

Permeability and the Time Lag for Downstream Absorptive Permeation with Concomitant Reaction across a Series–Parallel Path studied by the Matrix Method

Way-Gia Shi and Jenn-Shing Chen*

Department of Applied Chemistry, National Chiao-Tung University, Hsin-Chu, Taiwan 30050, Republic of China

Based on Siegel's theory, the permeability (P) and the downstream time lag (t_L) for absorptive unidirectional permeation, accompanying a first-order reaction, across a membrane composed of two parallel laminae in series with another lamina, have been calculated from the transmission matrix of the whole membrane. This matrix can be constructed from the transmission matrix of each component lamina. The transmission matrix of the whole membrane is first calculated from the matrices of the component laminae in the Laplace domain. P and t_L are then derived from the first row and second column of the transmission matrix of the whole membrane according to Siegel's theory. Thus, P and t_L can be represented in terms of the elements of the transmission matrix, and hence the diffusion parameters, of each component lamina. The directional symmetry of t_L is also proven, based on the unity value of the determinant of the transmission matrix. The advantage of the matrix method is also discussed.

A typical experiment for permeation across membranes involves maintaining the penetrant activity at constant levels a_u and a_d , at upstream and downstream faces, respectively. It is usually carried out under conditions such that $a_u > a_d = 0$ and the initial concentration of the penetrant inside the membrane is zero.^{1,2} It is then followed by measuring the total amount of penetrant released into the downstream compartment, $Q(t)$, as function of time, t . The steady-state permeability, P , and absorptive downstream lag time, t_L , are obtained, from the slope and the intercept (with the t -axis) of the linear asymptote of the curve plotted for $Q(t)$ vs. t .^{3–5} In some practical applications, the parameters P and t_L are adequate to predict $Q(t)$ in the long-time limit^{3–5} by

$$Q(t) = P(t - t_L) \quad (1)$$

Several attempts have been made to derive P and t_L for various diffusion systems. Earlier, Frisch used a very elegant method of repeated integration to formulate P and t_L in the system where the diffusivity, D , is concentration dependent.⁶ Similarly, diffusion across a heterogeneous membrane in which both D and the partition coefficient, K , are position-dependent^{7–10} was studied. The method of integration was also adapted by Chen and Rosenberger for permeation, without accompanying reaction, across laminates with or without periodic structure,¹¹ and a membrane composed of two parallel laminae in series with another lamina.¹²

Of increasing importance are membranes with imbedded reactive catalysts or enzymes to enhance the productivity of chemical or biological processes,¹³ to enhance the performance of biosensors¹⁴ or to simulate active transport using an uneven distribution of enzyme activities.¹⁵ However, the method of repeated integration fails to calculate P and t_L in the case of permeation with concomitant reaction. Therefore, we were forced to resort to other methods such as Laplace transform and change-of-variable.¹⁶ Leypoldt and Gough also chose the method of finite Fourier transform in conjunction with residual theorem in complex variable theory to deal with a reaction–diffusion problem.¹⁷ Siegel has given a detailed account of the matrix approach for the analysis of the diffusion problem including the formulation of permeability, time lags, time leads and mean first-passage times in terms of the elements of a transmission matrix.¹⁸ Earlier reports using a matrix approach to membrane diffusion problems are also in the literature.^{4,19,20}

The aim of this paper is to formulate, using the matrix approach, P and t_L for permeation, concomitant with a first-order reaction, across a membrane consisting of two parallel laminae in series with another lamina.

