at the interface of immiscible liquids; (e) Membrane layer interposed between two liquids; (f) Schulman cell, a macroscopic model of membrane transport.

traction of a gas bubble to estimate the diffusivity of hemoglobin and the kinetics of the oxyhemoglobin reaction. In this situation, only one interface is involved for the boundary conditions; the remaining boundary condition is one of chemical equilibrium at infinite distances from the bubble.

Finally, several authors have measured or analyzed facilitated diffusion in heterogeneous media, with the chemical reaction occurring in either the continuous or discontinuous phases in order to estimate the net effect of carrier transport in similar, important physiological systems (LaForce and Fatt, 1962; Stroeve et al., 1972).

Each of the configurations just discussed may have some special appeal for purposes of experimental or theoretical convenience. But it should be remembered that each configuration may exhibit differences in the detailed behavior of interactions due to chemical coupling because of essential differences in boundary conditions.

Model Systems for Carrier-Mediated Transport

Experimental work on membrane transport has expanded greatly in the past ten years. Indeed, the information on natural biological membranes is well beyond the scope of this review, and the reader is referred to several recent reviews and symposia for information on current trends of research activity (Schultz and Curran, 1970; Nystrom, 1973). The published information on model bilayer membranes is also quite extensive and will not be reviewed here in detail.

In Table 1 is a listing of the limited number of chemical reactions that have been considered for facilitated transport studies in simple membranes, for which all the species and chemical reactions were, more or less, well defined.

It is apparent from this table that most studies so far have dealt with two types of free or permeant species (soluble gases and simple ions), probably because the transport rates of these species can be measured with relative ease.

Only those studies which satisfy the criteria of global nonreactivity (vide infra.) are cited here for reasons that will be clarified in Section 3. These reactions are arranged roughly according to the mathematical complexity of the systems. As will be shown in the theoretical discussion to follow, one of the important determinants of mathematical and experimental complexity is the number F of permeant species that chemically interact with the constrained or nontransferred species. The permeant or transferred species, designated by a vertical arrow ($\uparrow$), shall also be referred to as *volatile* (or free) species, (not because they may happen in fact to be gaseous, but rather to emphasize that they can freely enter or leave the membrane phase.) The remaining species shall accordingly be called *nonvolatiles.*

The other parameters which will be important in this analysis are the number of independent chemical reactions R; the number of chemical species S; and the number of fixed stoichiometric invariants I'. This latter quantity is in a sense the number of fixed carriers that are under experimental control. In the left column of Table 1, reactions are listed in abstract form.

The analysis of carrier-mediated transport in the literature has been confined, for the most part, to the estimation of the flux through simple membranes. Thus, steady state analysis based on simple diffusional processes usually starts with local material-balance equations of the form

$$D_s \frac{d^2C_s}{dx^2} = -r_s, \quad s = 1, 2, \ldots \tag{2.1}$$

with given boundary conditions on the volatile species (v), $C_v(0)$, $C_v(L)$ and zero-flux boundary conditions for the nonvolatile species (n): $N_n(0) = N_n(L) = 0$.

Complete analytic solutions of these 2-point boundary-value problems are usually out of the question, except for linear kinetic laws. For example, the first reaction given in the table $\uparrow A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B$ with the rate law $r_B = k_1C_A - k_2C_B$. These differential equations can be solved exactly (Friedlander and Keller, 1965; Goddard et al., 1970). One useful conceptual aspect of these solutions is their indication of the regimes of near-diffusion and near-equilibrium according to the relative rates of diffusion and reaction in the membrane. These regimes correspond to similar ones in facilitated heat transfer, known respectively as the frozen and equilibrium regimes (Brian and Reid, 1962) and are representative of general diffusion-reaction phenomena, regardless of the particular details.

In the equilibrium regime, the limiting solutions of

Table 1. Types of Facilitated Transport Reactions and Experimental Studies

	F	R	S	I′	Chemical Reactions	References
1.	1	1	2	0		
	$nA\uparrow \rightleftarrows B$				$2HAc\uparrow \rightleftarrows (HAc)_2$	Olander (1960)
2.	1	1	3	1		
	$A\uparrow + B \rightleftarrows C$				$O_2\uparrow + Mb \rightleftarrows MBO_2$	Wittenberg (1970), Hemmingsen (1963)
					$NO\uparrow + Fe^{++} \rightleftarrows Fe(NO)^{++}$	Ward (1970b), Bdzil (1973)
					$M^+\uparrow + Polyether \rightleftarrows PolyetherM^+$	Pedersen (1968), Tosteson (1968), Lauger and Stark (1970)
3.	1	1	3	1	$H_2O + Cl\uparrow \rightleftarrows HOCl^- + H^+$	Friedlander and Keller (1965)
	$A\uparrow \rightleftarrows B + C$				$RN(Amine)\uparrow \rightleftarrows RN^+ + H^+$	Stehle and Higuchi (1967)
4.	1	2	4	1		
	$A\uparrow + B \rightleftarrows C$				$O_2\uparrow + Co(Hist)_2 \rightleftarrows O_2Co(Hist)_2$	Bassett and Schultz (1970)
	$B + C \rightleftarrows E$				$O_2Co(Hist)_2 + Co(Hist)_2 \rightleftarrows O_2[Co(Hist)_2]_2$	
5.	1	4	6	1		
	$A\uparrow + B \rightleftarrows AB$					
	$A\uparrow + AB \rightleftarrows A_2B$				$O_2\uparrow + Hb \rightleftarrows HbO_2$	Scholander (1960), Hemmingsen and Scholander (1960)
	$A\uparrow + A_2B \rightleftarrows A_3B$				. . . .	Wittenberg (1966, 1970), Keller and Friedlander (1966), Kutchai and Staub (1969)
	$A\uparrow + A_3B \rightleftarrows A_4B$				$O_2\uparrow + Hb(O_2)_3 \rightleftarrows Hb(O_2)_4$	
6.	1	5	9	3	$CO_2\uparrow + H_2O \rightleftarrows H_2CO_3$	Ward and Robb (1967)
						Enns (1967)
					$CO_2\uparrow + OH^- \rightleftarrows HCO_3^-$	Otto and Quinn (1971)
						Suchdeo and Schultz (1973)
					$H_2CO_3 \rightleftarrows H^+ + HCO_3^-$	
					$HCO_3^- \rightleftarrows H^+ + CO_3^=$	
					$MHCO_3 \rightleftarrows M^+ + HCO_3^-$	
					$H_2O \rightleftarrows H^+ + OH^-$	
7.	2	1	3	0		
	$A\uparrow + B\uparrow \rightleftarrows C$				$Fe^{++}\uparrow + NO\uparrow \rightleftarrows Fe(NO)^{++}$	Ward (1970a)
8.	$A\uparrow + B \rightleftarrows C\uparrow$					
9.	2	1	4	1		
	$A\uparrow + B \rightleftarrows C + D\uparrow$				$M^+\uparrow +$ R-COOH $\rightleftarrows$ R-COO$^-M^+ + H^+\uparrow$	Shean and Sollner (1966)
					Monensin	Pressman (1968), Ashton and Steinrauf (1970), Verhoff and Sundaresan (1973)
					Nigericin	
					$M^+ = Na^+, K^+, Li^+, Cs^+$, etc.	
10.	2	1	4	1		
	$A\uparrow + B\uparrow + C \rightleftarrows D$				$M^+\uparrow + A^- +$ Valinomycin (or) Polyethers $\rightleftarrows$ Valinomycin M^+ (complex) $+ A^-$	Pressman (1968), Ashton and Steinrauf (1970), Reusch and Cussler (1973)
					$A^- = CNS^-$, Picrate$^-$, etc.	
11.	2	2	5	1		
	$A\uparrow + B \rightleftarrows C$				$CO\uparrow + Mb \rightleftarrows MbCO$	Mochizuki and Forster (1962)
	$E\uparrow + B \rightleftarrows D$				$O_2\uparrow + Mb \rightleftarrows MbO_2$	Wittenberg (1966)
12.	2	5	10	3	$O_2\uparrow + Hb \rightleftarrows HbO_2$	Ulanowicz and Frazier (1970)
					$CO_2\uparrow + Hb \rightleftarrows HbCOO^- + H^+$	
					$H^+ + Hb \rightleftarrows HHb^+$	
					$H^+ + HbO_2 \rightleftarrows HHbO_2^+$	
					$CO_2\uparrow + H_2O \rightleftarrows H^+ + HCO_3^-$	
13.	F	F	2F + 1	1		Verhoff and Sundaresan (1972)
	$A_1\uparrow + B \rightleftarrows B_1$				glycine$\uparrow + B \rightleftarrows B(gly)$	
	$A_2\uparrow + B_1 \rightleftarrows B_2$				$Na^+\uparrow + B(gly) \rightleftarrows B(gly)\ Na^+$	
	$A_3\uparrow + B_2 \rightleftarrows B_3$				$Na^+\uparrow + B(gly)\ Na^+ \rightleftarrows B(gly)\ (Na^+)_2$	
					B = binding enzyme	

transport equations of type (2.1) can be derived by rather simple algebra and are exemplified in this case by

$$N_A = \frac{D_A}{L}[C_A(0) - C_A(L)] + \frac{D_C}{L}[C_C(0) - C_C(L)] \tag{2.2}$$

where C_C is presumed to be related through reaction equilibrium to C_A and C_B:

$$C_C = K C_A C_B \tag{2.3}$$

The facilitation factor defined as

$$\Phi = \frac{N_A - N_{A0}}{N_{A0}} \tag{2.4}$$

becomes

$$\Phi = \frac{D_C[C_C(0) - C_C(L)]}{D_A[C_A(0) - C_A(L)]} \tag{2.5}$$

The particular reaction system A + B $\rightleftarrows$ C has received much experimental, and the most theoretical, attention. It will be noted that there are four possible reaction schemes involving one reaction and three species, No's. 2, 3, 7, and 8 in Table 1, but the system A$\uparrow$ + B $\rightleftarrows$ C provides the basis for most of our present understanding of the main features facilitated transport systems. For example, the rather complicated oxygen-hemoglobin transport system, No. 5, has been treated using the simplified model A$\uparrow$ + B $\rightleftarrows$ C (Kutchai et al., 1970; Wyman, 1966).

A number of studies in the pharmaceutical literature relate to transport of drugs through membranes with simultaneous chemical reactions (Levy and Mroszczak, 1968; Stehle and Higuchi, 1967; Vaidynathan, 1971, 1972). However, in most of these cases the global nonreactivity restriction of this review is not satisfied.

As can be noted in Table 1, ionic species are involved in many of the facilitated transport systems that have been studied, and especially those of biological importance. The presence of reactive ions does not alter any of the stoichiometric generalizations with respect to reaction or system invariants developed below but does require that electrical potential gradients be considered in the field equations.

Methods for treating problems of nonequilibrium carrier-mediated transport in the presence of electrical fields are emerging (Ciani et al., 1973; Lauger and Stark, 1970; Markin, et al., 1969). Although the question of diffusion-induced electrical fields were raised by Bright (1967), most authors have assumed that their contribution to the flux was minor (compare Otto and Quinn, 1971; Ward and Robb, 1967). Bdzil et al. (1973) have shown that no electrical fields are developed for the system $\uparrow$NO + Fe^{++} $\rightleftarrows$ $NOFe^{++}$ when the ionic species are nonpermeant, and, simultaneously, the free and complexed carrier forms have equal diffusivities.

However, when ionic species do permeate, for example, as with the ion transporting antibiotics, the polyethers (Pressman, 1968; Tosteson, 1968; Ciani et al., 1969; Lauger and Stark, 1970), and/or electric currents are imposed (Ward, 1970a), then the electric-field contributions to the process should be taken into account.

Indeed, there are a class of membranes, in particular lipid bilayers with ionic binding sites, where the typical Debye length of about 10Å (Barry and Diamond, 1971) may be on the same order of magnitude as the membrane thickness. For these membranes, not only does the local electroneutrality condition become invalid, but the entire membrane may also assume a net charge (Ciani et al., 1969; Lauger and Stark, 1970). For example, the transport of cations through lipid membranes in the presence of neutral carriers (valinomycin, nonactin, polyethers) can proceed without a simultaneous transport of anions through the membrane, that is, the membranes are permselective. In the mathematical treatments of these systems, the assumption has been usually made that the relaxation times for the chemical reactions within the membrane phase are much smaller than the diffusion times and, therefore, that the chemical reactions within the membrane are in equilibrium. The predominate limiting kinetic step is presumed to be the interfacial reaction of ions with the carrier at the membrane surface (Ciani et al., 1973). Equilibrium criteria based on linearized analyses (Haydon and Hladky, 1972) may well be in error when large facilitations occur, as has been found for the simple (nonionic) carrier-mediated system discussed in Section 4 here.

The variety of facilitated transport systems increases rapidly as more species and more chemical reactions are admitted and may require a systems-theory attack, for example, through identification theory, for a systematic ordering of these problems.

Most authors have focused on solutions for particular chemical systems and not on general formulations of the problem. Olander (1960) first suggested that the chemical entities participating in a reaction be divided into radicals and used the device of total radical material-balances to obtain a reduced number of differential equations. Fox and Landahl (1965) recognized, in treating the hemoglobin-O_2 system, that the chemical reactions represent a coupling of the diffusion equations and that, by a suitable combination of equations for different species, equations independent of some coupling terms may be obtained. In a slightly different context, Nims (1968) also realized that linear combinations of certain species fluxes are independent of position and were called component fluxes. However, no systematic method for identifying components and using them to calculate fluxes was given.

The need for formulating the problem in terms of the independent chemical reactions is implicit in the treatment given by Ulanowicz and Frazier (1968). Because their analysis was restricted to linearized kinetics, where all the differential equations could be solved simultaneously, methods for identifying invariants and integral constraints were not developed there. These complexities have motivated us to try to formulate a somewhat uniform way of approaching these problems. By taking a global viewpoint we have found that there are common features to these problems when formulated in terms of the reaction invariants for the process.

3. SPECIFIC DEFINITION OF CARRIER-MEDIATED TRANSPORT AND CONSEQUENCES FOR MATHEMATICAL DESCRIPTION

Axioms for Carrier-Mediated Systems

Basic to any theory of mass transfer modified by chemical reaction is the notion that some given set of chemical species can permeate a physical medium, wherein they participate simultaneously in chemical interconversions.

As in the general problem of reaction-coupled transport, we deal with a presumably closed set of chemical species, S in number say, $\mathcal{S}^s$, s = 1, 2, ... S, that diffuse or otherwise flow through an inert medium and react with local (point-wise) volumetric rates, r_s, s = 1, 2, ..., S, where r_s denotes the rate of production (with units, say, moles/volume-time) of species s. Letting C_s and $\vec{N}_s$

denote, respectively, the local species concentration (mole/volume) and flux vector (mole/area time), we have the global species balance, applied to some (fixed) smoothly bounded region of physical space occupied by the medium, for example, Figure 4a:

$$\frac{dn_s}{dt} = p_s - q_s \tag{3.1}$$

where

$$n_s = \int_V C_s dV \tag{3.2}$$

$$p_s = \int_V r_s dV \tag{3.3}$$

and

$$q_s = \int_{\partial V} \vec{n} \cdot \vec{N}_s dA, \quad \text{for} \quad s = 1, 2, \ldots, S \tag{3.4}$$

designate, respectively, the total amount (moles) of species s present in V at time t, its net rate of production in V, and its net rate of efflux to the surroundings across the boundary of V, ∂V, whose outer unit normal is denoted by $\vec{n}$.

Since there is an enormous literature on reactive transport enhancement with the basic structure just described, it is clearly desirable to develop a rational and fairly general basis for distinguishing the types of systems that are to be associated here with facilitated transport. For this purpose, we shall adopt certain axioms which serve to define a (simple) carrier-mediated transport system.

