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An Analytical Solution for Diffusion and Nonlinear Uptake of Oxygen in the Retina

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Abstract. A simple mathematical model of steady state oxygen distribution subject to diffusive transport and non- linear uptake in a retinal cylinder has been developed. The approximate analytical solution to a reaction-diffusion equation are obtained by using series expansions. The computational results for the scaled variables are presented through graphs. The effect of the important parameters (1) diffusion coefficient (2) metabolic rate constant (3) retinal capillary concentration are examined and discussed

Keywords: Oxygen diffusion, Michaelis-Menten Kinetics, Taylor series.

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1. Introduction

The determination of oxygen concentration profiles in a single capillary and in a surrounding coaxial cylinder of tissue is a fundamental problem in the mathematical study of oxygen transport to tissue. Although the basic model was originally introduced by Krogh for the study of oxygen distribution in the highly regular capillary beds of skeletal muscle, it has also been applied to retinal capillaries into the retinal tissue.

Thus, retinal circulation [2] is responsible for the delivery of oxygen and nutrients to different structures of the retina without interfering with visual function. To achieve this complex task in mammals, human and other primates, two separate vascular systems: the retinal vascularization and the choroidal vascularization ,partake in the process. The former one supplies the inner two-thirds of the retina

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through three layers of capillary networks including the radial peripapillary capillaries and a superficial and deep layer of capillaries. The retinal circulation shows progressive slowing of linear flow rate in arterioles and capillaries [1, 7]. Therefore, retinal circulation is characterized by a low blood flow and a high level of oxygen extraction; arteriovenous difference in PO_2 is about 40%. To ensure selective exchanges of substances between the blood and the surrounding tissuses, retinal vascular endothelial cells are non-fenestrated, tightly joined and form an inner blood retinal barrier between the retinal capillaries and the retinal tissues.

Gases such as O_2 and CO_2 can transport across the capillary walls. The transport of oxygen from the lungs to the systematic capillaries is accomplished by a process of bulk flow as oxygenated blood is carried to the tissues. Once blood reaches the systematic capillaries [3], oxygen dissociates from hemoglobin which holds 97% of its maximum amount of O_2 from normal air or holds 100% when breathing pure O_2 diffuses through the red cell membranes into the plasma and from there into the tissue.

Many different local and systematic factors can exert an influence, local and systematic factors can exert an influence, local physical (variations in perfusion pressure) and metabolic factors(e.g variations in PO_2 and pH) attempt to adapt to local needs, while systematic factors regulate the distribution of the cardiac output different beds. Since the retinal tissue lacks vascular innervations, retinal arterial tone is largely regulated by local factors. The low through avascular bed is determined by both perfusion pressure and vascular resistance [10]. In the adult, retinal blood is maintained constant over a wide range of perfusion pressure from 45 Hg to 145 mm Hg.

In addition to a large number of experimental studies [5, 9] numerous mathematical models [4, 6, 8] for the oxygen transport in the systematic capillaries tissue in different organs of the body have been developed and analyzed. The first simple mathematical model for oxygen transport across the capillaries was formulated by Krogh. In Kroghs initial work only a highly simplified and rather elementary mathematical analysis of the model was presented. Middleman and the proceeding of a recent symposium on oxygen transport to tissue contains numerous accounts of mathematical studies of the Krogh cylinder, as this model is now called. The very complex nature of the governing equations has always resulted in significant simplifications being made at the outset, so that the mathematics becomes tractable. Therefore, the analytical treatment is still far from complete.Friedland developed a mathematical model of transmural transport of oxygen to the retina of the human eye. He included not only the tissue metabolism and time varying concentrations but also included hydrostatic transmural pressure gradients. The present work is concerned with the formulation of a simple mathematical model for the transport of oxygen from the surrounding retinal tissue.

