Biophysical Chemistry, 33 (1989) 303–310
Elsevier

BIOCHE 01365

Membrane transport equations with a time delay

A model for overshoot and oscillatory permeation

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Received 30 November 1988
Revised manuscript received 13 March 1989
Accepted 6 April 1989

Membrane transport; Time delay; Overshoot; Oscillatory permeation

Membrane transport equations with a time delay are proposed and their analytic solution is derived. This solution is found to exhibit under certain conditions overshoot and oscillatory permeation.

1. Introduction

Cell membrane permeation in some cases displays the phenomenon of overshoot (see, for example, refs. 1 and 2). Also, Ohara et al. [3] have recently observed oscillatory permeation of drugs into microcapsules with composite membranes. Oscillation is an important and interesting phenomenon observed in biological and chemical systems (see, e.g., ref.4). The purpose of the present paper is to demonstrate that membrane transport equations whose solution exhibits overshoot and oscillatory permeation can be derived by introducing a time delay into the usual membrane transport equations. The importance of the time delay has been emphasized in various fields, such as biology [5], ecology [6] and economics [7,8]. Since various small particles (mitochondria, Golgi bodies, microsomes, ribosomes, etc.) exist within the interior of a cell, trapping or accumulation of solutes inside the cell may occur during the permeation process, which may cause a time delay. In view of this factor, we introduce a time delay into the solute concentration in the cell interior.

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2. Membrane transport equations without time delay

Under quasi-steady-state conditions, permeation of diffusing solutes into cells through their membranes has often been described by the following transport equations [9]:

$$V_o \frac{dC_o(t)}{dt} = -JA, \tag{1}$$

$$V_i \frac{dC_i(t)}{dt} = +JA, \tag{2}$$

with

$$J = P[C_o(t) - C_i(t)] \tag{3}$$

where $C_o(t)$ and $C_i(t)$ denote the respective solute concentrations in the extracellular and intracellular regions at time t, J the solute flux flowing from the outside into the inside of the cell, V_o and

V_i the extracellular volume and total volume of the intracellular region, respectively, P membrane permeability and A the total area of the cell surface.

The solution to eqs. 1 and 2 (with eq. 3), subject to the initial conditions

$$C_o(0) = C_{o,0} \tag{4}$$

$$C_i(0) = 0, \tag{5}$$

is given by

$$C_o(t) = C_{o,0}(\phi e^{-\alpha t} + 1 - \phi), \tag{6}$$

$$C_i(t) = C_{o,0}(1-\phi)(1 - e^{-\alpha t}), \tag{7}$$

where

$$\phi = V_i/(V_o + V_i) \tag{8}$$

is the cell volume fraction and

$$\alpha = PA(1/V_o + 1/V_i). \tag{9}$$

Note that the following conservation relation holds between $C_o(t)$ and $C_i(t)$:

$$V_o C_o(t) + V_i C_i(t) = V_o C_{o,0}, \tag{10}$$

or

$$(1-\phi)C_o(t) + \phi C_i(t) = (1-\phi)C_{o,0}, \tag{11}$$

which implies that the membrane volume is small so that the amount of solutes within the membrane can be neglected.

The concentrations $C_o(t)$ and $C_i(t)$ given by eqs. 6 and 7 vary exponentially with time, tending monotonically to their equilibrium value $C_o(\infty) = C_i(\infty) = C_{o,0}(1-\phi)$ as $t \to \infty$, so that they exhibit neither overshoot nor oscillatory permeation.

