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OXYGEN CONCENTRATION PROFILES IN CAPILLARIES AND LIVING TISSUES FOR GENERAL LINEAR KINETICS WHEN AXIAL DIFFUSION IS CONSIDERED

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Blum (1960) obtained the oxygen concentration profiles in the living tissues for zero order kinetics i.e. he discussed the case when the metabolic rate function $d(c)$ in the tissue is a constant g_0, where c is the oxygen concentration. We consider the more general linear case when $d(c) = g_0 + kc$ which includes both zero-order kinetics $d(c) = g_0$ and first-order kinetics $d(c) = kc$ as special cases. This also enables us to give a method for the more realistic non-linear Michaelis-Menten kinetics. However Blum's solution and our generalisation of his solution are only partially successful since these are shown to be strictly valid only when in the capillary region, both axial diffusion and capillary convection can be neglected. We therefore give an alternative technique, based on Galerkin's method, for solving the partial differential equations for the tissue and capillary regions, which are coupled by the boundary conditions at the capillary wall.

1. THE BASIC EQUATIONS AND BOUNDARY CONDITIONS

The fundamental structure used is the Krogh (1919 a, b) cylinder wherein diffusion takes place from blood flowing in a capillary of radius r_c to a surrounding coaxial cylindrical tissue of outer radius r_t which is a surface of no flux. In the steady case, let $c_1(r, z)$ and $c_2(r, z)$ be the concentrations of oxygen at the point (r,z) in the tissue region $(r_{c+0} \leqslant r < r_t, 0 \leqslant z \leqslant h)$ and the capillary region $(0 \leqslant r \leqslant r_{c-0}, 0 \leqslant z \leqslant h)$ respectively (Fig. 1).

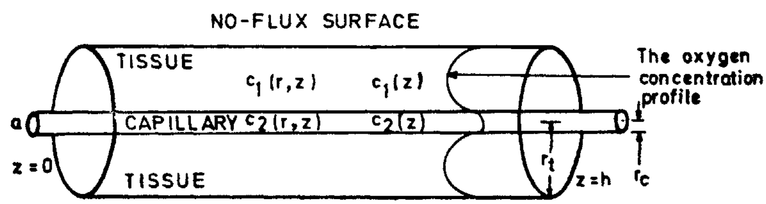

FIG. 1. The Krogh Cylinder.

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Let D_{1r} and D_{1z} be the diffusivities of oxygen in the tissue region in the radial and axial directions respectively and let the metabolic rate function be given by

$$d(c_1) = g_0 + kc_1 \qquad ...(1)$$

then the basic diffusion equation for the tissue region is

$$D_{1r}\left(\frac{\partial^2 c_1}{\partial r^2} + \frac{1}{r}\frac{\partial c_1}{\partial r}\right) + D_{1z}\frac{\partial^2 c_1}{\partial z^2} = g_0 + kc_1 \qquad ...(2)$$

which has to be solved subject to the boundary conditions :

(i) there is no flux at the outer surface of the tissue cylinder so that

$$\frac{\partial c_1}{\partial r} = 0 \text{ at } r = r_t \text{ for } 0 \leqslant z \leqslant h; \qquad ...(3)$$

(ii) there is no flux at the two ends of the tissue region so that

$$\frac{\partial c_1}{\partial z} = 0 \text{ at } z = 0 \text{ and } z = h \text{ for } r_c \leqslant r \leqslant r_t \qquad ...(4)$$

(iii) the amount of oxygen transported from the capillary to the tissue at any point of the capillary wall is proportional to the difference of concentrations of oxygen on the two sides so that

$$-D_{1r}\left[\frac{\partial c_1}{\partial r}\right] = P\,[c_2(z) - c_1(z)] \qquad ...(5)$$

where

$$c_1(z) = c_1(r_c, z),\ c_2(z) = c_2(r_c, z) \qquad ...(6)$$

are the concentrations of oxygen on the capillary wall on the tissue and capillary sides respectively.

Following Blum (1960), we shall, for the present, neglect variation with r, of the oxygen concentration $c_2(r, z)$ in the capillary region and consider it as a function $c_2(z)$ of z only so that the oxygen concentration profiles in the capillary region are assumed to be flat.

In order to apply the boundary condition (5), we have to know $c_2(z)$ which has to be determined from the balance equation in the capillary. Let v be the velocity of blood in the capillary, then the balance equation gives

$$v\frac{dc_2}{dz} = -\frac{2P}{r_c}[c_2(z) - c_1(z)]. \qquad ...(7)$$

The boundary condition (5) couples the differential equations for the tissue and capillary regions. The additional boundary conditions for the capillary region is

$$c_2(0) = c_{20} \qquad ...(8)$$

where c_{20} is the concentration of oxygen in the blood at the arterial end. If it is possible to determine c_{2h}, the concentration of oxygen at the venous end $z = h$, we may be able to use the boundary condition

$$c_2(h) = c_{2h}. \qquad ...(9)$$

2. Solution for the Tissue Region

Following Thews (1960) and Blum (1960), we assume a solution of the form

$$c_1(r, z) = F_1(r)\, G_1(z) + F_2(r) + G_2(z). \qquad \ldots(10)$$

Substituting in (2), we get

$$D_{1z} F_1(r)\, G_1''(z) + D_{1r}(F_1''(r) + 1/r\, F_1'(r)) - k\, F_1(r)\, G_1(z)$$

$$+ D_{1r}(F_2''(r) + 1/r\, F_2'(r)) - k\, F_2(r) + D_{1z}\, G_2''(z) - k\, G_2(z) = g_0. \qquad \ldots(11)$$