Transmission Matrix, Admittance Matrix of a Single Membrane

Mathematical analysis in the Laplace domain for a unidirectional absorptive permeation accompanying a first-order reaction across a membrane leads to a linear transport equation^{18,21}

$$\begin{bmatrix} \hat{a}_d(s) \\ \hat{J}_d(s) \end{bmatrix} = T(s) \begin{bmatrix} \hat{a}_u(s) \\ \hat{J}_u(s) \end{bmatrix} = \begin{bmatrix} T_{11}(s) & T_{12}(s) \\ T_{21}(s) & T_{22}(s) \end{bmatrix} \begin{bmatrix} \hat{a}_u(s) \\ \hat{J}_u(s) \end{bmatrix} \quad (2)$$

Here, s is the Laplace variable, $\hat{a}_u(s)$ and $\hat{J}_u(s)$ are the Laplace transforms of the activity $a_u(t)$ ($= \rho_u(t)/K_u$), and diffusion flux $J_u(t)$ into the membrane at the upstream face, $\rho_u(t)$ and K_u are the penetrant concentration and the partition coefficient at the upstream face. The counterparts at the downstream face are $\hat{a}_d(s)$, $\hat{J}_d(s)$, $\rho_d(t)$ and K_d . It should be remarked that while eqn. (2) is valid when D , K , and the first-order rate constant, k , are position-dependent, it is limited to concentration-independent diffusion.

Under some circumstances it is advantageous to present the transport equation in terms of the admittance matrix, $Y(s)$:²⁰

$$\begin{bmatrix} \hat{J}_u(s) \\ \hat{J}_d(s) \end{bmatrix} = Y(s) \begin{bmatrix} \hat{a}_u(s) \\ \hat{a}_d(s) \end{bmatrix} = \begin{bmatrix} Y_{11}(s) & Y_{12}(s) \\ Y_{21}(s) & Y_{22}(s) \end{bmatrix} \begin{bmatrix} \hat{a}_u(s) \\ \hat{a}_d(s) \end{bmatrix} \quad (3)$$

$Y(s)$ and $T(s)$ are interconvertible *via*

$$Y(s) = \begin{bmatrix} -\frac{T_{11}(s)}{T_{12}(s)} & \frac{1}{T_{12}(s)} \\ -\frac{1}{T_{12}(s)} & \frac{T_{22}(s)}{T_{12}(s)} \end{bmatrix} \quad (4)$$

$$T(s) = \begin{bmatrix} -\frac{Y_{11}(s)}{Y_{12}(s)} & \frac{1}{Y_{12}(s)} \\ \frac{Y_{12}(s)Y_{21}(s) - Y_{11}(s)Y_{22}(s)}{Y_{12}(s)} & \frac{Y_{22}(s)}{Y_{12}(s)} \end{bmatrix} \quad (5)$$

For a simple, homogeneous lamina with thickness, h , and constant D , K , and k , $T(s)$ acquires the form²¹

$$T(s) = \begin{bmatrix} \cosh(qh) & -\frac{\sinh(qh)}{DqK} \\ -DqK \sinh(qh) & \cosh(qh) \end{bmatrix} \quad (6)$$

with $q = [(k + s)/D]^{1/2}$.

P and t_L for Reaction–Diffusion across Two Parallel Laminae in series with another Lamina

In various situations of practical interest, diffusion may proceed in two or more parallel and/or series regions. For example, in the cornea of the eye, diffusion in the outer layer or epithelium occurs in numerous parallel porous, aqueous ducts.²² A similar situation arises in diffusion through the skin.²³ Hence, steady permeability parallel-diffusion models for drug delivery into the skin and cornea have been proposed.^{22,23} Extension of this model to other, more complicated, systems is also found. For example, it was used by Jefferson *et al.* to treat diffusion through a two-phase composite in which the discontinuous phase of uniform spheres were situated on a continuous phase of regular lattice,^{5,24} and by Tsao to treat composites in which the discontinuous phase consists of randomly distributed particles of irregular size and shape.^{5,25}