3. Membrane transport equations with a time delay

Eq. 3 is based upon Fick's first law that the solute concentration difference induces the solute flux, where the concentrations refer to those at the same time instant. However, if there is a time delay τ required for solutes in the intracellular region, $C_i(t)$ in the flux J (eq. 3) should be replaced by $C_i(t-\tau)$, viz.,

$$J = P[C_o(t) - C_i(t-\tau)]. \tag{12}$$

Substituting eq. 12 into eqs. 1 and 2 subject to the initial conditions (eqs. 4 and 5), and using the conservation relation (eq. 11), we obtain the following equation for $C_o(t)$:

$$\begin{aligned}\frac{dC_o(t)}{dt} &= -\alpha\phi[C_o(t) - C_i(t-\tau)] \\ &= -\alpha[\phi C_o(t) + (1-\phi)C_o(t-\tau) \\ &\quad -(1-\phi)C_{o,0}E(t-\tau)],\end{aligned} \tag{13}$$

where $E(t)$ is a step function defined by

$$E(t) = \begin{cases} 1, & t > 0, \\ 0, & t < 0, \end{cases} \tag{14}$$

ϕ and α having already been defined by eqs. 8 and 9. Eq. 13 can easily be integrated numerically. In order to find an analytic solution to eq. 13, we use the Laplace transform of $C_o(t)$, viz.,

$$\bar{C}_o(p) = \int_0^\infty e^{-pt} C_o(t)\, dt. \tag{15}$$

We then obtain, from eq. 13,

$$\begin{aligned}\bar{C}_o(p) &= \frac{p + \alpha(1-\phi)e^{-\tau p}}{p[p + \alpha\phi + \alpha(1-\phi)e^{-\tau p}]} C_{o,0} \\ &= \left[\frac{1}{p} - \frac{\alpha\phi}{p}\sum_{n=0}^{\infty}(-1)^n \right. \\ &\quad \left. \times \frac{\{\alpha(1-\phi)\}^n}{(p+\alpha\phi)^{n+1}} e^{-n\tau p}\right] C_{o,0},\end{aligned} \tag{16}$$

which gives

$$\begin{aligned}&C_o(t)/C_{o,0} \\ &= 1 - \sum_{n=0}^{\infty}(-1)^n \left(\frac{1-\phi}{\phi}\right)^n \\ &\quad \times \left[1 - e^{-\alpha\phi(t-n\tau)}\left(\sum_{r=0}^{n}\frac{\{\alpha\phi(t-n\tau)\}^r}{r!}\right)\right] \\ &\quad \times E(t-n\tau),\end{aligned} \tag{17}$$

Once the expression for $C_o(t)$ has been established, $C_i(t)$ is calculated via the conservation relation (eq.11), viz.,

$$C_i(t)/C_{o,0} = \frac{1-\phi}{\phi}[1 - C_o(t)/C_{o,0}], \tag{18}$$

Note that, since eq. 17 involves the step functions $E(t-n\tau)$, the summation in eq. 17 is carried out over $0 \leqq n \leqq m$ $(m = 0, 1, 2, \ldots)$ for the time domain $m\tau < t < (m+1)\tau$. Expressions for $c_o(t)$ over the time domains $0 < t < \tau$ and $\tau < t < 2\tau$ are given below.

$$C_o(t)/C_{o,0} = \exp(-\alpha\phi t), \quad 0 < t < \tau, \tag{19}$$

$$C_o(t)/C_{o,0} = (1-\phi)/\phi + \exp(-\alpha\phi t) - (1-\phi)/\phi \cdot e^{-\alpha\phi(t-\tau)}[1+\alpha\phi(t-\tau)], \quad \tau < t < 2\tau, \tag{20}$$

4. Results and discussion

We have obtained the solution (eqs. 17 and 18) to the membrane transport equation with a time delay τ (eq. 13). On the basis of the fact that there are a number of small particles (ribosomes, etc.) within the cell, which are expected to trap or accumulate the diffusing solutes within the cell interior, we have introduced a time delay only into the intracellular concentration $C_i(t)$; therefore, in our model, the inside and the outside of the cell are not equivalent. When $\tau \to 0$, eqs. 17 and 18 reduce to eqs. 6 and 7, showing neither overshoot nor oscillatory behavior. In contrast, for large τ, eqs. 17 and 18 can exhibit both of phenomena. Note that the equilibrium values of $C_o(t)$ and $C_i(t)$ are the same as those in the case of no time delay, viz.,

$$C_o(t)/C_{o,0}, \quad C_i(t)/C_{o,0} \xrightarrow[t\to\infty]{} 1-\phi. \tag{21}$$

