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Time course of oxygen depletion following reduction of blood flow.

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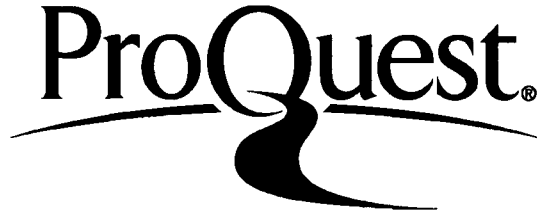
CERTIFICATE OF APPROVAL

This thesis is accepted and approved in partial fulfillment of the requirements for the degree of Master of Science in Chemical Engineering.

May 8, 1981
(Date)

Dr. Eric P. Salathe
(Professor in Charge)

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(Chairman of Department)

DEDICATION

To my parents, for their love and encouragement.

ACKNOWLEDGEMENTS

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ABSTRACT

Following reduction of arteriolar flow, tissue oxygen concentration decreases and anoxic tissue develops if the blood flow rate is small enough. Anoxia, if it develops, first appears in the region most distal to the capillary at the venous end, then spreads through the tissue until a final steady state is reached. In this thesis, the changing oxygen concentration, from the time blood flow changes until the anoxic tissue is fully developed, is examined mathematically. The equations governing oxygen concentration transport to tissue are solved by reducing them to a first order nonlinear partial differential-integral equation. The solution is valid until anoxia first appears. After anoxia develops, it is necessary to solve a moving boundary problem. This is done using the method of matched asymptotic expansions.

1. INTRODUCTION

Following partial arteriolar occlusion, the level of oxygen concentration in tissue begins to decrease, and anoxic tissue will develop provided that the capillary blood flow rate is small enough. Anoxia first appears in the tissue most distal to the capillary at the venous end, and the anoxic region grows and spreads toward the arterial end until it reaches a new steady state. During the initial period following occlusion, before anoxia appears, this process can be analyzed as an unsteady oxygen transport problem in a Krogh cylinder. An exact solution to the governing equations has been obtained by using a numerical solution to a non-linear first order partial differential-integral equation, and is presented in this thesis. Eventually, the oxygen concentration falls to zero, anoxic regions appear in the tissue, and the solution obtained is no longer valid. A steady state analysis was recently presented that shows the extent of the anoxic region in the tissue during various stages of hypoxia (Salathe and Beaudet, [4]). Another study, by Salathe and Wang, discusses anoxia development following total occlusion.

The analysis of the oxygen tranaport process after anoxia develops reduces to the solution of a moving boundary problem. Because of the non-linear oxyhemoglobin dissociation relationship and the three-dimensional geometry, exact solutions are impossible. However, when oxygen levels have dropped to a sufficiently low level that anoxic tissue appears, the nature of oxyhemoglobin dissociation is such that it is possible, as a first approximation, to neglect the time derivative term in the oxygen concentration equation for tissue. Although a corresponding simplification does not apply to the oxygen concentration equation for the blood, the reduction achieved is sufficient to permit the analysis to be carried out. Using the methods of asymptotic analysis, complete solutions have been obtained that permit an accurate description of the evolution of the oxygen concentration in the capillary and tissue, from the time blood flow is reduced until the final steady state is attained.

In the next section the analysis is described for the time from reduction of blood flow until the first appearance of anoxic tissue. The analysis of the development of anoxic tissue is given in the subsequent

section.   Results are presented for the analysis before

anoxia develops.

2. CONCENTRATION PROFILES FOLLOWING PARTIAL OCCLUSION

The Krogh model consists of a single capillary of length L' and radius R_c' surrounded by a concentric cylinder of tissue having radius R_t'. Oxygen transported by the blood diffuses from the capillary into the tissue, where it is consumed at constant rate M. Let z' denote distance along the capillary axis, $0 \leqslant z' \leqslant L'$, and r' distance normal to the axis, $0 \leqslant r' \leqslant R_t'$. If axial diffusion in the capillary and tissue are ignored, the governing equations for steady state oxygen transport to tissue are (see, for example, Salathe, et al., [5])

$$D\frac{1}{r'} \frac{\partial}{\partial r'}[r'\frac{\partial c_s'}{\partial r}] = M$$

$$q_i\frac{\partial}{\partial z'} F'[C_s'] = 2\pi R_c'D\frac{\partial c_s'}{\partial r}\Big|_{R_c'}$$

$$c_s' = C_s' \ , \ r' = R_c' \ ; \ \partial c_s'/\partial r' = 0 \ , \ r' = R_t'$$

$$C_s' = C_A \ , \ z' = 0$$

$$F'[C'] = C' + N'S'[C'] \ .$$

Where $C_s' = C_s'(r',z')$ and $C_s'(z')$ are the steady state oxygen concentrations in the tissue and in the capillary, respectively. Here D is the tissue oxygen diffusivity, q_i the initial volume blood flow rate, $S'(C')$ the

oxyhemoglobin dissociation relationship, N' the oxygen capacity of blood at 100% saturation, and C_A the oxygen concentration in arterial blood. The oxyhemoglobin dissociation relationship will be assumed to be given by the empirical formula $S'(C') = K'C'^n/(1+K'C'^n)$, for suitable choice of the constants K' and n.

The above equations can be readily solved to yield

$$C_S' = C_S'(z') + M[(r'^2 - R_c'^2)/2 - R_t'^2 \ln(r'/r_c')]/2D \qquad (2.1)$$

$$C_S' + N'S'(C_S') = F'(C_S') \qquad (2.2)$$

$$= F'(C_A) + \pi M(R_c'^2 - R_A'^2)z/q_i .$$

The latter equation gives z' explicitly in terms of C_S', and can easily be inverted numerically to yield $C_S'(z')$. Solutions of this type were obtained and discussed by Kety [1].

Upon partial occlusion, blood flow is reduced to q_f. Oxygen is still supplied to the tissue from the capillary, but the concentration in both the tissue and capillary decreases with time. Until the oxygen level falls to zero at the outer edge of the Krogh cylinder, the concentration at any location z' satisfies the

equations

$$\frac{\partial c'}{\partial t} = D\frac{1}{r'} \frac{\partial}{\partial r'}[r'\frac{\partial c'}{\partial r'}] - M \quad, \quad t' \geqslant 0 \quad, \quad R_c' \leqslant r \leqslant R_t' \qquad (2.3)$$

$$\frac{\partial c'}{\partial r'} = 0 \quad, \quad r = R_t', \quad t' \geqslant 0 \qquad (2.4)$$

$$c' = C' \quad, \quad r' = R_c', \quad t' \geqslant 0 \qquad (2.5)$$

$$c' = c_s' \quad, \quad t' = 0 \quad, \quad R_c' \quad r \quad R_t' \qquad (2.6)$$

$$[\pi R_c'^2\frac{\partial}{\partial t'} + q_f\frac{\partial}{\partial z'}]F'(C') = 2\pi R_c'D\frac{\partial c'}{\partial r'}\bigg|_{R_c'} \qquad (2.7)$$

$$C' = C_s' \quad, \quad t' = 0 \quad, \quad 0 \leqslant z' \leqslant L \qquad (2.8)$$

where $c' = c'(t',r',z')$ and $C' = C'(t',z')$ are the tissue
and capillary oxygen concentrations, respectively.