In formulating axioms, we have in mind two particular attributes of these systems, the first and foremost of which relates to internal structure. Specifically, we deal with systems containing some chemically reactive but nonvolatile species which, owing to solubility limitations or to other similar physical constraints such as semipermeable membranes, leave the system, if at all, only through chemical interconversion. Secondly, we wish to limit our analysis to systems whose net effect on their surroundings is primarily to transport materials spatially rather than to function as net chemical convertors that change the chemical form of matter. Hence attention will be directed uniquely to systems which are globally nonreactive, under steady state (or, for that matter, cyclical) conditions in time. As a result, we then show that there are certain salient features and generalizations which can be established for this particular subset of the much larger set of reaction-coupled transport systems (see Dankwerts, 1970).

Now, there are many real situations where carrier transport is operative in globally reactive systems, such as the mediated transport of substrates into cells accompanied by metabolic reactions (Murray, 1968; Wittenberg, 1970). However, it is neither practically nor theoretically an easy task to assess the precise contribution of carrier-mediated transport in such situations without detailed knowledge of reaction mechanisms, reaction-rate constants, and diffusivities of all chemical constituents involved. It is advantageous, then, to confine consideration of carrier-mediated transport to globally nonreactive systems, realizing of course that this theoretical viewpoint does not preclude the eventual application of the insights and methods developed here to systems involving other processes.

These considerations motivate, then, the following axioms, which serve to define succinctly the simple class of transport systems that will be the main object of analysis:

(i) Of the chemical species present in the system, one or more but not all are nonvolatile species, with the remaining species being volatile.

(ii) Every admissible stoichiometric chemical reaction (as defined below) in the system must involve at least one of the nonvolatile species.

These axioms are assumed to apply irrespective of internal transport mechanisms (diffusion, forced or natural convection, etc.) or complexity of the governing rate laws and field equations.

In the subsection immediately following it will be verified that the axioms do indeed ensure the global nonreactivity in the steady state. As a first result, however, it will be shown that systems satisfying the axioms are characterized by a certain number of (integral) composition invariants which can be derived solely from a postulated stoichiometry for the system.

Compositional Invariance and Global Nonreactivity

We restate the axioms of the preceding section in mathematical terms to consider some of their consequences. Let $s = 1, 2, \ldots, F$ refer to the set of volatile or free species and $s = F + 1, \ldots, S$ to the $F' = S - F$ nonvolatile species. If we then take the volume V and surface ∂V in Equations (3.2), (3.3), and (3.4) to refer to our entire system, Axiom (i) becomes

$$\vec{n} \cdot \vec{N}_s = 0 \quad \text{on} \quad \partial V, \quad \text{for} \quad s = F + 1, \ldots, S \quad (\text{with} \quad S > F' = S - F > 0) \tag{3.5}$$

On the other hand, Axiom (ii) is understood to mean the following:

$$\text{If} \quad r_s = 0, \quad \text{for} \quad s = F + 1, \ldots, S, \quad \text{then} \quad r_s = 0, \quad \text{for} \quad s = 1, \ldots, F \tag{3.6}$$

whatever the kinetic dependence of the r_s on the concentrations C_s.

As one consequence of the above conditions, we obtain a restriction on the compositional invariance of these systems.

First, we define, in general terms, a (vectoral) composition invariant to be any set of nontrivial (that is, not all zero) real numbers, I^s, $s = 1, \ldots, S$, such that the linear form

$$n\{I\} = I^s n_s \stackrel{\text{def}}{=} \sum_{s=1}^{S} I^s n_s \tag{3.7}$$*

in the total amounts of the S species present, satisfies

$$\frac{dn\{I\}}{dt} \equiv 0 \tag{3.8}$$

irrespective of the conditions imposed at the system boundaries, and, for unsteady as well as steady states. (Then, for each set of numbers I^s, $n\{I\}$ represents a scalar composition invariant.)

To satisfy the global species balance (3.1) will in general require, separately, that

$$p\{I\} \stackrel{\text{def}}{=} I^s p_s \equiv 0 \tag{3.9}$$

and

$$q\{I\} \stackrel{\text{def}}{=} I^s q_s \equiv 0 \tag{3.10}$$

(since $p\{I\}$ and $q\{I\}$ are to some extent under inde-

* Here, and in the following, we adopt the tensoral summation convention, wherein an index repeated as both superscript and subscript indicates a sum over the admissible indicial values.

pendent control through the imposed boundary conditions on the system.) We shall now establish the result that there are at least I' linearly independent composition invariants (that is, sets of I^s), for systems obeying the axioms above, where

$$I' = F' - R \equiv R' - F \geq 0 \qquad (3.11)$$

F' denotes, as before, the number of nonvolatiles, R denotes the (number of stoichiometrically) independent chemical reactions, and R' the number of stoichiometric (or reaction) invariants.

By stoichiometric independence of reactions the usual meaning is understood here but, instead of the standard approach (Aris and Mah, 1963), we choose to develop our definition from the notion of stoichiometric or reaction invariants. A stoichiometric invariant or, as we shall also call it, vector reaction invariant, relative to an abstract set of species, s = 1, ..., S, is understood here to be a set of numbers, E^s, s = 1, ..., S, such that

$$E^s r_s = 0 \qquad (3.12)$$

for all accessible reaction rates, as determined by the species concentrations and chemical kinetics.

Even in the absence of any knowledge of mechanisms or reaction-kinetic schemes, it is logical to define the admissible stoichiometry of reactions by a specification of the reaction invariants, which, as discussed below, can be identified in real chemical systems with the radicals or chemical bonds that are preserved under reaction. Thus, given a set of reaction invariants, that is, vectors E^s, we say that Equation (3.12) defines the set of (stoichiometrically) admissible reactions (or reaction rates r_s). Then, the (maximal) number of linearly (stoichiometrically) independent reactions

$$R = S - R' \qquad (3.13)$$

where R' is the (maximal) number of linearly independent reaction invariants (vectors E^s). For real (and nontrivial) chemical systems we can take $S > R' > 0$ or, equivalently, $S > R > 0$.

With some rather straightforward linear algebra, one can show that Equation (3.6) implies the following:

(a) There are exactly $F(\leq R')$ linearly independent reaction invariants relative to the volatile species alone, that is, invariants which satisfy

$E^s = 0$ for $s = F + 1, \ldots, S$, and therefore

$$E^v r_v \stackrel{\text{def}}{=} \sum_{s=1}^{F} E^s r_s = 0 \qquad (3.14)$$

for all admissible reaction rates r_s, s = 1, ..., F;

(b) There are exactly I' linearly independent reaction invariants relative to the nonvolatiles, such that

For $s = 1, \ldots, F$ $E^s = 0$, and therefore

$$E^n r_n \stackrel{\text{def}}{=} \sum_{s=F+1}^{S} E^s r_s = 0 \qquad (3.15)$$

where I' is given by Equation (3.11), and, hence,

(c) There are exactly R linearly independent reaction rates r_s among the nonvolatiles, s = F + 1, ..., S. In other words, an appropriate subset of the nonvolatiles, R in number, can be used as a stoichiometric basis for all the reaction rates; that is, the reaction rate of any species can be expressed as a linear combination of the rates for this subset of nonvolatiles.

To verify that Equation (3.11) gives the minimum number of composition invariants for the system, we note first that a reaction invariant E^s will obviously qualify, by Equation (3.9), to be a system invariant I^s provided it also satisfies Equation (3.10). Since, by hypothesis, the nonvolatiles have zero efflux rate, $q_s = 0$, s = F + 1, ..., S, Equation (3.10) will in general merely require that the reaction invariant satisfy

$$E^s = 0, \quad \text{for} \quad s = 1, \ldots, F \qquad (3.16)$$

However, because of (3.15), any reaction invariant relative to the nonvolatiles will do, whence (3.11) follows.

In special systems,* it is conceivable that there could be certain combinations of system parameters, for example, kinetic constants, diffusivities, etc., that give rise to more composition invariants than the minimum number I' indicated in (3.11). However, with no special restrictions on system parameters or rate laws, we may in general expect to have exactly I' system (composition) invariants that are simultaneously reaction invariants relative to the nonvolatiles.

The above notions of invariance have both practical and theoretical import for carrier-mediated transport. In particular, there is, corresponding to each of the I' independent composition invariants, an independent integral invariant for the system which is to be regarded as a constant, independent of time, and to be specified through some appropriate initial condition, say, at $t = 0$. Practically speaking, the number I' may be regarded as the degrees of freedom or number of composition parameters that enter into the state of preparation of a system such as the total amounts of various carrier species present in a membrane (for example, in Table 1, No. (5) total hemoglobin content; No. (2), total Fe^{++} content; etc.). In this sense, then, the parameter I' is a measure of the inherent chemical complexity or mobility of a carrier-mediated transport system.

This is easily illustrated for the simple reaction $A + B \rightleftarrows C$ (s = 1, 2, 3, = A, B, C, with $S = 3$, $R = 1$, $R' = 2$):

Reaction	F	F'	I'
$\uparrow A + B \rightleftarrows C$	1	2	1
$\uparrow A + \uparrow B \rightleftarrows C$	2	1	0
$\uparrow A + \uparrow B \rightleftarrows C\uparrow$	3	0	−1

In all cases shown, there are 2 reaction invariants (R') (for example, $E^A = 1$, $E^B = 0$, $E^C = -1$, with $1 \times r_A + 0 \times r_B - 1 \times r_C = 0$; and $E^A = 0$, $E^B = 1$, $E^C = -1$, with $0 \times r_A + 1 \times r_B - 1 \times r_C = 0$). However, the number of compositional invariants depends upon the number of volatile species.

In the first case, $I' = 1$, corresponding to the system invariant,

$$I^A = 0,\ I^B = 1,\ I^C = 1 \left(\text{that is, } \frac{d}{dt}\left[0 \times \int_V C_A dV \right] + \frac{d}{dt}\left[1 \times \int_V C_B dV \right] + \frac{d}{dt}\left[1 \times \int_V C_C dV \right] = 0 \right) \qquad (3.17)$$

and the total amount of B plus C in the membrane $\int_V (C_B + C_C) dV$ is a constant. Moreover, the global

* For example, in a system $A\uparrow \rightleftarrows B$ having linear kinetics, one has as a kind of system invariant

$$n_B - K n_A = 0,$$

where K is the equilibrium constant. However, this is a direct consequence of the assumed kinetics, and similar invariants arise generally for globally nonreactive systems with linear kinetics.

TABLE 2. MATRIX OF STOICHIOMETRIC COEFFICIENTS

s (species)		Reaction (k) (in the order of Table 1, No. 6) 1	2	3	4	5	6
1	(CO_2)	−1	−1				
2	(H_2O)	−1			−1		
3	(H_2CO_3)	+1					−1
4	(OH^-)		−1		+1		
5	(HCO_3^-)		+1	−1		+1	+1
6	(H^+)			+1	+1		+1
7	($CO_3^=$)			+1			
8	(M^+)					+1	
9	($MHCO_3$)					−1	

$\equiv [\alpha_s{}^k]$

where only the nonzero elements are shown.

transport properties of the membrane will depend on the initial loading of these carrier species.

However, in the second case, $I' = 0$, there is no compositional invariant for the membrane. Hence, whatever the initial loading nonvolatile of C in the membrane, the total amount of C in membrane in a given steady state is determined by the boundary conditions on A and B. In other words, C can enter or leave the system as the combination $(A + B)$.

In the final case, I' is negative, because Axiom (ii) set forth above has been violated and this system is in fact globally reactive. The reactive character of the membrane can be visualized by considering, for example, what would happen if A and B were maintained on both sides of the membrane at equal concentrations. One would then expect to find a steady state flux of species C emanating from both sides of the membrane, which would therefore behave much in the manner of a catalytic surface for the conversion of A and B to C.

In the present context, the notion of reaction invariants can be used to establish generally the global nonreactivity of the steady states of our system; for here, the species balance (3.4) gives

$$p_s = q_s, \quad \text{for} \quad s = 1, \ldots, S \tag{3.18}$$

that is, net production rate equals efflux rate for a steady state where of course $dn_s/dt = 0$. However, Equation (3.4) implies that the q_s and, hence, the p_s vanish for the nonvolatiles:

$$0 = q_s = p_s = \int_V r_s dV, \quad s = F + 1, \ldots, S \tag{3.19}$$

Because, moreover, we have R' linearly independent reaction invariants E^s satisfying

$$E^s p_s = \int_V E^s r_s dV = 0 \tag{3.20}$$

it follows from (3.19) and (3.20) that, we have R' equations

$$E^s p_s \equiv E^v p_v = 0 \tag{3.21}$$

in the F quantities, p_s ($s = 1, 2, \ldots, F$). Since $R' - F = I' \geq 0$, it follows that

$$p_s = 0, \quad \text{for} \quad s = 1, 2, \ldots, F$$

and, hence, that the system is globally nonreactive in the steady state. Simply stated, the global nonreactivity in a steady state of the nonvolatiles implies that of the volatiles because of the assumed (local) stoichiometric coupling in Axiom (ii).

Identification of Stoichiometric and System Invariants

To establish the reaction and system invariants for a particular transport system requires a knowledge of the stoichiometry of the system and a specification of which species are physically entrapped or nonvolatile.

The maximal set of linearly independent reaction invariants can always be obtained from matrix manipulation of the set of stoichiometry coefficients for a postulated set of reactions involved in the system (compare Aris and Mah, 1963). It is then convenient to start from the postulated set of reactions, usually corresponding to kinetic steps, say K in number, which can be written symbolically as

$$\alpha_s{}^k \mathcal{E}^s = 0, \quad k = 1, \ldots, K \tag{3.22}$$

where $\alpha_s{}^k$ is the ($S \times K$ matrix of) stoichiometric coefficients (with rank R) of species s in the kth reaction and $\mathcal{E}^s$ is the symbolic designation for the species.

That is, the species rates r_s are given by

$$r_s = \alpha_s{}^k \omega_k, \quad s = 1, \ldots, S \tag{3.23}$$

where ω_k is the known or postulated rate of the kth step (a function of C_s). Now, the reaction invariants, which we seek to determine, and the matrices of stoichiometric coefficients must satisfy the mathematical equivalent of (3.22),

$$E_i{}^s \alpha_s{}^k = 0, \quad (i = 1, \ldots, R'; \; k = 1, \ldots, K) \tag{3.24}$$

For example, for the CO_2-bicarbonate system in Table 1, the matrix of stoichiometric coefficients has the form shown in Table 2, which, with row-column operations, can be shown to have rank $R = 5$, the number of linearly independent reactions and 4 reaction invariants, $R' = S - R = 9 - 5$.

The straightforward application of this procedure shows that the reaction 6 is not stoichiometrically independent because $\alpha_s{}^6 = \alpha_s{}^4 - \alpha_s{}^1 - \alpha_s{}^3$, and the following are one set of reaction invariants:

$$r_{OH} + r_{H_2O} - r_{CO_2} = 0; \quad r_{M^+} + r_{MHCO_3} = 0;$$

$$r_{OH^-} - r_{CO_2} - r_{H_2CO_3} - r_{H^+} - r_{CO_3} = 0;$$

$$r_{M^+} + r_{OH^-} - 2r_{CO_2} - 2r_{H_2CO_3} - r_{H^+} - r_{HCO_3^-} = 0$$

which can be represented as given in Table 3. The reac-

TABLE 3. REACTION INVARIANTS

i invariant		Species (s) 1 CO_2	2 H_2O	3 H_2CO_3	4 OH^-	5 HCO_3^-	6 H^+	7 $CO_3^=$	8 M^+	9 $MHCO_3$
1	E_1	−1	1		1					
2	E_2								1	1
3	E_3	−1		−1	1		−1	−1		
4	E_4	−2		−2	1	−1			1	

$\equiv [E_i{}^s]$

tion invariants identified above are not particularly instructive for the analysis of carrier-mediated transport problems since the reaction invariants are not related to the chemistry of the system in an obvious way. In real chemical systems a reasonable approach is to choose reaction invariants that correspond to a set of stoichiometric radicals, that is, a set of chemical entities, consisting of the maximum assemblages of atoms or (ions), which preserve their chemical identity. Then the E_i^s, may be regarded as chemical indices being proportional to the number of radicals i = 1, ..., R′, contained in each chemical species s = 1, ..., S.