Some results are depicted in figs. 1–4. Figs. 1–3 display $C_o(t)/C_{o,0}$ and $C_i(t)/C_{o,0}$ plotted as functions of the scaled time, αt, for a cell volume fraction of $\phi = 0.5$, at three values of the scaled delay time $\alpha\tau$. Fig. 4 demonstrates the time course of $C_o(t)$ for higher values of $\alpha\tau$. One observes that for small τ there is neither overshoot nor oscillation whereas for large τ overshoot does occur and with further increase in τ damped oscillation appears. Note that the overshoot given by eqs. 17 and 18 does not represent a pure example of this phenomenon. Instead, the overshoot in our model is such that the amplitude of oscillation is damped

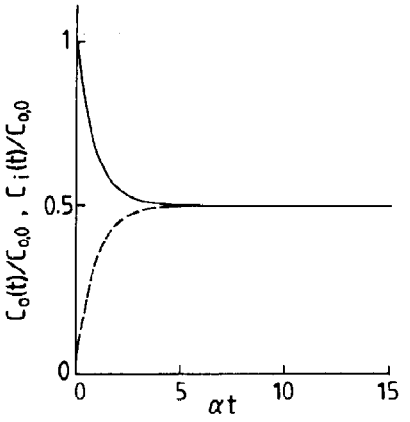

Fig. 1. Solute concentrations in the extracellular region, $C_o(t)$ (———), and intracellular region, $C_i(t)$ (- - - - -), plotted vs. dimensionless time αt for $\phi = 0.5$ and $\alpha\tau = 0.2$. $C_o(t)/C_{o,0}$ and $C_i(t)/C_{o,0}$ vary exponentially, tending to their equilibrium value $1-\phi$.

so rapidly that all extrema, except for the first minimum, are negligible and, therefore, that the oscillation is in practice observed as overshoot.

The reason why introduction of the time delay τ causes overshoot and oscillatory permeation can be explained as follows. During the time interval between $t = 0$ and $t = \tau$, only inward permeation, i.e., solute accumulation in the intracellular region, occurs following $C_o(t) = C_{o,0}\exp(-\alpha\phi t)$ (eq. 19) and $C_i(t) = \{(1-\phi)/\phi\}C_{o,0}(1-\exp(-\alpha\phi t))$. At the time instant $t = \tau$, in addition to inward

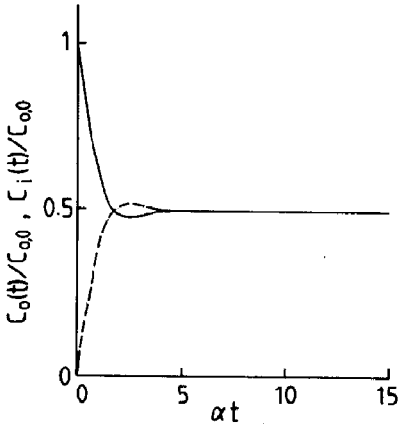

Fig. 2. Same as fig. 1, except for $\alpha\tau = 0.8$. $C_o(t)$ and $C_i(t)$ show overshoot.

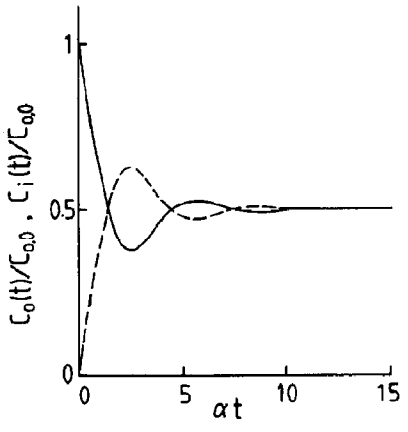

Fig. 3. Same as fig. 1, except for $\alpha\tau = 1.5$. $C_o(t)$ and $C_i(t)$ show oscillation.

permeation, outward permeation commences, i.e., solutes begin to diffuse out of the intracellular area into the extracellular region. Therefore, if τ is sufficiently large, the amount of solutes accumulated in the intracellular region between $t = 0$ and $t = \tau$ may exceed the equilibrium value $(1 - \phi)C_{o,0}$, resulting in overshoot or oscillation around the equilibrium value.