This will be satisfied if

$$D_{1r}\, [F_1''(r) + \frac{1}{r}\, F_1'(r)] + (\lambda^2 - k)\, F_1(r) = 0 \qquad \ldots(12)$$

$$D_{1z}\, G_1''(z) - \lambda^2\, G_1(z) = 0 \qquad \ldots(13)$$

$$D_{1r}\, (F_2''(r) + \frac{1}{r}\, F_2(r)] - k\, F_2(r) = g_0 \qquad \ldots(14)$$

$$D_{1z}\, G_2''(z) - k\, G_2(z) = 0, \qquad \ldots 15)$$

where λ^2 is a separation constant. We now define

$$\beta^2 = \frac{\lambda^2}{D_{1z}},\quad \epsilon^2 = \frac{\lambda^2 - k}{D_{1r}},\quad \alpha = \frac{g_0}{D_{1r}},\quad \gamma^2 = \frac{k}{D_{1r}},\quad \delta = \frac{k}{D_{1z}} \qquad \ldots(16)$$

so that eqns. (12) – (16) become

$$F_1''(r) + \frac{1}{r}\, F_1'(r) + \epsilon^2\, F_1(r) = 0 \qquad \ldots(17)$$

$$G_1''(z) - \beta^2\, G_1(z) = 0 \qquad \ldots(18)$$

$$F_2''(r) + \frac{1}{r}\, F_2'(r) - \gamma^2\, F_2(r) = \alpha \qquad \ldots(19)$$

$$G_2''(z) - \delta^2\, G_2(z) = 0. \qquad \ldots(20)$$

We get the solutions

$$F_1(r) = A_1\, J_0(\epsilon r) + A_2\, N_0(\epsilon r) \qquad \ldots(21)$$

$$G_1(z) = B_1 \cosh \beta z + B_2 \sinh \beta z \qquad \ldots(22)$$

$$F_2(r) = C_1 I_0(\gamma r) + C_2 I_0(\gamma r) - (\alpha/\gamma^2) \qquad \ldots(23)$$

$$G_2(z) = D_1 \cosh \delta z + D_2 \sinh \delta z \qquad \ldots(24)$$

where $J_0(r)$ and $N_0(r)$ are Bessel's and Neumann's functions and $I_0(r)$ and $K_0(r)$ are Bessel's modified functions of zero order. Substituting in (10)

$$c_1(r, z) = [A_1 J_0(\epsilon r) + A_2\, N_0(\epsilon r)]\, [B_1 \cosh \beta z + B_2 \sinh \beta z] + [C_1\, I_0(\gamma r)$$

$$+ C_2\, K_9(\gamma r) - \alpha/\gamma^2] + [D_1 \cosh \delta z + D_2 \sinh \delta z]. \qquad \ldots(25)$$

Using the boundary condition (3)

$$0 = \epsilon\,[A_1\,J_1\,(\epsilon\,r_t) + A_2\,N_1\,(\epsilon r_t)]\,[B_1 \cosh \beta z + B_2 \sinh \beta z] + \gamma\,[C_1\,I_1\,(\gamma r_t) - C_2\,k_1\,(\gamma r_t)] = 0 \text{ for all } z. \quad ...(26)$$

This will be satisfied if we take

$$A_1 = N_0\,(\epsilon r_c), \quad A_2 = -J_0\,(\epsilon r_c) \quad ...(27)$$

$$N_0\,(\epsilon r_c)\,J_1\,(\epsilon r_t) - N_1\,(\epsilon r_t)\,J_0\,(\epsilon r_c) = 0 \quad ...(28)$$

$$C_1 = CK_1\,(\gamma r_t), \quad C_2 = CI_1\,(\gamma r_t) \quad ...(29)$$

Let

$$Z_k\,(\epsilon r) = N_0\,(\epsilon r_c)\,J_k\,(\epsilon r) - J_0\,(\epsilon r_c)\,N_k\,(\epsilon r) \quad ...(30)$$

so that $Z_0\,(\epsilon r_c) = 0$ ...(31)

and using (28) $Z_0\,(\epsilon r_t) = 0.$ ...(32)

Equation (28) will give an infinite number of values of ϵ. Let ϵ_1, $\epsilon_2 \ldots \epsilon_n, \ldots$ be the simple zeros of the cylindrical function $Z_1\,(\epsilon r_t)$, then we get the solution

$$c_1\,(r, z) = \sum_{n=1}^{\infty} Z_0\,(\epsilon_n r\,[B_{1n} \cosh \beta_n z + B_{2n} \sinh \beta_n z] + C\,[K_1\,(\gamma\,r_t)\,I_0\,(\gamma r) + I_1\,(\gamma\,r_t)\,K_0\,(\gamma\,r)] - \alpha/\gamma^2 + D_1 \cosh \delta z + D_2 \sinh \delta z \quad ...(33)$$

where

$$\beta_n^2 = \frac{D_{1r}\,\epsilon_n^2 + k}{D_{1z}}. \quad ...(34)$$

The unknown constants are B_{1n}, B_{2n} $(n = 1, 2, 3, \ldots)$, C; D_1 and D_2.

