A model for capillary exchange

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JOHNSON, JOHN A., AND THEODORE A. WILSON. A model for capillary exchange. Am. J. Physiol. 210(1): 1296-1303. 1966.—A mathematical model based on previous experimental work for material exchange across capillary walls is developed for the case where both capillary flow and transcapillary exchange are taken into account. Solutions are given for very early times and for later times for which an asymptotic solution was obtained. These solutions give intracapillary concentration profiles as well as the concentration in the extracellular space as a function of time. The asymptotic solutions indicate that the rate constant for the tissue buildup is $Q/V(1 - e^{-PA/Q})$ when $Q$ is the perfusion rate, $V$ the tissue volume, $P$ the permeability coefficient, and $A$ is the capillary area. The early time solutions predict that there will be appearance of transported substance in the capillary at points beyond the convected material because of an extracellular space shunt due to the rapid extracellular diffusion postulated in the model. In the discussion criticisms are given of other models concerned with the quantification of transcapillary exchange.

**Abstract**

The complexity of the capillary circulation in many tissues has made it difficult to achieve a general, quantitative treatment of transcapillary exchange. This means that each tissue must be examined carefully to see if certain simplifying assumptions are plausible in order to set up models which lead to tractable equations. The following work grew out of an interest in transport of nonelectrolytes in the isolated perfused heart. The perfusion of this organ appears to be reasonably homogeneous and the extravascular diffusion distances are small.

Arguments have been put forward by Schafer and Johnson (14) that, for materials such as sucrose and inulin in the isolated heart, transport in the extracellular space is fast compared with passage across the capillary wall. This led us to consider the following model: A capillary penetrates a region in which the extracellular concentration of a substance is homogeneous with respect to its spatial distribution. Within the capillary, however, the substance is a function of both distance along the capillary and time. It is assumed that within the capillary there is no radial variation in concentration. The flow through the capillary is assumed to be block flow. This last assumption is an oversimplification, however, as Prothero and Burton (11) have pointed out it is more likely to be true when erythrocytes are present. The transported substance is also assumed to be conserved.

This model leads to two coupled equations (1) and (2) describing the concentration in the capillary and outside it in the extracellular space.

\[ \pi r^2 \frac{\partial C}{\partial t} + \pi r^2 \frac{\partial C}{\partial x} = 2\pi r h(C_t - C) \]  
\[ V \frac{\partial C_t}{\partial t} = \int_0^l 2\pi r h(C - C_t) \, dx \]

Where $r$ is the radius of the capillary, $C$ the concentration at a point within the capillary, $C_t$ the concentration outside the capillary in the tissue space, $V$ the volume of tissue space surrounding the capillary available for diluting the solute, $t$ represents time, $h$ the permeability coefficient of the capillary wall to the substances in question, $x$ distance along the capillary, $l$ is the length of the capillary, and $u$ the velocity of the fluid flowing through the capillary.

We seek a solution of these equations in which the following boundary and initial conditions are satisfied:

\[ C(x = 0, t > 0) = 1, \quad C(x, t = 0) = 0 \quad \text{and} \quad C_t(t = 0) = 0. \]

Introducing the nondimensional variables $\xi = x/l$ and $\tau = ut/l$ the equations become:

\[ \frac{\partial C}{\partial \xi} + \frac{\partial C}{\partial \tau} = \alpha(C_t - C) \]  
\[ K \frac{\partial C_t}{\partial \tau} = \alpha \int_0^1 (C - C_t) \, d\xi \]

where $K = V/\pi r^2 l$ and $\alpha = 2hlru$ are the appropriate nondimensional parameters of the problem. The char-
acteristic time required for the concentration in the tissue space to relax to its new equilibrium value is of the order of \( K/\alpha \) if \( \alpha < 1 \) or \( K \) if \( \alpha > 1 \).