Introduction of the time delay in some cases may cause an instability in the process of oscillatory permeation, as discussed below. Let t_e and t_m represent the respective time instants at which $C_o(t)$ passes through the equilibrium level for the first time and which $C_o(t)$ has its first minimum. For $\phi \geqq 0.5$, the decrease in $C_o(t)$ during the time interval between $t = t_e$ and $t = t_m$ can never exceed the decrease between $t = 0$ and $t = t_e$ (i.e., $C_{o,0} - (1 - \phi)C_{o,0} = \phi C_{o,0}$). In this case, the oscillation is stable; in other words, the amplitude of the oscillation decreases with time (convergent oscillation). For $\phi < 0.5$, however, the decrease in $C_o(t)$ between $t = t_e$ and $t = t_m$ may be greater than that between $t = 0$ and $t = t_e$ if τ is very large. In this situation the oscillation becomes unstable, i.e., either (i) the oscillation amplitude increases with time (divergent oscillation), or (ii) the first maximum of $C_o(t)$ exceeds the initial value $C_{o,0}$, even if the oscillation amplitude decreases with time after the first minimum. For values of $\alpha\tau$ and ϕ at which the above cases occur, the present model cannot be used.

We have demonstrated that three different forms of the time course of $C_o(t)$ (and $C_i(t)$) appear, namely, a simple exponential-type monotonic change without oscillation, stable damped oscillation and unstable oscillation, depending on the magnitudes of $\alpha\tau$ and ϕ. Fig. 5 shows three regions, I–III, corresponding to the different time courses. In region I, $C_o(t)$ and $C_i(t)$ vary mono-

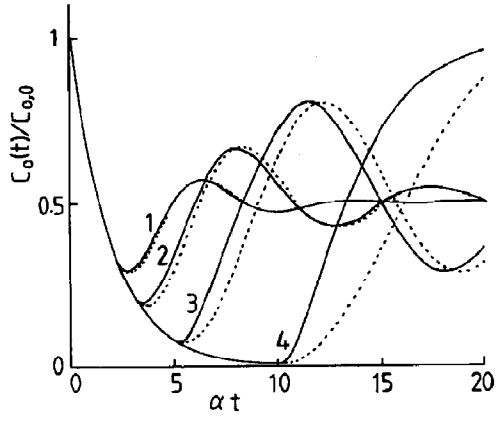

Fig. 4. Solute concentration $C_o(t)$ in the extracellular solution as a function of scaled time αt at $\phi = 0.5$ for several values of $\alpha\tau$. Curves: 1, $\alpha\tau = 2$; 2, $\alpha\tau = 3$; 3, $\alpha\tau = 5$; 4, $\alpha\tau = 10$. Dotted lines represent the approximate results (eq. 34).

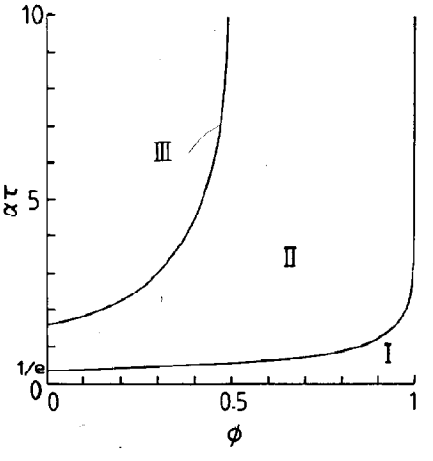

Fig. 5. Three regions I–III, in which different types of time course of $C_o(t)$ and $C_i(t)$ appear. I, monotonic exponential-type change without oscillation; II, stable oscillation; III, unstable oscillation. The boundary between I and II corresponds to values of $\alpha\tau$ and ϕ satisfying $\gamma = 1/e$ (γ defined by eq. 23).

tonically, tending to their equilibrium value. In region II, $C_o(t)$ and $C_i(t)$ show convergent oscillation around their equilibrium values. Region III corresponds to unstable oscillation. The boundaries between the three regions have been calculated from eq. 17. As shown later, the boundary between regions I and II coincides with $\gamma = 1/e$ (γ given in eq. 23).