Now using the boundary conditions (4), we get

$$\sum_{n=1}^{\infty} Z_0\,(\epsilon_n r)\,\beta_n\,B_{2n} + D_2\delta = 0 \text{ for all } r \quad ...(35)$$

$$\sum_{n=1}^{\infty} Z_0\,(\epsilon_n r)\,\beta_n\,[B_{1n} \sinh \beta_n h + B_{2n} \cosh \beta_n h] + \delta\,[D_1 \sinh \delta\,h + D_2 \cosh \delta\,h] = 0 \text{ for all } r. \quad ...(36)$$

Equations (35) and (36) will be identical if we choose

$$B_{1n} = B_{2n}\,\frac{(1 - \cosh \beta_n h)}{\sinh \beta_n h} = p_n\,B_{2n} \text{ (say)} \quad ..(37)$$

$$D_1 = D_2\,\frac{(1 - \cosh \delta\,h)}{\sinh \delta\,h} = q\,D_2 \text{ (say)}. \quad ...(38)$$

On multiplying (35) by $r\,Z_0\,(\epsilon_n r)$, integrating from r_c to r_t and using the orthogonality property of the cylindrical functions, we get

$$\frac{B_{2n}}{D_2} = \frac{\delta r_c\,[Z_1\,(\epsilon_n\,r_c)\,]^2}{\epsilon_n\,\{[r_t\,Z_1\,(\epsilon_n\,r_t)]^2 - [r_c\,Z_1\,(\epsilon_n\,r_c)]^2\}\,Z_1\,(\epsilon_n\,r_c)} = s_n \text{ (say)}. \quad ...(39)$$

Using (37), (38) and (39), we can express B_{1n}, B_{2n} and D_1 interms of D_2. Thus the only unknown constants that remain in (33) are C and D_2. In fact we get

$$c_1(r, z) = \sum_{n=1}^{\infty} Z_0(\epsilon_n r) D_2 s_n [p_n \cosh \beta_n z + \sinh \beta_n z] + C[K_1(\gamma r_t) I_0(\gamma r) + I_1(\gamma r_t) K_0(\gamma r)] - \alpha/\gamma^2 + D_2[q \cosh \delta z + \sinh \delta z]. \quad \ldots(40)$$

Substituting $r = r_c$, we get

$$c_1(r_c, z) = c_1(z) = \sum_{n=1}^{\infty} Z_0(\epsilon_n r_c) D_2 s_n [p_n \cosh \beta_n z + \sinh \beta_n z] + C[K_1(\gamma r_t) I_0(\gamma r_c) + I_1(\gamma r_t) K_0(\gamma r_c)] - \alpha/\gamma^2 + [D_2[q \cosh \delta z + \sinh \delta z]. \quad \ldots(41)$$

Substituting from (40) and (41) in (5)

$$c_2(z) = c_1(z) - \frac{D_{1r}}{p} \left[\frac{\partial c_1}{\partial r}\right]_{r=r_c}$$

$$= \sum_{n=1}^{\infty} Z_0(\epsilon_n r_c) D_2 s_n [p_n \cosh \beta_n z + \sinh \beta_n z] + C[K_1(\gamma r_t) I_0(\gamma r_c) + I_1(\gamma r_t) K_0(\gamma r_c)] - \alpha/\gamma + D_2[q \cosh \delta z + \sinh \delta z] - \frac{D_1 r}{P} \sum_{n=1}^{\infty} C_n Z_1(\epsilon_n r_c) D_2 s_n [p_n \cosh \beta_n z + \sinh \beta_n z] - \frac{D_{1r} C}{P} [K_1(\gamma r_t) I_1(\gamma r_c) - I_1(\gamma r_t) K_1(\gamma r_c)]. \quad \ldots(42)$$

If we make use of boundary conditions (8) and (9), the two constants are determined and the solution is completely known. If we make use of (8) only, then one constant has still to be determined.

3. Comparision with Blum's Solution

Blum (1960) had obtained the solution for $d(c) = g_0$, while we have obtained it for the more general linear metabolic rate function $d(c) = g_0 + kc$.

Substituting from (41) and (42) in (7), we get

$$v \sum_{n=1}^{\infty} Z_0(\epsilon_n r_c) D_2 s_n \beta_n (p_n \sinh \beta_n z + \cosh \beta_n z) + v D_2 \delta [q \cosh \delta z + \sinh \delta z] - v \frac{D_{1r}}{P} \sum_{n=1}^{\infty} \epsilon_n Z_1(\epsilon_n r_c) D_2 s_n \beta_n (p_n \sinh \beta_n z + \cosh \beta_n z)$$

$$= \frac{2D_{1r}}{r_c} \sum_{n=1}^{\infty} \epsilon_n Z_1(\epsilon_n r_c) D_2 s_n (p_n \cosh \beta_n z + \sinh \beta_n z)] + C\gamma [K_1(\gamma r_t) I_1(\gamma r_c) - I_1(\gamma r_c) K_1(\gamma r_c)]. \quad \ldots(43)$$

This equation is not an identity for any values of C and D. As such, our solution does not satisfy the capillary equation (7). This fact remains true even if we consider the case $k=0$ i.e. the case of constant rate of metabolism considered by Blum (1960). This means that the set of boundary conditions imposed by Blum is not consistent with his capillary equation. There are two alternatives viz. either we give up some of the boundary conditions or write another equation for the capillary.