Before proceeding further, we introduce
dimensionless variables

$$c_s = C_s'/C_A \quad, \quad C_s = C_s'/C_A \quad, \quad c = c'/C_A \quad, \quad C = C'/C_A \quad,$$

$$N = N'/C_A \quad, \quad K = K'(C_A)^n \quad, \quad F(C) = F'(C')/C_A \quad,$$

$$r = r'/R_t' \quad, \quad R_c = R_c'/R_t' \quad, \quad z = z'/L'$$

$$t = t'/t_c \quad, \quad \nu = q_f/q_i \quad, \quad t_c = \pi R_c'^2 L'/q_f.$$

Then eqs.(2.1) , (2.2) become

$$c_s = C_s + A_o[r^2 - R_c^2 - 2\ln(r/R_c)]/4 \qquad (2.9)$$

$$F(C_s) = F(1) - \nu E_o z \qquad (2.10)$$

and eqs.(2.3) to (2.8) become

$$\frac{2}{R_c B_o} \frac{\partial c}{\partial t} = \frac{1}{r} \frac{\partial}{\partial r}[r\frac{\partial c}{\partial r}] + A_o \ , \quad t \geqslant 0 \qquad (2.11)$$

$$\frac{\partial c}{\partial r} = 0 \ , \ r = 1 \ , \ t \geqslant 0 \qquad (2.12)$$

$$c = C \ , \ r = R_c \ , \ t \geqslant 0 \qquad (2.13)$$

$$c = c_s \ , \ R_c \leqslant r \leqslant 1 \qquad (2.14)$$

$$[\frac{\partial}{\partial t} + \frac{\partial}{\partial z}]F(C) = B_o \frac{\partial c}{\partial r} \Big|_{R_c} \qquad (2.15)$$

$$C = C_s \ , \ t = 0 \ , \ 0 \leqslant z \leqslant 1 \qquad (2.16)$$

$$C = 1 \ , \ z = 0 \qquad (2.17)$$

Introducing the transformation $c(t,r,z) = v(t,r,z) + C(t,z) - C_s(z) + c_s$ reduces eqs.(2.11)-(2.14) to the following equations for v:

$$\frac{2}{R_c B_o} \frac{\partial}{\partial r} = \frac{1}{r} \frac{\partial v}{\partial r} [r\frac{\partial v}{\partial r}] - \frac{2}{R_c B_o} \frac{\partial C}{\partial t}$$

$$\frac{\partial v}{\partial r} = 0 \ , \quad r = 1$$

$$v = 0 \ , \quad r = R_c$$

$$v = 0 \ , \quad t = 0 \ .$$

The solution to these equations can be obtained as an eigenfunction expansion (see Appendix I for details), so that

$$c = C(t,z) + c_s(r,z) - C_s(z) + \sum_{i=1}^{\infty} T_i(t,z) w_i(r) \quad (2.18)$$

where

$$w_i(r) = J_0(\lambda_i r) Y_0(\lambda_i R_c) - J_0(\lambda_i R_c) Y_0(\lambda_i r) \quad (2.19)$$

are eigenfunctions and λ_i are the roots of

$$J_0(\lambda R_c) Y_1(\lambda R_t) - J_1(\lambda R_t) Y_0(\lambda R_c) = 0 \quad . \quad (2.20)$$

Here J_n and Y_n are the n'th order Bessel functions of the first and second kind, respectively. The eigenvalues λ_i

have been calculated and tabulated by Wang [6] for choices of $\dot{R}_t$ and R_c of physiological interest. The functions $T_i(t,z)$ are given by

$$T_i(t,z) = \frac{2L_i}{\pi\lambda_i^2}\{C(t,z) - \exp[-\mu_i t]C_s(z) \qquad (2.21)$$

$$- \mu_i \int_o^t C(\tau,z)\exp[-\mu_i(t-\tau)]d\tau .$$

Where $L_i = (-2/\pi^2\lambda_i^2 + W_i^2(1)/2)^{-1}$, $\mu_i = R_c B_o \lambda_i^2/2$

Substituting this solution into eq.(2.15), we obtain a non-linear partial differential-integral equation for the capillary oxygen concentration:

$$[\frac{\partial}{\partial t} + \frac{\partial}{\partial z}]F(C) = \frac{4B_o}{\pi^2 R_c} \sum_{i=1}^{\infty} \frac{L_i}{\lambda_i^2}\{C_s(z)\exp[-\mu_i t] \qquad (2.22)$$

$$- C(t,z) + \mu_i \int_o^t C(\tau,z)\exp[-\mu_i(t-\tau)]d\tau\} - E_o .$$

This equation can be integrated numerically.

We divide t into n equal intervals, say $t = n\Delta$. Then the integral

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$$\mu_i \int_0^t C(\tau,z) \exp[-\mu_i(t-\tau)]d\tau$$

can be written as

$$\mu_i \sum_{j=1}^n \int_{(j-1)\Delta}^{j\Delta} C(\tau,z) \exp[-\mu_i(t-\tau)]d\tau .$$

Assuming the variation of $C(\tau,z)$ is small compared to $\exp[\mu_i\Delta]$ in each interval $[(j-1)\Delta, j\Delta]$, we then obtain

$$(1-\exp[-\mu_i\Delta]) \sum_{j=1}^n C(j\Delta,z) \exp[-\mu_i(n-j)\Delta] .$$

Substituting this result into eq.(2.22), we have

$$(\frac{\partial}{\partial t} + \frac{\partial}{\partial z})F(C) = \frac{4B_o}{\pi^2 R_c} \sum_{i=1}^\infty \frac{L_i}{\lambda_i^2}\{C_s(z)\exp[-\mu_i n\Delta] \qquad (2.23)$$

$$- C(n\Delta,z) + (1-\exp[-\mu_i\Delta]) \sum_{j=1}^n C(j\Delta,z)\exp[-\mu_i(n-j)]\}$$

$$- E_o$$

or

$$\left[\frac{\partial}{\partial t} + \frac{\partial}{\partial z}\right] C = \left(\frac{dF}{dt}\right)^{-1}\left[\frac{4B_o}{\pi^2 R_c} \sum_{i=1}^{\infty} \frac{L_i}{\lambda_i^2}\right.$$

$$\left\{C_s(z)\exp[-\mu_i n\Delta] + (1-\exp -\mu_i\Delta])\sum_{j=1}^{n-1} C(j\Delta,z)\exp\right.$$

$$\left.\left.[-\mu_i(n-j)\Delta] - C(n\Delta,z)\exp[-\mu_i\Delta]\right\} - E_o\right].$$

If we let $\Delta z = \Delta t = \Delta$ and $z = m\Delta$, then eq.(2.23) becomes

$$\frac{1}{\sqrt{2}\Delta}\{C([n+1]\Delta,[m+1]\Delta) - C(n\Delta,m\Delta)\}$$

$$= \left(\frac{dF}{dC}\right)^{-1}\left[\frac{4B_o}{\pi^2 R_c} \sum_{i=1}^{\infty} \frac{L_i}{\lambda_i^2} \{C_s(m\Delta)\exp[-\mu_i n\Delta]\right.$$

$$+ (1-\exp[-\mu_i\Delta])\sum_{j=1}^{n-1} C(j\Delta,m\Delta)\exp[-\mu_i(n-j)\Delta]$$

(2.24)

$$\left.\left. - C(n\Delta,m\Delta)\exp[-\mu_i\Delta]\right\} - E_o\right].$$

Now eq.(2.24) is changed into a form which is suitable for numerical computation:

$$C([n+1]\Delta,[m+1]\Delta) = C(n\Delta,m\Delta) + \sqrt{2}\Delta (dF/dC)^{-1} \qquad (2.25)$$

$$\left[\frac{4B_o}{\pi^2 R_c} \sum_{j=1}^{\infty} \frac{L_i}{\lambda_1^2} \{I1(i,n,m) + I2(i,n,m) + I3(i,n,m)\}\right.$$