When the values of $\alpha\tau$ and ϕ lie within region II, $C_o(t)$ and $C_i(t)$ show stable oscillation. Let us now consider the time instant at which $C_o(t)$ and $C_i(t)$ exhibit their extrema. Note that at the time instant where $C_o(t)$ reaches its maximum (or minimum), $C_i(t)$ shows its minimum (or maximum). The position of the extrema is given by setting $dC_o(t)/dt = -\{\phi/(1-\phi)\}\, dC_i(t)/dt = 0$. Differentiating eq. 17 with respect to t, we obtain

$$\sum_{n=0}^{\infty} \frac{(-1)^n}{n!}\gamma^n(t/\tau - n)^n E(t - n\tau) = 0, \qquad (22)$$

where

$$\gamma = \alpha(1-\phi)\tau \exp(\alpha\phi\tau). \qquad (23)$$

The solution to eq. 22 gives the positions of the extrema of $C_o(t)$ and $C_i(t)$. It is interesting to note that the position of the extrema (scaled by the delay time τ) may be determined by only one parameter, γ. Fig. 6 displays γ as a function of $\alpha\tau$ and ϕ in three-dimensional coordinates. Fig. 7 depicts the position of the extrema of $C_o(t)$ and $C_i(t)$ with respect to γ calculated via eq. 22. The curve for the initial minimum of $C_o(t)$ (or the first maximum of $C_i(t)$) has an asymptote $\gamma = 1/e$ and no extrema occur for $\gamma \leqq 1/e$. Hence only when $\gamma > 1/e$, do $C_o(t)$ and $C_i(t)$ exhibit oscillation. From this it follows that the boundary between regions I and II in fig. 5 is given by $\gamma = 1/e$. In the limit of large γ, the position of the extrema tends to $t/\tau = n$ ($n = 1, 2, \ldots$). Simple analytic expressions for the values of the time instants at which $C_o(t)$ and $C_i(t)$ have their extrema can be obtained provided they are located between $t = \tau$ and $t = 2\tau$ or between $t = 2\tau$ and $t = 3\tau$ (no extremum occurs between $t = 0$ and $t = \tau$). The results are:

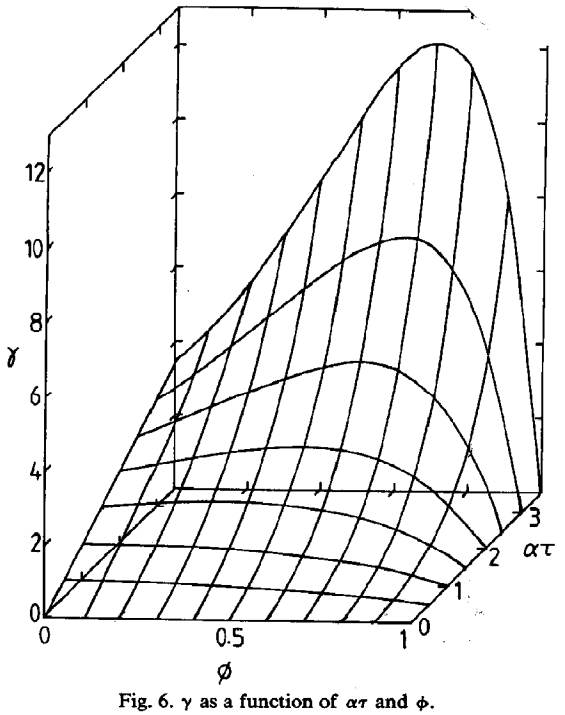

Fig. 6. γ as a function of $\alpha\tau$ and ϕ.