Again, referring to the CO_2-bicarbonate example Table 1, the reaction invariants for this example system can be determined from the set of postulated reactions by sequentially listing the radicals (Column 2 of Table 4) of the individual reactions. A set of reaction invariants or radicals for the system is then obtained according to the rather obvious rule that, from the list of radicals for the individual reactions, only those are selected which cannot be formed by (positive, linear) combinations of other radicals in the system.

The radicals rejected by this rule are simply omitted from column 3. It is worth noting that the radicals for reaction number 4 ($H^+ + OH^- = H_2O$) are H^+ and $O^=$, since the OH^- can be broken down by a similar reaction, which represents an exchange reaction. This merely illustrates the fact that not all stoichiometric radicals need appear necessarily as freely dissociated (that is, free radicals) in systems involving exchange reactions.*

Now an alternative basic vector of coefficients E_i^s (the reaction invariants) that relate the number of radical i to the species s in the system can be obtained simply by inspection as shown in the array of Table 5.

Furthermore, combinations of the scalar product of these coefficients with the total moles of each species in the system, that is, $n\{E\} = n_sE^s$, will be shown to be related to the material balance constraints on the system.

* In fact, the CO_2 molecule might, in reality, not be a radical, if one considers the possibility of internal bonds being broken. However, the consideration of subentities of the CO_2 molecule adds nothing new.

Table 4. Reaction Invariants for Individual Reactions

Reaction no.	Radicals for individual reactions	Reaction invariants (radicals) for the system of reactions
1	CO_2, H_2O	CO_2
2	CO_2, OH^-	...
3	H^+, $CO_3^=$	H^+
4	H^+, $O^=$	$O^=$
5	M^+, HCO_3^-	M^+
6	H^+, HCO_3^-	...

Thus, while one may always proceed from a given reaction scheme, typified by (3.22) and (3.23), and employ formal methods of linear algebra for the derivation of reaction invariants, it will often be easier practically to identify, by inspection, a set of actual chemical radicals for real (as opposed to abstract) chemical systems.

In many cases, then, one can readily identify the I' system invariants as corresponding physically to those of the R' reaction invariants which are permanently entrapped radicals, or else, as permanent restrictions on the relative amounts of different radicals present in the system (as generalized from the notion of stoichiometric excess).

In the above example, the system invariants can be readily identified with the entrapped radicals H^+, $O^=$, M^+, and therefore the numerical value of I' is 3. Also, there are three material-balance constraints associated with each of these entrapped radicals: that is,

$$n\{H^+\} = \text{constant},\ n\{O^=\} = \text{constant, and}$$
$$n\{M^+\} = \text{constant}$$

Incidentally, we note that the common notion of conservation of electrical charge implies that it is a reaction invariant and, hence, expressible as a linear combination of the invariants already identified, that is,

$$(n_{OH^-} + n_{HCO_3^-} + 2n_{CO_3^=}) - (n_{H^+} + n_{M^+})$$

is identical with

$$2n\{O^=\} - n\{H^+\} - n\{M^+\}$$

The fact that the species composition, as opposed to the invariant composition of the membrane may change after the membrane solution has been exposed to the permeant has not always been realized. For example, Enns (1967) adjusted the pH of a bicarbonate carrier solution prior to forming his model membranes and assumed that the average pH remained constant when the membrane was exposed to different CO_2 environments. Actually, in this case, the final mean pH in the membrane varies with the CO_2 atmosphere and is more dependent on the total base (MOH) in the membrane-forming solution rather than on initial pH of the membrane (Suchdeo, 1973).

In general, the radicals may not always be identical with the system invariants, as is illustrated by the decomposition reaction of example 3 in Table 1. Here, species B and C are obviously radicals (Species "A" being simply the chemical combination BC), but neither is permanently entrapped in the system. However, the reaction invariant $n\{B\} - n\{C\}$, representing the stoichiometric excess of B over C, is indeed a system invariant.

On the basis of the foregoing considerations, one arrives at two, rather abstract, but nevertheless useful, conceptual viewpoints into the type of carrier-mediated transport system defined by the axioms given above. As for the first, we note that our partition of species into the

Table 5. Alternative Basic Vector of Coefficients

		s (species)								
		1	2	3	4	5	6	7	8	9
i (radical)		CO_2	H_2O	H_2CO_3	OH^-	HCO_3^-	H^+	$CO_3^=$	M^+	$MHCO_3$
1	CO_2	1		1		1		1		1
2	H^+		2	2	1	1	1			1
3	$O^=$		1	1	1	1		1		1
4	M^+								1	1

$\equiv [E_i^s]$

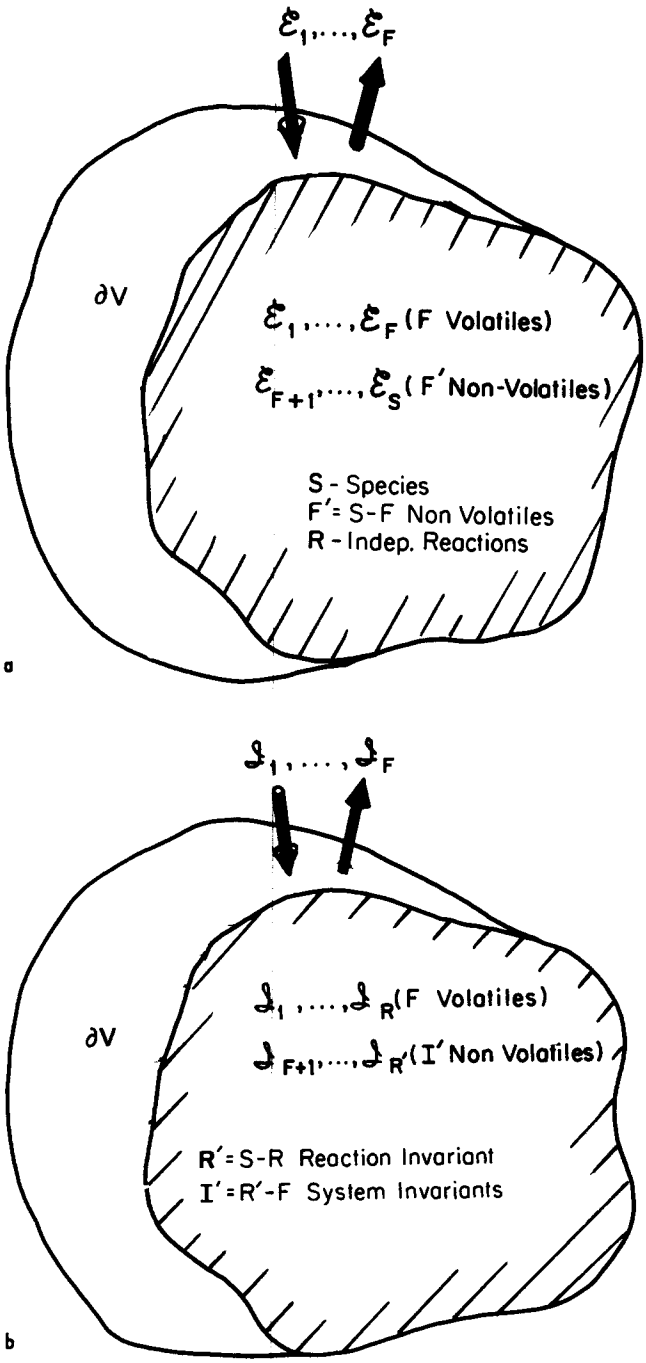


Fig. 4. Two conceptual views of the exchange of substances with a membrane phase corresponding to global-nonreactivity: (a) Exchange of volatile species $\mathcal{E}_v$ and reaction with nonvolatile species $\mathcal{E}_n$; (b) Exchange of volatile invariants $\mathcal{I}_v$, with nonvolatile invariants remaining $\mathcal{I}_n$ in the membrane.

set of volatiles, say $v = \{s{:}s = 1, \ldots, F\}$, and nonvolatiles, $n = \{s{:}s = F + 1, \ldots, S\}$ corresponds exactly to the decomposition of an S-dimensional linear vector space $\mathcal{S}$ into a direct sum $\mathcal{S} = \mathcal{V} \oplus \mathcal{N}$ of an F-dimensional subspace $\mathcal{V}$ and an F'-dimensional subspace $\mathcal{N}$, according to the partition (of components) of the associated vectors and matrices; for example, the partition of reaction invariants $E^s = E^n \oplus E^v$, stoichiometric coefficients, $\alpha_s{}^k = \alpha_n{}^k \oplus \alpha_v{}^k$, etc. Hence, we can abstractly regard our carrier-mediated transport system as a reaction between two species, say $\mathcal{E}^n$ and $\mathcal{E}^v$, with the obvious symbolism for the reaction:

$$\alpha_v{}^k \mathcal{E}^v \rightleftarrows -\alpha_n{}^k \mathcal{E}^n \tag{3.25}$$

We expect the reaction rates of volatile and nonvolatile species to be coupled, then, through the component kinetic functions

$$r_v = r_v(C_v; C_n) \quad \text{and} \quad r_n = r_n(C_v; C_n) \tag{3.26}$$

obtained from the complete kinetic function:

$$r_s = r_v \oplus r_n = r_s(C_v \oplus C_n) = r_s(C_v; C_n) \tag{3.27}$$

which, in terms of a set of kinetic steps such as (3.23), is made explicit by the partition of $\alpha_s{}^k$.

In general, we may also have such coupling of other terms of the field equations, but in any case we shall always have as the boundary conditions on the nonvolatile species:

$$\vec{n} \cdot \vec{N}_n = 0 \quad \text{on} \quad \partial V \tag{3.28}$$

As an alternative but complementary viewpoint to the above and instead of considering actual chemical species, we may choose to visualize the process as suggested in Figure 4b. Here, we have the transport of F itinerant or volatile reaction invariants, say $\mathcal{I}_j$, j = 1, . . . , F, through a system which also contains a number I' of permanent or nonvolatile reaction invariants, $\mathcal{I}_j$, j = F + 1, . . . , R′.

Implications of Invariants on the Field Equations

The ideas established above have a direct bearing on the formulation and treatment of boundary-value problems in carrier-mediated transport. In the case, say, of homogeneous reaction,* the local species balance corresponding to (3.1) will generally read

$$\vec{\nabla} \cdot \vec{N}_s = r_s - \frac{\partial C_s}{\partial t}, \quad s = 1, \ldots, S \tag{3.29}$$

And in addition to the partition into volatiles and nonvolatiles discussed above there is another type of partition possible according to reaction stoichiometry and invariants.

In particular, if we regard (3.29) as a vector equation subject to arbitrary nonsingular linear transformations or changes of coordinates, say $A_i{}^s$, it becomes in general compositional coordinates

$$\vec{\nabla} \cdot \vec{\nu}_i = \omega_i - \frac{\partial \xi_i}{\partial t} \tag{3.30}$$

where

$$\xi_i = A_i{}^s C_s, \quad \omega_i = A_i{}^s r_s \tag{3.31}$$

$$\vec{\nu}_i = A_i{}^s \vec{N}_s$$

for i = 1, . . . , S.

Given, then, a set of R' reaction invariants $E_i{}^s$, identified as shown in the previous section, we can choose $A_i{}^s$ to be any nonsingular transformation satisfying

$$A_i{}^s \equiv E_i{}^s, \quad \text{for} \quad i = 1, \ldots, R', \; s = 1, \ldots, S \tag{3.32}$$

with the remaining $(S \times R)$ components of $A_i{}^s$ (i = R′ + 1, . . . , S; s = 1, . . . , S) being otherwise freely disposable. Then, the reaction term ω_i in the first R' Equation of (3.30) is such that

$$\omega_i \equiv 0 \quad \text{for} \quad i = 1, \ldots, R' \tag{3.33}$$

with the new flux and concentration variables representing those associated with the corresponding invariants,

* This restriction to homogeneous, as opposed to heterogeneous, reactions is not essential to the main results. It merely allows us to write down field equations without introducing the notion of singular surface distributions for the reaction-rate term r_s.

TABLE 6. PARTITIONED TRANSFORMATION MATRIX RELATING THE CHEMICAL SPECIES TO THE INVARIANTS AND THE EXTENTS OF REACTION

	F volatile	S species	F′ non-volatile	
R′ reaction invariants	$E_i^1 \ldots$	$\ldots$	$\ldots E_1^S$	F "volatile" or "itinerant" radicals
	$E_F^1 \ldots$	$\ldots$	$\ldots E_F^S$	
	$0 \ldots 0$	$E_{F+1}^{F+1} \ldots$	$\ldots E^S_{F+1}$	I′ system composition invariants
$[E_i^s] =$	$0 \ldots 0$	$E_{R'}^{F+1} \ldots$	$\ldots E^S_{R'+1}$	
R "extents of reaction"	$0 \ldots 0$	$0 \ldots 0$	$E_{R'+1}^{R'+1} \ldots E^S_{R'+1}$	(3.39)
	$0 \ldots 0$	$0 \ldots 0$	$E_S^{R'+1} \ldots E_S^S$	
		I′	R	

$$\xi_i = C\{E_i\} \equiv E_i^s C_s \tag{3.34}$$

$$\vec{\nu}_i = \vec{N}\{E_i\} \equiv E_i^s \vec{N}_s, \quad i = 1, \ldots, R' \tag{3.35}$$

Equation (3.30) reduces then to a familiar continuity equation of the form

$$\vec{\nabla} \cdot \vec{N}\ \{E\} + \frac{\partial C}{\partial t}\{E\} = 0 \tag{3.36}$$

which of course dictates that invariants accumulate and flow without reacting. For the remaining R equations we have $\omega_i \neq 0$, in general, and the $(S \times R)$ disposable A_i^s $(i = R' + 1, \ldots, S, s = 1, \ldots, R)$ can be related to an admissible set of (linearly independent) stoichiometric coefficients, while the corresponding (R) concentration variables ξ_i, $i = R' + 1, \ldots, S$ represent generalized extents of reaction.

Based on the above representation, there is another partition possible, in the space of the new variables ξ_i, corresponding to R extents of reaction $(i = R' + 1, \ldots, S)$; F itinerant reaction invariants or radicals associated with volatile species (say, $i = 1, \ldots, F$); and finally, I' radicals, associated with nonvolatile species, or other such system invariants (say, $i = F + 1, \ldots, R'$). This follows directly from the results given in Equations (3.14) and (3.15), which also have for a consequence that there is no local efflux of system invariants at the system boundary, that is,

$$\vec{n} \cdot \vec{\nu}_i = 0, \quad i = F + 1, \ldots, R' \tag{3.37}$$

Hence, as mentioned earlier, there exists an associated integral

$$n\{E_i\} \equiv \int_V C\{E_i\}\, dV \equiv \int_V \xi_i dV = n_{tot}\{E_i\} \tag{3.38}$$

for these I' quantities $i = F + 1, \ldots, R'$ where $n_{tot}\{E_i\}$, a time-invariant constant of the system, represents an initial condition (at time $t = 0$, say) on the invariant E_i. From a mathematical point of view, the specification of all integral invariants for a system will generally be necessary to ensure uniqueness of solutions to the field equations governing the internal transport process.

The above ideas can be summarized quite succinctly through the concept of partitioned matrices, for we can arrange to choose the $A_i^s \equiv E_i^s$ such that the $S \times S$ matrix E_i^s (with columns $s = 1, \ldots, S$, and rows $i = 1, \ldots, S$) is partitioned into an upper-diagonal form, with (square, nonsingular) $F \times F$, $I' \times I'$, and $R \times R$ submatrices as the diagonal elements, as shown in Table 6.