We will consider the simplest prototype of the series–parallel configuration: a membrane composed of two parallel laminae A and B in series with lamina C. Each lamina has its characteristic diffusivity, $D_i(x)$, partition coefficient $K_i(x)$, rate constant $k_i(x)$, thickness h_i and cross-section σ_i ($i = A, B, C$). Without loss of generality, we specify that $\sigma_A + \sigma_B = \sigma_C = 1$, $h_A = h_B = h_{AB}$. The transmission matrix for this whole membrane is given by

$$T(s) = T^C(s)T^{AB}(s) \quad (7)$$

where $T^C(s)$ is in the transmission matrix of lamina C, $T^{AB}(s)$ is that of the parallel subregion AB. The $T^{AB}(s)$ is to be calculated from $Y^{AB}(s)$,²⁰

$$Y^{AB}(s) = \sigma_A Y^A(s) + \sigma_B Y^B(s) \quad (8)$$

followed by a transformation of eqn. (5). Thus the elements of $T^{AB}(s)$ are represented by the elements of $Y^A(s)$ or $Y^B(s)$, which can be further replaced by the elements of $T^A(s)$ and $T^B(s)$ by use of eqn. (4). We finally arrive at

$$T^{AB}(s) = \begin{bmatrix} T_{11}^{AB}(s) & T_{12}^{AB}(s) \\ T_{21}^{AB}(s) & T_{22}^{AB}(s) \end{bmatrix} \quad (9)$$

with

$$T_{11}^{AB} = \frac{\sigma_A \frac{T_{11}^A}{T_{12}^A} + \sigma_B \frac{T_{11}^B}{T_{12}^B}}{\sigma_A \frac{T_{22}^A}{T_{12}^A} + \sigma_B \frac{T_{22}^B}{T_{12}^B}} \quad (9a)$$

$$T_{12}^{AB} = \frac{1}{\sigma_A \frac{1}{T_{12}^A} + \sigma_B \frac{1}{T_{12}^B}} \quad (9b)$$

$$T_{21}^{AB} = -\left(\sigma_A \frac{1}{T_{12}^A} + \sigma_B \frac{1}{T_{12}^B}\right) + \frac{\left(\sigma_A \frac{T_{11}^A}{T_{12}^A} + \sigma_B \frac{T_{11}^B}{T_{12}^B}\right)\left(\sigma_A \frac{T_{22}^A}{T_{12}^A} + \sigma_B \frac{T_{22}^B}{T_{12}^B}\right)}{\sigma_A \frac{1}{T_{12}^A} + \sigma_B \frac{1}{T_{12}^B}} \quad (9c)$$

$$T_{22}^{AB} = \frac{\sigma_A \frac{T_{22}^A}{T_{12}^A} + \sigma_B \frac{T_{22}^B}{T_{12}^B}}{\sigma_A \frac{1}{T_{12}^A} + \sigma_B \frac{1}{T_{12}^B}} \quad (9d)$$

Hereinafter, if the dependency of the matrix elements on the Laplace variable s , is self-explanatory, it is not explicitly expressed for notational simplicity.

According to Siegel, P and t_L can be expressed, in terms of the limits of $T_{12}(s)$ and its first derivative as $s \rightarrow 0$.¹⁸ Thus, to calculate P and t_L , only the element $T_{12}(s)$ of $T(s)$ in eqn. (7) is used which reads

$$T_{12}(s) = T_{11}^C(s)T_{12}^{AB}(s) + T_{12}^C(s)T_{22}^{AB}(s) \quad (10)$$

P and t_L for reaction–diffusion across the series–parallel path are then calculated to be

$$\frac{1}{P} = \lim_{s \rightarrow 0} -T_{12}(s) = \lim_{s \rightarrow 0} -[T_{11}^C(s)T_{12}^{AB}(s) + T_{12}^C(s)T_{22}^{AB}(s)] \\ = \frac{(T_{11}^C)_{s=0}}{P^{AB}} + \frac{(T_{22}^{AB})_{s=0}}{P^C} \quad (11)$$