When $2 - \sqrt{2} \leqq \gamma < 1$, $C_o(t)$ (or $C_i(t)$) has its first minimum (or maximum) at $t = t_1$ ($2\tau < t_1 \leqq 3\tau$).

For $1 \leqq \gamma < 2 + \sqrt{2}$, $C_o(t)$ (or $C_i(t)$) has its first minimum (or maximum) at $t = t_2$ ($\tau < t_2 \leqq 2\tau$).

When $\gamma \geqq 2 + \sqrt{2}$, $C_o(t)$ (or $C_i(t)$) has its first minimum (or maximum) at $t = t_2$ and its initial maximum (or minimum) at $t = t_3$ ($2\tau < t_3 \leqq 3\tau$).

Here, t_1, t_2, and t_3 are defined by

$$t_1 = \tau\left[2 + \left\{1 - (2\gamma - 1)^{1/2}\right\}/\gamma\right], \qquad (24)$$

$$t_2 = \tau[1 + 1/\gamma], \qquad (25)$$

$$t_3 = \tau\left[2 + \left\{1 + (2\gamma - 1)^{1/2}\right\}/\gamma\right]. \qquad (26)$$

The exact solution (eq. 17) for $C_o(t)$ has different forms according to the particular time domains. We derive a simpler, approximate expression for $C_o(t)$ when $t > \tau$. If we assume $C_o(t)$ to be in the form $C_{o,0}[K \exp(pt) + (1-\phi)]$, where K is a constant and p may be a complex number, then p can be given by the poles of $C_o(p)$ (eq.

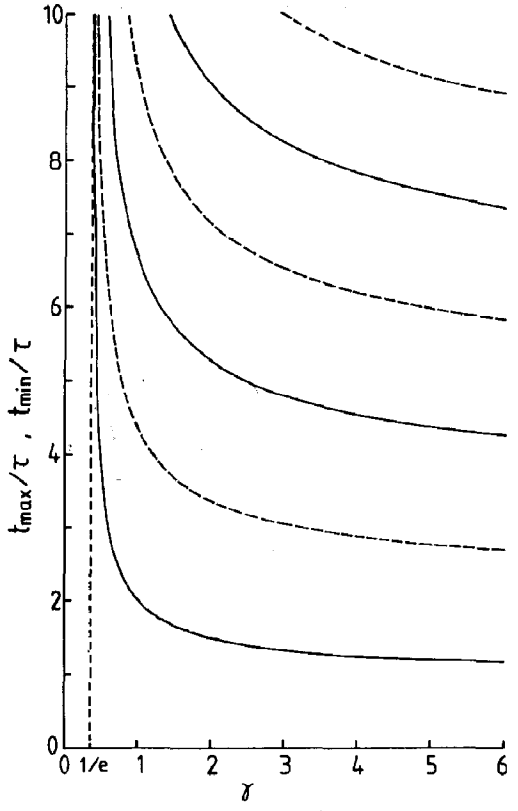

Fig. 7. Positions of maxima (t_{max}) and minima (t_{min}) of $C_o(t)$ and $C_i(t)$ as functions of γ. Solid curves, minima of $C_o(t)$ (maxima of $C_i(t)$); dashed curves, maxima of $C_o(t)$ (minima of $C_i(t)$). Dashed vertical line denotes the asymptote $\gamma = 1/e$.

16) i.e., by the solution to the characteristic equation,

$$r + \gamma \exp(-r) = 0 \tag{27}$$

with

$$r = (p + \alpha\phi)\tau \tag{28}$$

which appears in the denominator of the first equation of eq. 16. An equation similar to eq 27 has been considered by Frisch and Holme [7]. Let us firstly deal with the case $\gamma \leqq 1/e$. Here, $C_o(t)$ and $C_i(t)$ show an exponential-type change with time. In accordance with this, we then seek real roots of eq. 27, which has indeed a negative root $r = x$ for a given value of γ. Matching the solutions for $0 < t < \tau$ (eq. 19) and for $t > \tau$ at $t = \tau$, one can determine the value of the constant K with the result that