A formal solution of the equations can be obtained by the method of the Laplace transform. The transformed dependent variables in the transform variables will be denoted by a bar.

\[
C(\xi, \tau) = \int_0^\infty e^{-s\tau} C(\xi, \tau) \, d\tau
\]

\[
\bar{C}(\xi) = \int_0^\infty e^{-s\tau} \bar{C}(\tau) \, d\tau
\]

In terms of the transformed variables, equations 3 and 4 take the form given by equations 5 and 6.

\[
s\bar{\xi} + \frac{\partial \bar{C}}{\partial \xi} = \alpha (\bar{C}_t - \bar{C})
\]

\[
sK\bar{C}_t = \alpha \int_0^1 (\bar{C} - \bar{C}_t) \, d\xi
\]

The solution of these equations is given by equations 7 and 8.

\[
\bar{C} = \frac{1}{s} - \frac{c_0}{s} + \frac{(1 - c_0)(1 - c_0\xi)}{s[P(s) - e^{-\alpha\xi}]} \tag{7}
\]

\[
\bar{C}_t = \frac{(\alpha + \xi)(1 - e^{-\alpha\xi})}{\alpha s[P(s) - e^{-\alpha\xi}]} \tag{8}
\]

\( P(s) \) is a cubic given by equation 9.

\[
P(s) = \frac{(K/\alpha^2)s^3 + [(2K + 1)/\alpha]s^2 + (K + 1)s + 1}{(K^2 + K + 1)[\alpha(s^3 + 1) + \alpha(s^2 + 1) + \alpha(s + 1)]} \tag{9}
\]

\( P(s) \) is a cubic given by equation 9.

Each of the terms has a known inverse and the behavior for \( \tau < n \) could in principle be obtained by keeping \( n \) terms in the series. The algebra quickly becomes overwhelming and this expansion procedure is only useful in cases for which the characteristic time is of the order of one. By keeping only the first term an explicit solution can be obtained for \( \tau < 1 \). For \( \tau < 1 \) we have

\[
C = 1(\tau - \xi)\xi^{-a} + \int_{\tau - \xi}^\tau f(\xi) \, d\xi
\]

\[
\bar{C}_t = \frac{1}{\alpha} f'(\tau) \tag{10}
\]

\[
f = f + \frac{1}{\alpha} f'(\tau) + \frac{1}{\alpha} \left[ A_1 \xi + A_2 \xi^2 + A_3 \xi^3 \right] \tag{11}
\]

where \( s_1, s_2, \) and \( s_3 \) are the roots of \( P(s) \) and \( A_1, A_2, \) and \( A_3 \) are the coefficients of the partial fraction expansion of \( [P(s)]^{-1} \).

\[
\begin{bmatrix}
A_1 + A_2 + A_3 = 0 \\
A_2(s_1 + s_2) + A_3(s_1 + s_3) + A_3(s_1 + s_2) = 0 \\
A_3(s_2 s_3) + A_2(s_1 s_3) + A_1(s_1 s_2) = 1
\end{bmatrix}
\]

Relations (13) can be shown to be the requirements that must be met to satisfy the given boundary and initial conditions.

In Figs. 1, 2, and 3, solutions are shown for various

![FIG. 1. A display of curves relating concentration in the capillary (relative to that at the arterial end) to fractional distance along the capillary for the case where \( K = 5 \) and \( \alpha = 5 \). Concentration is indicated on ordinate and distance along the capillary is indicated on abscissa. Horizontal line segments indicate the values of the relative tissue concentration for different values of \( \tau \).](http://ajplegacy.physiology.org/doi/10.220.32.247/proxy?url=https://ajplegacy.physiology.org/doi/10.220.32.247/proxy?url=https://ajplegacy.physiology.org/doi/10.220.32.247/proxy)
values of the parameters $K$ and $a$. In Fig. 4, the venous concentration just before the arrival of the convected concentration jump ($r = 1$) and just after its arrival ($r = 1^+$) is plotted as a function of $K$ and $a$. Although the values of the concentration shown in Fig. 4 are complicated functions of $K$ and $a$, the difference between the concentrations just before and after the jump for a given $K$ is a simple function of $a$.

$$C(\xi = 1, r = 1^+) - C(\xi = 1, r = 1^-) = e^{\alpha}$$ (14)

