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ORIGINAL PAPER

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Theoretical analysis of time-dependent diffusion, reaction and electromigration in membranes

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Abstract The transport of material through a membrane of finite thickness via the process of diffusion is examined theoretically. The membrane is assumed to be sandwiched between a donor and a receptor compartment and it is assumed that infinite source and sink conditions pertain. The effect of an externally applied electric field and concurrent first-order chemical reaction of the diffusant species with sites in the membrane on the diffusion rate is examined via the formulation of a time-dependent differential equation and its subsequent solution via the technique of Laplace transformation. Closed form expressions for the diffusant lag time and permeability are derived and compared with expressions previously presented in the literature.

Key words Diffusion · Membranes · Diffusion equations · Iontophoresis · Active diffusion

Introduction

The analysis of material transport via diffusion in regions of finite spatial extent is a subject of much current interest. Time-dependent passive diffusion of material through membranes and thin films has been the subject of mathematical modelling for many years and reference may be made to the classic monographs produced by Carslaw and Jaeger [1] and Crank [2] for a comprehensive survey of progress made in this area. The analysis of bounded diffusion processes in which the diffusing material is also subjected to applied electric fields and can undergo chemical reaction with sites located in the diffusion medium is considerably more complicated and therefore has not received much attention to date.

Attention is focused on bounded diffusion/migration/reaction (DMR) problems because the latter processes describe the operation of systems of current technological importance, such as electric field assisted iontophoretic drug delivery devices [3] and polymer modified electrode sensors [4–8]. In the present paper we discuss the process of diffusion, reaction and migration through membranes of finite thickness L. Mathematical modelling of the latter system involves the formulation of a partial differential equation, a suitable initial condition, and physically reasonable boundary conditions. The differential equation is then solved to obtain a closed form expression for the concentration profile of diffusant as a function of distance and time. The latter expression may then be manipulated to obtain a closed form expression for the total quantity of material released from the membrane at any given time. The latter expression may then be used to evaluate a theoretical expression for the normalised lag time τ_L of penetrant species, which defines the time required for the attainment of steady state diffusion conditions, and the normalised permeability ρ, which is a measure of the steady state rate of material transport through the membrane material. Both of the latter quantities can be readily determined via experiment. In particular, for simple passive diffusion through a membrane, the lag time t_L may be used to obtain an estimate of the diffusion coefficient D of the transported species via the expression $t_L = L^2/6D$.

Aspects of material transport in membranes have been previously discussed in the literature. For instance, Ludolph and co-workers [9] presented an analysis to calculate the lag time expected for bounded diffusion coupled with chemical reaction and sorption of diffusing species. These workers showed that the lag time for bounded passive diffusion coupled with reversible penetrant immobilisation within the membrane is given

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by $t_L = (L^2/6D)\ (1 + K)$, where K represents the equilibrium constant relating free and bound penetrant. Leypoldt and Gough [10] examined the same system using finite Fourier transform methods. More recently, Keister and Kasting [11] modelled electric field enhanced active diffusion within a finite membrane by a separation of variables method, and derived an expression for the lag time. Chen and Rosenberger [12] derived closed form solutions for the steady state permeability and the lag time of a linear diffusion system with concurrent reaction and convection using the Laplace transform technique. In the present paper we present an alternative analysis of bounded diffusion with concurrent chemical reaction and electromigration and obtain closed form expressions for the concentration profile of penetrant, and total quantity of diffusant exiting the membrane, as a function of time. The effect of applied electric field and chemical rate constant on both the lag time and is also elucidated.

General description of the physical system and the formulation of the boundary value problem

The mathematical model presented can be used to analyse the following experimental arrangement. We consider a thin homogeneous membrane of thickness L that separates two bulk volumes (Fig. 1). We assume that the diffusion of penetrant is planar. Hence the spatial variable is defined over the range $0 \le x \le L$. The region $x < 0$ is designated as the donor compartment and the region $x > L$ is the receptor compartment. We also assume that the membrane is subjected to a constant uniform electric field. Furthermore, the diffusing penetrant reacts within the membrane according to a first-order kinetic expression with a rate constant k. Initially, the membrane is devoid of penetrant. At time $t = 0$ the face of the membrane adjacent to the donor compartment is exposed to a constant concentration c_0 while the other face in contact with the receptor compartment is maintained at zero concentration. It is also assumed that the solutions on both sides of the membrane are well stirred, and that the receiver solution acts as an infinite sink and that the donor solution serves as an infinite source.

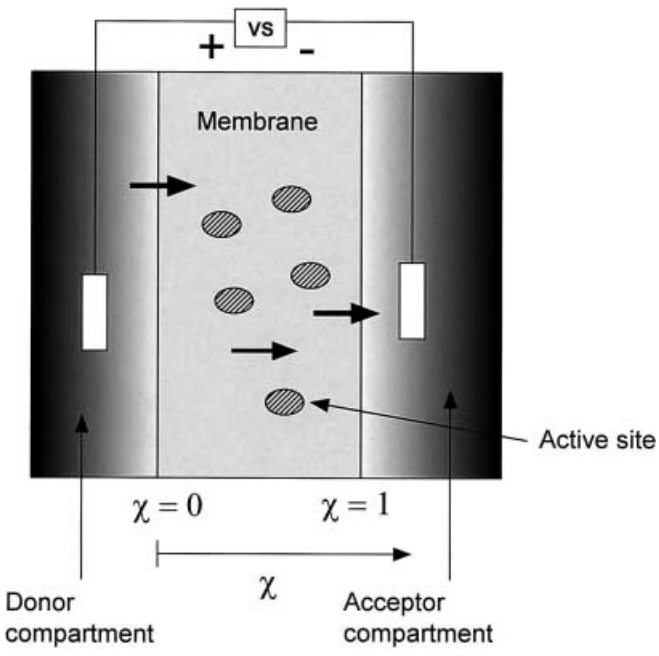


Fig. 1 Schematic representation of free standing membrane of finite thickness L, containing immobilised active binding/reaction sites. The penetrant species passes through the membrane from a donor to a receptor compartment. A uniform electric field is present in the membrane, which can facilitate transport of penetrant

The mathematical description of the problem involves a time-dependent diffusion equation of the following type:

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \chi^2} - \beta \frac{\partial u}{\partial \chi} - \gamma u \tag{1}$$

This expression is presented in non-dimensional form. This is done via definition of the following normalised parameters:

$$u = \frac{c}{\kappa c_0} \chi = \frac{x}{L} \gamma = \frac{kL^2}{D} = \frac{j_R}{j_D} \beta = \frac{\mu E L}{D} = \frac{j_M}{j_D} \tau = \frac{Dt}{L^2} \tag{2}$$

where u represents a non-dimensional penetrant concentration at any point in the membrane which is scaled with respect to the concentration c_0 at the donor solution/membrane interface, χ is a normalised distance variable scaled to the total thickness L of the membrane, and τ is a normalised time parameter. Hence we note that $0 \le u \le 1$ and $0 \le \chi \le 1$. Furthermore, γ and β represent normalised diffusion/reaction and diffusion/migration parameters, respectively. In fact the diffusion/reaction parameter γ is defined as the ratio of the flux due to chemical reaction to the flux arising from species diffusion through the membrane. In a similar way, the parameter β defines the ratio of the migration flux to the diffusion flux and compares the magnitudes of the transport rate of penetrant through the membrane via migration and diffusion, respectively. Consequently, the ratio γ/β compares the rate of penetrant species reaction at a site in the membrane to the rate of electromigration of penetrant species within the membrane. The parameter β depends directly on both the electric field strength E within the membrane and on the ionic mobility μ of the penetrant species. It also depends on the membrane thickness and is inversely proportional to the diffusion coefficient D of the penetrant. In contrast, the parameter γ is directly proportional to the first-order rate constant for species removal within the membrane and is inversely proportional to the diffusion coefficient D. The effect of species partitioning at the donor solution/membrane interface is quantified via the partition coefficient κ. The latter parameter accounts for the continuity of the diffusant's chemical potential at the

interface. The expression presented in Eq. 1 should be compared with the equation governing simple passive diffusion within the membrane, which is well described by the time-dependent Fick diffusion equation:

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \chi^2} \tag{3}$$

The problem is defined mathematically in terms of the following initial and boundary conditions:

$$u(\chi,\ 0) = 0 \qquad u(0,\ \tau) = 1 \qquad u(1,\ \tau) = 0 \tag{4}$$

We shall initially present a solution of the simple passive diffusion problem governed by Eq. 3 and then outline how the more complex situation of diffusion coupled with concurrent electromigration and chemical reaction, which is governed by the differential equation presented in Eq. 1, is tackled. In both cases we utilise the technique of Laplace transformation, which is the solution technique of choice when bounded diffusion problems are examined.

Passive diffusion in a finite membrane

We initially indicate the manner in which the Fick diffusion equation (Eq. 3) is solved subject to the initial and boundary conditions presented in Eq. 4. The diffusion flux at the membrane/receptor compartment interface corresponding to $\chi = 1$ is given by:

$$j = -\frac{D\kappa c_0}{L}\left(\frac{\partial u}{\partial \chi}\right)_{\chi=1} \tag{5}$$

and the normalised diffusion flux ψ is given by:

$$\psi = \frac{jL}{D\kappa c_0} = -\left(\frac{\partial u}{\partial \chi}\right)_{\chi=1} \tag{6}$$

We take Laplace transforms of Eq. 3 to obtain the following ordinary differential equation:

$$\frac{\mathrm{d}^2 \bar{u}}{\mathrm{d}\chi^2} - p\bar{u} = 0 \tag{7}$$

where p denotes the Laplace parameter and $\bar{u}$ represents the concentration of penetrant in Laplace space. Equation 7 is subject to the following transformed boundary conditions:

$$\bar{u}(0,\ p) = \frac{1}{p} \qquad \bar{u}(1,\ p) = 0 \tag{8}$$

As outlined in Appendix A, the solution of Eq. 7 is given by:

$$\bar{u}(\chi,\ p) = \frac{\cosh\left[\sqrt{p}\chi\right]}{p} - \frac{\sinh\left[\sqrt{p}\chi\right]}{p\tanh\sqrt{p}} = \frac{\sinh\left[\sqrt{p}(1-\chi)\right]}{p\sinh\sqrt{p}} \tag{9}$$

We use the complex inversion theorem to obtain the inverse Laplace transform and invert Eq. 9 (see Appendix A) to obtain the following expression for the normalised concentration profile:

$$u(\chi,\ \tau) = 1 - \chi - 2\sum_{n=1}^{\infty}\frac{\sin[n\pi\chi]}{n\pi}\exp\left[-n^2\pi^2\tau\right] \tag{10}$$

Typical diffusant concentration profiles through the membrane obtained using Eq. 10 are presented in Fig. 2.

We can use Eqs. 6 and 10 to obtain the following expression for the diffusion flux at the membrane/receptor compartment interface:

$$\psi(\tau) = 1 + 2\sum_{n=1}^{\infty}(-1)^n\exp\left[-n^2\pi^2\tau\right] \tag{11}$$

The total quantity $N(t)$ of penetrant passing through the membrane after a time t is given by:

$$N(t) = A\int_0^t j(t)\mathrm{d}t \tag{12}$$

where A is the membrane surface area. Since $\mathrm{d}t = L^2/D_s\,\mathrm{d}\tau$, then using Eq. 6 we can readily show that:

$$N(\tau) = N_\infty\int_0^\tau \psi(\tau)\mathrm{d}\tau \tag{13}$$

where the total quantity of material released into the receptor compartment at very long times is given by $N_\infty = AL\kappa c_0$. The ratio $Q(\tau) = N(\tau)/N_\infty$ versus τ defines the quantity of primary experimental interest.