$$C_o(t)/C_{o,0} = K_1 \exp[(x/\tau - \alpha\phi)(t - \phi)] + 1 - \phi, \quad t > \tau, \tag{29}$$

with

$$K_1 = \exp(-\alpha\phi\tau) - (1 - \phi). \tag{30}$$

Since $x < 0$, $C_o(t)$ given by eq. 29 decays monotonically to the equilibrium value $(1 - \phi)C_{o,0}$. Consider next the case $\gamma > 1/e$, where $C_o(t)$ and $C_i(t)$ show oscillation. In this situation, eq. 27 has many imaginary roots for a given value of γ, corresponding to oscillations. Substituting $r = x \pm iy$ ($y > 0$) into eq. 27 (when r is the solution to eq. 27, the conjugate value r^* also satisfies eq. 27), we obtain the following equations which are satisfied by x and y

$$\gamma = y/\sin y \cdot \exp(-y/\tan y), \tag{31}$$

$$x = -y/\tan y. \tag{32}$$

Note that y represents the frequency of oscillation and

$$T = 2\pi\tau/y \tag{33}$$

corresponds to the period of oscillation. It can be shown that the smallest root y lies within the range $(0, \pi)$ together with a series of higher values of y in the ranges $(2\pi, 3\pi)$, $(4\pi, 5\pi)$... The exact solution (eq. 17) contains all of the contributions for every frequency y. However, the smallest y (or, the longest period T) can be expected to make a major contribution, since higher frequency oscillations (or longer period oscillations) complete their cycles within the delay time so that they contribute less to the entire time course of $C_o(t)$. On the basis of this idea, we derive an approximate formula for $C_o(t)$ by retaining only the smallest y and neglecting contributions from higher frequencies. Matching $C_o(t)$ and $dC_o(t)/dt$ with those for $0 < t < \tau$, we obtain

$$C_o(t)/C_{o,0} = \exp[(x/\tau - \alpha\phi)(t - \tau)] \times [K_1 \cos\{y/\tau \cdot (t - \tau)\} + K_2 \sin\{y/\tau \cdot (t - \tau)\}] + 1 - \phi, \quad t > \tau, \tag{34}$$

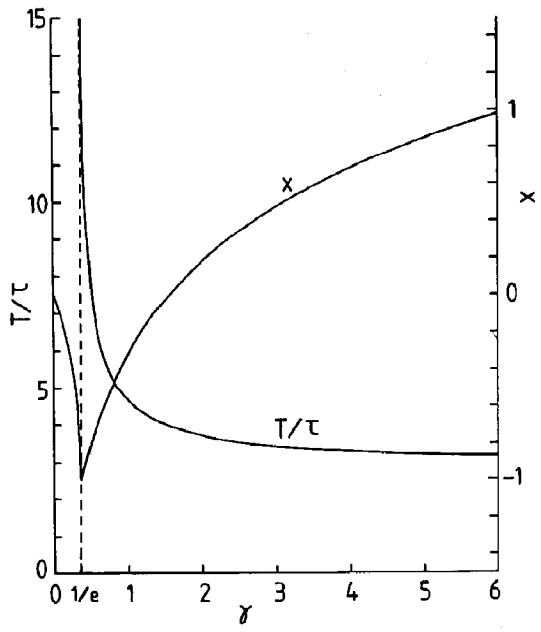

Fig. 8. Values of the longest period T ($= 2\pi\tau/y$) and the corresponding x values appearing in eq. 34 as functions of γ ($> 1/e$). The value of x in eq. 29 is also plotted vs. γ ($\leqq 1/e$).