In most cases, the characteristic time will be large compared to one and the asymptotic solution of equations 1 and 2 will provide the most useful description. In order to obtain the asymptotic behavior of $C$, the transform of $C - 1$ must be put in the form $g(s)/(s - s_0)$ where $s_0$ is the solution of equation 15 with the largest real part.

$$P(s) = e^{-(\alpha + \beta) s} = 0$$ (15)

then

$$C \sim 1 + g(s_0)e^{\alpha s}$$

If $K$ is large as is frequently the case an approximate value of $s_0$ can be obtained by considering the linear terms in $s$ in equation 15.

$$s_0 \approx -(1 - e^{-\alpha})/K$$ (16)

$$C \sim 1 - (1 - e^{-2\alpha}) e^{\alpha s}$$ (17)

$$C_1 \sim 1 - e^{\alpha s}$$ (18)

Equation 18 verifies the earlier statement that the characteristic relaxation time for the process is the larger of the two numbers $K$ and $K/\alpha$.

If the approximation for large $K$ is not appropriate then equation 15 must be solved numerically for $s_0$, and the asymptotic forms for $C$ and $C_1$ are given by equations 19 and 20.

$$\frac{a^2(1 - e^{-(\alpha + \beta) s})(1 - e^{-(\alpha + \beta) s_0})c_s}{[gKs^2 + 2a(2K + 1)s + \alpha^2(K + 1) + \alpha^2e^{-(\alpha + \beta) s_0}]^{1/2}}$$ (19)

$$C_1 \sim 1 + \left(\frac{\alpha + s_0}{\alpha}\right)$$ (20)

In Fig. 5 the exact value of $s_0$ computed from equation 15 is compared with the approximation given by equation 16 for various values of $K$ and $a$. The best agreement between the approximate and exact values is obtained in the region in which the asymptotic solution is most valuable.

**DISCUSSION**

It is of interest to compare the results of this paper with related work that has appeared in the literature. Morales and Smith (7) wrote extensively on the exchange of materials between blood and tissues. They averaged the capillary concentration and thus avoided the use of partial differential equations. This, however, precluded any description of the capillary concentration profile. Schmidt (15, 16) set up partial differential equations for exchange of materials at tissues including the parameters of plasma flow and capillary permeability and, in
addition, included factors for the influence of diffusion in the extracellular space. However, because of the complexity of the resulting Laplace transforms he did not try any complete inversion but attempted to approximate the solution for certain limiting cases in which all early events are neglected. Cotlove (2) applied some of Schmidt's equations in the uptake of materials in muscle and tendon.

Renkin (12) and Crone (3) have also dealt with mathematical models of capillary transport. However, they have neglected back exchange from the tissues and also have assumed that the concentration at a point within the capillary changes slowly compared with the change with distance along the capillary. This would be the same as solving equation 1 in our paper for the simplified case of $\partial C/\partial t = 0$ and $C_1 = 0$.

Perl (9) has given a very interesting account of exchange for both heat and material. He has dealt with functional units which involve more course graining than we have and has included the influence of capillary flow on transport between these functional units.

Goresky (4) has devised a model which seems to be peculiarly suited to the liver. Here the exchanging units all apparently have concurrent flow, the radial diffusion distances are small, and the longitudinal distances are large. This anatomical arrangement has led Goresky to assume that diffusion in a radial direction is rapid compared to the transfer of material by flow in the capillary. This treatment neglects any influence of the capillary wall and therefore cannot be used to detect or predict the influence of capillary permeability on exchange in the liver. This may, however, be justified in that organ. A somewhat similar model including capillary permeability has been given by Sangren and Shepperd (13).

Bellman, Jacquez, and Kalabe (1), in attempting to give a quantitative approach to the distribution and uptake of drugs in organs, have set up differential equations similar to Schmidt's and to those in this paper. They, however, give no information on solutions showing short time behavior which they say is a "difficult problem analytically." Their asymptotic solution assumes a linear profile within the capillary and this would appear to be useful only for those cases where the permeability is relatively low.