$- E_o]$

where

$$I1(i,n,m) = C_s \exp[-\mu_i n\Delta]$$

$$I2(i,n,m) =$$
$$\{1 - \exp[-\mu_i \Delta]\} \sum_{j=1}^{n-1} C(n\Delta,m\Delta) \exp[-\mu_i(n-j)\Delta]$$

$$I3(i,n,m) = - C(n\Delta,m\Delta) \exp[-\mu_i \Delta] .$$

The folloing recursive formulas are also easy to derive :

$$I1(i,n+1,m) = I1(i,n,m)\exp[-\mu_i \Delta]$$

$$I2(i,n+1,m) =$$
$$I2(i,n,m)\exp[-\mu_i \Delta] - (1 - \exp[-\mu_i \Delta])I3(i,n,m)$$

$$I3(i,n+1,m) = - C_b([n+1]\Delta,m\Delta)\exp[-\mu_i \Delta]$$

and

$$I1(i,1,m) = C_s(m\Delta)\exp[-\mu_i \Delta]$$

$$I2(i,1,m) = 0$$

$$I3(i,1,m) = - C(\Delta,m\Delta)\exp[-\mu_i \Delta] .$$

Using the same principle, we can approximate $T_i(t,z)$ by

$$T_i(n,m) = - \frac{2}{\pi} \frac{L_i}{\lambda_1^2}[I1(i,n,m) + I2(i,n,m) \qquad (2.26)$$

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+ I3(i,n,m)] .

Substituting eq.(2.26) into eq.(2.18), we obtain a computational formula for $c(t,r,z)$:

$$c(n\Delta,r,m\Delta) = C(n\Delta,m\Delta) - A_0[r^2 - R_C^2 - 2\ln(r/R_C)] \qquad (2.27)$$

$$- \frac{2}{\pi} \sum_{i=1}^{\infty} \frac{L_i}{\lambda_i^2} w_i(r) \cdot [I1(i,n,m)$$

$$+ I2(i,n,m) + I3(i,n,m)] .$$

Both eq.(2.25) and eq.(2.27) are used in the numerical calculation for capillary and tissue oxygen concentration before anoxia develops.

The solution obtained in this section is valid at and location z only until the time $t^*(z)$ at which c=0 at r=1. Regions of anoxia then develop in the tissue and grow with increasing time. The analysis of the oxygen concentration profiles and the determination of the growth of these anoxic regions will be carried out in the next section.

3. THE DEVELOPMENT OF ANOXIA

At any axial location z, the solution obtained in the previous section determines the time $t^*(z)$ following occlusion at which the oxygen concentration falls to zero at the outer edge of the Krogh cylinder. For larger values of time, those solutions are no longer valid, and a completely different type of analysis must be given. Anoxic tissue first devlops at the venous end, z=1, at time $t^*(1)$. With increasing time, this region grows, moving toward the capillary, as well as toward the arterial end of the Krogh cylinder. Eventually, concentration profiles will reach a new steady state.

At any location z, a new time $t^\sim = t - t^*(z)$ will be introduced, measured form the time at which the oxygen concentration falls to zero at r=1. The governing equation for $t^\sim$ 0 are

$$\frac{2}{R_c B_o} \frac{\partial c_t}{\partial r} = \frac{1}{r} \frac{\partial}{\partial r} r \frac{\partial c_t}{\partial r} + A_o \tag{3.1}$$

$$c_t = \frac{\partial c_t}{\partial r} = 0 \qquad \text{at} \quad r = H(t^\sim, z) \tag{3.2}$$

$$c_t = C_b \qquad \text{at} \quad r = R_c , \qquad t^\sim \geqslant 0 \tag{3.3}$$

$$[\partial/\partial t^\sim + \partial/\partial z] F(C_b) = B_o \partial c_t / \partial r |_{R_c} \qquad , \quad t^\sim \geqslant 0 \tag{3.4}$$

$$H(t\tilde{\ },z) = 1, \ C_b = C_i \ , \ c_t = c_i(r,z) \text{ at } t\tilde{\ } = 0 \quad (3.5)$$

where c_t and C_b are the tissue and blood oxygen concentrations, respectively, and $c_i(r,z)$, $C_i(z)$ are the solutions for tissue and blood obtained from the last section at $t = t^*(z)$.

Equation (3.1) assumes that the tissue consumes oxygen at a constant rate A_o (M) as long as the concentration is greater than zero, but falls to zero discontinuously when the concentration vanishes. The significance of this assumption has been discussed previously (Salathe and Beaudet, [4]).

The determination of c_t and C_b involves the analysis of a moving boundary problem, characterized by the fact that the domain of definition of equation (3.1), $R_c < r < H(t\tilde{\ },z)$, is not known a priori, but must be determined as part of the solution. Such problems are extremely complex, even in their most simple form. The present problem is further complicated by the axisymmeteric geometry and the coupling of the tissue and capillary concentrations through eqs. (3.3) and (3.4). In addition, the nonlinear oxyhemoglobin dissociation

realtionship makes the analysis virtually intractable, either by analytic or numerical methods. However, the form of the oxyhemmoglobin dissociation relation makes possible an approximate method of soluton by means of perturbation techniques that provides sufficiently accurate results under a wide range of physiological conditions.

Under normal physiological conditions, capillary oxygen concentration is sufficiently high that it corresponds to the flat portion of the oxyhemoglobin dissociation relationship. Therefore, immediately following occlusion, the concentration drops rapidly, with relatively little bound oxygen released. By the time anoxic tissue begins to develop, the oxygen concentration in the capillary has fallen to values corresponding to the steep portion of the dissociation relationship. The hemoglobin then supplies relatively large amounts of oxygen to the tissue with much smaller changes in concentration. Mathematically, this follows from equ.(3.4), which can be written in the form $(\partial/\partial t^{\sim} + \partial/\partial z)C_b = \partial c_t/\partial r|_{R_c}/[1+NS'(C_b)]$. Clearly, $\partial C_b/\partial t^{\sim}$ is small when $S'(C_b)$ is large, and from eq.(3.3), $\partial(c/\partial t^{\sim}$ should also be small. It follows that the dominant

behavior during this period can be described by using a quasi-steady approximation for tissue concentration, achieved by neglecting the $\partial c_t / \partial \tilde{t}$ term in eq.(3.1). The effect of this term can be ascertained, and the accuracy of the solution improved, by obtaining the next term in a perturbation or iteration scheme.