$$t_L = \lim_{s \rightarrow 0} \frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \\ = \lim_{s \rightarrow 0} \frac{\left(\frac{d/ds T_{11}^C}{T_{11}^C}\right)T_{11}^C T_{12}^{AB} + \left(\frac{d/ds T_{12}^{AB}}{T_{12}^{AB}}\right)T_{11}^C T_{12}^{AB} \\ + \left(\frac{d/ds T_{12}^C}{T_{12}^C}\right)T_{12}^C T_{22}^{AB} + \left(\frac{d/ds T_{22}^{AB}}{T_{22}^{AB}}\right)T_{12}^C T_{22}^{AB}}{T_{11}^C T_{12}^{AB} + T_{12}^C T_{22}^{AB}} \\ = \left(\frac{(T_{22}^{AB})_{s=0}}{P^C} + \frac{(T_{11}^C)_{s=0}}{P^{AB}}\right)^{-1} \\ \times \left(\frac{(T_{22}^{AB})_{s=0}}{P^C} (t_L^+ + \bar{t}_+^{AB}) + \frac{(T_{11}^C)_{s=0}}{P^{AB}} (\bar{t}_-^C + t_L^{AB})\right) \quad (12)$$

where the definitions of P and t_L are used.¹⁸ The negative sign is added in eqn. (11) since we define the direction of downstream flux to be from the membrane to the downstream compartment, while Siegel defined it to be in the reverse sense. \bar{t}_+^{AB} is the forward mean first-passage time of the parallel subregion AB, and \bar{t}_-^C the backward mean first-passage time of the lamina C.¹⁸ They are defined by

$$\bar{t}_-^C = \lim_{s \rightarrow 0} \frac{\frac{d}{ds} T_{11}^C}{T_{11}^C} \quad (13)$$

$$\bar{t}_+^{AB} = \lim_{s \rightarrow 0} \frac{\frac{d}{ds} T_{22}^{AB}}{T_{22}^{AB}} \quad (14)$$

Various quantities related to the AB subregion in eqn. (11) and (12) can be evaluated in terms of the diffusion parameters of the component lamina A or B. Namely

$$\frac{1}{P^{AB}} = \frac{1}{\sigma_A P^A + \sigma_B P^B} \quad (15)$$

$$(T_{22}^{AB})_{s=0} = \frac{\sigma_A P^A (T_{22}^A)_{s=0} + \sigma_B P^B (T_{22}^B)_{s=0}}{\sigma_A P^A + \sigma_B P^B} \quad (16)$$

$$t_L^{AB} = \frac{\sigma_A P^A t_L^A + \sigma_B P^B t_L^B}{\sigma_A P^A + \sigma_B P^B} \quad (17)$$

$$\bar{t}_+^{AB} = \frac{\sigma_A P^A (T_{22}^A)_{s=0} (\bar{t}_+^A - t_L^A) + \sigma_B P^B (T_{22}^B)_{s=0} (\bar{t}_+^B - t_L^B)}{\sigma_A P^A (T_{22}^A)_{s=0} + \sigma_B P^B (T_{22}^B)_{s=0}} + t_L^{AB} \quad (18)$$

Thus, it is seen that P in eqn. (11) and t_L in eqn. (12) for the whole membrane can be expressed in terms of various diffusion parameters of its component lamina.

Till now the derivation is sufficiently general to be valid even when all laminae are heterogeneous, except for the case of concentration-dependent diffusivity. For a simplest application we may assume each component lamina i , ($i = A, B$ or C) are homogeneous, characterized by h_i and constant D_i , K_i , k_i . Various diffusion parameters related to a single lamina A, B or C used in calculating the resultant P and t_L are then readily evaluated to be

$$P^i = \phi_i \operatorname{csch}(\phi_i) \frac{D_i K_i}{h_i} \quad (19)$$

$$(T_{11}^i)_{s=0} = (T_{22}^i)_{s=0} = \cosh(\phi_i) \quad (20)$$

$$t_L^i = \left[\frac{3(\phi_i \coth \phi_i - 1)}{\phi_i^2} \right] \frac{h_i^2}{6D_i} \quad (21)$$

$$\bar{t}_- = \bar{t}_+ = \left[\frac{\coth \phi_i - \operatorname{sech} \phi_i \operatorname{csch} \phi_i}{\phi_i} \right] \frac{h_i^2}{2D_i} \quad (22)$$

with $\phi_i = (k_i/D_i)^{1/2} h_i$.