As pointed out above, these results have both theoretical and practical import for the treatment of the carrier-mediated transport problem, especially for the steady state diffusion-reaction systems considered in this review. As a general consideration, for example, one can obtain immediately the I' integrals

$$\vec{\nu}_i = 0, \quad \text{for} \quad i = F + 1, \ldots, R' \tag{3.40}$$

for the steady state form of (3.30) governing the system invariants, an integral which of course satisfies the boundary condition of (3.37). In the absence of forced migration or convection and with the classical linear diffusion laws, these same integrals should generally apply to steady state systems. In this case, they can be used to reduce the order of the field equations and, at the same time, are seen to be directly connected with the integral invariants of Equation (3.38).

Steady State Membrane Diffusion

The preceding relations take on an especially simple form in the case of a steady state system with unidirectional spatial flux, as is often assumed to occur in membranes. In particular, if x denotes the direction of flux, normal to the membrane surfaces, at $x = 0$ and $x = L$, say, then the x-components of flux in (3.34) associated with the reaction invariants or radicals reduce by means of (3.36).

$$N\{E_i\} = E_i^s N_s(x) \equiv \nu_i, \quad \text{a constant for} \quad 0 \leq x \leq L \tag{3.41}$$

for $i = 1, \ldots, R'$; that is, the fluxes of the radicals are constants independent of x.

As in the general relations (3.40), one can always choose I' of the ν_i, corresponding to the system invariants, to be identically zero. Then, as will be discussed in Part II, it follows that the transmembrane flux of volatile, $v = 1, \ldots, F$ is related to the species fluxes at any interior point $0 \leq x \leq L$ of the membrane by

$$N_v \overset{\text{def}}{=} N_v(0) \equiv N_v(L) = Z_v{}^m N_m(x) \tag{3.42}$$

where

$$Z_v{}^m = \sum_{i=1}^{F} (E^{-1})_v{}^i E_i^m, \quad m = 1, \ldots, S \tag{3.43}$$

with E_i^m and $(E^{-1})_m{}^i$ denoting, respectively, the components of the partitioned matrix of (3.39) and its inverse.

The (constant) numbers $Z_v{}^m$ $(m = 1, \ldots, S, v = 1, 2, \ldots, F)$ may be regarded as chemical transport numbers which play a role in the transport of volatiles that is entirely analogous to that of ionic charge in the transport

of electrolytic current. It is, moreover, evident that these numbers are determined uniquely by the specification of the reaction invariants and the nonvolatile species.

Here, we are mainly concerned with the situation where species transport occurs solely by molecular diffusion, without appreciable motion due to convection or forced migration. We shall further assume that the diffusive fluxes can be expressed in terms of the relevant concentration gradients, as

$$J_s = - D_s{}^m \frac{\partial C_m}{\partial x}, \quad s = 1, \ldots, S \tag{3.44}$$

where $D_s{}^m$ (m, s = 1, 2, ..., S) represent the (matrix) components of coupled diffusivities (with the dimensions units of area per unit time). In the usually-assumed case of simple diffusion with no direct coupling diffusivities we may further write

$$D_s{}^m = \begin{cases} 0, & \text{for} \quad m \neq s \\ D_s, & \text{say, for} \quad m = s \end{cases} \tag{3.45}$$

and the sum implied in (3.44) reduces to a single term. Since many of the analytical methods and results discussed herein are equally applicable to coupled diffusion processes, we prefer however to leave (3.44) in a more general form.

We focus attention here, then, on systems where the local flux is entirely by diffusion so that

$$N_s \equiv J_s \tag{3.46}$$

in (3.42). As discussed in Part II, Equation (3.41) provides a set of R' first integrals of the relevant differential equations for diffusion with reaction. [Previously, we have used the term kinetic constraints for R' second integrals of Equation (3.41) (Goddard et al., 1970)].

Whenever the diffusivities $D_s{}^m$ may be taken as constants, independent of concentration, the relations (3.43) and (3.44) provide, on further integration, an expression for transmembrane flux of volatiles:

$$N_v = Z_v{}^m D_m{}^s \left(\frac{C_s(0) - C_s(L)}{L} \right) \tag{3.47}$$

in terms of transport numbers, diffusivities, and overall gradients of all the species involved. This is, in fact, the generalization of an often-used relation for simple cases of carrier-mediated diffusion in membranes as is illustrated by Equation (2.2).

As an example of the utility of the preceding formula, it is worthwhile to consider a system of the type proposed by Verhoff and Sundaresan (1972) (No. 13, Table 1), as a model of coupled transport in biological cells. In this model, one has a number of volatile or transferred species which are presumed to combine with a number F' of nonvolatile species in a number of reactions, any of which has stoichiometry that can be represented schematically by

$$\mathbf{A}\uparrow + \mathbf{B} \rightleftarrows \mathbf{B}' \tag{3.48}$$

where **A** denotes any one of the volatiles, while **B** and **B'** denote nonvolatiles. It becomes immediately obvious then that the volatile species **A** are reaction invariants or radicals as defined in the present work and hence that the uppermost $F \times F$ square submatrix on the diagonal in Equation (3.39), $E_i{}^s$ (s, i = 1, ..., F) reduces to an $F \times F$ idemfactor or identity matrix. Therefore, the corresponding submatrix of the inverse transformation $(E^{-1})_s{}^i$ (s, i = 1, 2, ..., F) has the same form, and the expression for volatile flux in (3.47) reduces consequently to the simpler form

$$N_v = \frac{E_v{}^s D_s{}^m}{L} [C_m(0) - C_m(L)]$$

$$\equiv \frac{D_v{}^m}{L} [C_m(0) - C_m(L)]$$

$$+ \frac{E_v{}^n D_n{}^m}{L} [C_m(0) - C_m(L)] \tag{3.49}$$

where now the relevant transport numbers

$$Z_v{}^s \equiv E_v{}^s \equiv E_i{}^s, \quad \text{for} \quad i = v = 1, \ldots, F$$

is the number of molecules of volatile (radical) i per molecule of species s, and where

$$E_v{}^n D_n{}^m = \sum_{s=F+1}^{S} E_v{}^s D_s{}^m, \quad m = 1, \ldots, S \tag{3.50}$$

denotes a sum over the nonvolatile species. We note also that Equation (3.50) can be further simplified in the special case of uncoupled diffusion actually treated by Verhoff and Sundaresan.

However, the most important point to be made here is that the present general formulation, based on the elementary notion of reaction invariants, leads to an easy derivation of the expressions of the above authors for flux, without the necessity of imposing, a priori, their restrictive conditions on the sequence of chemical reactions which are assumed to govern the combination of volatiles with nonvolatiles. Furthermore, with the above authors' ultimate assumption of reaction equilibrium, Equation (3.50) provides an almost immediate path to their final results for the equilibrium mediation or enhancement of mass transfer.

STEADY STATE PROPERTIES OF CARRIER-MEDIATED MEMBRANE TRANSPORT SYSTEMS

Regimes

Because of the many factors that influence transport it is possible to see clearly the relationships of physical and chemical parameters only in various asymptotic regimes wherein some exact results can be derived for simple systems.

In the following sections, primary attention is devoted to steady state problems where the generalization of Equation (2.1) takes on the familiar form

$$D_s{}^m \nabla^2 C_m = - r_s(C_l), \quad (l, s = 1, \ldots, S) \tag{4.1}$$

or, *in direct notation*

$$\mathbf{D} \cdot \nabla^2 \mathbf{C} = - \mathbf{r}(\mathbf{C})$$

for the case of homogeneous reaction and constant diffusivity **D**. The general boundary-value problem for carrier-mediated transport (in three spatial dimensions) consists of finding solutions to (4.1), in the interior V of our system, which must also satisfy the zero-flux condition of (3.28) for (F') nonvolatiles which specializes here to

$$\vec{n} \cdot \vec{J}_m = - D_m{}^s \frac{\partial C_s}{\partial n} = 0 \quad \text{on} \quad \partial V,$$

$$\text{for} \quad m = F + 1, \ldots, S \tag{4.2}$$

Furthermore, one will in general require such a solution to satisfy certain boundary conditions on the (F) volatile species. In the usual physical arrangement the volatiles are exchanged with a surrounding phase of known composition, and, whenever limitations on external mass trans-

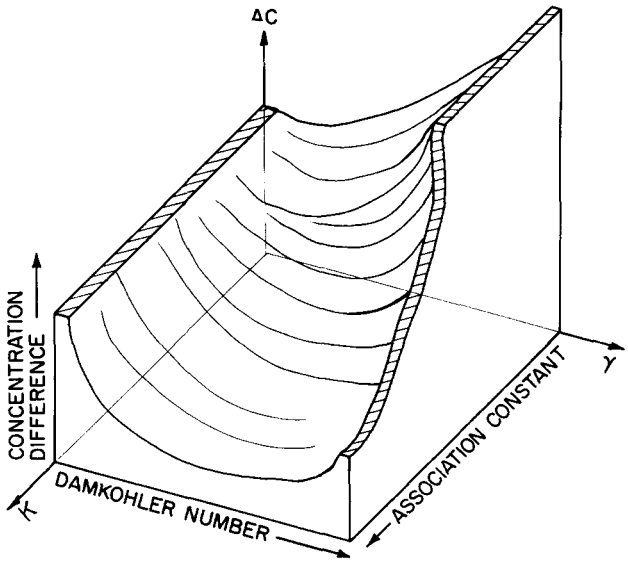


Fig. 5. Shaded areas are regions of parameters where approximate analytical solutions can be constructed.

fer rates and interfacial kinetic processes are absent,* one can employ the usual prescription of the (externally equilibrated) volatile species concentrations on ∂V. This may not be a trivial matter for ion transport when some ions do not distribute across the membrane phase boundaries. In the latter case due to the Donnan effect, one may expect the nonpermeant ions to influence the distribution of the permeant ions (compare Tanford, 1967).

At any rate, one should expect to have F boundary conditions** on the volatile concentration fields, which with (4.2) gives formally a total of S such conditions. However, because there can be fewer independent reactions (R) than chemical nonvolatile species (F'), the conditions of (4.2) will generally be neither independent nor otherwise sufficient to provide for unique mathematical solutions. As pointed out above (and, for some simpler special cases, by Bassett and Schultz, 1971; Goddard et al., 1970), this fact will necessitate the specification of integral constraints on a number ($I' = F' - R$) of composition invariants for the system.

It must be admitted at the outset that most reactions of interest are bimolecular at least and therefore have kinetics $\mathbf{r}(\mathbf{C})$ which are nonlinear in the concentrations $\mathbf{C}$. It is primarily this term in the differential equations that introduces the nonlinearity into the problem. Because of the resultant analytical intractability, all the analytical treatments of facilitated diffusion that have been developed to date are based on one or more special simplifications of the problem. It is perhaps not surprising that these simplifications are associated with the physical regimes of fast or slow reactions, and of weakly perturbed systems with linearized kinetics.

A qualitative indication of the regimes that have been found amenable to analytic exact or approximate solutions is shown in Figure 5 for a single-reaction, single-permeant system. The major parameters of interest are the equilibrium or binding constant for the reaction K; the Damköhler number γ, which characterizes the rate of reaction [see Equation (4.11) below]; and the concentration difference for the permeant across the membrane, ΔC. We shall see that in the limiting plane of vanishing concentration gradients $\Delta C \rightarrow 0$ analytical treatments based on linear kinetic laws become valid, and that at low and high values of the Damköhler number analytic solutions are also available. As the binding constant increases, the region of validity for these asymptotic solutions decreases.

Weakly Perturbed Systems—Linear Kinetics

As in much of the literature on diffusion with chemical reaction, the special case of a linear-kinetics law for reaction rates provides a valuable limiting form of carrier-mediated diffusion. Here, the reaction rate term in (4.1) is taken to be

$$\mathbf{r} = -\mathbf{K} \cdot \mathbf{C} \tag{4.3}$$

that is,

$$r_s = -k_s{}^m C_m$$

where the (matrix of) rate coefficients $k_s{}^m$ are constants independent of $\mathbf{C}$. This linearity, together with the constancy of diffusivities, allows for the application of linear-algebraic (matrix) methods to derive formal analytic solutions of Equation (4.1), for several simple system geometries.* As will be shown below, this provides for a general closed-form solution of the unidirectional carrier-mediated diffusion problem, for constant diffusivities, and with any number of chemical reactions (Ulanowicz and Frazier, 1968).

Such solutions can be useful in that they provide exact analytic results, which require only algebraic operations for computation; they display much of the parametric complexity of the problem; and, they also serve as a basis of comparison with other more difficult computations. Furthermore, as will be discussed below, they provide some signals for the kind of singular behavior that can render other computations difficult or almost impracticable.

As an approximation to most real chemical kinetics, the range of applicability of the idealized rate-law (4.3) is quite limited. Indeed, it is only in the limit of thermodynamically near-equilibrium systems, that is to say, those perturbed infinitesimally from a uniform equilibrium state of composition (or chemical potential), that (4.3) has universal validity. In the systems of interest here, this means generally speaking that the concentrations of the volatile or transferable species must be nearly the same on all boundary points, such that the driving force for diffusional transfer is likewise infinitesimally small.

By the usual type of perturbation analysis one can formalize this as follows: Given an unperturbed, equilibrium state of a system where the species concentrations have spatially uniform steady state values, $\mathbf{C}^*$ say, such that all fluxes and reaction rates vanish, then in the slightly perturbed state one has formally that

$$\mathbf{r} = \left(\frac{\partial \mathbf{r}}{\partial \mathbf{C}}\right)^* \cdot (\mathbf{C} - \mathbf{C}^*) + 0(|\mathbf{C} - \mathbf{C}^*|^2) \tag{4.4}$$

where $\mathbf{C} - \mathbf{C}^*$ is the perturbation in concentration and where the derivatives of reaction rate (with components $\partial r_s/\partial C_m$, say) are evaluated at the unperturbed state. Thus, regardless of the actual kinetics, to terms

* Of course, one usually attempts in carrier-transport studies to eliminate, whenever possible, such effects, for example, to provide for large mass transfer coefficients by stirring, etc., and thereby, to eliminate extraneous experimental variables such as external mass transfer coefficients (see Section 2).

** In some treatments of the problem (Murray, 1971) this fact has not been fully exploited.

* Also, one is able to treat a number of unsteady state problem analytically, but these will not be discussed here.

$0(|\mathbf{C} - \mathbf{C}^*|^2)$, the rate law is approximated by (4.3) with

$$-k_s^m \equiv (\partial r_s/\partial C_m)^* \tag{4.5}$$

and with C_m replaced by $C_m - C_m^*$, for m = 1, . . . , S.

This mode of reasoning is essentially that of linear irreversible thermodynamics, which Friedlander and Keller (1965), followed by Blumenthal and Katchalsky (1969), and others first proposed to treat boundary-value problems of the carrier-mediated-diffusion type although their treatments dealt with only one chemical reaction.

With regard to the validity of (4.3) as an approximation, it should be pointed out that the required maximum differences in the imposed volatile concentrations necessary to ensure approximately uniform concentration profiles of the nonvolatile constituents is highly dependent on the specific chemical reactions that occur in the membrane.

An example where very nonuniform concentration profiles within the membrane may develop in the face of apparently equal permeant concentrations at the boundaries is given by Ward (1970a) for electrically induced flux of NO through $FeCl_2$ solutions [Figure 6 (from Ward)]. In this case the Fe^{++} ions also behave as permeants and the imposed current may force a large variation in the concentrations of Fe^{++}.