where K_1 is given by eq. 30 and

$$K_2 = -\left[xK_1 + \alpha\phi\tau(1-\phi)\right]/y. \tag{35}$$

Excellent agreement is obtained between the approximate results (eqs. 29 and 34) and the exact results for small $\alpha\tau$. In figs. 1–3, the approximate and exact results agree within the linewidth. In fig. 4, the approximate results are denoted by dotted lines. Deviation from the exact results increases as $\alpha\tau$ increases, implying that contributions from higher values of y are not negligible for large τ. In fig. 8, the values of the longest period T and the corresponding values of x are plotted as functions of γ ($> 1/e$) together with the values of x for $\gamma \leqq 1/e$. In order for oscillation to be stable (or, convergent), it is necessary that the real part of p is negative. This is a necessary but not sufficient condition for stable oscillation. That is, even if Re p is negative, the first maximum of $C_o(t)$ may exceed $C_{o,0}$ when $\phi < 0.5$ and $\alpha\tau$ is very large. In accordance, above the boundary between regions II and III in fig. 5, there occurs a boundary between the region for Re $p > 0$ and that for Re $p < 0$.

The prediction from the present model is of oscillation around the final equilibrium level. On the other hand, Ohara et al. [3] observed that, for permeation of a number of drugs into microcapsules with composite membranes, the drug concentration outside the microcapsules shows exponential-type decay modulated by sinusoidal change. It is possible to obtain this type of time course for the solution concentration in the extracellular phase by assuming that there exist sites in the intracellular phase that adsorb solutes irreversibly. Then, eq. 13 is modified as follows:

$$\frac{dC_o(t)}{dt} = -\alpha\phi\left[C_o(t) - C_i(t-\tau)\right] - \beta\phi C_o(t), \tag{36}$$

where the second term on the right-hand side corresponds to irreversible adsorption of solutes in intracellular phases, β denoting a constant. An example of results calculated via eq. 36 is given in fig. 9, which shows that as $\alpha\tau$ increases, oscillatory behavior becomes appreciable whereas it disappears for $\alpha\tau \to 0$. Lee and Lee [10] have recently, proposed a theory that differs completely from ours, to explain the data of Ohara et al. [3]. Although further experimental analyses on the system considered by Ohara et al. [3] would be required for detailed comparison between the present theory and that of Lee and Lee [10], which

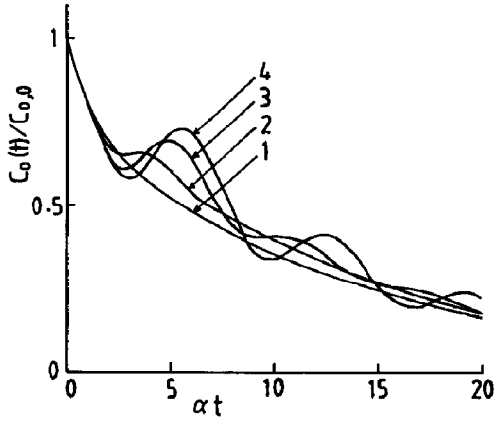

Fig. 9. Exponential-type decay modulated by sinusoidal change of the solute concentration in the extracellular solution. Calculated using eq. 36 for $\phi = 0.2$ and $\beta = 0.5\alpha$. Curves: 1, $\alpha\tau = 0$; 2, $\alpha\tau = 1$; 3, $\alpha\tau = 1.5$; $\alpha\tau = 1.8$.

involve quite different parameters, we believe that the time delay plays a particular role in oscillatory permeation and overshoot.

References

1 R. Neihof and K. Soliner, J. Phys. Chem. 61 (1957) 159.
2 N. Takeguchi, I. Horikoshi and S. Tanaka, Bull. Chem. Soc. Jap. 48 (1957) 3044.
3 Y. Ohara, M. Arakawa, T. Kondo and K.B. Lee, J. Membrane Sci. 23 (1985) 1.
4 P. Glansdorff and I. Prigogine, Thermodynamic theory of structure, stability and fluctuations (Wiley, London, 1971).
5 J.B. Milsum, Biological control systems analysis (McGraw-Hill, New York, 1967).
6 R.M. May, Nature 261 (1976) 459.
7 R. Frisch and H. Holme, Economics 3 (1935) 225.
8 R.G.D. Allen, Mathematical economics (Macmillan, London, 1956).
9 W. Jost, Diffusion in solids, liquids, gases (Academic Press, New York, 1960) p. 11.
10 K.B. Lee and Y.H. Lee, J. Microencapsulation 6 (1989) 59.