The dominant approximations to c_t, C_b and $H(\tilde{t}, z)$, denoted by c_o, C_o and H_o, respectively, satisfy the equations

$$\frac{1}{r} \frac{\partial}{\partial r}[r \frac{\partial}{\partial r} c_o] = A_o \quad \tilde{t} \geqslant 0, \ R_c \leqslant r \leqslant H_o \quad (3.6)$$

$$c_o = \partial c_o / \partial r = 0 \quad \text{at } r = H_o; \ c_o = C_o \text{ at } r = R_c \quad (3.7)$$

$$(\partial / \partial \tilde{t} + \partial / \partial z) F(C_o) = B_o \ \partial c_o / \partial r|_{R_c} . \quad (3.8)$$

From eqs.(3.6), (3.7) it follows that

$$c_o = A_o[r^2 - H_o^2 - 2H_o^2 \ln(r/H_o)]/4 \quad (3.9)$$

$$C_o = A_o R_c^2 [2(H_o/R_c)^2 \cdot \ln(H_o/R_c) - (H_o/R_c)^2 + 1]/4 \quad (3.10)$$

$$\partial c_o / \partial r|_{R_c} = A_o R_c [1 - (H_o/R_c)^2]/2 . \quad (3.11)$$

Substituting these results into eq.(3.8) gives

$$(\partial / \partial \tilde{t} + \partial / \partial z) F(C_o) = -A_o B_o R_c [(H_o/R_c)^2 - 1]/2 . \quad (3.12)$$

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In order to solve eq.(3.12), we introduce new dependent and independent variables:

$$\eta = \tilde{t}$$

$$\sigma = z - \tilde{t}$$

$$U_0(\eta,\sigma) = \left[\frac{H_0(\tilde{t},z)}{R_c}\right]^2 .$$

Then eq.(3.12) becomes

$$\frac{\partial U}{\partial \eta} = -\frac{2B_0}{R_c}\frac{U_0-1}{\ell n U_0 F'[C_0]} . \tag{3.13}$$

With the initial condition $U_0 = R_c^{-2}$ at $\eta = 0$, eq.(3.13) can readily be integrated numerically to give U_0, and therefore H_0 in a parametric form.

At $\tilde{t} = 0$, $H_0 = 1$ and eqs.(3.9) and (3.10) give

$$c_0 = A_0[r^2-1+2\ln(r)]/4$$

$$C_0 = A_0[R_c^2-1+2\ln(R_c)]/4 .$$

Clearly, $c_0=0$ at $r=H_0$, as required. However, these solutions are not in agreement with the solutions obtained in the previous section, at the time t^* at which

oxygen concentration falls to zero at r=1. The reason is that the expansion used in this section is singular, and is not applicable at $t^\sim=0$. The assumption that the $\partial c/\partial t$ term is negilible in eq.(3.1) breaks down at $t \approx t^*$, when the transition between the two types of solutions occurs. A completely new type of expansion is required during the brief period in which the soluions at $t=t^*$ evolve to the solution obtained here for $t > t^*$. This assertion is verified and a brief description of the nature of the solution in this transition layer is given in Appendix III.

It can be seen that the dominant solution depends only on η, so that the concentration profiles evolve in an identical manner in η once anoxia begins to develop, at least to this approximation.

The solution obtained above can be improved upon by obtaining the next iteration, C_1, c_1, H_1, in which the neglected term in eq(3.1) is approximated by . This approximation satisfies the equations

$$\frac{1}{r}\frac{\partial}{\partial r}[r\frac{\partial}{\partial r}c_1] = A_o + \frac{2}{B_o R_c}\frac{\partial c_o}{\partial t}, \quad t^\sim > 0 \qquad (3.14)$$

$$c_1 = \partial c_1/\partial r = 0 \;,\; r = H_1 \;;\; c_1 = C_1 \;,\; r = R_c \qquad (3.15)$$

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$$\left(\frac{\partial}{\partial \tilde{t}} + \frac{\partial}{\partial z}\right) F(C_1) = B_o \left. \frac{\partial c_1}{\partial r} \right|_{R_c} \tag{3.16}$$

From (3.9), it is easy to show that

$$\frac{\partial C_o}{\partial \eta} = \frac{A_o}{4} \, \ell n U_o \, \frac{\partial U_o}{\partial \eta} \quad .$$

It can be shown (see Appendix II) from (3.14), (3.15) that

$$c_1 = [\zeta(U_o,2)+2M(U_o)\ell nR_c][(r/R_c)^2-U_1] + \tag{3.17}$$

$$2[\zeta(U_o,2)-2M(U_o)\ell nU_1]U_1\ell n(H_1/r) +$$

$$M(U_o)(H_1^2\ell nH_1-r^2\ell nr)/2$$

$$C_1 = \zeta(U_o,2)(1-u_1) + G(U_o,U_1) \quad . \tag{3.18}$$

Where

$$U_1 = (H_1/R_c)^2$$

$$M(U_o) = \frac{A_o(1-U_1)}{(1-dt^*/dz)\ell nU_o F'(C_o)}$$

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$$\zeta(U_o, \alpha) = R_c^2 [A_o + M(U_o)(\ell n U_o + \alpha - 2\ell n R_c)]/4$$

$$G(U_o, U_1) = [\zeta(U_o, 2) - R_c^2 M(U_o) \ell n U_o/4] U, \ell n U_1 \ .$$

Substituting these results into (3.16) gives an equation for U_1, which, after some manipulation, can be put into the form

$$\frac{\partial U_1}{\partial \eta} = [\Psi(U_o, U_1) - \Phi(U_o, U_1)]/ \quad\quad (3.19)$$

$$\Theta(\bar{U}_o, U_1)$$

where

$$\Psi(U_o, U_1) = R_c[\zeta(U_o, 1) + M(U_o)U_1 \ell n U_1]$$

$$\Phi(U_o, U_1) = \frac{\partial \zeta(U_o, 2)}{\partial U_o}(1 - U_1) + \frac{\partial G(U_o, U_1)}{\partial U_o} \frac{\partial U_o}{\partial \eta}$$

$$\Theta(U_o, U_1) = \frac{\partial G(U_o, U_1)}{\partial U_1} - \zeta(U_o, 2) \ .$$

With the provision of an initial condition for U_1 at $\eta = 0$, this equation can be readily integrated numerically to provide U_1. Substituting U_1 into (3.17) and (3.18)

then provides the solution for the concentration c_1, C_1.

It is not possible to satisfy, at $t^{\sim} = 0$, both the initial condition $U_1 = R_c^{-2}$ and the requirement that C_1 should equal the value given by the earlier solution (for $t \leqslant t^*$) at $t = t^*$. As pointed out earlier, the two solutions (for $t \leqslant t^*$ and $t > t^*$) do not match at $t = t^*$, and a transition layer in which the $\partial c/\partial t$ term in (2.3) is not negligible must be constructed to join the two solutions. It can be shown (Appendix III) that the correct initial condition on U_1 at $t^{\sim} = 0$ is $U_1 = (1 - \lambda)/R_c^2$, where λ is chosen so that C_1 at $t^{\sim} = 0$ has the same value as that given by the earlier solution at $t = t^*$. Denoting this value of C_b by C_b^*, and reconginzing λ as a small perturbation quantity (Appendix III), it follows from eq.(3.18) that

$$\lambda = \frac{(C_b^* - \zeta_0 [1/R_c^2 - 1] + 2\ell n R_c \cdot \xi_0)}{2(1 + \ell n R_c)\xi_0} \qquad (3.20)$$

where

$$\zeta_0 = \zeta(1/R_c^2, 2)$$

$$M_0 = M(1/R_c^2)$$

$$\xi_0 = [\zeta_0/R_c^2 + M_0 \ell n R_c/2] \ .$$

4. NUMERICAL RESULTS

Numerical results will be presented for the data shown in Table 1. These results apply before the time that anoxic tissue develops. Figure 1 illustrates the variation in blood oxygen concentration along the capillary at various times. It shows that there is an intensive variation of concentration profile in the capillary during the first second. Figure 2 is the variation in oxygen concentration along the outer edge of the Krogh cylinder. The time $t^*(z)$ as a function of z is shown in Figure 3. From Figure 3 it can be seen that the new steady state is reached as t^* goes to infinity for certain z, so that anoxia will not develop any further.