Martin and Yudilevich (6) have proposed a model for quantification of transcapillary exchange of substances by a tracer-dilution method. They then apply their technique to experimental work they have carried out on the isolated perfused dog heart (17). Permeability surface products are calculated by a relationship which they say has been justified by Crone (3) and Renkin (12). However, for the substances used (sodium, iodide, and rubidium) the criticism given by Schafer and Johnson (14) would appear to make the interpretation invalid. The criticism has to do with applying the extraction ratio to substances which approach the flow-limited case, in which case the permeability coefficient ratio can appear to be close to unity when actually this may not be true at all. Furthermore, it is stated by Yudilevich and Martin (17) that the extraction ratio $E = 1 - \lim_{t \to \infty} c(t)/C(t)$ is one in the flow-limited case. $C(t)$ is the venous concentration of the reference tracer which does not pass across the capillary walls and $c(t)$ is the venous concentration of the permeable tracer. That this is not true for finite values of $K$ (extracapillary-capillary volume ratio) can be seen from examining Fig. 4 of this paper. If we take $C(t)$ to be one ($C(0) = 1$, $\tau = 1^+$ for $\alpha \to 0$) and $c(t) = C(\xi = 1, \tau = 1^+)$ for $\alpha$ large) we see that the ratio $c(t)/C(t)$ can approach zero only if $K \to \infty$. This would indicate that, at least as far as the model presented here is concerned, a flow-limited case would not give $E = 1$ but would approach 1 only for large $K$.

To the extent that the present model does not consider factors such as the velocity distributions within blood vessels and varying path lengths between the larger arteries and veins its practical application may seem limited. However, it does focus attention on and predicts what will be the influence of some of the important variables in the problem of blood tissue exchange. For example, it clearly indicates the importance of the permeability to blood flow ratio on the intracapillary concentration profile. At high values of $\alpha$ the intracapillary concentration is essentially equal to the tissue space concentration over most of its length. This gives a flow-limited pattern where the flow-to-tissue volume ratio determines the kinetics of distribution. See for example reference 5 for experimental results which are consistent with this situation. In this case most of the capillary area is not used for the transfer of material. The very small area over which some difference between capillary and tissue space concentration exists is of importance, however, for the osmotic transfer of fluid which occurs even for highly permeable substances such as sodium chloride in the heart (Johnson, unpublished work) and skeletal muscle (8). The negligible utilization of a large

![Graph](image-url)
fraction of the capillary area which exists for highly permeable substances such as cyclopropane and nitrous oxide has been used by Perl et al. (10) as an explanation for the relative importance of diffusive gas transfer from adjacent tissues in adipose tissue. As methods improve and we are able to obtain an early sample of blood at the venous end of the capillary the relationships given in Fig. 4 should be of help in obtaining information about the permeability of the capillaries if the other parameters such as flow velocity and ratio of extracellular space-to-capillary volumes are known.

If the over-all transport process is slow enough to allow samples to be taken (the relaxation time should be longer than a few seconds with present techniques) and if \( K \) is large enough so that the tissue concentration can be determined by subtracting the concentration due to the blood, then tissue sampling can be used to estimate \( C_t \) as was done by Schafer and Johnson (14). Under these circumstances equations 16 and 18 can be used. When the symbols are the same as those used by Schafer and Johnson we find from equation 18 that the rate constant for the tissue buildup is:

\[
\frac{Q}{V + V_{cap}} \left( 1 - \exp \left( -\frac{PA}{Q} \right) \right)
\]

where \( Q \) is the perfusion rate, \( V \) the tissue volume, \( P \) the permeability coefficient (defined as \( h \) in this paper), and \( A \) the capillary area. Schafer and Johnson give as the rate constant

where \( V_{cap} \) is the capillary volume. Since, when \( K \) is large, \( V + V_{cap} \simeq V \) the two results are essentially the same. The rate constant obtained by Schafer and Johnson came from a limiting case of an equation given by Schmidt (16) which included diffusion in the extracellular space.

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REFERENCES