In fact Blum himself did not at first use the no-flux condition (4) at $z=0$ and $z=h$ and used only the boundary conditions (3), (5) and (8) and the capillary equation (7). From (5) and (7), he deduced

$$\frac{dc_2}{dz} = \frac{2}{r_c v} D_{1r} \left[\frac{\partial c_1}{\partial r}\right]_{r=r_c} \qquad \ldots(44)$$

and integrated it to get $c_2(z)$. On substituting it, he got an equation to determine the constants B_{1n}, B_{2n}, but he stated : "It is not profitable to compare the coefficients of the terms in sinh $\beta_n z$ or in cosh $\beta_n z$, since these comparisions do not lead to the evaluation of the remaining constants. Instead we turn to the boundary condition (4)". He was able to obtain the values of the constants, but he did not substitute back in the earlier equations to see that that equation was not satisfied. In fact he replaced (5) and (7) by the single equation (44).

Thus his solution and our more general solution are valid for differential equations (2) and (44) and with boundary conditions (3), (4) and (8). In our case, substituting from (41) in (44), we get

$$\frac{dc_2}{dz} = \frac{2}{r_c v} D_{1r} \left[\sum_{n=1}^{\infty} \epsilon_n Z_1(\epsilon_n r_c) D_2 s_n \left[p_n \cosh B_n z + \sinh \beta_n z\right]\right. \qquad \ldots(45)$$

Integrating

$$c_2(z) - c_{20} = \frac{2}{r_c v} D_{1r} \left\{ \sum_{n=1}^{\infty} Z_1(\epsilon_n r_c) D_2 s_n \beta_n^{-1} \left[p_n \sinh \beta_n z + \cosh \beta_n z\right] \right.$$

$$\left. - \sum_{n=1}^{\infty} Z_1(\epsilon_n r_c) D_2 \; s_n \; \beta_n^{-1} \right\}. \qquad \ldots(46)$$

Blum (1960) also noted that "The concentration inside the capillary is independent of the membrane premeability when the tissue consumes the substrate at a zero-order rate, but not when the substrate is consumed at a first order rate. This comes about because in the zero order case, the tissue is necessarily consuming substrate at a constant rate, so that in the steady state, the influence of the membrane comes to be felt in the capillary. The membrane simply lowers the average profile in the tissue and it must be remembered that the assumption of zero order kinetics should break down if the concentration at any point in the tissue becomes so small that zero-order kinetics cannot be obeyed".

However our discussion shows that the independence of concentration of the membrane permeability is not due to the difference between zero order and first order kinetics since our solutions (40) and (46) for the general linear kinetics for the same conditions as Blum's is also independent of P. This independence arises simply because (5) and (7) used by Blum for zero order kinetics have been replaced by (4) and (44) for the first order kinetics and neither (4) nor (44) depends on P. It is obvious that if the problem is reformulated to an equivalent problem independent of P, its solution cannot depend on P.

4. Solution for the Capillary Region

If D_{2r} and D_{2z} be the radial and axial diffusivities in the capillary region, the basic diffusion equation is

$$D_{2r}\left(\frac{\partial^2 c_2}{\partial r^2} + \frac{1}{r}\frac{\partial c_2}{\partial r}\right) + D_{2z}\frac{\partial^2 c_2}{\partial z^2} = v(r)\frac{\partial c_2}{\partial z}. \qquad \ldots(47)$$

The magnitudes of the axial diffusion and capillary convection terms relative to the radial diffusion term are of the order

$$\frac{D_{2z}/h^2}{D_{2r}/r_c^2} \text{ and } \frac{\bar{v}/h}{D_{2r}/r_c}, \qquad \ldots(48)$$

where $\bar{v}$ is the average velocity in the capillary. Now some typical values of the parameters involved are (Middleman 1972, Reneau *et al.* 1967).

$$r_c = 3\mu,\ h = 180\ \mu,\ \bar{v} = 400\ \mu/\text{sec},\ D_{2r} = D_{2z} = 1000\mu^2/\text{sec} \qquad \ldots(49)$$

so that the relative magnitudes are of the order

$$1/3600 \text{ and } 1/50. \qquad \ldots(50)$$

Thus in general axial diffusion can be neglected and as a first approximation, we can even neglect capillary convection so that (47) give

$$\frac{\partial^2 c_2}{\partial r^2} + \frac{1}{r}\frac{\partial c_2}{\partial r} = 0 \text{ or } \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_2}{\partial r}\right) = 0. \qquad \ldots(51)$$

Integrating

$$c_2(r, z) = \alpha(z)\ln r + \beta(z). \qquad \ldots(52)$$

Since $\frac{\partial c_2}{\partial r} = 0$ when $r = 0$ ...(53)

and $c_2(r_c, z) = c_2(z)$ ...(54)

we get $c_2(r, z) = c_2(z), \quad 0 \leqslant r < r_c$ ...(55)

so that to this approximation, the concentration in the capillary region does not depend on r.

To this approximation, equations (40), (41), (42) and (55) give the complete solution of our problem.

In fact to this approximation, we can also take oxygen dissociation in the capillary into account so that equation (51) becomes

$$\frac{1}{r}\frac{\partial}{\partial r}\left\{r\left[c_2 + \frac{kc_2^n}{1+Kc_2^n}\right]\right\} = 0. \qquad \ldots(56)$$

Integrating

$$c_2 + \frac{kc_2^n}{1+Kc_2^n} = \alpha(z)\ln r + \beta(z). \qquad \ldots(57)$$

Using $\partial c_2/\partial r = 0$ at $r = 0$ and $c_2(r_c, z) = c_2(z)$ we get

$$c_2(r, z) + \frac{k\,c_2^n(r, z)}{1+K\,c_2^n(r,z)} = c_2(z) + \frac{k\,c_n^n(z)}{1+K\,c_2^n(z)} \qquad \ldots(58)$$

or $c_2(r, z) = c_2(z)$ ...(59)

i. e. the oxygen dissociation will not influence, the oxygen profile in the capillary region when axial diffusion and capillary convection are neglected.
From (48), we see that capillary convection can be neglected if r_c is small and h is large, Thus if $r_c = 10\ \mu$ and $h = 100\ \mu$, then the capillary convection term is of the same order as radial diffusion term and cannot be neglected.