Appendix I: Properties of eigenfunction $w_i(r)$

The solution obtained in eq.(2.18) can be derived by representing $v(t,r,z)$ as an eigenfunction expansion in the form $v = \sum_{i=1}^{\infty} T_i(t,z)w_i(r)$. The eigenfunctions w_i, defined in eq.(2.19), have the orthogonality property

$$\int_{R_c}^{1} rw_i(r)w_j(r)\,dr = \delta_{ij}[1/\pi^2\lambda_1^2 + w_i^2(1)/2] = \delta_{ij}L_i^{-1} \quad (I.1)$$

where $\delta_{ij} = 0$, $i \neq j$; $\delta_{ij} = 1$, $i=j$; and the eigenvalues are defined in eq.(2.20). It therefore follows that

$$T_i(t,z) = L_i \int_{R_c}^{1} rw_i v\,dr . \quad (I.2)$$

Differentiating T_i with respect to t, integrating by parts, making use of the equation and boundary conditions satisfied by v and the properties of the eigenfunction such as,

$$1 = -\sum_{i=1}^{\infty} \frac{2L_i}{\pi\lambda_i^2} w_i(r)$$

it can shown that

$$\partial T_i/\partial t + \mu_i T_i = {}^2L_i/\pi\lambda_i^2 \, \partial C_b/\partial t . \quad (I.3)$$

Applying the initial condition $v=0$ at $t=0$ to eq.(I.2) gives $T_i(0,z) = 0$. The solution to eq.(I.3) subject to

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the initial condition gives the result shown in eq.(2.21).

Appendix II: Intermediate result used in section 3

In section 2 eqs.(3.14) , (3.15) can be written in the following simplified form :

$$\frac{1}{r}\frac{\partial}{\partial r}[r\frac{\partial}{\partial r} c] = A - B\ell n(r/R_c) . \tag{II.1}$$

$$c = \partial c/\partial r = 0 \quad \text{at } r = H .$$

Integrating once and applying boundary condition, it follows that

$$\frac{\partial c}{\partial r} = \left[\frac{A}{2} + \frac{B}{4}\right](r - \frac{H^2}{r}) + \frac{B}{2}\frac{H^2}{r}\ell n(\frac{H}{R}) - r\ell n(\frac{r}{R_c}) . \tag{II.2}$$

Integrating again, it can be shown that

$$c = \frac{A+B}{4}[r^2 - H^2] + \frac{1}{4}[(2A+B) - B\ell n(H/R_c)]H^2\ell n(H/r) \tag{II.3}$$

$$+ \frac{B}{4}H^2\ell n(H/R_c) - r^2\ell n(r/R_c) .$$

Letting $r = R_c$, the expression for C is readily obtained

$$C = \frac{A+B}{4}[R_c^2 - H^2] + \frac{1}{4}[2(A+B) - 2B\ell n(H/R_c)]H^2\ell n(H/R_c) . \tag{II.4}$$

With eq.(II.3), (II.4), the derivation of eq.(3.17) and (3.18) can be easily obtained.

Appendix III: Perturbation analysis

When tissue oxygen concentration reaches zero at the outer edge of the Krogh cylinder and anoxia begins to develop, there is a brief period during which a perturbation expansion with the quasi-steady solution as the dominant term is not applicable. In this appendix, a simplified two-dimensional model which has the essential features of the original problem will be examined, and it will be shown how the solutions for $t \leqslant t^*$ and for $t > t^*$ are properly joined at $t = t^*$. This will be done by assuming that the $\partial c / \partial t$ term is small for all t, so that both the solution for $t < t^*$ and $t > t^*$ can be obtained as asymptotic expansions. A boundary layer in the neighborhood of $t = t^*$ will then be constructed and joined to these solutions using the method of matched asymptotic expansions.

Consider a simplified two-dimensional tissue and capillary system. The non-linear oxyhemogoblin dissociation relation will not be considered in the present case, and the time rate of change in tissue is assumed to be small compared to other terms. Therefore the dimensionless steady concentration profile satisfies

$$\frac{\partial^2 C_s}{\partial x^2} = M \ , \quad 0 \leqslant x \leqslant 1 \ , \quad 0 \leqslant z \leqslant 1$$

$$\frac{1}{\nu} \frac{\partial C_s}{\partial z} = \left. \frac{\partial c_s}{\partial x} \right]_{x=0}$$

$$C_s = 1 \ , \quad z = 1$$

$$\frac{\partial C_b}{\partial x} = 0 \ , \quad x = 1 \ ; \quad c_s = C_s \ , \quad x = 0 \ .$$

This system can be solved and gives

$$C_s = 1 - \nu M z$$

$$c_s = C_s + M(x^2/2 - x) \ .$$

If the capillary flow rate is reduced to 1, both the oxygen concentration in the tissue and in the capillary decrease with increasing time. Before anoxia develops, the concentration at any location z satisfies the equations

$$\varepsilon \frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} \quad 0 \leqslant x \leqslant 1 \tag{III.1}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial x} \right) C = \left. \frac{\partial c}{\partial x} \right|_{x=0} \tag{III.2}$$

$$c_t = C_b \text{ at } x=0 \ ; \quad \partial c / \partial x = 0 \text{ at } x = 1 \quad \text{for } t < t^* \tag{III.3}$$

$$C_b = C_c = 1 - \nu M z \tag{III.4}$$

$$c_t = c_s = 1 - \nu M z + M(x^2 - 2x)/2 \tag{III.5}$$

$$C_b = 1 \quad \text{at } z = 0 \tag{III.6}$$

where c_t, C_b are the concentration in the tissue and capillary, respectively.

After partial occlusion there are two kinds of blood that have to be considered:

1. Blood that is in the capillary when occlusion occurs.

2. Blood that enters the capillay after occlusion.

These two kinds of blood give different boundary condition for eq.(III.2) . They are eq.(III.5) and (III.6).

Writing $c_t = c_0 + \varepsilon c_1$, $C_b = C_0 + \varepsilon C_1$, where it is assumed that $\varepsilon \ll 1$, it can easily be shown that for $t > z$ everything is steady. In this case, one has to consider only the part for $t \leqslant z \leqslant L$, for which the solutions are

$$c_0 = C_0 + M(x^2/2 - x)$$

$$C_0 = 1 - M(\nu z + (1 - \nu)t] .$$

Clearly, at $t = 0$, this solution satisfies the initial condition. Also, $c_0 = 0$ at $x = 1$ at $t = t_0 = (1/M - \nu z - 1/2)/(1 - \nu)$, which is the first approximation to t^*.

The next term in the perturbation expansion for $t \leq t^*$ is given by

$$c_1 = C_1 - M(1-\nu)[x^2/2 - x]$$

$$C_1 = M(1-\nu)[g_1(z-t)+t].$$

Applying the initial condition $C_b = C_0 + \varepsilon C_1 = C_s$ at $t=0$ gives $g_1(z-t) = 0$. However $c_t = c_0 + \varepsilon c_1$ doesn't reduce to c_s at $t=0$ for any choice of $g_1(z-t)$. The solution generated by this perturbation expansion is not applicable near $t=0$, and the initial conditions cannot be satisfied. It turns out that the dominant term does in fact satisfy the initial conditions, given by the steady state profile, since it is a quasi-steady solution. However, when the higher order terms are included, the initial conditions cannot be satisfied. A boundary layer exists at $t=0$ that satisfies the initial conditions and joins them to the above solution. Therefore, it cannot be inferred that $g_1(z-t) = 0$. Only through an analysis of the boundary layer can this function be determined, and

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the solution for $t < t^*$ completed.