From Eqs. 11 and 13 we can show (Appendix A) that:

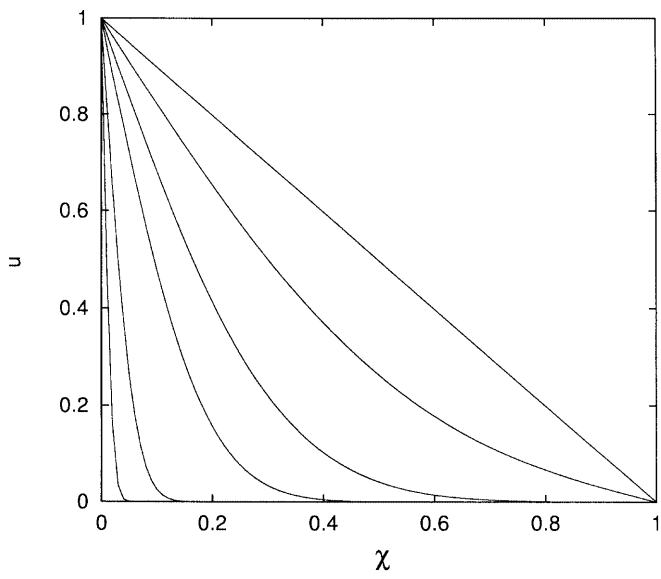


Fig. 2 Typical concentration profiles computed using Eq. 10 for simple passive diffusion through a membrane of finite thickness. The concentration profiles are presented for normalised times (*from left to right*) of 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, 0.1 and 0.6 respectively

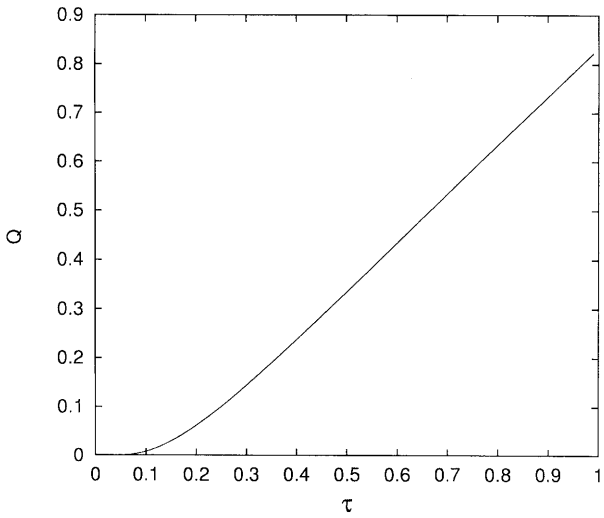


Fig. 3 Variation of quantity of penetrant delivered to the receptor compartment as a function of normalised time. The curve was computed using Eq. 14

$$Q(\tau) = \tau - \frac{1}{6} - 2\sum_{n=1}^{\infty} \frac{(-1)^n}{n^2\pi^2} \exp\left[-n^2\pi^2\tau\right] \tag{14}$$

and we can identify the normalised lag time as $\tau L = 1/6$. A typical release profile is presented in Fig. 3.

We can obtain useful limiting expressions for the normalised release function $Q(\tau)$ in the limit of short and long times τ. We return to Eq. 9 and note:

$$\bar{u} = p^{-1}\mathrm{cosech}\sqrt{p}\sinh\left[\sqrt{p}(1-\chi)\right] \tag{15}$$

Now short times correspond to $\tau \ll 1$ and to $p \gg 1$. Under such conditions we note that: $\mathrm{cosech}\sqrt{p} \cong 2\exp\left[-\sqrt{p}\right]$. Also $(\mathrm{d}\bar{u}/\mathrm{d}\chi)_{\chi=1} = -p^{1/2}\ \mathrm{cosech}\sqrt{p} \cong -2p^{-1/2}\exp\left[-\sqrt{p}\right]$, and so the normalised release profile is given by:

$$Q(\tau) = -\mathrm{L}^{-1}\left\{\int_0^{\tau}\left(\frac{\mathrm{d}\bar{u}}{\mathrm{d}\chi}\right)_{\chi=1}\mathrm{d}\tau\right\} = -\mathrm{L}^{-1}\left\{p^{-1}\left(\frac{\mathrm{d}\bar{u}}{\mathrm{d}\chi}\right)_{\chi=1}\right\} \tag{16}$$

where L^{-1} represents the inverse Laplace transformation operator and we have used the fact that integration with respect to time τ is equivalent to division by the Laplace parameter p. Hence the diffusant release profile at short times is obtained via inverting the expression:

$$Q(\tau) \cong 2\mathrm{L}^{-1}\left\{p^{-3/2}\exp\left[-\sqrt{p}\right]\right\} \tag{17}$$

We note that [13]:

$$\mathrm{L}^{-1}\left\{\frac{\exp\left[-\alpha\sqrt{p}\right]}{p^{3/2}}\right\} = 2\sqrt{\frac{\tau}{\pi}}\exp\left[-\frac{\alpha^2}{4\tau}\right] - \alpha\,\mathrm{erfc}\left[\frac{\alpha}{2\sqrt{\tau}}\right]$$
$$= 2\sqrt{\tau}\ \mathrm{ierfc}\left[\frac{\alpha}{2\sqrt{\tau}}\right] \tag{18}$$

where $\alpha \geq 0$. If we set $\alpha = 1$ we obtain:

$$Q(\tau) \cong 4\sqrt{\tau}\,\mathrm{ierfc}\left[\frac{1}{2\sqrt{\tau}}\right] \tag{19}$$

where we note that ierfc denotes the complementary error function integral which is defined as [14]:

$$\mathrm{ierfc}[x] = \frac{2}{\sqrt{\pi}}\int_x^{\infty}(\theta - x)\exp\left[-\theta^2\right]\mathrm{d}\theta = \int_x^{\infty}\mathrm{erfc}[\theta]\mathrm{d}\theta$$
$$= \int_x^{\infty}(1 - \mathrm{erf}[\theta])\mathrm{d}\theta \tag{20}$$

where θ is a dummy integration variable and erf $[x]$ represents the well-known error function. It can be shown [14] that the following asymptotic expansion is useful when the argument of the repeated integral of the complementary error function is large:

$$\mathrm{i}^n\mathrm{erfc}[x] \cong \frac{2\exp\left[-x^2\right]}{\sqrt{\pi}(2x)^{n+1}}\sum_{j=0}^{\infty}\frac{(-1)^j(n+2j)!}{n!j!(2x)^{2j}} \tag{21}$$

Specifically for $n = 1$ and setting $\eta = 1/2\sqrt{\tau}$ we obtain for $\eta \gg 1$ (or $\tau \ll 1$):

$$\mathrm{ierfc}[\eta] \cong \frac{2\exp\left[-\eta^2\right]}{(2\eta)^2\sqrt{\pi}} \tag{22}$$

and so an expression for the release profile valid for short times is given by:

$$Q(\tau) \cong 4\sqrt{\tau}\left\{\frac{2\exp[-1/4\tau]}{\sqrt{\pi}(1/\sqrt{\tau})^2}\right\} = \frac{8}{\sqrt{\pi}}\tau^{3/2}\exp\left[-\frac{1}{4\tau}\right] \tag{23}$$

This expression is valid up to $\tau \cong 0.02$ (error 10%). For $\tau = 0.1$ there is a 50% error in using Eq. 23 to estimate the quantity of diffusant released from the membrane. The full expression must be used for τ values greater than 0.02.

Conversely, for long times when $p \ll 1$ we use the fact that $\mathrm{cosech}\sqrt{p} \cong 1/\sqrt{p} - \sqrt{p}/6$ to obtain $p^{3/2}\mathrm{cosech}\sqrt{p} \cong 1/p^2 - 1/6p$ and when the latter is substituted in Eq. 16 we obtain:

$$Q(\tau) \cong \tau - \frac{1}{6} = \tau - \tau_{\mathrm{L}} \tag{24}$$

The latter expression, valid at long times, is used experimentally to evaluate the lag time τ_{L} and hence the diffusion coefficient D_{S} of the penetrant through the membrane. Now the permeability in normalised form is defined as:

$$\rho = \frac{LP}{\kappa D} = \left(\frac{\mathrm{d}Q}{\mathrm{d}\tau}\right)_{\tau\to\infty} \tag{25}$$

Hence from Eq. 24 we note that $\rho = 1$, as expected for a system exhibiting simple passive diffusion. Furthermore, the normalised lag time is:

$$\tau_{\mathrm{L}} = \frac{Dt_{\mathrm{L}}}{L^2} = \frac{1}{6} \tag{26}$$

Hence the lag time for passive diffusion through a membrane of thickness L is predicted to be $t_L = L^2/6D$, as is well known.

Electric field assisted diffusion with concurrent first-order chemical reaction in a finite membrane

We now present a solution of Eq. 1 which describes electric field assisted diffusion with concurrent first-order reaction kinetics in a finite membrane. Such a situation would typically correspond to iontophoretic transport of charged drug species across a membrane barrier in which the drug can be metabolised via first-order kinetics. The analysis could also be used to describe substrate transport and reaction within a free-standing electronically conducting polymer membrane in which the diffusing substrate reacts with sites located on the polymer chains via first-order kinetics.

We apply the Laplace transform to Eq. 1 to obtain:

$$\frac{d^2\overline{u}}{d\chi^2} - \beta\frac{d\overline{u}}{d\chi} - (p+\gamma)\overline{u} = 0 \tag{27}$$

This ordinary differential equation with constant coefficients is solved using the Laplace transformed boundary conditions presented in Eq. 8. The general solution to Eq. 27 is:

$$\overline{u}(\chi,p) = \exp[\xi\chi]\left\{A\cosh\left[\sqrt{\zeta+p}\chi\right] + B\sinh\left[\sqrt{\zeta+p}\chi\right]\right\} \tag{28}$$

where we note that:

$$\xi = \frac{\beta}{2} \qquad \zeta = \gamma + \xi^2 = \gamma + \frac{\beta^2}{4} \tag{29}$$

and A and B are integration constants which are evaluated from the boundary conditions presented in Eq. 8. As outlined in Appendix B, we can show readily that:

$$\overline{u}(\chi,p) = \exp[\xi\chi]\left\{\frac{\sinh\left[\sqrt{\zeta+p}(1-\chi)\right]}{p\sinh\sqrt{\zeta+p}}\right\} \tag{30}$$

When the diffusion is passive, $\xi = 0 = 0$, and if there is no loss of penetrant via first-order chemical reaction then $\zeta = 0$ and we note immediately that Eq. 30 reduces directly to Eq. 9 which we have previously examined. The Laplace transform presented in Eq. 30 may be inverted using the Heaviside expansion theorem [15] or via the complex inversion formula [16]. In Appendix B we use the former strategy to show that the normalised penetrant concentration profile within the membrane is given by:

$$u(\chi,\tau) = u_S(\chi) - u_T(\chi,\tau) \tag{31}$$

where u_S represents the steady state component and u_T is the transient contribution to the concentration profile. The latter quantities are given by:

$$u_S(\chi) = \frac{\sinh\left[\sqrt{\zeta}(1-\chi)\right]}{\sinh\sqrt{\zeta}}\exp[\xi\chi] = \frac{\sinh\left[\sqrt{\gamma+\frac{\beta^2}{4}}(1-\chi)\right]}{\sinh\left[\sqrt{\gamma+\frac{\beta^2}{4}}\right]}\exp\left[\frac{\beta\chi}{2}\right] \tag{32}$$

and

$$u_T(\chi,\tau) = 2\exp[\xi\chi]\sum_{n=1}^{\infty}\frac{n\pi}{n^2\pi^2+\zeta}\sin[n\pi\chi] \times \exp[-(n^2\pi^2+\zeta)\tau] = 2\exp\left[\frac{\beta\chi}{2}\right]\sum_{n=1}^{\infty}\frac{n\pi}{n^2\pi^2+\gamma+\frac{\beta^2}{4}}\sin[n\pi\chi] \times \exp\left[-\left(n^2\pi^2+\gamma+\frac{\beta^2}{4}\right)\tau\right] \tag{33}$$