As mentioned above, Friedlander and Keller (1965) pioneered the use of the thermodynamic affinity function to obtain analytical solutions for diffusion in reacting systems near chemical equilibrium and to establish an analogy with similar problems in heat transfer. Their analysis clearly showed for the first time the boundary-layer character of facilitated diffusion in membranes. In particular, they employed the concept of relaxation length for diffusion with chemical reaction and showed that chemical reactions are farthest from equilibrium at interfacial boundaries and approach equilibrium at distances from the interface on the order-of-magnitude of the relaxation length. The result of their analysis gives the following formula for facilitation*:

$$\Phi = \frac{N - N_0}{N_0} = \frac{(1 - w)\beta^1\alpha_1}{1 + (w - 1)\beta^1\alpha_1} \tag{4.6}$$

where

$$w = \frac{2}{\lambda}\tanh\frac{\lambda}{2},\quad \beta^1 = -\left(\frac{L}{\lambda}\right)^2\frac{k^1}{D_1},$$

$$\left(\frac{\lambda}{L}\right)^2 = -\sum_1^S \frac{k^s\alpha_s}{D_s}$$

A typical and instructive calculation of reaction rates profiles for linear kinetics was given by Blumenthal and Katchalsky (1969) and reproduced here as Figure 7. Note that for high values of the Damköhler number, the reaction rates are highest at the membrane surfaces and almost zero in the central core of the film. Whereas for lower values of the reaction rate constants, the reaction rate is a linear function, significantly different from zero, throughout the whole membrane.

Similar concentration profiles are obtained for nonlinear kinetics, as in the case of CO_2 diffusing through bicarbonate solutions, Figure 8. Here the general nature of large reaction rates at the surface is still maintained, but there is a definite asymmetry of the reaction-rate profile in the membrane.

As discussed later, this insight of reaction at the interface and equilibrium within the core of the membrane has been the basis for several other mathematical approaches to obtain asymptotic solutions to the facilitated-diffusion equations in the regime of fast reactions with large concentration differences (shown on the right-hand side of Figure 5) (Goddard, et al., 1970; Murray, 1971; Kreuzer and Hoofd, 1972; Smith et al., 1973).

Mathematically, the use of the affinity function A for linearized analysis of this class of problems is strictly an exact procedure only in the limit of $A \to 0$, as expressed by Friedlander and Keller (1965) where the exponential $e^{-A/RT}$ is well approximated by $1 - A/RT$. This linear representation of this exponential can be expected to be valid within 5% if the group A/RT is less than 0.3. However, while necessary, this is not a sufficient criteria

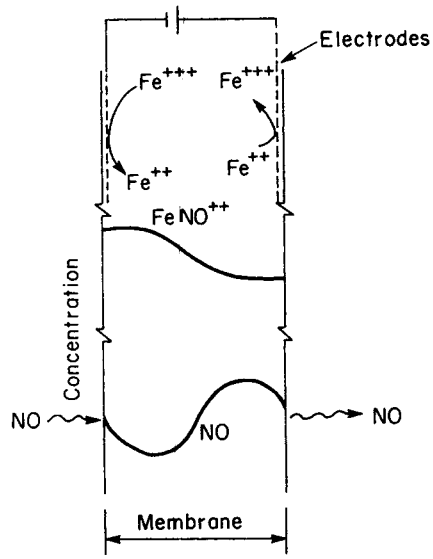


Fig. 6. Anomalous concentration profiles (NO) with equal concentrations at the boundaries (Ward, 1970a).

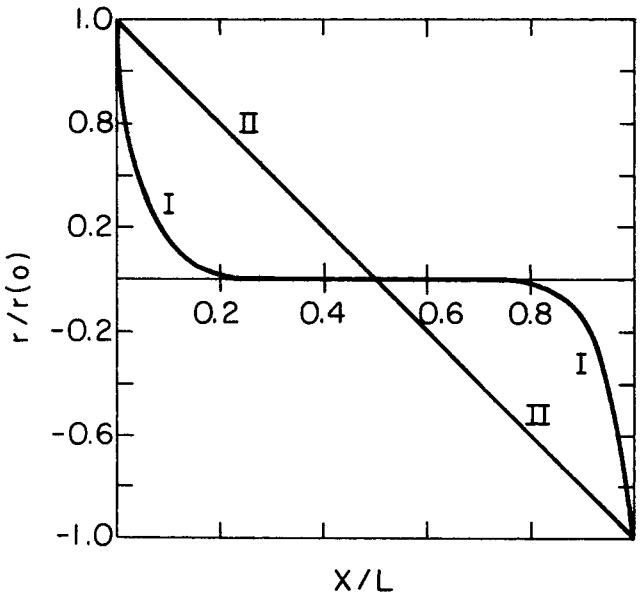


Fig. 7. Symmetrical reaction rate profiles throughout membranes as obtained by the linear analysis (Bluemthal and Katchalsky, 1969) curve I high Damköhler numbers-near equilibrium regime and II Low Damköhler numbers-near diffusion regime.

* The function denoted by F in Friedlander and Keller (1965) is identical with $(1-w)$ in the present notation.

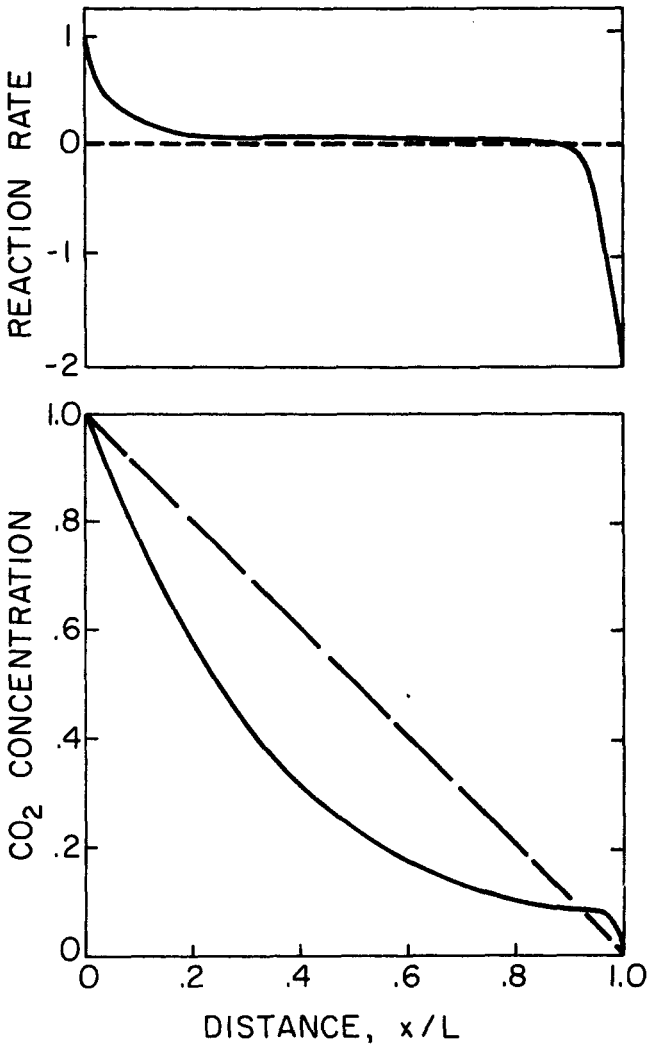


Fig. 8. Nonsymmetrical profiles for CO_2 diffusion through bicarbonate solutions (Suchdeo, 1973): (a) Reaction rate more intense at downstream boundary; (b) Concentration of CO_2 changes rapidly at membrane surfaces. Conditions: CO_2 partial pressure, upstream = 1 atm; Downstream = 0.01 atm, 1N $NaHCO_3$ in membrane; membrane thickness = 0.5 cm.

for assuming that the kinetics can be linearized. Although the reaction rate for a reversible reaction can generally be put into the form $r = r_f(1 - e^{-A/RT})$, the forward rate r_f depends on the concentration of all reactive species, and the requirement that A/RT be small does not of course guarantee that the function r_f is a constant over the concentration range of interest.

Another related problem in applying this theory as an approximation to real membranes with finite driving forces is that the theory itself does not provide a procedure for evaluating various rate constants, such as the k_s^m. For any finite concentration gradient, the rate constants k_s^m are of course not constants, but change with position, especially for the volatile species. (Normally, one resorts to evaluating constants at the arithmetic-mean interfacial volatile concentration, taking $A = 0$ there). It might be expected that this approach, which appears to be a perturbation from the equilibrium or unperturbed state, would be most correct in the limit of large Damköhler numbers, a condition in which the affinity approaches zero in a central core of the membrane which extends closer and closer to the interfacial boundaries, as indicated in Figure 7. Indeed, both Friedlander and Keller (1965) and Ulanowicz and Frazier (1968) in their linearized theory indicate that the limit of large Damköhler numbers corresponds to equilibrium throughout the film and that Olander's results are obtained as an asymptotic limit of this theory. However, a closer inspection reveals that in this limit, the facilitation factor given by the linearized theory does not in fact approach the facilitation predicted by the equilibrium theory, as is clearly demonstrated in calculations given by Smith et al. (1973). A similar comparison is made in Figure 9 for the CO_2 system. The discrepancies arise because various terms in the linearized equations are evaluated at the average boundary concentrations of permeant, whereas the correct equilibrium expression (for example, of Olander, 1960) uses the actual boundary concentrations to calculate the flux. That Olander's (1960) approach gives the correct equilibrium asymptote is demonstrated by the work of Goddard et al. (1970) where it emerges as the first term in a perturbation scheme.

Ulanowicz and Frazier (1968) earlier attempted to extend the concept of linearized kinetics to multiple reactions and multiple volatiles by exploiting the fact that the equations can readily be treated by matrix methods. An important aspect of their analysis is that for several independent simultaneous reactions, several characteristic values (eigenvalues) are generated, which can be individually related to the relaxation lengths of individual diffusion-reaction modes. This series of relaxation lengths provides some basis for judging which reactions are likely to be rate-determining for a given membrane thickness. At the present time, there appears to be no better general criterion for deciding which reactions are in the nonequilibrium regime, if several are possible.

In terms of the behavior of carrier-mediated transport systems, one drawback of their work is that, in the convective mass-transfer model chosen, the reaction rate integrated over the whole region or film, is not zero, a situation which does not correspond to global nonreactivity. Since the net reaction is nonzero, in general there must be a continual transport of the carrier species from the bulk to the interface. Therefore, the enhancement

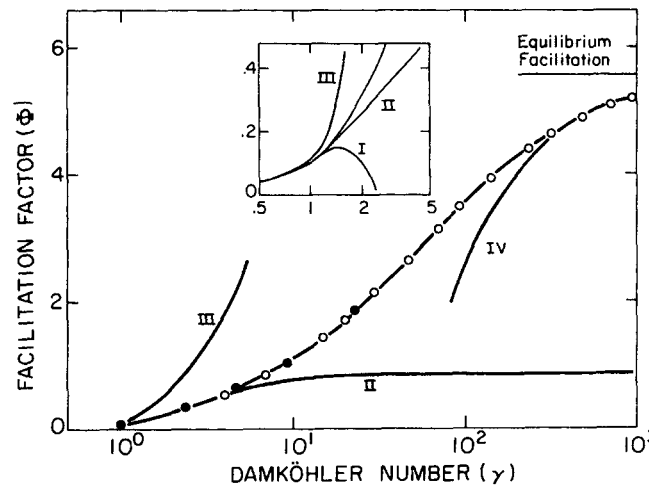


Fig. 9. Regions of validity of various analytical and numerical methods for estimating the facilitated flux of CO_2 through bicarbonate solutions. Conditions: CO_2 partial pressures, upstream—1 atm., downstream—0.01 atm; 1N $NaHCO_3$ in membrane; 25°C. $\alpha = k_{Hydration}L^2/D_{CO_2}$. Curve I. Near-diffusion model (Suchdeo and Schultz, 1971; Smith et al., 1973). II. Linearized model (Friedlander and Keller, 1965). III. Weak boundary layer model (Goddard et al., 1970). V. Strong boundary layer model (Kreuzer and Hoofd, 1972; Smith et al., 1973).

predicted by this model is not, strictly speaking, due to carrier effects alone, but falls into a more general class of reaction-augmented transport phenomena, as discussed, for example, by Dankwerts (1970). Thus, for example, in the discussion of co- or countertransport of CO_2 and O_2 through hemoglobin solutions by Ulanowicz and Frazier (1970), it is not possible at the outset to distinguish between competitive carrier effects alone, and effects due to variations in the transport of carriers from the bulk to the interfacial membrane-layer.

Linear reaction-rate expressions can also arise from a variety of factors which tend to produce nearly uniform concentrations of several species within the membranes and, thereby, lead to pseudo-linear kinetics. An example of this is illustrated in the inserts of Figure 10 where it is indicated that relatively large or small equilibrium constant for the chemical reaction can lead to carrier concentrations that are nearly constant throughout the film.

If the extent of reaction is uniformly small throughout the membrane region because of slow reaction rates relative to diffusion (small Damköhler numbers) a situation which has been referred to as the near-diffusion regime, concentrations of the nonvolatile species again tend to be constant.

Ward and Robb (1967) applied a type of linear-kinetic treatment to the transport of CO_2 through bicarbonate solutions, assuming the concentrations of OH^-, H^+, and HCO_3^- to be constants in the appropriate differential equation:

$$D_{CO_2}\frac{d^2C_{CO_2}}{dx^2} = r\,(CO_2, H^+, OH^-, HCO_3^-) \quad (4.7)$$

Otto and Quinn (1971) used this approach, previously outlined by Ward and Robb (1967), to calculate the flux of CO_2 through bicarbonate solutions. Otto and Quinn showed, however, that the proper constant average values for bicarbonate can be obtained by requiring that the flux of CO_2 into and out of the membrane be equal. In more general terms this is equivalent to the requirement that the global reaction rate be zero.

Ward (1970b) again used the linear-kinetic approximation to provide an estimate of fluxes of NO through $FeCl_2$ solutions. His suggested method of determining the proper average concentrations of Fe^{++} and $FeNO^{++}$ is to require that

$$\left.\frac{dC_{NO}}{dx}\right|_{x=0} = \left.\frac{dC_{NO}}{dx}\right|_{x=L} \quad (4.8)$$

or that

$$\left.\frac{d^2C_{NO}}{dx^2}\right|_{x=0} = -\left.\frac{d^2C_{NO}}{dx^2}\right|_{x=L} \quad (4.9)$$

The latter condition is admissible only because for linear kinetics the reaction-rate profiles are antisymmetrical about the center point of the membrane (as will be shown generally below). In general, the proper average nonvolatile concentrations for a single reaction should be obtained from the (linear) equilibrium condition

$$r\left\{\frac{\overline{C}+\underline{C}}{2}, C_2, C_3, \ldots\right\} = 0 \quad (4.10)$$

where C_2, C_3, ... are the desired constant average values of the nonvolatile species, and $\overline{C}$, $\underline{C}$ are the boundary values for the concentration C_1 of the volatile species. [While the type of approximation proposed by Ward (1970b) is not restricted to kinetics that are linear in permeant concentration the simplifications (4.9) and (4.10) will not hold in general].

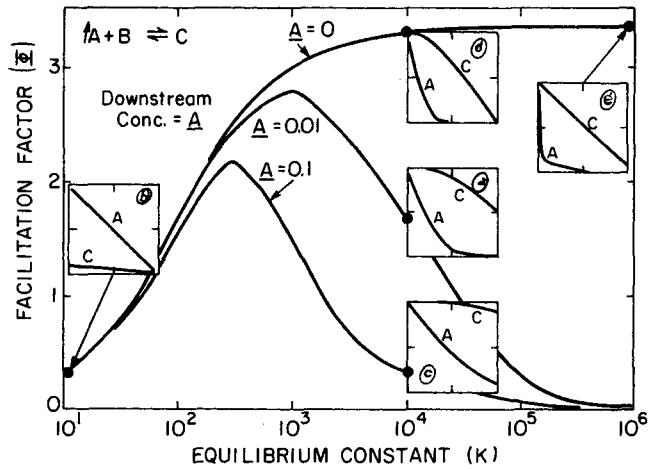


Fig. 10. Effect of equilibrium binding and downstream pressure concentration on carrier-mediated facilitation in equilibrium regime. Inserts show concentration profiles at points indicated.