Introducing the boundary layer varible $T = t/\varepsilon$, which has the property $t \to 0$ as $\varepsilon \to 0$, T fixed, the governing equation for $c^\sim(r,T,z) = c_t(r, \varepsilon t, z)$ becomes $C_T^\sim = C_{xx}^\sim - M$, while the equation for $C^\sim(T,z) = C_b(T,z)$ is $(\partial/\partial T + \varepsilon\, \partial/\partial z)C_b = \varepsilon\, \partial c/\partial x|_{x} = 0$. The boundary conditions at $x=0$ and $x=1$, and the initial condition remains the same. In order to obtain a boundary layer solution that matches with the solution obtained above for t bounded away form zero , it is necessary to examine that solution as $t \to 0$. Writing $t = \varepsilon T$ and expanding the above solution in a series in ε gives

$$C_b \simeq C_s + \varepsilon M(1-\nu)[g_1(z) - T] + 0\ (\varepsilon^2)$$

$$c_t \simeq C_s + \varepsilon M(1-\nu)\ g_1(z) - T - x^2/2 + x + 0\,(\varepsilon^2).$$

It therefore follows that the boundary layer expansion is of the form

$$c_t^\sim = c_s + \varepsilon\psi(x,z,T)$$

$$C_b^\sim = C_s + \varepsilon P(z,T)$$

where ψ and P satisfy the equation and boundary

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conditions

$$\frac{\partial^2 \psi}{\partial T} = \frac{\partial^2 \psi}{\partial x^2} \qquad\qquad (III.8)$$

$$dP/dT = - m(1 - \nu)$$

$$\psi = 0 \qquad P = 0 \quad \text{at } T = 0$$

$$\psi = P \quad \text{at } x=0 ; \quad \frac{\partial \psi}{\partial x} = 0 \quad \text{at } x=1 \cdot$$

The form of the expansion, eq.(III.7), also shows that as $t \to 0$,

$$P \to M(1 - \nu)[g_1(z) - T] \qquad\qquad (III.9)$$

$$\psi \to M(1 - \nu)[g_1(z) - x^2/2 + x] \cdot$$

Equations (III.8) and (III.9) provide a complete set for the determination of ψ and P. Equation (III.8) gives $P = -M(1 - \nu)T$, so that, from equation (III.9), it follows that $g_1(z-t) = 0$. This provides the missing constant in the solution for t bounded away from zero. The solution for ψ and further investigation of the boundary layer will not be persued here.

The time $t = t^* = t_0 + \varepsilon t_1$ at which $c_t = 0$ at $x = 1$ can be determined form this solution. The dominant term,

t_0, has been given above and $t_1 = t_0 + 1/2$. At time $t = t^*$, it can be shown that the solutions are

$$c_b = M/2 - \varepsilon M(1 - \nu)/2$$

$$c_t = M(x - 1)^2[1 - 2(1 - \nu)\varepsilon].$$

For $t > t^*$, the solution can be obtained as an asymptotic expansion, $c_t = c_0 + \varepsilon c_1$, $c_b = C_0 + \varepsilon C_1$, instead of by the iterative method used in the text, so the matching of the solution for $t \leqslant t^*$ and $t > t^*$ can be carried out. With H expanded in the series $H = H_0 + \varepsilon H_1$, the dominent terms, c_0, C_0, H_0, are given by

$$c_0 = M(H_0 - x)^2/2$$

$$C_0 = MH_0^2/2$$

$$H_0 = 1 - (1-\nu)(t-t_0)$$

and the first order term can be shown to be

$$C_1 = \frac{M}{6}(1-\nu)H_0^2 + MH_0 H_1$$

$$c_1 = \frac{M}{6}(1-\nu)(x-H_o)^2 + MH_1(H_o-x)$$

$$H_1 = (1-\nu)g_2(z-t)$$

where $g_2(z-t)$ is to be determined.

These solution evaluated $t = t^*$ do not agree with the solution obtained above for $t \leqslant t^*$, eq.(III.10), for any choice of the function $g_2(z-t)$. The solutions are the same only for the dominant term, but the order ε terms do not match. In order to join the two solutions, and obtain the unknown function $g_2(z-t)$, it is necessary to analyze the boundary layer at $t = t^*$. Defining $\tilde{T} = (t - t^*)/\varepsilon$, which has the property $t \to t^*$ as $\varepsilon \to 0$, $\tilde{T}$ fixed, the boundary layer equations are the same as those for the boundary layer at $t = 0$, except that $\partial\tilde{c}/\partial x = 0$ at $x = 1$ is replaced by $\tilde{c} = \partial\tilde{c}/\partial x = 0$ at $r = \tilde{H} = H(t^*+ \tilde{T})$, where $\tilde{H}(0) = 1$. The boundary layer solution must be constructed in such a way that it satisfies the initial condition at $\tilde{T}=0$ (given by the solution for $t \leqslant t^*$ at $t = t^*$, eq.(III.10)) and matches with the solution obtained for $t > t^*$. An expansion of the solution for $t > t^*$ gives

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$$c_{t} = M(1-x^2)/2 + \varepsilon M(1-\nu)[(1-x)g_2(z-t)-(1-x)|\tilde{} (1-x)^3/6]$$

$$C_b = \frac{M}{2} + \varepsilon M(1-\nu)[g_2(z-t)-T^{\sim}-1/6].$$

This demonstrates that the boundary layer expansion must be of the form

$$C^{\sim} = \frac{M}{2} + \varepsilon M(1-\nu)Q(z,t^{\sim})$$

$$c^{\sim} = \frac{M}{2}(1-x)^2 + \varepsilon M(1-\nu)\alpha(x,z,T^{\sim})$$

and that Q, α satisfy the equations and boundary conditions

$$\frac{\partial \alpha}{\partial T^{\sim}} = \frac{\partial^2 \alpha}{\partial^2 x}$$

$$\alpha = Q, \quad x = 0$$

$$\alpha = 0,$$

$$\frac{\partial \alpha}{\partial x} = -h(T^{\sim}), \quad x = 1$$

$$\alpha = -(x-1)^2, \quad \text{at } T^{\sim} = 0$$

$$\frac{\partial Q}{\partial T^{\sim}} = -1$$

$$Q = -\frac{1}{2} \text{ at } T^{\sim} = 0$$

$$\alpha \to L(T^{\sim},z,x) \text{ as } T^{\sim} \to \infty$$

$$Q \to L(T,z,0)$$

where $H^\sim = 1 + \varepsilon h(T^\sim)$ is the expansion for the anoxic border in this boundary layer, and $L(T^\sim, z, x) = \{(1 - x)g_2(z-t) - (1 - x)T^\sim - (1 - x)^3/6\}$. This provides a complete set of equations for the determination of α, Q and h.

The equation and initial condition for Q give $Q = -1/2 - T^\sim$. The coefficient of $T^\sim$ in this solution can be shown to be the same as the coefficient of $T^\sim$ in $L(T^\sim, z, 0)$, so that this solution can be made to satisfy the matching condition at infinity if $g_2(z-t)$ is properly chosen. This completes the solution for $t > t^*$, valid for the region bounded away from $t = t^*$. It gives $g_2(z-t) = -1/3$. It can be shown that the value for g_2 so obtained results in the capillary concentrations $C_0 + \varepsilon C_1$ for the solution $t > t^*$, and the capillary concentration obtained from the solution for $t \leqslant t^*$, being equal at $t = t^*$.