We can readily show that the expressions presented in Eqs. 32 and 33 reduce to that outlined in Eq. 10 when the parameters β and γ are both zero and simple passive diffusion pertains. Typical normalised concentration profiles for penetrant are presented in Fig. 4 for typical values of the migration parameter β and the reaction/diffusion parameter γ. These profiles are presented in a three-dimensional format for ease of representation. For instance, in Fig. 4a we show how the normalised concentration profile u varies with β at different values of

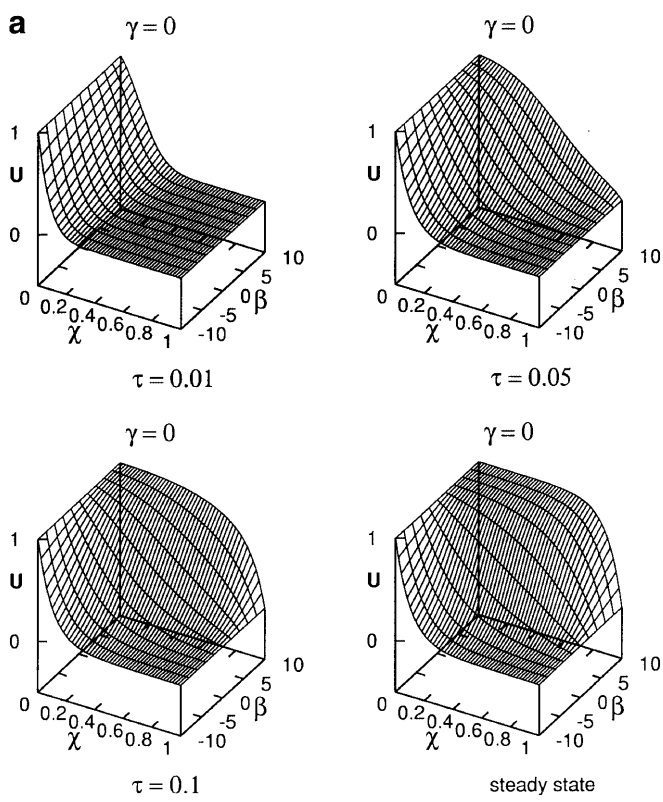


Fig. 4a

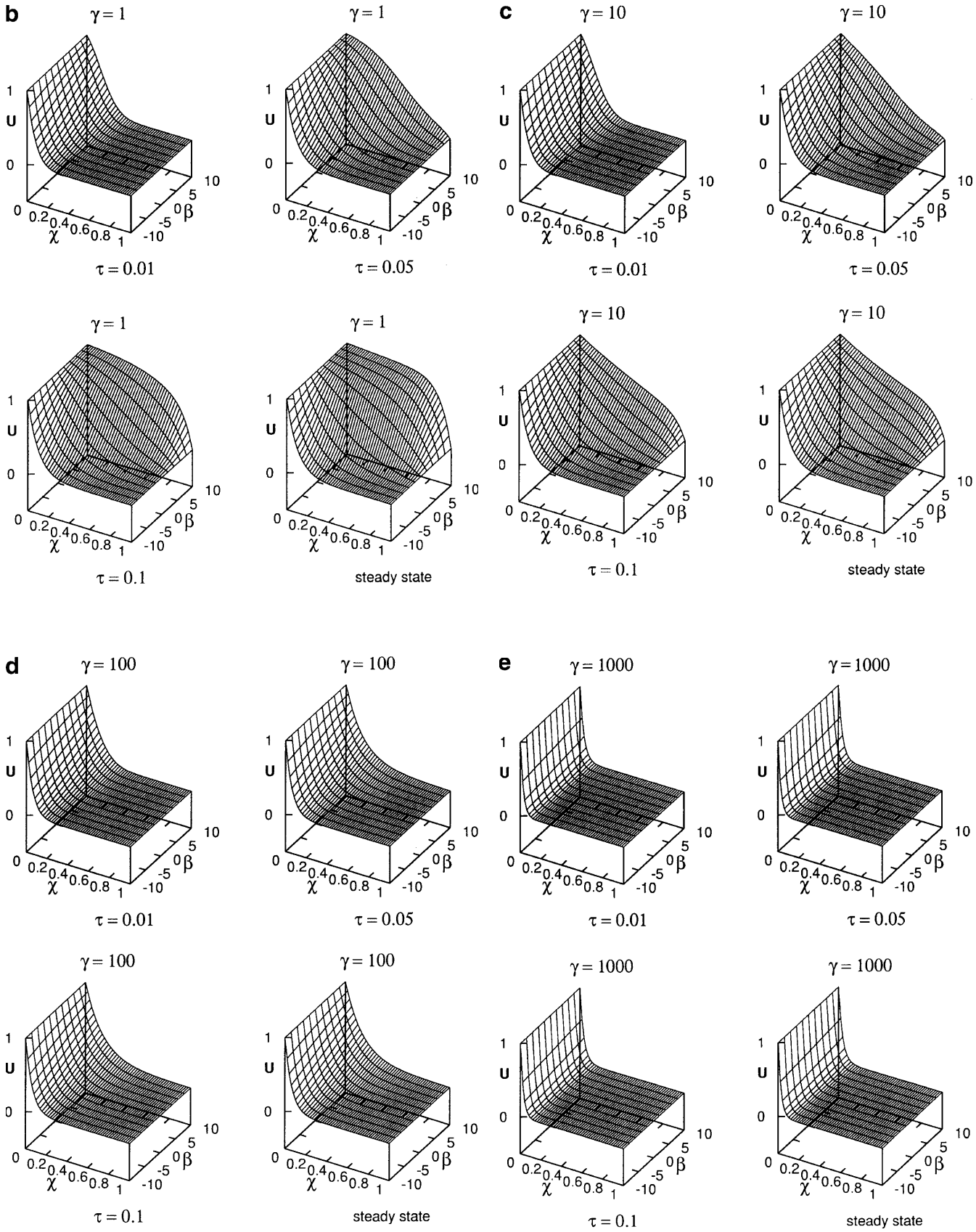
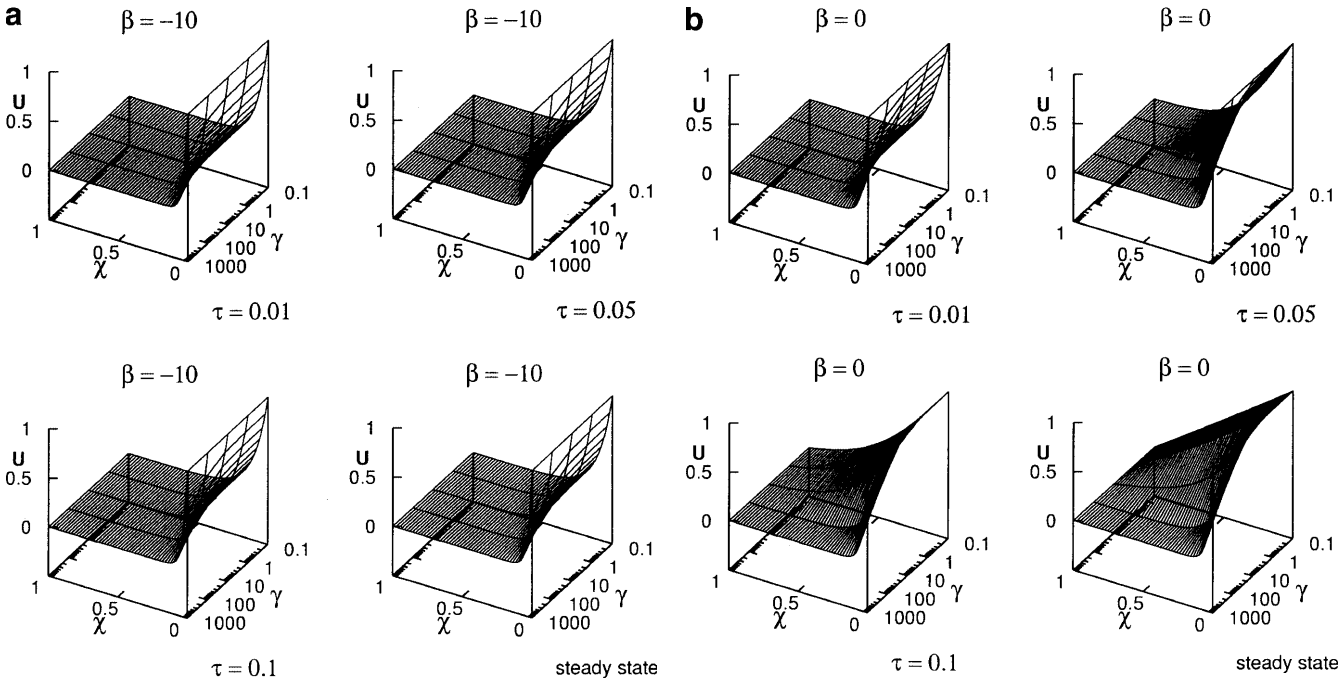


Fig. 4a–e Development of the (u, χ, β) surface as a function both of normalised time τ and reaction/diffusion parameter γ: **a** $\gamma = 0$; **b** $\gamma = 1$; **c** $\gamma = 10$; **d** $\gamma = 100$; **e** $\gamma = 1000$



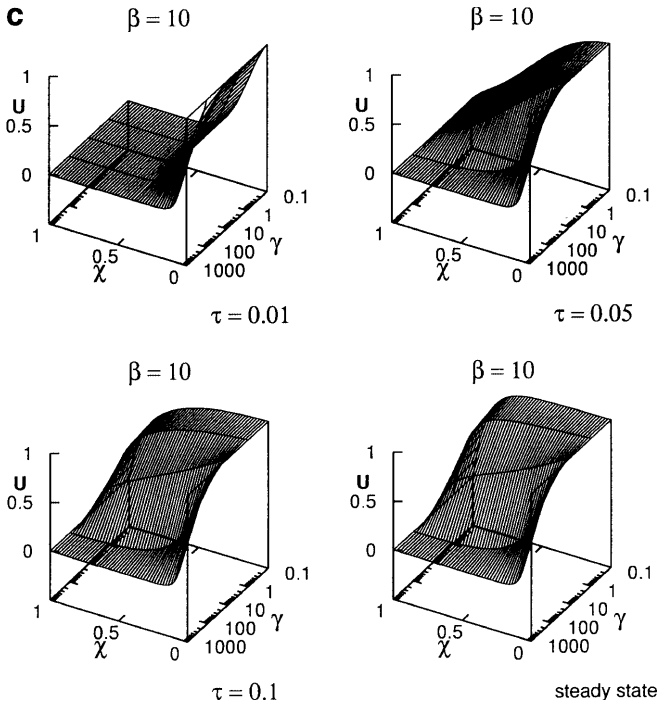


Fig. 5a–c Development of the (u, χ, γ) surface as a function both of normalised time τ and migration parameter β: **a** $\beta = -10$; **b** $\beta = 0$; **c** $\beta = 10$

normalised time τ ranging from $\tau = 0.01$ to steady state when the reaction/diffusion parameter γ is zero. In Fig. 4b, concentration profiles are presented for various β and τ values, but in this case $\gamma = 1$. The same computation is repeated in Fig. 4c, 4d and 4e but in this case $\gamma = 10$, 100 and 1000, respectively. A further set of concentration profiles is presented in Fig. 5. In this case the effect of the sign and magnitude of the migration parameter β on the shape of the (u, χ, γ) surface is explored. In Fig. 5a the effect of a negative β value on the (u, χ, γ) surface is presented. Here the field opposes the migration of penetrant through the membrane. In Fig. 5b, $\beta = 0$ and the time development of, and the effect of the reaction/diffusion parameter γ on, the (u, χ, γ) surface is clearly presented. In Fig. 5c the time variation of the (u, χ, γ) surface when $\beta = 10$ is presented. Here the field enhances penetrant transport through the membrane.