Thus in general, we will have to solve (47) subject to (8), (53), (54) and

$$D_{2r}\left[\frac{\partial c_2}{\partial r}\right]_{r=r_c} = P\,[c_2(z) - c_1(z)]$$

$$= -D_{1r}\,[\sum_{n=1}^{\infty} \epsilon_n Z_1(\epsilon_n r_c)\, D_2\, s_n\,(p_n \cosh \beta_n z + \sinh \beta_n z)$$

$$+ C\gamma\,(K_1(\gamma r_t)\, I_1(\gamma r_c) - I_1(\gamma r_t)\, K_1(\gamma c_r))] \quad \ldots(60)$$

i.e. we have to solve the capillary diffusion equation including capillary convection term subject to the values of $c_2(r, z)$ and $\partial c_2/\partial r$ being prescribed at $r = r_c$, its value being a known constant at $z = 0$ and its derivative vanishing at r=0. The solution may be obtained by numerical methods, but if numerical method have to be used, it may be better to use them for both the regions rather than use analytical method for the tissue region and numerical method for the capillary region, since in the latter case matching of conditions at the interface may be more troublesome.

However in the next section, we give another technique for solving the complete partial differential equations for the two regions based on Galerkin's method.

5. Solution by using Galerkin's Method

We have to solve

$$D_{1r}\left(\frac{\partial^2 c_1}{\partial r^2} + \frac{1}{r}\frac{\partial c_1}{\partial r}\right) + D_{1z}\frac{\partial^2 c_1}{\partial z^2} = g_0 + kc_1 \quad ..(61)$$

$$D_{2r}\left(\frac{\partial^2 c_2}{\partial r^2} + \frac{1}{r}\frac{\partial c_2}{\partial r}\right) + D_{2z}\frac{\partial^2 c_2}{\partial z^2} = v(r)\frac{\partial c_2}{\partial z} \quad ..(62)$$

subject to the boundary conditions

$$\frac{\partial c_1}{\partial r} = 0 \text{ at } r = r_t, \quad \frac{\partial c_2}{\partial r} 0 = 0 \text{ at } r = 0 \quad \ldots(63)$$

$$-D_{1r}\left[\frac{\partial c_1}{\partial r}\right]_{r=r_c} = -D_{2r}\left[\frac{\partial c_2}{\partial r}\right]_{r=r_c} = P\,[c_2(r_c, z) - c_1(r_c, z)]$$

$$= P\,[c_2(z) - c_1(z)] \quad \ldots(64)$$

$$c_1 = c_{10}, \quad c_2 = c_{20} \text{ at } z = 0 \quad \ldots(65)$$

$$\frac{\partial c_1}{\partial z} = 0, \quad \frac{\partial c_2}{\partial z} = 0 \text{ at } z = 0. \quad ..(66)$$

No boundary conditions are imposed at $z = h$. Defining the Laplace transforms

$$\bar{c}_1(r, s) = \int_0^\infty e^{-sz} c_1(r, z)\, dz, \quad \bar{c}_2(r, s) = \int_0^\infty e^{-sz} c_2(r, z)\, dz, \quad \ldots(67)$$

taking the Laplace transforms of (61) and 62) and using (65) and (66), we get

$$D_{1r}\left(\frac{\partial^2 \bar{c}_1}{\partial r^2}+\frac{1}{r}\frac{\partial \bar{c}_1}{\partial r}\right)+D_{1z}(s^2\bar{c}_1-s\,c_{10})=\frac{g_0}{s}+k\,\bar{c}_1 \qquad ...(68)$$

$$D_{2r}\left(\frac{\partial^2 \bar{c}_2}{\partial r^2}+\frac{1}{r}\frac{\partial \bar{c}_1}{\partial r}\right)+D_{2z}(s^2\bar{c}_2-s\,c_{20})=v(r)(s\,\bar{c}_2-c_{20}). \qquad ...(69)$$

The boundary conditions (63) and (64) become

$$\frac{\partial \bar{c}_1}{\partial r}=0 \text{ at } r=r_t, \quad \frac{\partial \bar{c}_2}{\partial r}=0 \text{ at } r=0 \qquad ...(70)$$

$$-D_1\left(\frac{\partial \bar{c}_1}{\partial r}\right)_{r=r_c}=-D_2\left(\frac{\partial \bar{c}_2}{\partial r}\right)_{r=r_c}=P[\bar{c}_2(s)-\bar{c}_1(s)] \qquad ...(71)$$

where $\bar{c}_1(s)$, $\bar{c}_2(s)$ are the Laplace transforms of $c_1(z)$ and $c_2(z)$. These have also to be determined.