In conclusion, therefore. an analysis of the boundary layer separating the solutions for $t < t^*$ and for $t > t^*$ shows that the solution for $t > t^*$ is correctly and uniquely determined by choosing the capillary concentration at $t = t^*$ to be equal to the

capillary concentration given by the solution for t t^*

at $t = t^*$. The tissue concentration profiles for the two

solutions do not agree at $t = t^*$. The transition between

these two solutions is given by the boundary layer

solution.

In the text an exact solution was obtained for $t \leqslant$

t^*, since the perturbation method is not generally

applicable during this period under most physiological

conditions. An iteration procedure was used for $t > t^*$,

rather than an asymptotic expansion. The two methods are

basically similar, and in fact the first iteration and

the first term in the expansion are identical. However,

the iteration procedure has the advantage of not

expanding the function $F(C)$ in a series, since in general

$F'(C)$ is not small. It also avoids expanding the location

of the anoxic border, H , in a series, but deterimines

its location as part of the solution. However, the

conclusions reached in this appendix are applicable to

the iteration solution, and justify the assertions made

in the text regarding the joining of the solutions at $t =$

t^*. Since the two solution agree to lowest order at $t =$

t^*, the statement that   is a small perturbation is also

verified. Finally, eq.(III.10) shows that c_b , c_t are

independent of z at $t = t^*$, at least to order ^{2}, so that C_1^* (c.f., eq.(3.18)) is virtually independent of z, as asserted.

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Table 1: Value of Parameters Used in Examples

Parameter	Value
Arterial blood oxygen concentration C_A ($cm^3 O_2/cm^3$ blood)	3×10^{-3}
Tissue diffusivity D (cm^2/sec)	1.1×10^{-5}
Oxygen capacity of the blood at 100% saturation N ($cm^3 O_2/cm^3$ blood)	0.204
Tissue oxygen consumption rate M ($cm^3 O_2/cm^3$ tissue-sec)	5×10^{-4}
Capillary length L (cm)	2.4×10^{-2}
Capillary length R_c (cm)	4×10^{-4}
Tissue radius R_t (cm)	4×10^{-3}
Volume blood flow rate (cm^3/sec) Initial Final	2.01×10^{-8} 1.105×10^{-8}
Constant K in oxyhemoglobin dissociation relationship	6.69×10^{6}
Constant n in oxyhemogolobin dissociation relationship	2.2

Table 2: The definition of dimensionless constant

$$A_o = \frac{M R_t'^2}{DC_A}$$

$$B = \frac{2\pi R_c DL}{g_f}$$

$$E_o = \frac{\pi(1-R_c^2)R_t'^2 LM}{q_f C_A}$$

$$\mu = \frac{R_c B_o \lambda_i^2}{2}$$

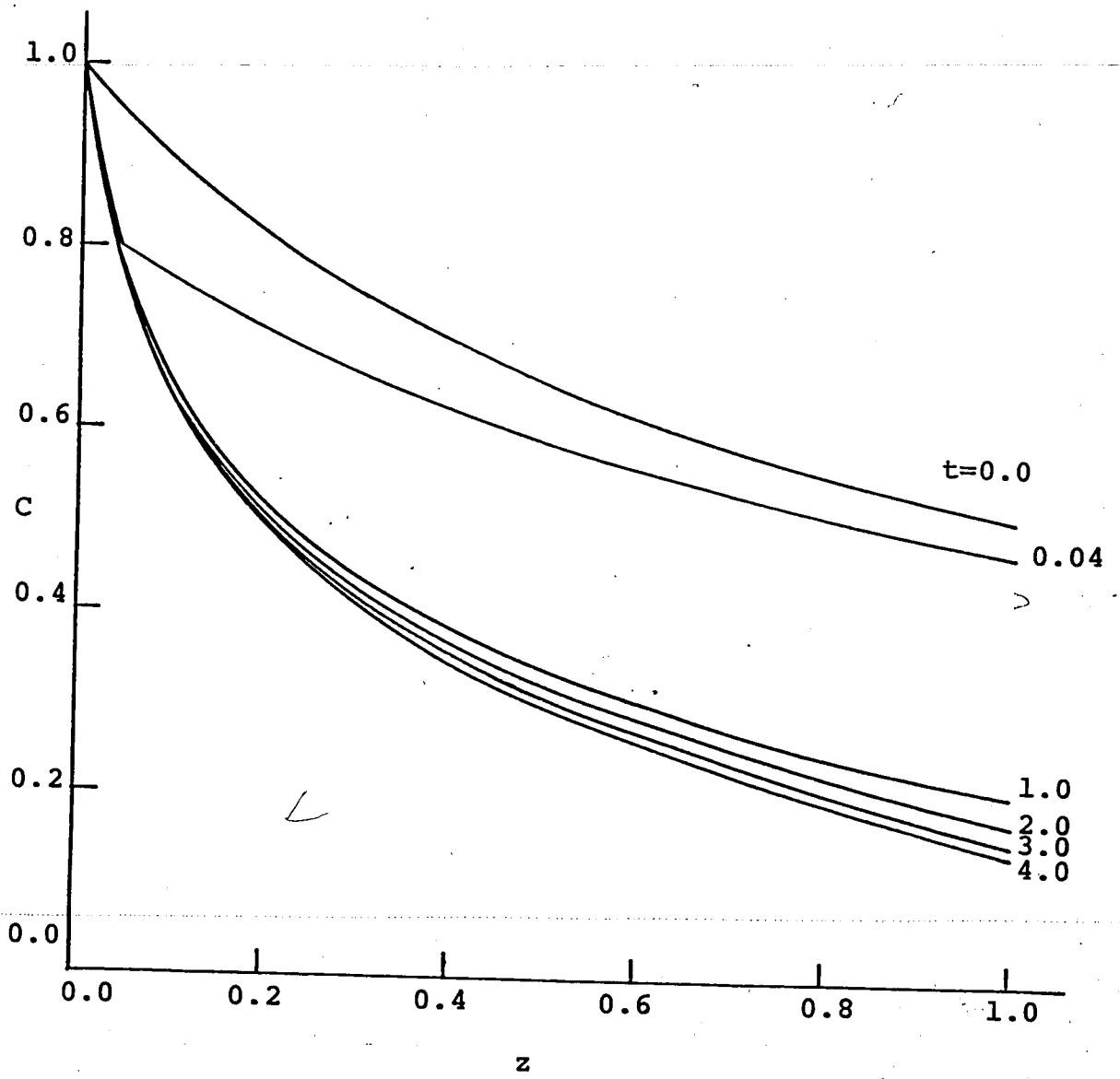$$L_i = (-2/\pi^2 \lambda_i^2 + w_i^2(1)/2)^{-1}$$