In Appendix C we show that Eq. 1 may be integrated to obtain an analytical expression for the concentration profile of penetrant if a solution of the following form is assumed:

$$u(\chi, \tau) = \exp[\xi\chi]\exp[-\zeta\tau]\omega(\chi, \tau) \tag{34}$$

where $\omega(\chi, \tau)$ satisfies the simple Fick diffusion equation:

$$\frac{\partial\omega}{\partial\tau} = \frac{\partial^2\omega}{\partial\chi^2} \tag{35}$$

and also satisfies the following initial and boundary conditions:

$$\omega(\chi, 0) = 0 \qquad \omega(0, \tau) = \exp[\zeta\tau] \qquad \omega(1, \tau) = 0 \tag{36}$$

where we define: $\xi = \beta/2$ and $\zeta = \gamma + \xi^2$. This alternative strategy can prove to be very useful when other types of bounded diffusion problems in membranes are considered.

As outlined in Appendix B, we can show that the normalised release profile of penetrant from the membrane as a function of time is given by:

$$Q(\tau) = \sqrt{\zeta}\exp[\xi]\text{cosech}\left[\sqrt{\zeta}\tau\right]\tau + 2\exp[\xi]\sum_{n=1}^{\infty}\frac{(-1)^n n^2\pi^2}{(n^2\pi^2+\zeta)^2} - 2\exp[\xi]\sum_{n=1}^{\infty}\frac{(-1)^n n^2\pi^2}{(n^2\pi^2+\zeta)^2} \times \exp\left[-(n^2\pi^2+\zeta)\tau\right] \quad (37)$$

We follow Leypoldt and Gough [10] and note that complex variables theory (specifically the method of contour integration) may be used to express the following infinite series in terms of a closed form expression involving hyperbolic functions:

$$\sum_{n=1}^{\infty}\frac{(-1)^n n^2\pi^2}{(n^2\pi^2+\zeta)^2} = -\frac{1}{4}\left\{\text{cosech}\sqrt{\zeta}\left(\coth\sqrt{\zeta}-\frac{1}{\sqrt{\zeta}}\right)\right\} \quad (38)$$

and so the normalised release profile of penetrant becomes:

$$Q(\tau) = \sqrt{\zeta}\exp[\xi]\text{cosech}\left[\sqrt{\zeta}\tau\right]\tau - \frac{1}{2}\exp[\xi]\text{cosech}\sqrt{\zeta}\left\{\coth\sqrt{\zeta}-\frac{1}{\sqrt{\zeta}}\right\} - 2\exp[\xi]\sum_{n=1}^{\infty}\frac{(-1)^n n^2\pi^2}{(n^2\pi^2+\zeta)^2} \times \exp\left[-(n^2\pi^2+\zeta)\tau\right] \quad (39)$$

In the limit of long time the last term of Eq. 39 reduces to zero and we obtain that:

$$Q(\tau\to\infty) = \sqrt{\zeta}\exp[\xi]\text{cosech}\sqrt{\zeta}\tau - \frac{1}{2}\exp[\xi]\text{cosech}\sqrt{\zeta}\left\{\coth\sqrt{\zeta}-\frac{1}{\sqrt{\zeta}}\right\} \quad (40)$$

The normalised permeability may immediately be evaluated from the latter expression and is given by:

$$\rho = \left(\frac{\mathrm{d}Q}{\mathrm{d}\tau}\right)_{\tau\to\infty} = \sqrt{\zeta}\exp[\xi]\text{cosech}\sqrt{\zeta} \quad (41)$$

We also note that Eq. 40 can be written in the form:

$$Q(\tau\to\infty) = \rho(\zeta,\xi)\tau - \rho(\zeta,\xi)\tau_{\mathrm{L}}(\zeta) \quad (42)$$

and so the normalised lag time for electric field assisted diffusion with concurrent first-order chemical reaction is given by:

$$\tau_{\mathrm{L}}(\zeta) = \frac{1}{2\sqrt{\zeta}}\left\{\coth\sqrt{\zeta}-\frac{1}{\sqrt{\zeta}}\right\} = \frac{1}{2\sqrt{\zeta}}L(\sqrt{\zeta}) \quad (43)$$

where $L(x)$ is the well-known Langevin function which is given by:

$$L(x) = \coth x - \frac{1}{x} \quad (44)$$

Equation 43 may also be written in another way:

$$\tau_{\mathrm{L}}(\zeta) = \frac{1}{6}\left\{\frac{3}{\sqrt{\zeta}}L\left(\sqrt{\zeta}\right)\right\} = \tau_{\mathrm{L}}(0)\left\{\frac{3}{\sqrt{\zeta}}L\left(\sqrt{\zeta}\right)\right\} \quad (45)$$

where $\tau_{\mathrm{L}}(0)$ denotes the normalised lag time for passive diffusion. Equations 41 and 45 may be used to examine the way in which the permeability and the lag time vary with the diffusion/migration parameter β and the diffusion reaction parameter γ. When the ζ parameter is small we note that $\coth\sqrt{\zeta} \cong (1/\sqrt{\zeta})\{1+\zeta/3\}$ and $(3/\sqrt{\zeta})L(\sqrt{\zeta}) \cong 1$ and we obtain that $\tau_{\mathrm{L}}(\zeta) \cong \tau_{\mathrm{L}}(0)$, as one would expect. Also since $\text{cosech}\sqrt{\zeta} \cong 1/\sqrt{\zeta}$ and $\exp[\xi] \cong 1 + \xi$ for small values of ζ and ξ, then from Eq. 41 we note that the normalised permeability ρ reduces to $\rho \cong 1 + \xi \cong 1$, as indeed it should.

For the specific case of active diffusion or iontophoresis corresponding to $\gamma = 0$, the pertinent expressions for the permeability and lag time are given by:

$$\rho(\beta) = \frac{\beta}{2}\exp\left[\frac{\beta}{2}\right]\text{cosech}\left[\frac{\beta}{2}\right] = \frac{\beta}{1-\exp[-\beta]} = \frac{j_{\mathrm{E}}}{j_{\mathrm{P}}}$$

$$\tau_{\mathrm{L}}(\beta) = \tau_{\mathrm{L}}(0)\left\{\frac{6}{\beta}L\left(\frac{\beta}{2}\right)\right\} = \tau_{\mathrm{L}}(0)\left\{\frac{6}{\beta^2}\left(\beta\coth\left[\frac{\beta}{2}\right]-2\right)\right\} \quad (46)$$

The first expression in Eq. 46 provides an analytical expression for the degree of current or flux enhancement at the membrane receptor interface owing to iontophoresis under steady state conditions. The second expression in Eq. 46 indicates how the normalised lag time varies with migration parameter β[1]. The expressions provided in Eq. 46 are represented graphically in Fig. 6. In Fig. 6a the current enhancement factor is plotted as a function of the migration parameter β. The same function is displayed in semi-logarithmic format in Fig. 6b. Now $\beta = \mu EL/D = z\mathrm{F}\Delta V/RT$, where ΔV denotes the applied potential difference across the membrane and z is the valence of the diffusing species. Hence from Fig. 6a we note that the enhancement ratio, or the ratio of steady state flux with applied voltage to the steady state passive diffusion flux, is an asymmetric function of the applied voltage ΔV. For large positive β values the enhancement factor is a linear function of β. For negative values of β when the applied voltage inhibits the flow of charged species through the membrane the en-

[1] Following a query expressed by one of the referees, we can readily show how the expression for the normalised lag time reduces to the value $\tau_{\mathrm{L}} = 1/6$ in the limit as $\beta \to 0$. To achieve this aim we use the fact that $\coth x \cong (1/x) + (x/3)$ when the parameter x is small. Hence in the limit of small β we note that Eq. 46 reduces to

$$\tau_{\mathrm{L}}(\beta) = \tau_{\mathrm{L}}(0)\left\{\frac{6}{\beta^2}\beta\left[\left(\frac{2}{\beta}+\frac{\beta}{6}\right)-2\right]\right\} = \tau_{\mathrm{L}}(0) = \frac{1}{6}$$

where we have used the result obtained in Eq. 26.

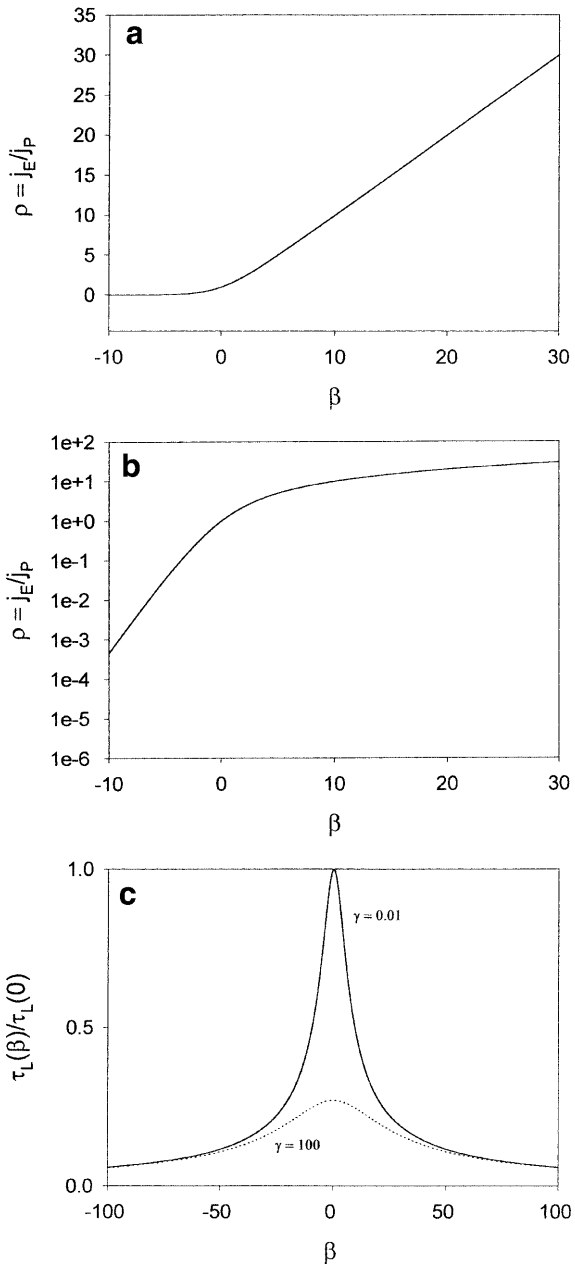


Fig. 6 **a** Variation of flux enhancement parameter ρ with migration parameter β. **b** The same data expressed in semi-logarithmic format. The curves in both cases were computed using Eq. 46. **c** Variation of the ratio of the penetrant lag time in the presence of a field $\tau_L(\beta)$ with that due to simple passive diffusion $\tau_L(0)$ with migration parameter β. The curves were computed using Eq. 46. Note that the lag time ratio function exhibits symmetry with respect to the migration parameter. The symmetry is maintained regardless of the value of the reaction/diffusion parameter adopted