Now we try the solution

$$\bar{c}_1(r,s)-\bar{c}_2(r_c,s)=\sum_{i=1}^{n} h_{i1}(r)f_i(s)=\sum_{i=1}^{n}(a_{i1}+b_{i1}(r-r_t)^{i+1})f_i(s) \qquad ...(72)$$

$$\bar{c}_2(r,s)-\bar{c}_1(r_c,s)=\sum_{i=1}^{n} h_{i2}(r)g_i(s)=\sum_{i=1}^{n}[a_{i2}+b_{i2}\,r^{i+1}]g_i(s). \qquad ...(73)$$

The boundary conditions (90) are satisfied. The boundary conditions (71) give

$$-D_1\left[\sum_{i=1}^{n} b_{i1}(i+1)(r_c-r_t)^i f_i(s)\right]=-D_2\left[\sum_{i=1}^{n} b_{i2}(i+1)\,r_c^i\,g_i(s)\right.$$

$$=P\left[\sum_{i=1}^{n}(a_{i2}+b_{i2}\,r_c^{i+1})g_i(s)\right]=-P\left[\sum_{i=1}^{n}(a_{i1}+b_{i1}(r_c-r_t)^{i+1}\right]f_i(s)]. \qquad ...(74)$$

These will be satisfied if we choose

$$-D_1\,b_{i1}(i+1)(r_c-r_t)^i=1, \quad -D_2\,b_{i2}(i+1)\,r_c^i=1 \qquad ...(75)$$

$$P\,(a_{i2+bi2}\,r_c^{i+1})=1, \; -P\,(a_{i1+bi1}(r_c-r_t))^{i+1}=1 \qquad ...(76)$$

$$\sum_{i=1}^{n} f_i(s)=1/s, \; \sum_{i=1}^{n} g_i(s)=1/s. \qquad ...(77)$$

Equation (75) and (76) determine $a_{i1}, a_{i2}, b_{i1}, b_{i2}$ for $i=1,2,\ldots,n$. Equations (77) give conditions on the $2n$ unknown functions $f_1(s), f_2(s),\ldots, f_n(s); g_1(s),\ldots, g_n(s)$.

If we choose $a_{i1}, a_{i2}, b_{i1}, b_{i2}$ to satisfy (75) and (76) and $f_i(s)$, $g_i(s)$ to satisfy (77), $\bar{c}_1(r,s)$, $\bar{c}_2(r,s)$ as defined by (72) and (73) satisfy the boundary conditions exactly. These may not satisfy the partial differential equations (68) and (69) exactly In fact when we substitute from (72) and (73) in (68) and (69), we get the residuals

$$R_1(r,s)=D_{1r}\left[\sum_{i=1}^{n}\left(h_{i1}''(r)+\frac{1}{r}h_{i1}'(r)\right)f_i(s)\right]$$

$$+D_{1z}\left[s^2\bar{c}_2(r_c,s)+s^2\sum_{i=1}^{n}h_{i1}(r)f_i(s)-sc_{10}\right]$$

$$-\frac{g_0}{s}-k\left[\bar{c}_2(r_c,s)+\sum_{i=1}^{n}h_{i1}(r)f_1(s)\right] \qquad ...(78)$$

$$R_2(r, s) = D_{2r}\ [\sum_{i=1}^{n} ((h''_{i2}\ (r) + \frac{1}{r}\ h'_{i2}(r)\ ]\ g_i(s)\ ]$$

$$+\ D_{2z}\ [s^2\ \bar{c}_1(r_c, s) + s^2 \sum_{i=1}^{n} h_{i2}(r)\ g_i\ (s) - s c_{20}\ ]$$

$$-\ v(r)\ [\ s\ \bar{c}_1(r_c, s) + s \sum_{i=1}^{n} h_{i2}(r)\ g_i(r) - c_{20}\ ]. \qquad \ldots(79)$$

These residuals depend on the $(2n+2)$ functions $f_1(s), \ldots, f_n(s)$; $g_1(s), \ldots, g_n(s)$, $\bar{c}_1(s), \bar{c}_2(s)$. However (79) already gives two relations between these. As such we have to get n more equation to determine all of them.

These are given by the conditions that $R_1(r, s)$ should be orthogonal to $h_{j1}(r)$ for $j=1, 2, \ldots, n$ and $R_2(r, s)$ should be orthogonal to $h_{j2}(r)$ for $j=1, 2, \ldots, n$. Thus we get

$$\int_{r_c}^{r_t} R_1(r, s)\ h_{j1}(r)\ r dr = 0, \quad \int_{0}^{r_c} R_2(r, s)\ h_{j2}(r)\ r dr = 0, \quad i=1, 2, \ldots, n. \qquad \ldots(80)$$

Substituting from (78) and (79) in (80), we get

$$\sum_{i=1}^{n} a_{ij} f_i(s) + \sum_{i=1}^{n} b_{ij}\ s^2 f_i(s) + [D_{1z}\ s^2 - k]\ p_j\ \bar{c}_2(s) - [D_{1z}\ c_{10}\ s + \frac{g_0}{s}]\ p_j = 0 \qquad \ldots(81)$$

$$\sum_{i=1}^{n} a_{ij}\ g_i(s) + \sum_{i=1}^{n} b'_{ij}\ s^2\ g_i(s) + \sum_{j=1}^{n} c'_{ij}\ s\ g_i(s)$$

$$+\ D_{2z}\ s^2\ p'_j\ \bar{c}_1(s) - s q'_j\ \bar{c}_1(s) + c_{20}\ g'_j = 0 \qquad \ldots(82)$$

where

$$a_{ij} = \int_{r_c}^{r_f} D_{1r}\ (h''_{i1}\ (r) + \frac{1}{r}\ h'_i(r) - k\ h_{i1}(r))\ h_{j1}(r)\ r\ dr \qquad \ldots(83)$$