When no reaction occurs, $k_i = 0$ then $\phi_i = 0$, eqn. (19)–(22) are simplified to be $P^i = (D_i K_i/h_i)$, $(T_{11}^i)_{s=0} = (T_{22}^i)_{s=0} = 1$, $t_L^i = (h_i^2/6D_i)$, $\bar{t}_- = \bar{t}_+ = (h_i^2/2D_i)$, and the resultant P and t_L become

$$\frac{1}{P} = \frac{1}{P^C} + \frac{1}{P^{AB}} \quad (23)$$

$$t_L = \frac{\bar{t}_-^C}{1 + \frac{P^C}{P^{AB}}} + \frac{t_L^{AB}}{1 + \frac{P^C}{P^{AB}}} + \frac{t_L^C}{1 + \frac{P^C}{P^{AB}}} + \frac{\bar{t}_+^{AB}}{1 + \frac{P^C}{P^{AB}}} \quad (24)$$

which are identical to the previous results¹² obtained from repeated integration.

Directional Symmetry of Lag Times for Absorptive Permeation

The absorptive permeation may be run in reverse mode by exchanging the upstream and downstream compartments.^{1,2} The extensive theoretical studies of Petropoulos and co-workers^{1,8,26,27} revealed that the directional symmetry, *i.e.* the equality of the forward and reverse downstream absorptive time lags, holds once D and K are dependent only on position x . Since D and K are functions of both x and the concentration, ρ , the directional symmetry holds only if there is a symmetry about the midplane of the membrane. Otherwise, a distinction between separable and non-separable x and ρ may be made by checking the directional symmetry or non-symmetry of flux.²⁶ We will examine whether the directional symmetry holds for reaction–diffusion through a serial–parallel path.

In a previous paper²¹ we have proven that directional symmetry is valid for diffusion accompanying reaction across laminae in series, when D , K , and k are only a function of position and the reaction is of first-order. The proof hinges on the unity value of the determinant of the transmission matrix, $\det T(s)$, of each component lamina. In the system of reaction–diffusion across a series–parallel path considered here, the parallel region can be considered as an equivalent lamina, AB, characterized by a transmission matrix T^{AB} . AB is then in series with the lamina C characterized by a trans-

mission matrix T^C . Since $\det T^{AB} = 1$, as calculated from eqn. (9a)–(9d), and $\det T^C = 1$, as has been proven elsewhere,²¹ we have $\det T^C T^{AB} = 1$. As a consequence, the directional symmetry holds for the adsorptive downstream lag time in this system.

Discussion and Conclusion

When either σ_A or σ_B is equal to zero, the whole membrane reduces to laminae in series; when $\sigma_C = 0$, it reduces to laminae in parallel. Thus, we have demonstrated the use of the matrix method in calculation of the P and t_L for reaction–diffusion in series or in parallel paths, or a combination of both. The concept of a hypothetical, equivalent transmission matrix in the parallel subregion is a crucial point in this calculation. When using the matrix approach, the requirement of the continuity of the activity and flux at the interfaces between neighbouring laminae is automatically taken into account in the matrix operation. Thus, only the boundary conditions at the upstream and downstream faces need to be considered in the calculation. Furthermore, calculation by the matrix method can easily be combined with commercially available software such as MATLAB or MATHEMATICA. When dealing with reaction–diffusion problems, the matrix demonstrates its advantage over repeated integration in that the latter can accomplish the calculation of P and t_L only when reaction is not involved.

In conclusion, we have extended a mathematically elegant method for diffusion time lag to laminated membranes with first-order reaction. The method is limited to the case where diffusivity, partition coefficient and rate constant are dependent on position only. Although none of the results obtained here are new, the formulation is potentially a powerful one to deal with more complicated diffusion systems.

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