hancement factor is a rapidly decreasing function of β (Fig. 6b). Typically for $\beta = -10$, $\rho = 4.54 \times 10^{-4}$ or $j_E = 4.54 \times 10^{-4} j_P$. The species flow is therefore strongly inhibited. As noted from Fig. 6c, the ratio $\tau_L(\beta)/\tau_L(0)$ is a symmetric function of the β parameter. The lag time for active diffusion relative to that observed for passive diffusion is reduced with increasing positive values of β. However, owing to the symmetry of the function $\tau_L(\beta)/\tau_L(0)$ the lag time is also reduced for increasingly more negative values of the β parameter. Keister and Kasting [7] have also made a similar observation. It is interesting to note that Chen and Rosenberger [8] have determined that the symmetry exhibited by the lag time expression arises mathematically from the symmetry with respect to the exchange of coordinate variables exhibited by the corresponding Green's function for the general diffusive/convective boundary value problem. The latter observation does not shed additional physical insight, however. This result may be explained physically as follows[2]. The lag time indicates how quickly the steady state condition within the membrane is established, i.e. how quickly the flux at $\chi = 1$ becomes constant. A zero lag time indicates that the steady state is immediately established. It should be noted that the lag time is independent of the flux itself. Both very small and very big fluxes can correspond to the same numerical value of the lag time. This fact can be noted from Figs. 4 and 5. Now if the parameter $\beta < 0$ the electric field acts against the diffusional transport and the net flux will be small, but the steady state concentration profile appears for $\tau = 0.01$ (Figs. 4a and 5a). If the parameter $\beta > 0$, the electric field enhances the flux, but on the other side of the membrane it creates a very low concentration gradient for normalised distances less than 0.4 (Fig. 4a), which controls the flux. So again the steady state condition is established more rapidly than that pertaining for $\beta = 0$ (Fig. 4a, $\tau = 0.1$).

The results presented in Eq. 46 derived from the more general expressions presented in Eqs. 41 and 45 are in exact agreement with those previously published by Keister and Kasting [11], who examined iontophoretic drug transport through a finite membrane via solution of the diffusion/migration equation by means of the separation of variables technique.

For the specific case of passive diffusion coupled with concurrent first-order chemical reaction corresponding to the situation of $\beta = 0$, the normalised permeability and lag time are given by the following expressions:

$$\rho(\gamma) = \sqrt{\gamma}\,\mathrm{cosech}\sqrt{\gamma}$$

$$\tau_L(\gamma) = \frac{1}{2\sqrt{\gamma}}\left\{\coth\sqrt{\gamma} - \frac{1}{\sqrt{\gamma}}\right\} = \frac{\tau_L(0)}{\sqrt{\gamma}}\left\{3\left(\coth\sqrt{\gamma} - \frac{1}{\sqrt{\gamma}}\right)\right\} \tag{47}$$

When γ is small, then noting that $\mathrm{cosech}\sqrt{\gamma} \cong 1/\sqrt{\gamma}$ and $\coth\sqrt{\gamma} \cong (1/\sqrt{\gamma}) + (\sqrt{\gamma}/3)$, we can readily show that $\rho(\gamma) \to 1$ and $\tau_L(\gamma) \to \tau_L(0)$. Conversely, when γ is large, then $\mathrm{cosech}\sqrt{\gamma} \cong 2\exp[-\sqrt{\gamma}]$ and $\coth\sqrt{\gamma} \cong 1 + 2\exp[-\sqrt{\gamma}]$ and therefore:

$$\rho(\gamma) \cong 2\sqrt{\gamma}\exp[-\sqrt{\gamma}] \to 0 \tag{48}$$

[2] The authors are very grateful to one of the referees for helping us to understand this observation.

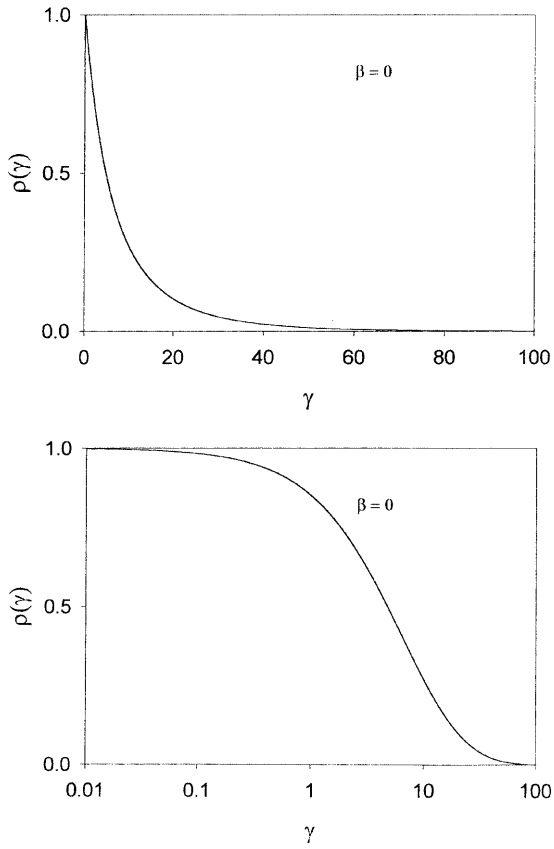


Fig. 7 Variation of flux enhancement factor ρ with reaction/diffusion parameter γ. The curves are generated via Eq. 47, and $\beta = 0$ is assumed. The data are presented both in linear and semi-logarithmic format for clarity

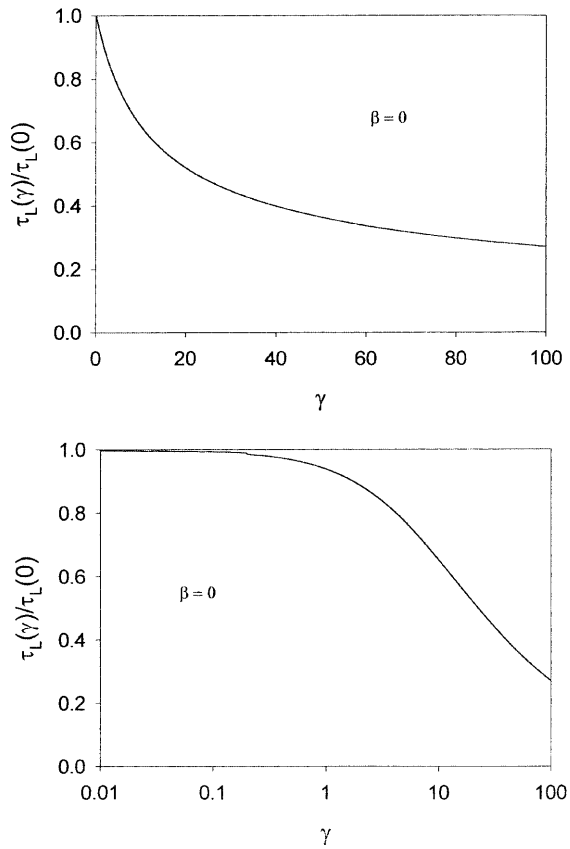


Fig. 8 Variation of normalised lag time ratio with reaction/diffusion parameter γ. The curves are generated via Eq. 47 and $\beta = 0$ is assumed. The data are presented both in linear and semi-logarithmic format for clarity

$$\tau_L(\gamma) \cong \frac{3\tau_L(0)}{\sqrt{\gamma}}\left\{1 - \frac{1}{\sqrt{\gamma}} + 2\exp[-\sqrt{\gamma}]\right\}$$
$$\cong \frac{3\tau_L(0)}{\sqrt{\gamma}}\left\{1 - \frac{1}{\sqrt{\gamma}}\right\} \tag{49}$$

Hence we expect that the normalised permeability and the lag time decrease rapidly with increasing values of γ when the latter parameter is large. This contention is supported by the computations presented in Figs. 7 and 8. We note from Fig. 7 that if a semi-logarithmic scale is used, the normalised permeability exhibits only a small decrease with increasing γ up to a value close to 0.5. It then decreases quite rapidly with increasing values of the reaction/diffusion parameter. A similar behaviour is observed for the normalised lag time (Fig. 8).

The general situation corresponding to finite values of β and γ is described by Eqs. 41 and 45. In Fig. 9 we indicate the manner in which the normalised permeability ρ varies with the migration parameter β for various values of the reaction/diffusion parameter γ. When the reaction/diffusion parameter is small, then ρ varies linearly with β. Hence we observe a marked enhancement in steady state flux with increasing value of electric field. When γ becomes significant the ρ versus β behaviour changes. We note from Fig. 9 that ρ still increases with increasing β, but when γ is significant the strictly linear increase is not observed for all values of β. Indeed, for β values in the range 0.01–1, ρ can be less than unity if γ is finite. Hence if the electric field is small and the concurrent chemical reaction is operative, then the steady state flux of penetrant can be less than that observed for simple passive diffusion in the absence of electric fields and chemical reaction. Penetrant flux enhancement is only observed for β values greater than 1, and indeed the operation of a chemical reaction within the membrane reduces the enhancing effect of the electric field on the transport rate of penetrant species. This statement can be noted more readily from Fig. 10, where we show the variation of ρ with γ for different β values. We see from this figure that ρ decreases smoothly with increasing γ value for all values of β examined, but the disenhancing effect of γ on ρ is not as marked for β values.

The variation of lag time with β and γ given by Eq. 45 is illustrated in Figs. 11 and 12. Here the computational datum is the ratio of the normalised lag time for finite β and γ to that expected for simple passive diffusion. In Fig. 11 we indicate how the latter quantity varies with migration parameter β for given values of the reaction/diffusion parameter γ. The lag time decreases significantly with increasing β value for all values of γ examined, although the rate of decrease is not as marked when γ is

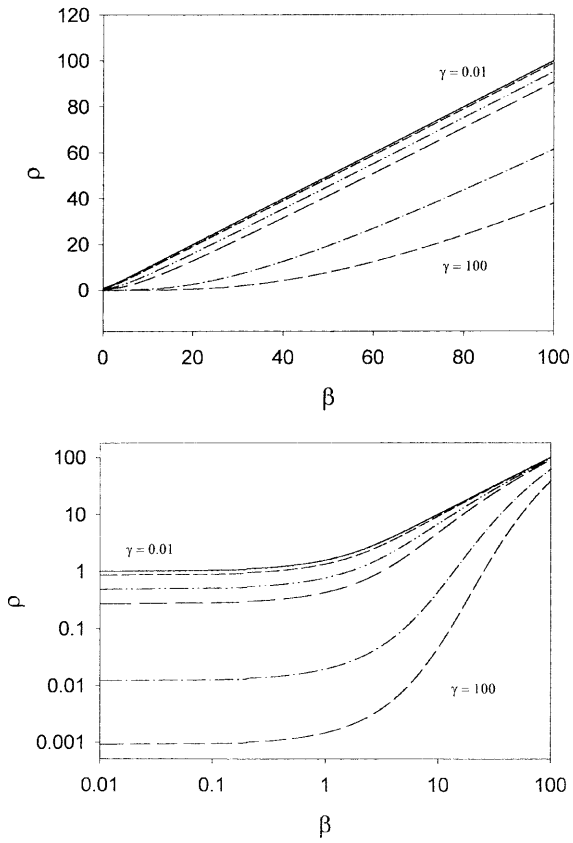


Fig. 9 Variation of flux enhancement factor ρ with migration parameter β for various fixed values of the reaction/diffusion parameter γ. The curves were computed using Eq. 41 for various g values in the range 0.01–100. The data are presented both in linear and semi-logarithmic format for clarity