$$b_{ij} = D_{2z} \int_{r_c}^{r_t} h_{i1}(r)\ h_{j1}(r)\ r\ dr \qquad \ldots(84)$$

$$p_j = \int_{r_c}^{r_t} h_{j1}(r)\ r\ dr \qquad \ldots(85)$$

$$a'_{ij} \int_{0}^{r_c} D_{2r}\ [\ h''_{i2}\ (r) + \frac{1}{r} h_{i2}(r)]\ h_{j2}(r)\ r\ dr \qquad \ldots(86)$$

$$b'_{ij} = \int_{0}^{r_c} D_{2z}\ h_{i2}(r)\ h_{j2}(r)\ r\ dr \qquad \ldots(87)$$

$$c'_{ij} = -\int_{0}^{r_c} v(r)\ h_{i2}(r)\ h_{j2}(r)\ r\ dr \qquad \ldots(88)$$

$$p'_j = \int_{0}^{r_c} h_{j2}(r)\ r\ dr \qquad \ldots(89)$$

$$q'_j = \int_{0}^{r_c} v(r)\ h_{j2}(r)\ r\ dr. \qquad \ldots(90)$$

If $v(r)$ can be replaced by the average velocity $\bar{v}$, then

$$c'_{ij} = -\bar{v}\frac{b'_{ij}}{D_{2z}}, \quad q_j = -\bar{v}\,p_j. \qquad \ldots(91)$$

In this case (81) and (82) give

$$\sum_{i=1}^{n}(a_{ij}+s^2 b_{ij})f_i(s) = p_j\left[D_{1z}\,c_{10}\,s + \frac{g_0}{s} - (D_{1z}\,s^2 - k)\,\bar{c}_2(s)\right],$$
$$j = 1, 2, \ldots, n. \qquad \ldots(92)$$

$$\sum_{i=1}^{n}\left[a'_{ij} - \bar{v}\frac{b'_{ij}}{D_{iz}}s + b'_{ij}\,s^2\right]g_i(s)$$
$$= -p'_j\left[D_{2z}\,s^2\,\bar{c}_1(s) + s\bar{v}\,\bar{c}_1(s) - s\,c_{20}\,\bar{v}\right]. \qquad \ldots(93)$$

We have to solve either (77), (81), (82) or (77), (92), (93) for the $(2n+2)$ functions $f_i(s)$, $g_i(s)$, $\bar{c}_1(s)$, $\bar{c}_2(s)$.
Substituting

$$F_i(s) = \frac{f_i(s)}{D_{1z}\,c_{10}s + \frac{g_0}{s} - (D_{1z}\,s^2 - k)\,\bar{c}_2(s)} \qquad \ldots(94)$$

$$G_i(s) = \frac{g_i(s)}{s\,c_{20}\,\bar{v} - s\bar{v}\bar{c}_1(s) - D_{2z}\,s^2\,\bar{c}_1(s)} \qquad \ldots(95)$$

we get

$$\sum_{i=1}^{n}(a_{ij}+s^2 b_{ij})\,F_i(s) = p_j \qquad \ldots(96)$$

$$\sum_{i=1}^{n}\left[a_{ij} - \bar{v}\frac{b'_{ij}}{D_{2z}}s + b'_{ij}\,s^2\right]G_i(s) = p_j. \qquad \ldots(97)$$

From (96) and (97) we can easily solve for $F_i(s)$ and $G_i(s)$, then (77), (94), (96) give

$$(k - D_{1z}\,s^2)\,\bar{c}_2(s) + D_{1z}\,c_0\,s + \frac{g_0}{s} \frac{1/s}{\sum_{i=1}^{n} F_i(s)} \qquad \ldots(98)$$

$$[D_{2z}\,s^2 + s\bar{v}]\,\bar{c}_1(s) - s c_{20}\,\bar{v} = \frac{1/s}{\sum_{i=1}^{n} G_i(s)} \qquad \ldots(99)$$

and thus $\bar{c}_1(s)$ and $\bar{c}_2(s)$ are obtained. Finally (94) and (95) give $f_i(s)$ and $g_i(s)$ and on inverting the Laplace transforms, (71), (72) give $c_1(r, z)$ and $c_2(r, z)$ giving a complete solution to our problem.

Since $F_i(s)$, $G_i(s)$, $\bar{c}_1(s)$, $\bar{c}_2(s)$ are all rational functions of s, their inverse Laplace transforms can be easily obtained.

$F_i(s)$ and $G_i(s)$ are rational functions of which numerators are polynomials of $(2n-2)$ th degree denominators are polynomials of $2n$ th degree so that

$$\sum_{i=1}^{n} F_i(s) = \frac{P_{2n-2}(s)}{Q_{2n}(s)}, \quad \sum_{i=1}^{n} G_i(s) = \frac{R_{2n-2}(s)}{S_{2n}(s)} \qquad ...(100)$$

where P_{2n-1}, R_{2n-1}, Q_{2n}, R_{2n} are polynomials of degrees indicated.

Similarly we find that each of $f_i(s)$, $g_i(s)$, $F_i(s)$, $G_i(s)$, $\bar{c_1}(s)$, $\bar{c_2}(s)$ is a rational function whose numerator is at least of one degree more than that of the denominator.