Again, it should be pointed out that since linear rate laws are not generally obtained for reactions one does not know a priori when mathematical solutions based on them will be valid. However, one can expect such solutions to be valid for a particular system, over the entire near-diffusion to reaction-equilibrium regimes, if the concentration profiles calculated by the assumption of interfacial equilibrium (that is, the most nonlinear regime) are compatible with the assumed linear kinetics.

Asymptotic Solutions for Slow or Rapid Reactions

Asymptotic representations or perturbation series, based on small or large values of certain parameters, can often provide useful approximate solutions for carrier-mediated transport problems. Although such representations will usually be limited in their range of practical applicability, they can nevertheless provide some useful criteria for assessing the relative importance of different physical effects.

In diffusion-reaction problems, the most evident asymptotic regimes, at least those that can be treated with any degree of generality, correspond to the respective extremes of slow and rapid reaction. These well-known approximations in the literature on mass transfer with chemical reaction (compare Brotz, 1965) have been related to facilitated diffusion (Perelson and Katchalsky, 1972) and need no detailed introduction here. We merely recall that these limits correspond, respectively, to the large or small magnitudes for the ratios of certain characteristic times for diffusion (τ_D) to certain characteristic (or relaxation) times for reaction (τ_R); or alternatively, to the ratios of some characteristic diffusion-reaction length scales to the dimension of the system (Thiele modulus). In the case of a single homogeneous reaction, this can be formally stated in terms of a Damköhler number:

$$\gamma = \left(\frac{1}{\tau_R}\right)(\tau_D) = \left(\frac{r^*}{C^*}\right)\left(\frac{L^2}{D^*}\right) = \left(\frac{L}{\delta^*}\right)^2 \begin{cases} \nearrow 0, & \text{slow reaction} \\ \searrow \infty, & \text{fast reaction} \end{cases} \quad (4.11)$$

where r^*, C^*, D^*, L are, respectively, a typical reaction rate, concentration level, diffusivity, and system length. Then, $\delta^* \equiv \sqrt{D^*C^*/r^*}$ represents a characteristic reac-

tion-diffusion (reaction-layer) length scale.

For the case of a single chemical reaction, both these limits, and the associated perturbation analyses, have received considerable attention in the recent literature on carrier-mediated diffusion. In Part II we shall review the techniques involved and, at the same time, consider their most direct extensions to multiple reactions, in which all reaction rates are assumed to be inherently of the same order of largeness or smallness.

Slow Reactions

Several authors have presented solutions to the facilitated diffusion equations in the limits of low reaction rates or small Damköhler numbers (Ward, 1970; Otto and Quinn, 1971; Suchdeo and Schultz, 1971; Smith et al., 1973). The first two papers cited assume linear kinetics for slow reactions, while the latter papers develop a regular perturbation solution to the problem. As pointed out by Smith et al. (1973), some advantages of the perturbation method are that it provides a self-consistency check to determine the region of validity and that it represents a general approach applicable to arbitrarily complex kinetic schemes. Suchdeo and Schultz (1973) have developed the flux equation for a single reaction with generalized kinetics* and showed how experiments in the region of low Damköhler numbers can be used to obtain the nonreactive (Fickian) physical permeability of permeants which may react within the membrane. The results are of the form

$$N/N_0 = 1 + \frac{1}{12}\gamma Y_0 + (0)\gamma^2 \qquad (4.12)$$

where Y_0 is determined from the kinetics.

Fast Reactions

In the past, several authors have considered carrier-mediated diffusion-reaction equations of the form (Olander, 1960; Mochizuki and Forster, 1962)

$$D_s \frac{d^2C_s}{dx^2} = r_s(C_1, C_2, \ldots), \quad (\text{No sum};\ s = 1, \ldots, S) \qquad (4.13)$$

Snell and Stein (1966) recognized the difficulty in solving such equations and suggested, on a somewhat ad hoc basis, that approximate fluxes could be calculated by a reaction-equilibrium approximation, with some appropriate correction factor to be derived from the equilibrium flux itself.

Wyman (1966) was one of the first to exploit the fact that the simultaneous differential equations for the single reaction $A + B \underset{k_2}{\overset{k_1}{\rightleftarrows}} C$ could be reduced to a single differential equation in one concentration variable if $D_B = D_C$

$$D_A \frac{d^2C_A}{dx^2} = g(C_A, x) \qquad (4.14)$$

He also showed, by inspection of the magnitude of the terms on the left and right side of this equation, that there are conditions (for example, corresponding to the experiments of Wittenberg, 1966) where the left-hand side can become negligible with respect to terms on the right-hand side so that as a first approximation

$$0 = g(C_A, x) \qquad (4.15)$$

This insight, which is the basis of a perturbation approach to solving these second-order differential equations, was explicitly recognized and fully developed by Goddard et al. (1970). These authors developed a general series solution for the near-equilibrium regime based on asymptotic, singular-perturbation techniques. For the system at hand, the following equation for facilitation was obtained:

$$(1 + \Phi)/(1 + \Phi_{eq}) = 1 - [\bar{Z}^2\delta(\bar{Z}) + \underline{Z}^2\delta(\underline{Z})] + 0(\epsilon^2) \qquad (4.16)$$

where

$$\Phi_{eq} = \bar{Z}\underline{Z}; \quad \sigma^2 = \frac{KD_B}{D_A} C_{tot}\{B\}; \quad \gamma = \frac{k_1L^2}{D_A}$$

$$Z = \frac{\sigma}{1 + KC_A}; \quad \delta(Z) = \left\{ \frac{\sigma}{\gamma} \frac{Z}{1 + Z^2} \right\}^{1/2}$$

The derivation given by these authors shows precisely how the equilibrium solution represents the asymptotic limit of very fast reactions. An other merit of the singular-perturbation technique is that it can provide rigorously exact correction factors for the facilitated flux to account for departures from interfacial equilibrium. Unfortunately, the series solution previously derived by this technique converges well only for small facilitation factors.* However, such series do provide valid estimates of the departure from equilibrium and can therefore be used to determine the necessary conditions, for example, membrane thickness, diffusivities, and rate constants required to achieve a state of reaction equilibrium with respect to the interfacial concentrations.

Murray (1971a, 1971b) in the specialized context of the equation proposed by Wyman (1966) has also given several discussions of the reaction-equilibrium approximation and the associated singular-perturbation problem. He does not carry the analysis significantly beyond the zeroth-order or equilibrium solution to the equations.

Another type of boundary-layer analysis, developed by Kreuzer and Hoofd (1972) and Smith et al. (1973) leads to solutions which are valid over a wide range of Damköhler numbers.* An approximate solution related to Equation (4.16) takes the form

$$\frac{1 + \Phi}{1 + \Phi_{eq}} \doteq (1 + [\bar{Z}^2\delta(\bar{Z}) + \underline{Z}^2\delta(\underline{Z})])^{-1} \qquad (4.17)$$

To summarize, then at large (near-equilibrium) Damköhler numbers the flux of a single permeant through a membrane is given by equations of the form presented earlier:

$$N_A = (N_A)_{eq} = \frac{D_A}{L}(\bar{C}_A - \underline{C}_A) + \sum_{n=2}^{s} \frac{Z_A{}^n D_n}{L}(\bar{C}_n - \underline{C}_n) \qquad (4.18)$$

where the boundary concentrations of the nonvolatiles $\bar{C}_n, \underline{C}_n$ are assumed to be in equilibrium with the boundary concentration of the volatile species. This upper or equilibrium bound is shown in Figure 9 as the uppermost curve. [The range of validity of Equation (4.17) can be determined from the first correction term in the asymptotic expression given by Goddard et al., (1970)].

Criteria for Near-Equilibrium and Near-Diffusion Regimes

At present no one has devised a generally valid analytical technique for evaluating whether a particular

* A general result for multiple reactions is provided in Part II.

* For reasons indicated in the discussion of Part II.

TABLE 7. REGIMES FOR SOME REPORTED CARRIER-MEDIATED TRANSPORT SYSTEMS

System	Membrane thickness, microns	Facilitation factor	Regime	Investigator
$O_2 + Hb \rightleftarrows HbO_2$	25-300	0.5-10	NE-ND	Wittenberg (1966)
	160	0.6-6	NE	Kutchai and Staub (1969)
$NO + Fe^{++} \rightleftarrows NO\,Fe^{++}$	1,000		Intermediate	Ward (1970a)
$CO + Hb \rightleftarrows HbCO$	150	4-30	ND	Mochiziki and Forester (1962)
$O_2 + 2Co(Hist)_2 \rightleftarrows O_2[CO\,(Hist)]_2$	25-300	0.25-3.5	>ND	Bassett and Schultz (1971)
$CO_2 + CO_3^{=} \rightleftarrows H_2O\ 2HCO_3^{-}$	100-900	0-1	>ND	Otto and Quinn (1971)

carrier transport system, involving several reaction steps and more than one volatile component, falls into the near-equilibrium or near-diffusion limits of behavior. One approach is strictly correct only for systems with either linear or linearized kinetics (Friedlander and Keller, 1965; Ulanowicz and Frazier, 1968).

The technique of matched asymptotic expansions (Goddard et al., 1970) can provide generally valid criteria for establishing whether a system is in the equilibrium regime. But so far, simple, analytical expressions have only been obtained for single reactions with one or two volatile components.

Approximate Limits for Near-Equilibrium and Near-Diffusion Regimes

It seems natural to develop a criteria for these regimes in terms of observable fluxes, that is, the flux of the volatile species. In the near-equilibrium regime, it is the approach of the carrier-mediated component of the flux to its maximum that is more of interest than the total flux. This distinction is important when the enhancement due to facilitation is small compared to simple diffusive transport. For example, if under some boundary conditions the maximum facilitated component is only 10% of the simple diffusion flux, (that is, $\Phi_{eq} = 0.1$) and an arbitrary number, say 95% approach to total maximum flux, is used as a criteria of near-equilibrium then one would mistakenly assume the chemical reactions to be near-equilibrium when in actuality only half of the carrier-mediated component is being expressed. Therefore, we define nearness to equilibrium when ζ as calculated below is less than some arbitrary small value. What is desired is an approximate evaluation of Φ and Φ_{eq} for a given system so that one can judge the behavior of the system before undertaking a computer analysis. An example for an accurate approximate solution in this regime is given in Equation (4.16) for a single volatile species with equal diffusivities of the carrier species, that is, $\uparrow A + B \rightleftarrows C$ if we define ζ as the deviation of the facilitated component of the flux from the equilibrium maximum, then

$$\zeta_1 = 1 - \frac{N - N_0}{N_{eq} - N_0} = \frac{\overline{Z}^2\delta(\overline{Z}) + \underline{Z}^2\delta(\underline{Z})}{1 - 1/(\overline{Z}\underline{Z} + 1)} \tag{4.19}$$

Based on an earlier linearized analysis, Friedlander and Keller proposed that when the function $(1 - w)$ in Equation (4.6) approaches one, then the system is in the equilibrium regime. This criteria, also used by others (for example, Cussler, 1973) reduces to $\zeta_2 << 1$, where

$$\zeta_2 = \frac{2}{\lambda} \tag{4.20}$$

However, for large facilitation factors, this criteria is insufficient because of the large number which multiplies the function $(1 - w)$ in Equation (4.6), and a better general criterion is obtained from the complete equation in the limit

$$\zeta_2 = \frac{2}{\lambda(1 - \alpha_1\beta^1)} \tag{4.21}$$

which for the special case $A + B \rightleftharpoons C$, becomes

$$\zeta_2 = 2(Z^2 + 1)\,\delta(Z) \tag{4.22}$$

Comparing this equation for linear kinetics to that obtained above from asymptotic analyses [Equation (4.19)], we see the difference lies in the method for averaging the boundary concentration. In the linear analyses the terms involving concentrations are evaluated at some mean value of the surface concentrations, whereas in (4.19) these terms are evaluated separately at each surface of the membrane. The distinction is rather important, for according to the linearized equations (4.6) and (4.21), the equilibrium regime is approached monotonically as the average concentration of the volatile species is increased. However, if this is achieved by increasing the upstream concentration while maintaining the downstream concentration constant, Equation (4.19), indicates that the function ζ goes through a minimum. That the membrane may be driven from the equilibrium regime as the upstream concentration while maintaining the downstream illustrated by the numerical calculations of Kreuzer and Hoofd (1972) for the myoglobin-oxygen system.

A similar line of reasoning can provide some criteria for the near-diffusion regime. In this case we require that the ratio of the facilitated component to the maximum facilitation is less than some small number, that is,

$$\zeta' = \frac{\Phi}{\Phi_{eq}} = \frac{N - N_0}{N_{eq} - N_0} = 1 - \zeta \tag{4.23}$$

Again resorting the same example as above, $\uparrow A + B \rightleftarrows C$, we can derive two approximations for ζ' based on a linear or a perturbation approach.

In the linear analysis, the factor $\alpha_1\beta^1$ is less than one, and the function $(1 - w) \doteq 1/3\ (\lambda/2)^2$ so that the following approximation will hold

$$\zeta_1' = \frac{1}{3}\left(\frac{\lambda}{2}\right)^2 (1 - \alpha_1\beta^1) \tag{4.24}$$

which becomes

$$\zeta_1' \doteq \frac{\gamma}{12\sigma\,Z} \tag{4.25}$$

Using the perturbation analysis one finds (Suchdeo and Schultz, 1973; Smith et al., 1973)

$$\zeta_2' = \frac{\gamma}{12\sigma\left[\frac{\bar{Z}+\underline{Z}}{2}\right]} \qquad (4.26)$$

Again, the two approaches give slightly different equations related to the way the boundary concentrations are averaged. If for a given membrane, the value for ζ' is less than 0.1 say, then one might consider the systems to be in the near-diffusion regime.

Characterization of Experimental Data

Some of the available experimental data on carrier-mediated transport can be put into perspective, based on the regime of behavior according to the criteria outlined above, or as Smith et al. (1973) have expressed it, whether the membrane can be considered a thick or thin film. The designation ND or NE* are listed for a number of experimental studies in Table 7. It is apparent that the entire range of near-diffusion to near-equilibrium behavior for a given reaction system has been achieved in relatively few studies. This lack of comprehensive data is especially apparent for systems where the facilitation factor is greater than 10, a regime where prediction of fluxes by numerical or semi-analytical methods becomes very difficult.

Wittenberg (1966) carried out a comprehensive set of experiments with a variety of hemoglobins with a large range in kinetic properties. In so doing he obtained measurements which ranged from near-equilibrium to near-diffusion in behavior. He attributed the pattern observed in facilitation with the off kinetic constant of the hemoglobins. But as Equations (4.19) to (4.26) show, changes in the equilibrium constant are also important in determining the regime of membrane behavior.

All the experiments of Kutchai and Staub (1969) fall in the equilibrium regime and therefore are consistent with the analysis they present.

Ward's (1970) experiments with NO and Fe^{++} do not approach either limit, and therefore the failure of the limiting approximate analytical expressions to estimate the measured fluxes is not surprising. But a numerical method of solution was successfully fitted to the data.

Mochiziki and Forster (1962) measured the diffusion of CO through hemoglobin solutions, a reaction which has a high association constant. Their expectation to find very high facilitations was not valid because the thin membranes put the system into the near-diffusion regime (Suchdeo et al., 1973).

Although the experiments of Bassett and Schultz (1970) covered a wide range of parameter values, most of the fluxes were close to the near-diffusion regime.