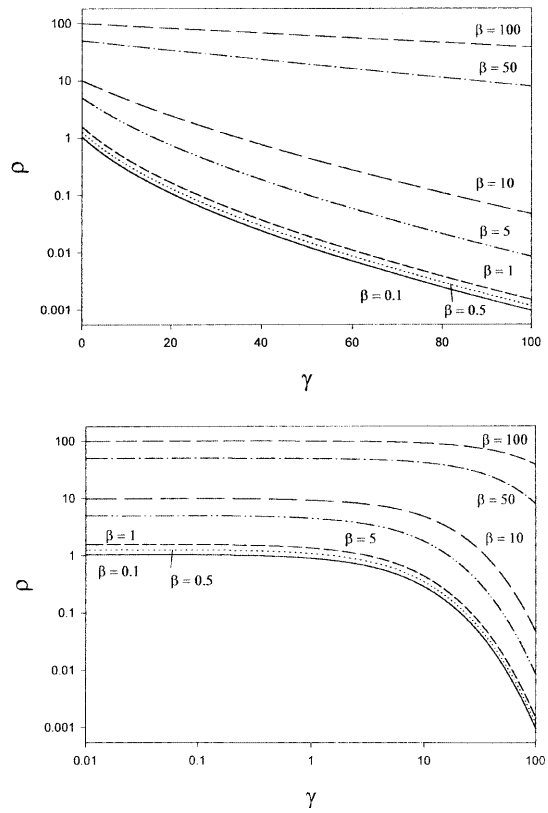


Fig. 10 Variation of flux enhancement factor ρ with reaction/diffusion parameter γ for various fixed values of the migration parameter β. The curves were computed using Eq. 41 for various β values in the range 0.1–100. The data are presented both in linear and semi-logarithmic format for clarity

large. Furthermore, any effect that γ has on the lag time ratio is not resolvable for β values greater than 70. In Fig. 12 we indicate the manner in which the lag time ratio varies with γ for various β values. Again the lag time ratio decreases with increasing γ value for small to intermediate β values, but when β becomes significant (>20) very little variation in lag time ratio with γ is observed.

Concluding comments

In the initial sections of the paper we have examined passive diffusion through a membrane of finite thickness and derived, via Laplace transform analysis of the time-dependent Fick diffusion equation, closed form analytical solutions for the concentration profile of penetrant through the membrane as a function of time, and for the amount of penetrant released into a receptor compartment as a function of time. From the latter expression the lag time and penetrant permeability can be derived.

In the second part of the paper we have shown that the technique of Laplace transformation provides a useful protocol for the solution of material transport problems in finite membranes in which diffusion, migration and concurrent first-order chemical kinetics are considered. The variation of the substrate permeability and lag time with both reaction/diffusion parameter and migration/diffusion parameter is computed via analytical solution of the diffusion/reaction/migration equation to obtain closed form expressions. The latter expressions are used to compute dimensionless working curves for the steady state permeability and the lag time which can be compared with experimental data.

Appendix A

The general solution to Eq. 7 is given by:

$$\bar{u}(\chi,p) = A\sinh\lfloor\sqrt{p}\chi\rfloor + B\cosh\lfloor\sqrt{p}\chi\rfloor \tag{A1}$$

Note that we choose hyperbolic functions since the diffusion space is finite and lies in the range (0, 1).When $\chi = 0$, $\bar{u} = 1/p$ and so $B = 1/p$. Also when $\chi = 1$, $\bar{u} = 0$ and so $A = -1/p\ \tanh\sqrt{p}$. Hence substitution of these quantities into Eq. 7 immediately produces:

$$\bar{u} = \frac{1}{p}\cosh[\sqrt{p}\chi] - \frac{\cosh\sqrt{p}\sinh\lfloor\sqrt{p}\chi\rfloor}{p\sinh\sqrt{p}}$$

$$= \frac{1}{p}\left\{\frac{\sinh\sqrt{p}\cosh[\sqrt{p}\chi] - \cosh\sqrt{p}\sinh[\sqrt{p}\chi]}{\sinh\sqrt{p}}\right\}$$

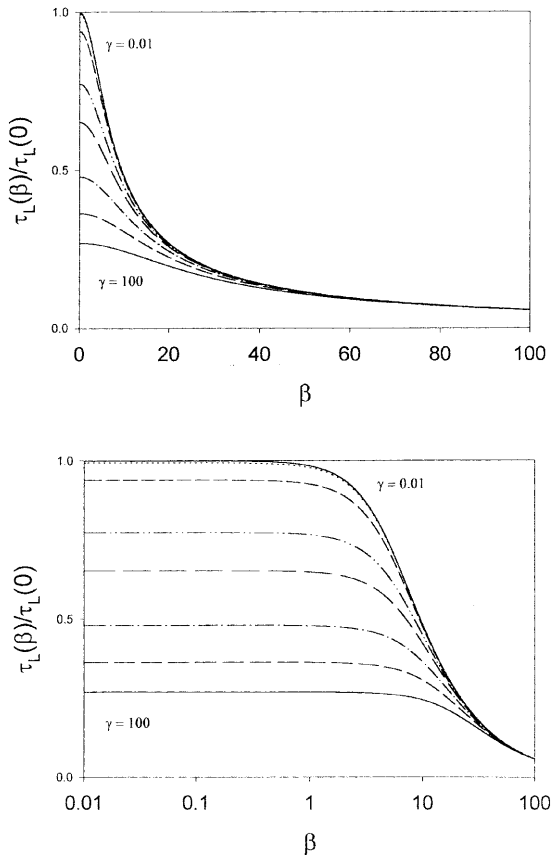


Fig. 11 Variation of normalised lag time ratio with migration parameter β. The curves were computed via Eq. 45 and various γ values in the range 0.01–100 were used. The data are presented both in linear and semi-logarithmic format for clarity

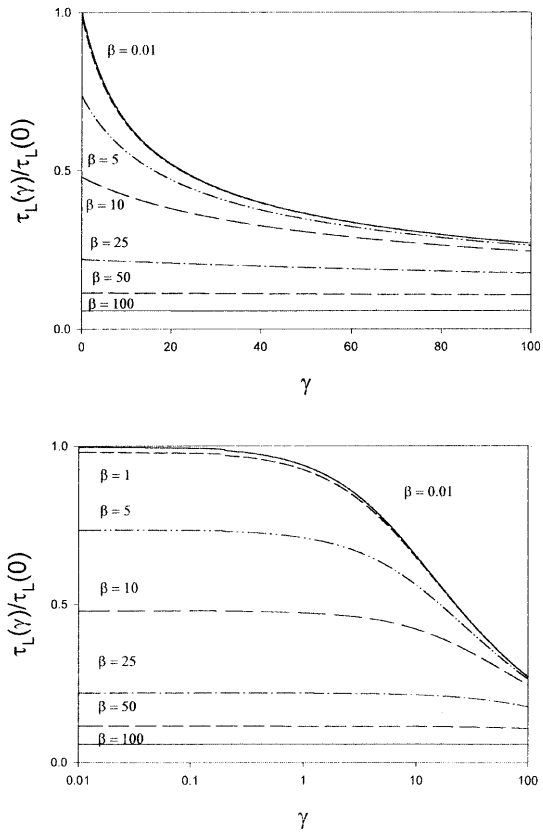


Fig. 12 Variation of normalised lag time ratio with the reaction/diffusion parameter γ. The curves were computed via Eq. 45 and various β values in the range 1–100 were used. The data are presented both in linear and semi-logarithmic format for clarity

$$= \frac{1}{p}\left\{\frac{\sinh[\sqrt{p}(1-\chi)]}{\sinh\sqrt{p}}\right\} \tag{A2}$$

which results in Eq. 9 of the paper.

We now use the complex inversion formula to invert Eq. 9. We recall that if $\bar{y}(p)$ represents the Laplace transform of a function $y(\tau)$, then according to the complex inversion formula we can state that:

$$y(\tau) = \frac{1}{2\pi i}\int_{c-i\infty}^{c+i\infty} \exp[p\tau]\bar{y}(p)\mathrm{d}p = \frac{1}{2\pi i}\oint_{c} \exp[p\tau]\bar{y}(p)\mathrm{d}p \tag{A3}$$

where the integration in Eq. A3 is to be performed along a line $p = c$ in the complex plane where $p = x + iy$. The real number c is chosen such that $p = c$ lies to the right of all the singularities, but is otherwise assumed to be arbitrary. In practice, however, the integral is evaluated by considering the contour integral presented on the r.h.s. of Eq. A3, which is evaluated using the so-called Bromwich contour. The contour integral is then evaluated using the residue theorem which states for any analytic function $F(z)$:

$$\oint_{c} F(z)\mathrm{d}z = 2\pi i\sum_{n} \mathrm{Res}[F(z)]_{z=z_n} \tag{A4}$$

where the residues are computed at the poles of the function $F(z)$. Hence from Eq. A3 we note that:

$$y(\tau) = \sum_{n} \mathrm{Res}[\exp[p\tau]\bar{y}(p)]_{p=p_n} \tag{A5}$$

From the theory of complex variables we can show that the residue of a function $F(z)$ at a simple pole at $z = a$ is given by:

$$\mathrm{Res}[F(z)]_{z=a} = \lim_{z\to a}\{(z-a)F(z)\} \tag{A6}$$

Hence in order to invert Eq. 9, we need to evaluate $\mathrm{Res}\left[\sinh[\sqrt{p\chi'}\,]/p\,\sinh\sqrt{p}\right]$ at the poles. Note that we have set $\chi' = 1 - \chi$. Now the poles are obtained from $p\,\sinh\sqrt{p} = 0$. Hence there is a simple pole at $p = 0$ (this will ultimately produce the steady state contribution to the concentration profile) and there are infinitely many poles given by the solution of the equation $\sinh\sqrt{p_n} = 0$ and so $p_n = -n^2\pi^2$ with $n = 1, 2, 3,$ These will ultimately produce the transient contribution to the concentration profile. Hence we note that:

$$\begin{aligned} u(\chi,\tau) &= \mathrm{Res}\left[\frac{\sinh[\sqrt{p}\chi']}{p\sinh\sqrt{p}}\right]_{p=0} + \mathrm{Res}\left[\frac{\sinh[\sqrt{p}\chi']}{p\sinh\sqrt{p}}\right]_{p=p_n} \\ &= \lim_{p\to 0}(p-0)\left\{\exp[p\tau]\frac{\sinh[\sqrt{p}\chi']}{p\sinh\sqrt{p}}\right\} \\ &\quad + \lim_{p\to p_n}(p-p_n)\left\{\exp[p\tau]\frac{\sinh[\sqrt{p}\chi']}{p\sinh\sqrt{p}}\right\} \end{aligned} \tag{A7}$$

The following Taylor series expansions of the hyperbolic terms are useful:

$$\begin{aligned} \frac{\sinh[\sqrt{p}\chi']}{\sinh\sqrt{p}} &\simeq \frac{\sqrt{p}\chi' + (\sqrt{p}\chi')^3/3! + \cdots}{\sqrt{p} + (\sqrt{p})^3/3! + \cdots} \\ &= \frac{\chi' + p\chi'^3/3! + \cdots}{1 + p/3! + \cdots} \end{aligned} \tag{A8}$$