For $n = 1$, we get

$$f_1(s) = \frac{1}{s}, \ \bar{c_1}(s) = \frac{A_{11}}{s} + \frac{A_{21}}{s^2} + \frac{A_{31}}{s-\alpha} \qquad ...(101)$$

$$g_1(s) = \frac{1}{s}, \ \bar{c_2}(s) = \frac{A_{12}}{s} + \frac{A_{22}}{s-\beta} + \frac{A_{32}}{s+\beta} \qquad ...(102)$$

$$c_1(r, z) = A_{12} + A_{22}\, e^{\beta z} + A_{32}\, e^{-\beta z} + [\, a_{11} + b_{11}\,(r-r_i)^2\,] \qquad ...(103)$$

$$c_2(r, z) = A_{11} + A_{21}\, z + A_{31}\, e^{\alpha z} + [a'_{11} + b'_{11}\, r^2\,]. \qquad ...(104)$$

For general values of n, we shall get solutions of the form

$$c_1(r, z) = c_2(z) + \sum_{j=1}^{n} [a_{ij} + b_{ij}\,(r-r_i)^{i+1}]\, F_j(z) \qquad ...(105)$$

$$c_2(r, z) = c_1(z) + \sum_{j=1}^{n} [a'_{ij} + b'_{ij}\, r^{i+1})\, G_j(z) \qquad ...(106)$$

where

$$\sum_{i=1}^{n} F_j(z) = \sum_{i=1}^{n} G_i(z) = 1. \qquad ...(107)$$

5. Generalisation for Michaelis-Menten Kinetics

Blum (1960) has suggested that the metabolic rate function $(d)\ c_1$ may as a first approximation be replaced by general linear kinetic function by expanding $d(c_1)$ in a Taylor series about some suitable point c^* so that

$$d(c_1) = \frac{A\, c_1}{B+c_1} = \frac{A\, c^*}{B+c^*} + (c_1-c^*)\frac{A\, B}{(B+c^*)^2} = g_0 + kc_1 \qquad ...(108)$$

This is equivalent to replacing the non-linear hyperbolic curve by its linear tangent at a suitable point (Figure 2)

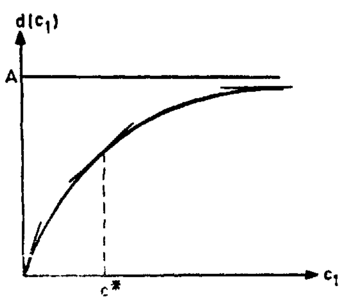

Fig. 2 A Linear Approximation to Michaelis-Menten Kinetics.

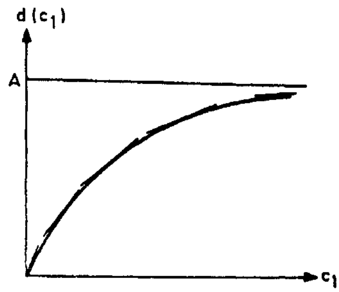

Fig. 3 A sequence of linear approximation.

However the straight line (108) always gives an overestimate at all points except c^*.

If $c^* = 0$, (108) gives

$$d\,(c_1) = \frac{A}{B}\, c_1 \qquad \text{...(109)}$$

which gives first order kinetics. If c^* is very large $d\,(c_1) \to A$ and this corresponds to zero order kinetics. Thus zero order and first order kinetics correspond to replacing the hyperbolic curve by tangent at infinity and origin respectively.

Since (108) always overestimates, it would be a better policy to choose g_0 and k by using the least square principle. We choose them so that

$$\int_0^{c_{20}} \left(\frac{A\,c}{B+c} - g_0 - k\,c \right)^2 dc \qquad \text{...(110)}$$

in minimum so that we solve for g_0 and k from the equations

$$\int_0^{c_{20}} \left(\frac{A\,c}{B+c} - g_0 - k\,c \right) dc = 0\,, \quad \int_0^{c_{20}} \left(\frac{A\,c}{B+c} - g_0 - kc \right) dc = 0 \qquad \text{...(111)}$$

or $$g_0 + \tfrac{1}{2}\, k\, c_{20} = A - \frac{A\,B}{c_{20}} \ln \frac{B + c_{20}}{B} \qquad \text{..(112)}$$

$$g_0 + \tfrac{2}{3}\, k\, c_{20} = -\frac{2\,A\,B}{c_{20}} + A + \frac{2\,AB^2}{c_{20}^2} \ln \frac{B + c_{20}}{B}. \qquad \text{...(113)}$$

Instead of replacing the entire curve by a single straight line, we can replace it by a sequence of straight line segments (Fig. 3), find solutions for each of these segments and then match the solution at the consecutive ends of the segments (Kapur 1980).

6. Concluding Remarks

Contributions to study of steady-state diffusion of oxygen in the capillaries and living tissues have been made by Krogh (1919 a, b), Hill (1928), Opitz and Schneider (1950), Kety (1957), Blum (1960), Thews (1960), Reneau *et al.* (1967) and others and these have been described in detail by Reneau *et al.* (1967) and Middleman (1972), Kapur (1980) has applied Galerkin's method while Reneau *et al.* (1967) have applied numerical methods.

Blum (1960) tried to discuss the problem for zero order kinetics when axial diffusion in the tissue region is taken into account. We have extended discussion to the first order kinetics and the general linear kinetics. We have also applied Galerkin's method to obtain oxygen concentration profiles when axial diffusion is taken into account in both tissue and capillary regions.

For extending the solution to non-linear kinetics, we have to modify the solutions for the case when c_{10} and c_{20} are not necessarily constants but are known functions of r. This does not create any problem in our method. In (78) and (79), c_{10} and c_{20} will be replaced by $c_{10}\,(r)$ and $c_{20}\,(r)$ and there will be some minor adjustments in (81) and (82).

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