In Otto and Quinn's (1971) work on carrier mediated transport of CO_2, the facilitation factors were low because the support membranes prevented the achievement of high concentration gradients across the active membrane region. In similar experiments by Suchdeo (1973), a much wider range of conditions was achieved because the membrane surface was directly exposed to the gas atmosphere.

Our ability to check the mathematical models for carrier-mediated transport may rest to some extent on the availability of accurate data for diffusion coefficients and kinetic constants and the regime in which the experiments are conducted. For example, in the near-diffusion regime, the calculated flux is not very sensitive to the diffusivity of carrier, whereas in the near-equilibrium regime the kinetic constants play less of a role (Suchdeo, 1973). Because of this lack of sensitivity, the possibility of determining kinetic constants for fast reactions by measurements of transport through carrier-mediated membranes suggested by Otto and Quinn (1971) does not seem promising.

Because of lack of information on kinetics, an assessment of the transport required for carrier transport in lipid bilayers must be very speculative. Blumenthal and Katchalsky (1969) have suggested that equilibrium is achieved in these very thin membranes because chemical reaction relaxation times were assumed to be very small; however, the effects of large concentration gradients and the association constant were not considered.

5. PROPERTIES OF THE REACTION-EQUILIBRIUM REGIME

Effect of Binding Constant

When the number of system invariants of the facilitated transport system is one or greater, that is, when there are some fixed species or carriers in the membrane, the affinity of the permeant for the carrier has an important influence on the behavior of the system. In the extremes of very high or very low affinity or binding constant between permeant and carriers, the facilitation effect is diminished or entirely eliminated.

In the realm of application to chemical separation processes, one would like to choose a carrier to maximize the facilitation factor for one substance in order to increase its rate of transport relative to other substances (Ward, 1967; Cussler, 1971). Presumably then the other substances would permeate the membrane by simple diffusion alone.

The effect can be visualized rather completely with reference to the bimolecular reaction (type 2 of Table 1)

$$\uparrow A + B \rightleftarrows C$$

If the diffusivities of carrier in forms B and C are equal, then from Equation (4.16) the facilitation factor is

$$\Phi_{eq} = \frac{C_{tot}\{B\}\, KD_B/D_A}{(1 + K\underline{C}_A)(1 + K\bar{C}_A)} \qquad (5.1)$$

One can see immediately that for fixed values of the boundary concentrations $\underline{C}_A$, $\bar{C}_A$, the facilitation factor goes through a maximum as the binding constant K goes from zero to infinity.

A graph of this equation is given in Figure 10 for some hypothetical constants. For a fixed value of the upstream volatile boundary concentration, the optimum moves to higher values of the binding constant K with decreasing concentration at the downstream boundary, according to the equation

$$K_{opt.} = \frac{1}{(\bar{C}_A\underline{C}_A)^{1/2}} \qquad (5.2)$$

As demonstrated by Olander (1960), one can get a good qualitative appreciation for the behavior of the system by considering the concentration profiles within the membrane. In the region of $K_{opt.}$, the concentration profiles in the membrane show a normal nonlinear character, Figure 10a.

At low values of the affinity constant, facilitation is more directly related to the upstream permeant concentration and is rather independent of the downstream concentration. A typical concentration profile in this regime is given in Figure 10b. Qualitatively, over a wide range of K values, the carrier is only slightly saturated in this

* ND and NE denote near diffusion and near equilibrium, respectively.

regime, as can be noted from the rather low concentration of carrier complex in the figure. In this regime the carrier-complex gradient and consequently the facilitated flux increases directly with the upstream permeant concentration.

On the other side of the graph at high affinity constants, facilitation decreases rather abruptly with increasing backpressure concentration of permeant. In this regime most of the carrier is fully complexed everywhere in the film as shown in Figure 10c. Again the carrier-complex gradient across the membrane is small, and little facilitation occurs.

For still higher values of the affinity constant K, and for back pressures of permeant approaching zero, this graph also shows the potential for highly singular behavior in facilitated transport. Here the reaction of permeant and complex begins to take on an irreversible character, as illustrated by the profiles in Figure 10d, and only at extremely low back pressures will facilitation be manifest.

It is also in this region that the homogeneous-reaction transport system can begin to approach the heterogeneous-reaction model of carrier transport usually invoked by membrane biologists (Wilbrandt and Rosenberg, 1961) and referred to earlier in Figure 1b. In this model, the permeant solubility in the membrane is considered to be negligibly small so that effectively the only species in the membrane are the various forms of the carrier B and C. Also, for this reason the concentration profiles of the carriers in the membrane phase are almost linear.

Most of the permeant A in the membrane will be in the form of the carrier-complex (AB) if the following holds $[D_B C_{AB}/HD_A C_A] >> 1$, or

$$\frac{D_B C_{tot}\{B\}}{D_A\left(\frac{1}{K} + HC_A\right)} >> 1 \qquad (5.3)$$

Although a variety of factors can combine to make this inequality valid and, therefore, to produce linear profiles of the carrier in the membrane, the system will approach the heterogeneous-reaction limit only if the value of H is small in relation to the quantities. This behavior, at low permeant concentrations and high affinities is illustrated in Figure 10e.

Competitive Interactions

As illustrated in Table 1, it can be expected that more than one volatile will be capable of interacting with nonvolatile, carrier species. These interactions will in general result in a different transport rate through the membrane than would be obtained if each volatile were present alone. The results of such interactions have been given various names in different contexts, for example, uphill transport (Wilbrandt and Rosenberg, 1961), counterflow and chemical pumping (Cussler, 1971).

These effects, which arise because of a competition between two or more species for the same transport path, can be illustrated by considering the bimolecular reactions

$$(1)\ \uparrow A + B \rightleftarrows AB \quad K_1$$

$$(2)\ \uparrow C + B \rightleftarrows CB \quad K_2$$

where, say, K_1 and K_2 are the equilibrium constants for the respective reactions. In order to obtain explicit algebraic solutions, we let $D_{AB} = D_B = D_{CB}$; then in the equilibrium regime for the flux of A we obtain from (4.16)

$$N_A = \frac{D_A}{L}(\bar{C}_A - \underline{C}_A) + \frac{D_B}{L}(\bar{C}_{AB} - \underline{C}_{AB}) \qquad (5.4)$$

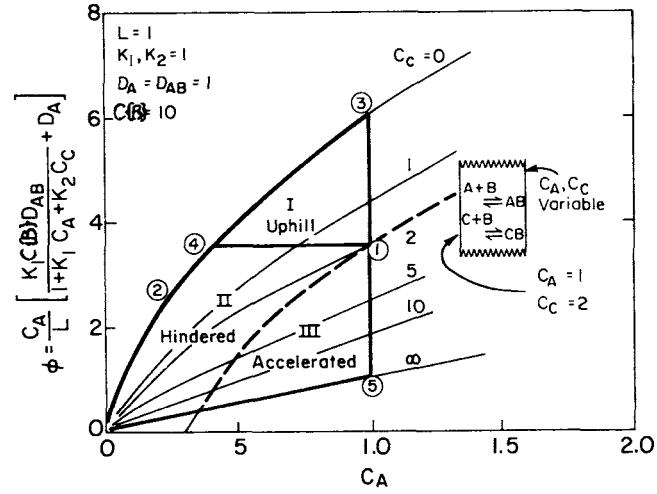


Fig. 11. Competitive carrier-mediated transport, two permeants completing for a single carrier. Regions showing uphill, hindered, and accelerated diffusion.

$$N_A = \frac{D_A}{L}(\bar{C}_A - \underline{C}_A) + \frac{D_B}{L} C_{tot}\{B\}$$

$$\left\{ \frac{\bar{C}_A}{\frac{1}{K_1} + \bar{C}_A + \frac{K_2}{K_1}\bar{C}_C} - \frac{\underline{C}_A}{\frac{1}{K_1} + \underline{C}_A + \frac{K_2}{K_1}\underline{C}_C} \right\} \qquad (5.5)$$

which can be written simply as

$$N_A = \bar{\phi}(\bar{C}_A, \bar{C}_C) - \underline{\phi}(\underline{C}_A, \underline{C}_C) \qquad (5.6)$$

where $\phi(C_A, C_C)$ is the function defined by

$$\phi = \frac{D_A C_A}{L} + \frac{D_B C_{tot}\{B\}}{\left(\frac{1}{K_1} + C_A + \frac{K_2}{K_1} C_C\right) L} \qquad (5.7)$$

The function ϕ can be plotted with respect to the concentration of A for various parametric values of C_C as shown in Figure 11. This graph is convenient for showing the various types of competitive phenomena, that is, uphill, hindered, and accelerated transport.

One can deduce the net flux of A through the membrane for any boundary concentrations of species A and C merely by locating the various boundary compositions on the graph and subtracting the corresponding values of the function ϕ. For example, as shown in the inset figure, if the upstream boundary is at $C_A = 1.0$ and $C_C = 2.0$ concentration units, this is found at point 1, and if the downstream boundary is at $C_A = 0.2$ and $C_C = 0.0$ units, this is located at point 2. The net flux of A will be $\phi_1 - \phi_2 = 3.5 - 2.0 = 1.5$ units; and since the difference is a positive number, the flux can be considered positive with respect to the gradient in A. That is, the transport of A is in the normal direction, from high to low concentrations of A.

All possible values of the function ϕ lie in the region bounded by the curves $C_C = 0$ and $C_C = \infty$; and, if the upstream concentration of A, $\bar{C}_A$, corresponds to the highest A concentration in the membrane, the region of possible boundary concentrations is further limited to values of $C_A \leq \bar{C}_A$. For example, referring to Figure 11, if $\bar{C}_A = 1.0$ the region of possible boundary concentration is shown as the shaded portions of the Figure bounded by the lines $C_C = 0$, $C_C = \infty$, $C_A = 1.0$.

The region can be further subdivided according to the flux of A in the presence of C, relative to the flux of A obtained in the absence of C. The latter may be obtained graphically from differences in ϕ along the curve $C_C = 0$.

The various types of behavior can be illustrated by choosing an upstream boundary condition, for example, $\overline{C}_A = 1$, $\overline{C}_C = 2.0$, and considering all possible downstream boundary values of A and C. If the downstream concentration lies in Zone I of the graph, then the transport of A may be called uphill transport (Willbrandt and Rosenberg, 1961) or chemical pumping (Cussler, 1971). That is, $\phi_1 - \phi_2$ will always be negative and species A will flow against its concentration gradient.

The maximum rate of uphill transport for given upstream concentration of A is found on the vertical line through C_A and is represented by the difference $\phi_1 - \phi_3$. In this limiting case, transport of A is obtained with no net driving force in free A at the boundaries. But, the difference in AB concentration across the membrane accounts for the net transport of A in this limit.

The uphill region is one situation where the concept of effective diffusivity (Keller and Friedlander, 1966; Verhoff and Sundaresan, 1973) becomes meaningless for if the flux equation is written in the form

$$D_{\text{eff}} = \frac{N_A L}{(\overline{C}_A - \underline{C}_A)} \tag{5.8}$$

then one must conclude that D_{eff} is negative and in the limit of the vertical line, negatively infinite, since $(\overline{C}_A - \underline{C}_A)$ vanishes while N_A is finite.

The lower bound to this region, given by the line 1 – 4 represents the case of a concentration difference in A, but no flux of A in either direction. The effective diffusivity under these conditions is zero, but actually this case represents, for uphill transport, the limit of the maximum concentration difference that can be sustained by a flux in C, for the assumed upstream concentrations of $\overline{C}_A = 1.0$, $\overline{C}_C = 2.0$. Relating this phenomena to a separation process the concentration of A at point 4 is the lowest value that can be increased to the concentration of A at 1 by a flux of C in the opposite direction. In this particular instance, a two-fold increase in A concentration can be achieved by counterflow of C.

In the next region, Zone II, the flux of A is less than would be obtained if no C were present at either surface of the membrane; hence, the phenomenon that has been called *hindered diffusion*. The lower bound of this zone is given by the fluxes that would be obtained in the absence of C. Graphically this bound is easily found by displacing the $C_C = 0$ curve vertically downwards until it goes through the reference point ($\overline{C}_A = 1.0$, $\overline{C}_C = 2.0$), shown as a dashed curve in the figure.

If the downstream concentrations of A and C fall into Zone III, the flux of A will be increased in comparison to what its value should be at the same boundary concentrations of A with no C in the system. The region may be termed one of accelerated transport. Again, the maximum increase in the flux of A is along the vertical line 1 – 5 where there is no gradient in A across the membrane. The lower line ($C_C = \infty$) represents the Fick's law flux of A through the membrane. As the diffusivity of A in the membrane is increased, the slope of this line is also increased and the curves move closer together. Because the Fick's flux represents a separate leakage pathway through the membrane, all the effects mentioned above tend to be lessened if the Fickian component of flux for species A through the membrane is increased.

Tracer Diffusion

The use of tracers for experimental measurement of transfer rates through membranes is a common procedure in the biological literature. The method allows for distinction between solutes of similar structure and properties. However, the interpretation of data on tracer fluxes is not as straightforward as that of total or absolute transport rates.

There are two types of tracer experiments that are often used. In one type, an absolute concentration difference of the permeant is established across a membrane, with the same specific activity of tracer maintained on both interfaces. In this case, the tracer flux merely serves to monitor the absolute permeant flux; that is, the permeant flux is given by the tracer flux divided by the specific activity of tracer.

Another experimental procedure used to determine membrane characteristics is to establish equal, total concentration of tracer-plus-unlabeled-permeant on the membrane boundaries, but with a gradient in specific activity of tracer. The tracer is then competitive with one of the permeants, and experiments of this type are not easy to interpret in terms of the physical and chemical properties of the membrane in the nonequilibrium regime. But, a general rigorous interpretation of this type of tracer experiment can be given if the membrane is in the reaction-equilibrium regime.

To show this, we consider an experiment where the external concentrations of permeants are maintained at the same level at both membrane boundaries. At equilibrium, the concentration of each species within the membrane will be the same at all positions in the membrane and in chemical equilibrium with the boundary concentrations. These constant concentrations are obtained by solving the equilibrium relations and system constraints simultaneously. For example, in the system

$$\text{A}\uparrow + \text{B} \rightleftarrows \text{C} \tag{5.9}$$

$$C_A = C_{A,\text{eq}} = \overline{C}_A = \underline{C}_A \tag{5.10}$$

$$C_{B,\text{eq}} = \frac{C_{tot}\{B\}}{1 + KC_A} \qquad C_{C,\text{eq}} = \frac{KC_A C_{tot}\{B\}}{1 + KC_A} \tag{5.11}$$

Now, conceptually speaking, some of the permeant is removed from the external medium and replaced with a solution of the same total composition, but with a tracer of different specific activity than at the other boundary. Since the total concentration of permeant has not changed, the concentration profile of the total of each species within the membrane will be unchanged. At each boundary the specific activity of every species in the membrane which interacts with the permeant will be the same specific activity as in the respective external phases, but there will be a variation in tracer concentration across the membrane.

In the steady state, tracer will diffuse across the membrane at a rate given by relations of the type given by Equation (4.16)

$$N_A^* = Z_A^s D_s(\overline{C}_s^* - \underline{C}_s^*) \tag{5.12}$$

where $\overline{C}_s^*$ and $\underline{C}_s^*$ are the concentrations of the tracer form of any species s at the boundaries.