Using this expansion we note that the first residue in Eq. A7 is given by:

$$\mathrm{Res}\left[\frac{\sinh[\sqrt{p}\chi']}{p\sinh\sqrt{p}}\right]_{p=0} = \lim_{p\to 0}\left\{\exp[p\tau]\left(\frac{\chi' + p\chi'^3/3! + \cdots}{1 + p/3! + \cdots}\right)\right\} = \chi' \tag{A9}$$

The second residue in Eq. A7 can be evaluated as follows. It is established that if $F(z)$ can be expressed as $F(z) = f(z)/g(z)$, where the functions f and g are analytic at $p = p_n$ and $g(p_n) = 0$ while $g'(p_n) \neq 0$ and $f(p_n) \neq 0$, then $\mathrm{Res}[F(z)]_{p=p_n} = \sum_{n=1}^{\infty} \frac{f(p_n)}{g'(p_n)} \exp[p_n\tau]$. Consequently from Eq. A7 we set $f(p_n) = \sinh\left[\sqrt{p_n}\chi'\right]/p_n$ and $g(p_n) = \sinh\sqrt{q_n}$. Noting that $p_n = -n^2\pi^2$ then $g'(p_n) = (1/2n\pi\mathrm{i})\cosh[n\pi\mathrm{i}] = \cos[n\pi]/2n\pi\mathrm{i} = (-1)^n/2n\pi\mathrm{i} \neq 0$. Also $f(p_n) = \sinh\left[\sqrt{-n^2\pi^2}\chi'\right]/(-n^2\pi^2) = \sinh[in\pi\chi']/(-n^2\pi^2) = \mathrm{i}\sin[n\pi\chi']/(-n^2\pi^2)$. Hence we can show that:

$$\mathrm{Res}\left[\frac{\sinh[\sqrt{p}\chi']}{p\sinh\sqrt{p}}\right]_{p=p_n} = \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{(-1)^n}{n}\sin[n\pi\chi']\exp[-n^2\pi^2\tau] \tag{A10}$$

and the concentration profile is given by:

$$u(\chi,\tau) = 1 - \chi - 2\sum_{n=1}^{\infty}\frac{1}{n\pi}\sin[n\pi\chi]\exp[-n^2\pi^2\tau] \tag{A11}$$

which is Eq. 10 in the text. In arriving at the result in Eq. A11 we have noted that $\sin[n\pi\chi'] = \sin[n\pi(1-\chi)] = -(-1)^n\sin[n\pi\chi]$. Note that the transient contribution to the concentration profile subtracts from the steady state contribution, as it should.

We now indicate the manner in which Eq. 14 of the paper is obtained. Using Eqs. 11 and 13 we obtain:

$$Q(\tau) = \int_0^{\tau}\left\{1 + 2\sum_{n=1}^{\infty}(-1)^n\exp[-n^2\pi^2\tau]\right\}\mathrm{d}\tau \tag{A12}$$

This expression simplifies to:

$$Q(\tau) = \tau + 2\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2\pi^2} - 2\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2\pi^2}\exp[-n^2\pi^2\tau] \tag{A13}$$

We recall that $\pi^2/12 = -\sum_{n=1}^{\infty}(-1)^n/n^2$. Hence using the latter identity we note that Eq. A13 reduces to Eq. 14 of the paper, as desired.

We note that the solution of the simple Fick diffusion expression presented in Eq. 3 of the paper can also be solved without using the complex inversion formula[3]. We begin with the Laplaced transformed diffusion equation presented in Eq. 7 and state that the latter expression admits the following solution:

$$\bar{u} = K_1\exp\lfloor\sqrt{p}\chi\rfloor + K_2\exp\lfloor-\sqrt{p}\chi\rfloor \tag{A14}$$

where

$$K_1 = -\frac{1}{p}\left\{\frac{1}{\exp[2\sqrt{p}] - 1}\right\} \qquad K_2 = \frac{1}{p} - K_1 \tag{A15}$$

Substituting Eq. A15 into Eq. A14, simplifying and noting that

$$\frac{1}{1 - \exp[-2\sqrt{p}]} = \sum_{n=0}^{\infty}\exp[-2n\sqrt{p}] \tag{A16}$$

we can show that Eq. A14 reduces to

$$\bar{u} = \sum_{n=0}^{\infty}\frac{\exp[-(2n+\chi)\sqrt{p}]}{p} - \sum_{n=0}^{\infty}\frac{\exp[-(2(n+1)-\chi)\sqrt{p}]}{p} \tag{A17}$$

This expression can be readily inverted to yield the normalised concentration profile by noting that for $k \geq 0$:

$$\mathrm{L}^{-1}\left\{\frac{\exp[-k\sqrt{p}]}{p}\right\} = \mathrm{erfc}\left[\frac{k}{2\sqrt{\tau}}\right] \tag{A18}$$

Applying the latter identity to Eq. A17 results in

$$u = \sum_{n=0}^{\infty}\mathrm{erfc}\left[\frac{2n+\chi}{2\sqrt{\tau}}\right] - \sum_{n=0}^{\infty}\mathrm{erfc}\left[\frac{2(n+1)-\chi}{2\sqrt{\tau}}\right] \tag{A19}$$

We compare the concentration profile predicted by Eq. A19 with that presented in Eq. A11 in Fig. 13a. It is clear from this figure that the expression in Eq. A19 involving the difference of two infinite series involving error function complement terms is completely equivalent to that presented in Eq. A11 for all values of the normalised time parameter τ.

We can differentiate Eq. A14 with respect to normalised distance to obtain an expression for the transient normalised flux in Laplace space:

$$\bar{\psi} = -\left(\frac{\partial\bar{u}}{\partial\chi}\right)_{\chi=1} = \frac{2\exp\lfloor-\sqrt{p}\rfloor}{\sqrt{p}\{1 - \exp[-2\sqrt{p}]\}} = 2p^{-1/2}\sum_{n=0}^{\infty}\exp[-(2n+1)\sqrt{p}] \tag{A20}$$

where we have used Eq. A16 in the analysis. The expression in Eq. A20 may be readily inverted by noting that

$$\mathrm{L}^{-1}\{p^{-1/2}\exp[-k\sqrt{p}]\} = (\pi\tau)^{-1/2}\exp\left[-\frac{k^2}{4\tau}\right] \tag{A21}$$

Hence we note that the transient diffusion flux is given by

$$\psi = \frac{2}{\sqrt{\pi\tau}}\sum_{n=0}^{\infty}\exp\left[-\frac{(2n+1)^2}{4\tau}\right] \tag{A22}$$

In Fig. 13b we compare Eq. A22 with Eq. 11 previously presented in the paper. We note that both expressions are totally equivalent.

We finally note that in Laplace space the normalised amount released into the receptor compartment is given by

$$\bar{Q} = \mathrm{L}\left\{\int_0^{\tau}\psi\,\mathrm{d}\tau\right\} = \frac{\bar{\psi}}{p} = 2\sum_{n=0}^{\infty}p^{-3/2}\exp[-(2n+1)\sqrt{p}] \tag{A23}$$

We immediately note that

$$\mathrm{L}^{-1}\left\{p^{-3/2}\exp[-k\sqrt{p}]\right\} = 2\sqrt{\frac{\tau}{\pi}}\exp\left[-\frac{k^2}{4\tau}\right] - k\,\mathrm{erfc}\left[\frac{k}{2\sqrt{\tau}}\right] \tag{A24}$$

Hence in real space the total quantity of material released into the receptor compartment at any time τ is given by

$$Q(\tau) = 2\sum_{n=0}^{\infty}(2n+1)\mathrm{erfc}\left[\frac{2n+1}{2\sqrt{\tau}}\right] - 4\sqrt{\frac{\tau}{\pi}}\sum_{n=0}^{\infty}\exp\left[-\frac{(2n+1)^2}{4\tau}\right] \tag{A25}$$

In Fig. 13c we compare Eq. A25 with Eq. 14 presented in the body of the paper. We note that both expressions produce exactly equivalent results. However, unlike Eq. 14, Eq. A25 does not immediately produce a term for the normalised lag time.

[3] Again we wish to convey our thanks to one of the referees for pointing out this method of approach.

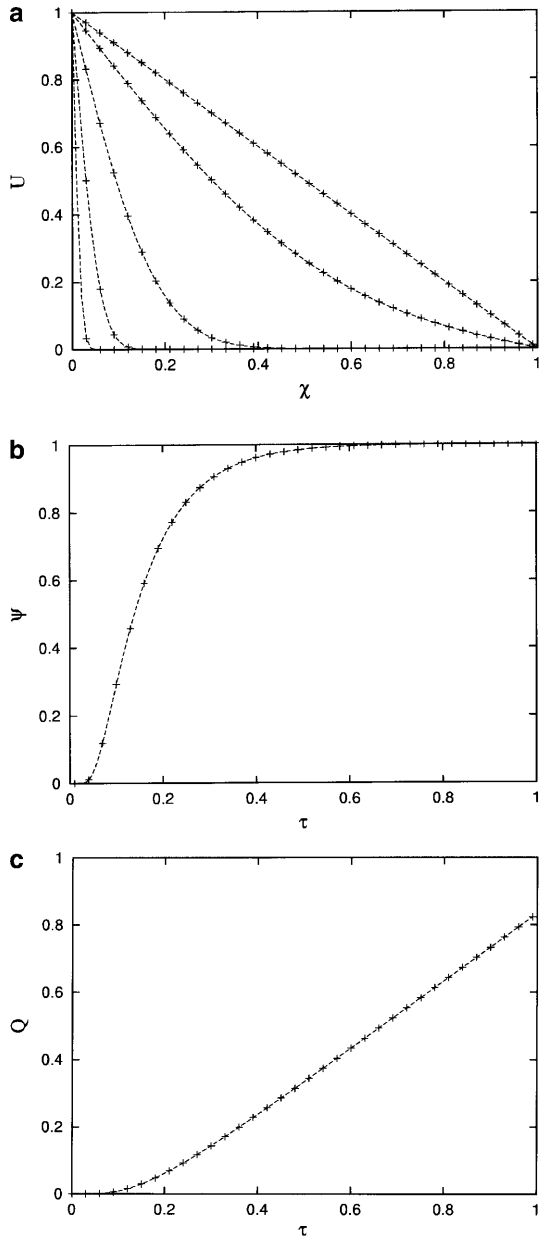


Fig. 13 **a** Typical concentration profiles computed using Eq. 10 (*dashed line*) and Eq. A19 (*discrete crosses*) for simple passive diffusion in a finite membrane. Values for the normalised time τ utilised in the computations are 1×10^{-4} (*bottom curve*), 1×10^{-3}, 1×10^{-2}, 0.1 and 1.0 (*top curve*). **b** Variation of normalised diffusion flux ψ with normalised time τ. The *dashed curve* corresponds to Eq. 11 and *discrete crosses* represent Eq. A22. **c** Variation of normalised release function Q with normalised time t. The *dashed curve* corresponds to Eq. 14 and *discrete crosses* represent Eq. A25

Appendix B

In this Appendix we indicate how Eq. 30 in the paper is derived. We begin with Eq. 28 and evaluate the constants A and B. When $\chi = 1$, $\bar{u} = 0$ and so from Eq. 28 we note that:

$$A = -B \tanh\left[\sqrt{\zeta + p}\right] \tag{B1}$$

Also when $\chi = 0$, $\bar{u} = 1/p$ and so

$$A = \frac{1}{p} \tag{B2}$$

From Eqs. B1 and B2 we get:

$$B = -\frac{1}{p \tanh\left[\sqrt{\zeta + p}\right]} \tag{B3}$$

Hence the normalised concentration profile in Laplace space is given by:

$$\begin{aligned}\bar{u}(\chi,p) &= \exp[\xi\chi]\left\{\frac{\cosh\left[\sqrt{\zeta+p}\chi\right]}{p} - \frac{\sinh\left[\sqrt{\zeta+p}\chi\right]}{p\tanh\sqrt{\zeta+p}}\right\} \\ &= \exp[\xi\chi]\left\{\frac{\cosh\left[\sqrt{\zeta+p}\chi\right]\sinh\sqrt{\zeta+p} - \sinh\left[\sqrt{\zeta+p}\chi\right]\cosh\sqrt{\zeta+p}}{p\sinh\sqrt{\zeta+p}}\right\} \\ &= \exp[\xi\chi]\left\{\frac{\sinh\left[\sqrt{\zeta+p}(1-\chi)\right]}{p\sinh\sqrt{\zeta+p}}\right\}\end{aligned} \tag{B4}$$

which is Eq. 30 of the paper.