Figure 1. Capillary oxygen concentration as a function
of axial location at various times. (All
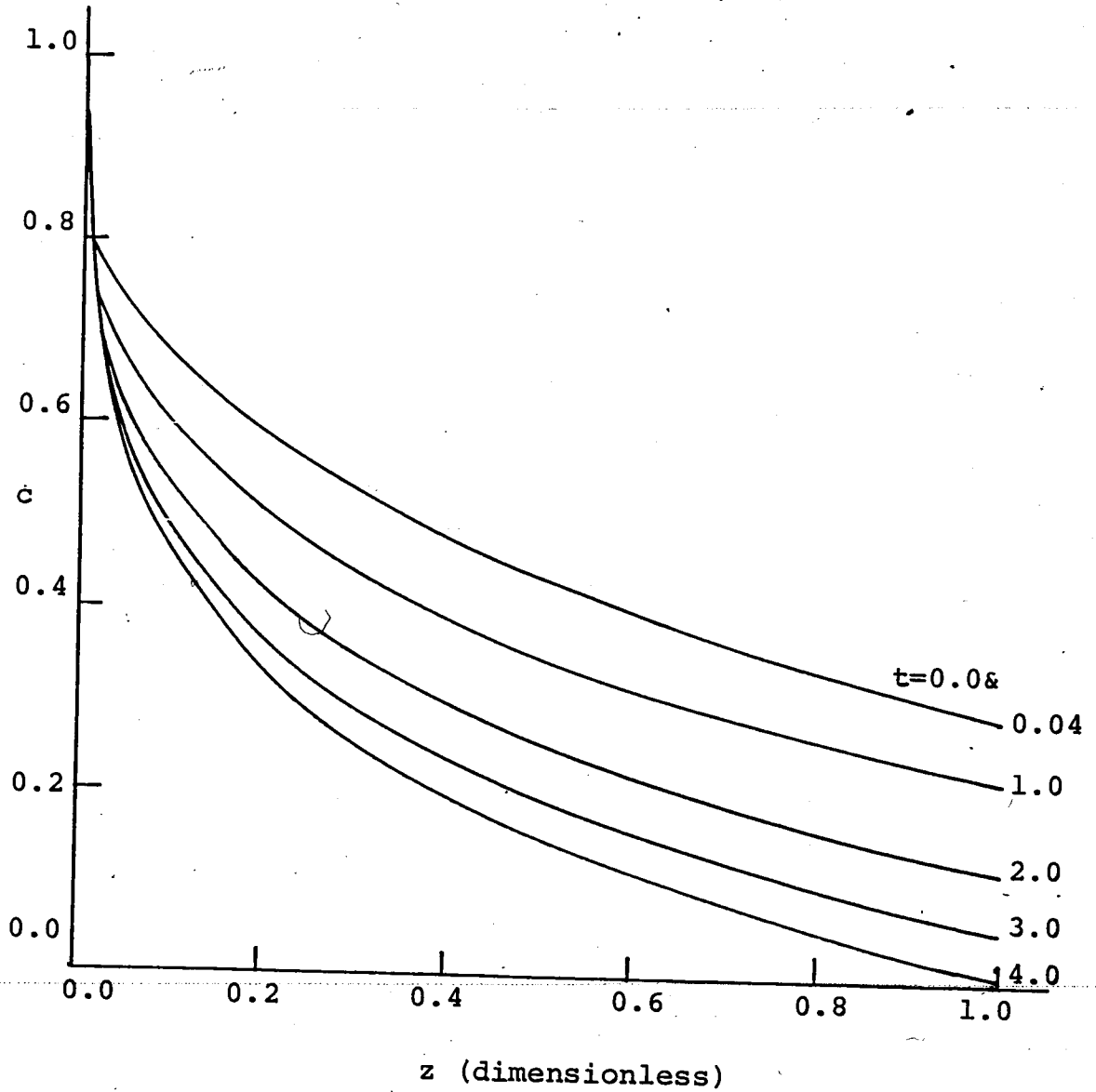variables are dimensionless.)

Figure 2.   Tissue oxygen concentration at the outer edge of the tissue as a function of axial position for various times.
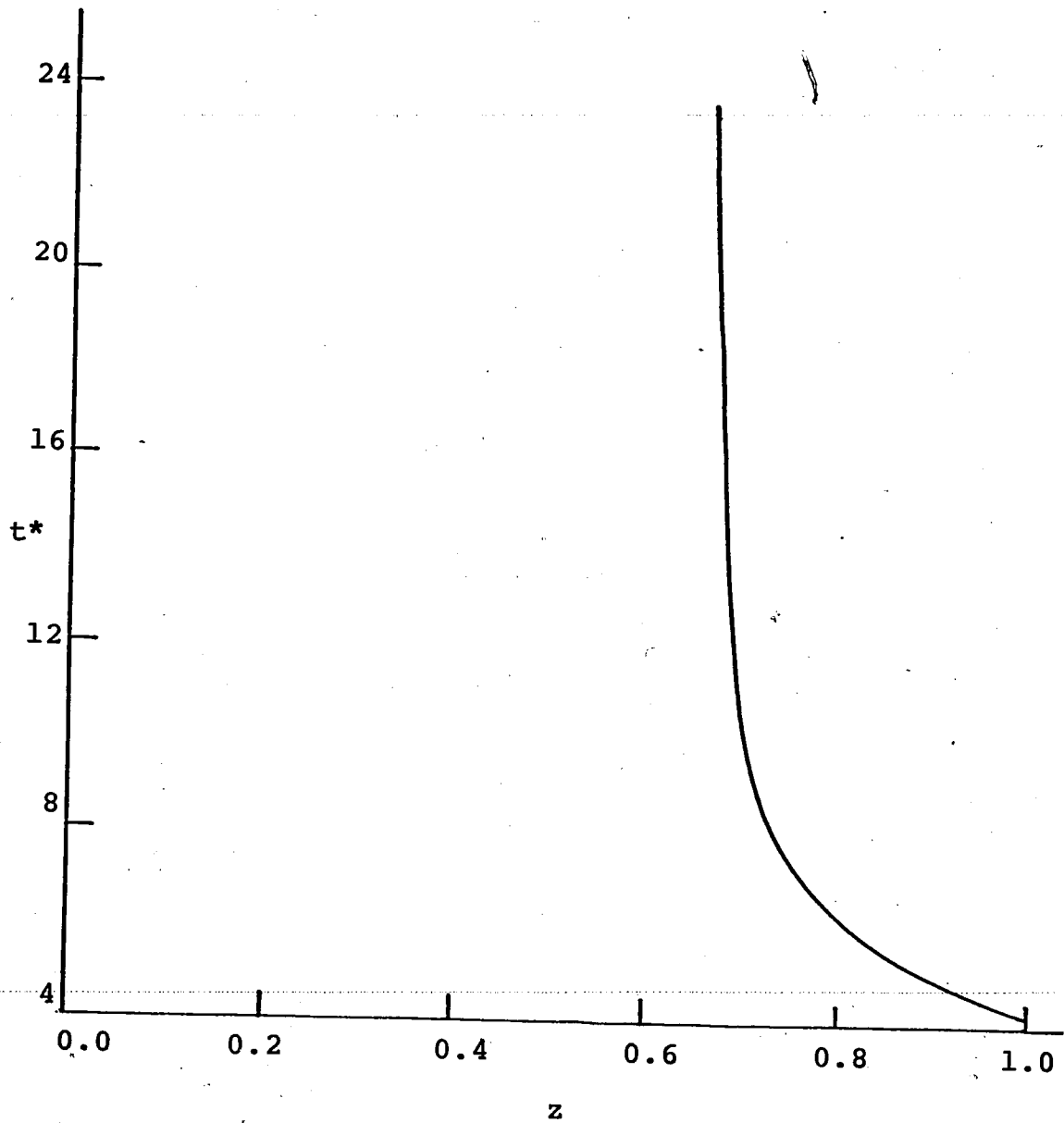
Figure 3. Time for anoxic tissue to develop at outer edge
of Krogh cylinder as a function of axial
location.

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