If we let ρ designate the ratio of tracer to nontracer atoms in a species, then

$$\frac{\overline{C}_A^*}{\overline{C}_A} = \rho\frac{\overline{C}_s^*}{\overline{C}_s} \tag{5.13}$$

and

$$\frac{\bar{C}_A^*}{\bar{C}_{A'}} = \frac{\bar{C}_A^*}{\bar{C}_A + C_A^*} = \frac{1}{1 + \frac{1}{\bar{\rho}}} = \frac{\bar{C}_s^*}{\bar{C}_s^* + \bar{C}_s} = \frac{\bar{C}_s^*}{\bar{C}_{s'}} \tag{5.14}$$

where $\bar{C}_{s'} = \bar{C}_s + \bar{C}_s^*$ is the total concentration of both tracer and nontracer forms which is in local equilibrium with the other species in the system. Then

$$N_A^* = \sum_s Z_A^s D_s \left[\frac{\bar{\rho}}{1+\bar{\rho}} \bar{C}_{s,eq} - \frac{\underline{\rho}}{1+\underline{\rho}} \underline{C}_{s,eq} \right] \tag{5.15}$$

and, since

$$\bar{C}_{s,eq} = \underline{C}_{s,eq} = \bar{C}_s \tag{5.16}$$

$$N_A^* = \sum_s Z_A^s D_s \bar{C}_{s,eq} \left[\frac{\bar{\rho}}{1+\bar{\rho}} - \frac{\underline{\rho}}{1+\underline{\rho}} \right] \tag{5.17}$$

This relation is valid for any specific activity, ρ, of tracer at the boundaries. In usual the case where $\bar{\rho}, \underline{\rho} << 1$, then

$$\frac{N_A^*}{(\bar{\rho} - \underline{\rho})} = \sum_s Z_A^s D_{(s)} C_s' \tag{5.18}$$

For the example given above, we find therefore that

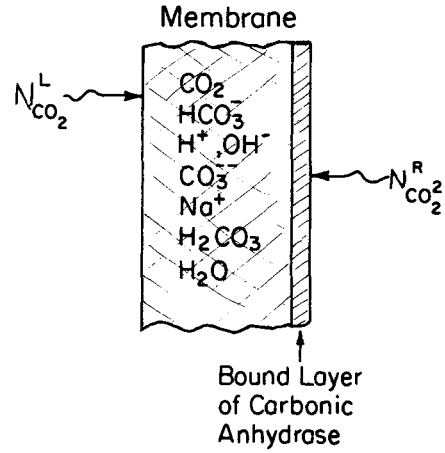
$$\frac{N_A^*}{\bar{\rho} - \underline{\rho}} = D_A C_A' + D_C C_C' \equiv \frac{D_A}{L} \bar{C}_{A'} + \frac{D_C K \bar{C}_A' C'_{tot}\{B\}}{L(1 + K\bar{C}_A')} \tag{5.19}$$

In other words, the tracer flux, divided by the difference in specific activity in tracer across the membrane, is equal to the absolute flux obtained in a nontracer study where the downstream concentration of permeant is maintained at zero.

In order to interpret tracer fluxes by equations of the type (5.18), the experiments must be in the near-equilibrium regime; these requirements were not met in the experiments of Hemingsen (1962). Hence, the experimental tracer fluxes obtained by him could be directly related to the O_2 saturation curves of hemoglobin and myoglobin, which appear as the ratio $\left(\frac{C_A'}{1 + KC_A'} \right)$ in the second term of Equation (5.19).

However, the tracer fluxes given by Enns (1967) for CO_2 transport through bicarbonate solution cannot be related to the chemical reactions by Equation (5.18) because the thickness of the film used by Enns; about 150 microns was too small for chemical equilibrium to be established everywhere within the membrane. This points up the fact that the exact interpretation of tracer fluxes, when reactions are not at equilibrium, is a problem that has yet to be systematically worked out.

If the tracer experiment is conducted with different total concentrations of permeant imposed at the membrane boundaries, then the fluxes will not generally follow Equation (5.17) since condition (5.16) will not be satisfied. Rather, one may encounter such effects as described in the section on competitive interactions, where component A can be regarded as a tracer of C if $K_1 = K_2$ in Equation (5.5). That is, Equation (5.5) becomes



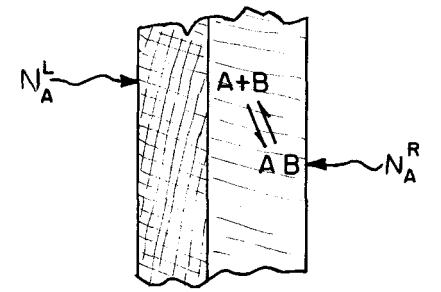


Fig. 12. Membrane structures which produce asymmetric transport. (a) Reaction catalysis at one surface; (b) Composite membrane of Fickian layer and carrier-mediated layer.

$$N_A^* = \frac{D_A}{L} (\bar{C}_A^* - \underline{C}_A^*) + \frac{D_{AB} C_{tot}\{B\}}{L} \left\{ \frac{\bar{C}_A^*}{\frac{1}{K_1} + \bar{C}_A^* + \bar{C}_A} - \frac{\underline{C}_A^*}{\frac{1}{K_1} + \underline{C}_A^* + \underline{C}_A} \right\} \tag{5.20}$$

One may expect to find extremely anomalous effects, such as a net tracer flux with no gradient in tracer concentration, for example, if $\bar{C}_A^* = \underline{C}_A^* = C_A^*$

$$N_A^* = \frac{D_{AB} C_{tot}\{B\}}{L} C_A^* \left(\frac{1}{1/K_1 + C_A^* + \bar{C}_A} - \frac{1}{1/K_1 + C_A^* + \underline{C}_A} \right) \tag{5.21}$$

Or conditions can be found where there will be no net tracer flux even if there is a gradient in tracer concentration, that is, let $\bar{C}_A^* \neq \underline{C}_A^*$ and $N_A^* = 0$ in Equation (5.20).

Asymmetric Transport

Asymmetric transport may be said to occur if the absolute magnitude of the flux of a volatile species changes upon reversing the boundary concentrations of the external medium.

At least three conditions that can result in asymmetric behavior which can be attributed to kinetic, structural, or competitive effects have been discerned to date.

Kinetical asymmetry, which has been postulated and

discussed in detail by Wilbrandt and Rosenberg (1961) is primarily a nonequilibrium phenomena caused by nonhomogeneities resulting in a difference in reaction kinetic constants at the opposite surfaces of a membrane. Such a variation in intrinsic reaction rates across the membrane can be produced by a variety of causes, one of which is a difference in enzymatic activity on the surfaces of the membrane, Figure 12. For example, carbonic anhydrase bound to one surface of a membrane can result in an asymmetrical CO_2 flux across the membrane (Selegny et al., 1971). However, if the reaction rates at the membrane boundaries are sufficiently fast to put the system into the equilibrium regime, then the asymmetric character disappears.

However, it should be recognized that many of the enzyme-bound asymmetric membranes are in fact reactors and therefore do not fit into the set of global-nonreactive transport barriers that are being considered here as facilitated transport systems.

Asymmetric transport due to structural properties has been discussed previously (Schultz, 1971, 1973; Naftilin, 1971; Wilbrandt, 1973). As applied to facilitated transport systems, asymmetry is produced if the membrane is composed of a series of barriers due to associated boundary layers with unequal permeabilities for the volatile species—Figure 12b. In this type of situation, the absolute values of the volatile concentrations at the interfaces of the facilitated layer change when the concentrations external to the membrane complex are interchanged. Since in general the flux across a carrier-mediated membrane is not linear with concentration difference, the overall effect is that the absolute magnitude of the flux changes when the concentrations are reversed with respect to the membrane.

A third type of asymmetric transport can arise, although not strictly in accordance with the proposition that all external species be changed. If a third component interacts with the carrier to change its availability to the volatile species, as C in Figure 11, then a reversal of concentration of the volatile species A will result in the change in the magnitude of the flux of A, if the concentration of the species C is unchanged. This apparent asymmetry may show up in bimembrane studies with whole cells, where the interior may not be accessible and where unknown competitive species are not under experimental control.

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NOTATION

A = affinity
A_i^s = coefficients of transformation
C = concentration, mole/cm^3
$\mathbf{C}(C_s)$ = vector of concentrations (and components), mole/cm^3
D = diffusivity, cm^2/s
D_{eff} = effective or apparent diffusivity, cm^2/s
E^s, E_i^s = reaction invariant components
$\mathcal{E}$ = chemical species
F = number of free or permeant species
F' = number of nonvolatile or trapped species
H = Henry's Law constant, mole/cm^3-atm
I^s, I_i^s = composition invariants
I' = number of fixed stoichiometric invariants
$\mathcal{I}_i$ = reaction composition invariant
J_s = diffusion flux of a chemical species, mole/cm^2-s
k = reaction rate constant
$\mathbf{K}$, (k_s^m) = matrix of kinetic constants (and components)
K = equilibrium constant
L_1 = membrane thickness, cm
n = surface normal
$\vec{N}$ = flux vector, mole/cm^2-s
$N\{\ \}$ = total molar flux or transmembrane flux of a permeant mole/cm^2-s
$n\{\ \}$ = amount {species, or entity}, mole
$\mathcal{N}$ = linear space of nonvolatile species
$p\{\ \}$ = local production rate {species}, mole/s
$q\{\ \}$ = transport {species} across surface, mole/s
RT = gas constant and absolute temperature
R = number of independent chemical reactions
R' = number of reaction invariants or radicals
r_s = rate of reaction of species s, mole/cm^3-s
$r(r_s)$ = vector of species reaction rates (and components)
S = number of chemical species
$\mathcal{S}$ = linear space of chemical species
t = time, s
$\mathcal{U}$ = linear space of volatile species
V = volume, cm^3
$w(\lambda)$ = function defined by Equation (4.6)
x = distance, cm
Z = parameters defined in Equation (3.43)
Z_s^m = transport numbers

Greek Letters

α_s = stoichiometric coefficients
β^s = Damköhler number for species s, Equation (4.6)
γ = a Damköhler number defined by Equation (4.11)
δ^* = reaction-layer dimension
$\delta(Z)$ = reaction-layer dimension defined by Equation (4.16)
ζ = deviation from equilibrium facilitated flux, Equation (4.19)
ζ' = deviation from diffusion regime, Equation (4.23)
λ = dimensionless inverse reaction layer thickness, Equation (4.6)
ξ_i = composition coordinate
ρ = specific radioactivity of tracer
ϕ = carrier saturation function, Equation (5.7)
Φ = facilitation factor, Equation (2.5)
σ = parameter, Equation (4.16)
τ_R, τ_D = reaction and diffusion time constants
ω_i = reaction rate coordinate
ν_i = flux coordinate

Superscripts

n = nonvolatile species
s = species
v = volatile species
* = typical or equilibrium value; also can indicate tracer

Subscripts

A, B, C = value for species A, B, C ...
eq = value evaluated at reaction equilibrium
0 = value in the absence of chemical reactions
n = nonvolatile species
s = chemical species
v = volatile species
tot = initial average carrier concentration added to membrane

Overbar indicates value evaluated at left boundary and underbar indicates value evaluated at right boundary.

Arrows denote physical space vectors and lowered dots their scalar products. Bold face refers to chemical-species space vectors and matrices, and centered dot their matrix products.

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THE AUTHORS

This joint effort, which started out as a rather modest, straightforward review, eventually grew into something of a Hydra. We hope that through our diverse interests our final product was enriched in addition to being expanded.

J. S. Schultz started his career in chemical engineering at Columbia where his interests in biology were kindled. It was while obtaining a doctorate in biochemistry at the University of Wisconsin that he learned of the marvels of the biological membrane. And while employed at Lederle Laboratories in antibiotics research, he had the opportunity to mull over some ideas on model systems that could be used to investigate membrane phenomena. At the University of Michigan, he has made the study of carrier-mediated membrane diffusion and hindered diffusion in microporous membranes his major research emphasis.

J. D. Goddard entered the University of Illinois as a Student of art, but he found his element in chemical engineering. His career picked up momentum as a graduate student at Berkeley where he was enveloped into the fold of fluid mechanics. After

a stint at the Petroleum Institute in Paris, he came to the University of Michigan, where his main interest is the rheology of viscoilastic fluids. After having been seduced into the area of membrane transport he has found it an ever-deepening and widening area of activity.

S. R. Suchdeo, has been an essential part of our effort. He came to Michigan via Bombay University and a M.S. from the University of Mississippi. As he has been involved in both the experimental and theoretical research he has provided some of the insights which ehlped our effort to obtain a broader perspective on the problem. He is now employed at Air Products and Chemicals, Allentown, Pennsylvania.

Scale-Up of Agitated Vessels Gas-Liquid Mass Transfer

Procedures are developed for predicting liquid film controlled mass transfer in gas sparged contactors with and without mechanical agitation. Mass transfer is shown to depend on mean bubble size. Bubble shape, motion, and interface fluctuations are all properties that are associated with bubble size, which, in turn, can be determined from the physical characteristics of the contacting system.

Experimental measurements were made on CO_2 stripping from aqueous solution with air in 0.00252, 0.0252, and 0.252 m^3 tanks. The vessels were geometrically similar, fully baffled, and equipped with four flat-blade impellers and spargers. These measurements are used to evaluate earlier correlations and to develop improved scale-up procedures.

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SCOPE

One of the most frequent problems in chemical reactor design involves scale-up in which mass transfer has an important influence on overall rate. Reactions with interphase mass transfer are often carried out in agitated vessels. The selection of design and operating parameters necessary for reliable scale-up in units of this type is of particular importance.

Reference is made in this study to one important rate process—that of liquid film controlled mass transfer. This can be important in liquid-solid, liquid-liquid, and gas-liquid contacting. Among these systems, analysis of performance is simplest for liquid-solid mass transfer because the size of the particulate phase can be independently controlled. Analysis with gas-liquid contacting is the most complicated. This is true because certain properties of the dispersed phase that affect mass transfer—bubble size, shape, motion and the frequency and extent of interface fluctuations—are determined by the contacting system itself.

The first consideration in agitated vessel scale-up is maintenance of geometric similarity. This requires that all corresponding linear dimensions in two vessels of different size be in the same ratio. Beyond this, for gas-liquid systems, there is the question of selecting an appropriate sparger design. Further, if mechanical agitation is imposed, a choice must be made of the proper impeller speed.

This study was undertaken to relate liquid film controlled mass transfer to the established physical characteristics of sparged and mechanically agitated systems. The ultimate objective through this analysis is to identify the appropriate scale-up requirements.

CONCLUSIONS AND SIGNIFICANCE

It is important in the scale-up and design of gas-liquid reaction equipment to be able to predict mass transfer rates reliably. Procedures have been developed for calculating liquid film controlled mass transfer in gas sparged systems both with and without mechanical agitation. These procedures are based on experimental measurements of the stripping of CO_2 from aqueous solution with air.

Liquid film controlled mass transfer in gas-liquid contacting is shown to depend on mean bubble size. Bubble shape, motion, and any tendency for the interface to ripple, fluctuate, or otherwise deform might also be expected to influence mass transfer. These effects are all related to bubble size, however, which in turn is determined by the physical characteristics of the contacting system.

After leaving the sparger in a gas-liquid contactor, bubbles either break up or coalesce as they move upward through the bulk liquid, shifting toward an equilibrium size limit. Mean bubble size can be approximated by taking the geometric mean between the bubble size produced at the sparger and the equilibrium bubble size.

Most commercial scale spargers operate in the turbulent chain bubbling flow regime. Within this flow regime, bubble size depends on the volumetric gas flow rate through each sparger opening and is independent of hole dimensions. Equilibrium bubble size is primarily dependent on the energy content of the liquid phase.

When mechanical agitation is imposed in a sparged system, it augments the energy content of the liquid phase and bubble size is reduced. With this situation, the separate power input contributions of gas sparging and mechanical agitation must be combined in an effective, overall value for use in prediction of bubble size.

Mechanically agitated vessels under 0.25 m^3 in size require correction for surface aeration. A correction term is derived based on impeller tip speed, superficial sparged gas velocity, and clear liquid depth above the impeller. This can be applied to the sparged gas rate as a multiplying factor to obtain total gas input inclusive of both sparging and surface entrainment.

Geometric similarity and equal effective power input, combining sparged gas and mechanical energy sources, are the basic requirements for duplicating liquid film controlled mass transfer in scale-up. This would be true