We now indicate how Eq. B4 may be inverted using the Heaviside expansion theorem. We firstly set $\phi^2 = p + \zeta$ and hence $\sinh\left[\sqrt{\zeta + p}(1 - \chi)\right]/p\sinh \quad \sqrt{\zeta + p} = \sinh[\phi(1 - \chi)]/p\sinh\phi$. Now the Heaviside expansion theorem states that if we can express a Laplace transform as $\bar{y}(p) = f(p)/g(p)$ and if we can set $g(p) = (p - \alpha_1)(p - \alpha_2)\cdots(p - \alpha_n)$ where α_k, $k = 1, 2, 3\ldots$ are constants then the inverse Laplace transform is given by:

$$y(\tau) = \sum_{k=1}^{n} \frac{f(\alpha_k)}{g'(\alpha_k)} \exp[\alpha_k \tau] \tag{B5}$$

We need to evaluate the zero's of $p\sinh\phi = 0$. Clearly, $p = 0$ is a zero and the others are given by $\sinh\phi_n = -\mathrm{i}\sin[\mathrm{i}\phi_n] = 0$. Hence $\sin[\mathrm{i}\phi_n] = 0$ or $\phi_n = \mathrm{i}n\pi$, $n = 1, 2, 3$. Now $p_n = \phi_n^2 - \zeta = -n^2\pi^2 - \zeta$. Thus we have our roots. We can readily show that $\frac{\mathrm{d}}{\mathrm{d}p}\{p\sinh\phi\} = \sinh\phi + p\cosh\phi\frac{\mathrm{d}\phi}{\mathrm{d}p}$. Since $\phi = \sqrt{\zeta + p}$, then $\frac{\mathrm{d}\phi}{\mathrm{d}p} = \frac{1}{2\sqrt{\zeta+p}} = \frac{1}{2\phi}$. Hence $\frac{\mathrm{d}}{\mathrm{d}p}\{p\sinh\phi\}_{p=p_n} = \sinh\phi_n + p_n\cosh\phi_n\frac{1}{2\phi_n}$. We can obtain an expression for the concentration profile by considering each root in turn, $p = 0$ and $\mathrm{p} = p_n$ and using the Heaviside expansion formula presented in Eq. B5.

The term for $p = 0$ gives the steady state concentration profile. Here $\phi = \sqrt{\zeta}$ and so:

$$u_{\mathrm{S}}(\chi) = \exp[\xi\chi]\left\{\frac{\sinh\left[\sqrt{\zeta}(1 - \chi)\right]}{\sinh\sqrt{\zeta}}\right\} \tag{B6}$$

which is Eq. 32 of the paper. The transient contribution to the concentration profile is given by:

$$\begin{aligned}u_{\mathrm{T}}(\chi,\tau) &= \exp[\xi\chi] \\ &\times \sum_{n=1}^{\infty} \frac{\sinh\left[\sqrt{\zeta + p_n}(1 - \chi)\right]}{\left(\sinh\left[\sqrt{\zeta + p_n}\right] + \frac{p_n}{2\sqrt{\zeta+p_n}}\cosh\left[\sqrt{\zeta + p_n}\right]\right)} \\ &\times \exp[p_n\tau]\end{aligned} \tag{B7}$$

where $p_n = -n^2\pi^2 - \zeta = -n^2\pi^2 - \gamma - \beta^2/4$. We readily show that $\sinh\sqrt{\zeta + p_n} = \sinh[\mathrm{i}n\pi] = \mathrm{i}\sin[n\pi] = 0$. Also $p_n/2\sqrt{\zeta + p_n} = (-n^2\pi^2 - \zeta)/2\mathrm{i}n\pi$ and we note that $\cosh\sqrt{\zeta + p_n} = \cosh[\mathrm{i}n\pi] = \cos[n\pi] = (-1)^n$. We finally note that $\sinh\left[\sqrt{\zeta + p_n}(1 - \chi)\right] = \mathrm{i}\sin[n\pi(1 - \chi)] = -\mathrm{i}(-1)^n\sin[n\pi\chi]$. If we substitute the latter identities into Eq. B7 we obtain:

$$u_T(\chi,\tau) = -2\exp[\xi\chi]\sum_{n=1}^{\infty}\frac{n\pi\sin[n\pi\chi]}{n^2\pi^2+\zeta} \times \exp\left[-\left(n^2\pi^2+\zeta\right)\tau\right] \tag{B8}$$

which is Eq. 33 in the paper.

We now indicate how Eq. 37 is derived. The normalised release profile is given by:

$$Q(\tau) = -\int_0^{\tau}\left(\frac{\partial u}{\partial\chi}\right)_{\chi=1}\mathrm{d}\tau \tag{B9}$$

We differentiate Eq. B6 and set $\chi = 1$ to obtain:

$$\left(\frac{\mathrm{d}u_S}{\mathrm{d}\chi}\right)_{\chi=1} = -\sqrt{\zeta}\exp[\xi]\mathrm{cosech}\sqrt{\zeta} \tag{B10}$$

Similarly, from Eq. B8 we can show that

$$\left(\frac{\mathrm{d}u_T}{\mathrm{d}\chi}\right)_{\chi=1} = -2\exp[\xi]\sum_{n=1}^{\infty}\frac{(-1)^n n^2\pi^2}{n^2\pi^2+\zeta} \times \exp\left[-\left(n^2\pi^2+\zeta\right)\tau\right] \tag{B11}$$

Hence using Eq. B9 we obtain

$$\begin{aligned} Q(\tau) &= \int_0^{\tau}\sqrt{\zeta}\exp[\xi]\mathrm{cosech}\sqrt{\zeta}\,\mathrm{d}\tau \\ &\quad + 2\exp[\xi]\int_0^{\tau}\sum_{n=1}^{\infty}\frac{(-1)^n n^2\pi^2}{n^2\pi^2+\zeta}\exp\left[-\left(n^2\pi^2+\zeta\right)\tau\right]\mathrm{d}\tau \\ &= 2\exp[\xi]\sum_{n=1}^{\infty}\frac{(-1)^n n^2\pi^2}{\left(n^2\pi^2+\zeta\right)^2} + \sqrt{\zeta}\exp[\xi]\mathrm{cosech}\sqrt{\zeta}\tau \\ &\quad - 2\exp[\xi]\sum_{n=1}^{\infty}\frac{(-1)^n n^2\pi^2}{\left(n^2\pi^2+\zeta\right)^2}\exp\left[-\left(n^2\pi^2+\zeta\right)\tau\right] \end{aligned} \tag{B12}$$

which is Eq. 37 of the paper.

Appendix C

In this Appendix we discuss the use of the substitution presented in Eq. 34 of the paper as an alternative way of solving the RDM boundary value problem. We begin with Eq. 34 of the paper:

$$u(\chi,\tau) = \exp[\xi\chi]\exp[-\zeta\tau]\omega(\chi,\tau) \tag{C1}$$

and propose that ω obeys the simple Fick diffusion equation:

$$\frac{\partial\omega}{\partial\tau} = \frac{\partial^2\omega}{\partial\chi^2} \tag{C2}$$

Now the initial and boundary conditions for the u function are $u(\chi,0) = 0,\ u(0,\tau) = 1,\ u(1,\tau) = 0$. Utilising the latter conditions and substitution into Eq. C1 immediately yields that ω satisfies the following initial and boundary conditions:

$$\omega(\chi,0) = 0 \qquad \omega(0,\tau) = \exp[\zeta\tau] \qquad \omega(1,\tau) = 0 \tag{C3}$$

We now take Laplace transforms of Eq. C2 to obtain:

$$\frac{\mathrm{d}^2\overline{\omega}}{\mathrm{d}\chi^2} - p\overline{\omega} = 0 \tag{C4}$$

and the boundary conditions transform as

$$\overline{\omega}(0,p) = \frac{1}{p-\zeta}\ \ \overline{\omega}(1,p) = 0 \tag{C5}$$

The solution to Eq. C4 has the form:

$$\overline{\omega} = A\cosh\left[\sqrt{p}\chi\right] + B\sinh\left[\sqrt{p}\chi\right] \tag{C6}$$

Now when $\chi = 1$, $\bar{\omega} = 0$ and so $A = -B\tanh\sqrt{p}$. Also when $\chi = 0$, $\bar{\omega} = -1/(p-\zeta)$ and so $A = 1/(p-\zeta)$. Hence $B = -1/(p-\zeta)\tanh\sqrt{p}$. Substituting the latter results into Eq. C6 yields:

$$\begin{aligned} \overline{\omega} &= \frac{\cosh\left[\sqrt{p}\chi\right]}{p-\zeta} - \frac{\sinh\left[\sqrt{p}\chi\right]}{(p-\zeta)\tanh\sqrt{p}} \\ &= \frac{\cosh\left[\sqrt{p}\chi\right]\sinh\sqrt{p} - \sinh\left[\sqrt{p}\chi\right]\cosh\sqrt{p}}{(p-\zeta)\sinh\sqrt{p}} \\ &= \frac{\sinh\left[\sqrt{p}(1-\chi)\right]}{(p-\zeta)\sinh\sqrt{p}} \end{aligned} \tag{C7}$$

which must be inverted. This can be done using tables of inverse Laplace transforms to obtain:

$$\begin{aligned} \omega(\chi,\tau) &= \frac{\sinh\left[\sqrt{\zeta}(1-\chi)\right]}{\sinh\sqrt{\zeta}}\exp[\zeta\tau] \\ &\quad + 2\sum_{n=1}^{\infty}\frac{(-1)^n n\pi}{n^2\pi^2+\zeta}\sin[n\pi(1-\chi)]\exp[-n^2\pi^2\tau] \end{aligned} \tag{C8}$$

Substituting this result into Eq. C1 affords:

$$\begin{aligned} u(\chi,\tau) &= \frac{\sinh\left[\sqrt{\zeta}(1-\chi)\right]}{\sinh\sqrt{\zeta}}\exp[\xi\chi] \\ &\quad + 2\exp[\xi\chi]\sum_{n=1}^{\infty}\frac{(-1)^n n\pi}{n^2\pi^2+\zeta}\sin[n\pi(1-\chi)] \\ &\quad \times \exp\left[-\left(n^2\pi^2+\zeta\right)\tau\right] \end{aligned} \tag{C9}$$

which is equivalent to Eqs. 32 and 33 of the paper.

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