2. Mathematical Formulation

The retinal tissue is represented as an array of uniformly cylinders along the axes. Each tissue cylinder is assumed to be supplied with oxygen exclusively within it where $< c >$ area averaged oxygen concentration in the retinal capillary; c_T, the oxygen concentration in the tissue, $< v >$, the measured average blood speed in the capillary, R_1, the radius of the retinal capillary, R_2, the radius of the tissue and L, the length of the capillary. Blood enters the retinal capillary at its arteriole end $z = 0$ and exits its venule end $z = L$. As blood flows along the capillary ,oxygen is extracted from the capillary wall. The transport of oxygen in the tissue occurs by molecular diffusion and the consumption of oxygen occurs in the surrounding

retinal tissue only. Within the retinal capillary, we assume that its size is so small, and the flow condition is such that the radial concentration and velocity gradients can be neglected and that we can instead use their area averaged value of $< c >$ and $< v >$ respectively. The equations governing the transport of intravascular oxygen in the retinal capillary and the transport of extravavscular oxygen in the retinal tissue are written in simplified form by taking into account the convection of oxygen in axial direction in the capillary and the radial diffusion in the tissue and non-linear metabolic consumption rate in the retinal tissue.

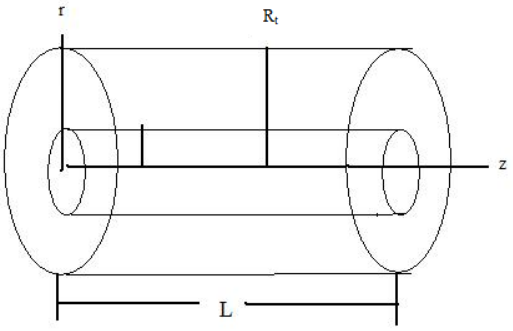

Figure 1. Systematic diagram of oxygen transport into the retinal tissue

3. Assumptions

1. Intravascularly flow in capillary may be far from poiseuille flow due to turbulence, non Newtonian viscosity effects and limiting of red blood cell.
2. We assume the each capillary only feeds its surrounding mantle of capillary tissue.
3. The capillary is assumed to be assumed to be surrounded by a mantle of retinal tissue which is metabolized by retinal cells.
4. Within the capillary, we assume that its size is so small, and the flow condition is such that the radial concentration and velocity gradient can be neglected.
5. In the retinal tissue, the longitudinal diffusion is neglible, hence we neglected the longitudinal diffusion term.

4. Governing Equations

Using a differential macroscopic mass balance over a length dz and rearranging the resulting expression, we obtain the following steady state equation governing the transport of oxygen in the retinal capillary:

$$\frac{dc}{dz} = \frac{-2\beta}{R_1 < v >}(c - c_{T1}) \tag{1}$$

The above equation mentioned states that the change of the moving intravascular concentration gradient in the retinal capillary. Where , retinal capillary oxygen permeability constant and c_{T1}, the concentration of oxygen in the tissue at $r = R_1$.

The transport of oxygen in the retinal tissue depends upon the molecular diffusion and oxygen consumption during the metabolic process. Oxygen diffusion in the axial direction in the tissue is neglected as evidenced by the fact that oxygen concentration gradients are much stepper in the radial direction than axial direction Ficks law of diffusion and conservation of mass lead to the corresponding nondimensional governing equation which can be written as,

$$\frac{D_r}{r}\frac{\partial}{\partial r}(r\frac{\partial c_T}{\partial r}) = \frac{Ac_T}{B+c_T} \tag{2}$$

$$\frac{D_r}{r}[\,r\frac{\partial^2 c_T}{\partial r^2} + \frac{\partial c_T}{\partial r}] = \frac{Ac_T}{B+c_T} \tag{3}$$

$$D_r\frac{\partial^2 c_T}{\partial r^2} + \frac{D_r}{r}\frac{\partial c_T}{\partial r} - \frac{Ac_T}{B+c_T} = 0 \tag{4}$$

The governing equation is a steady state reaction diffusion equation representing oxygen transport by linear diffusion in a cylinder with cylindrical symmetry. The oxygen uptake is described by the non linear Michaelis-Menten model with a maximum reaction rate A and the half-saturation concentration rate B .

4.1 *Boundary Conditions*

The physichologically relevant and mathematically consistent boundary and interface conditions are prescribed below:

$$(c)_{z=0} = 0 \tag{5}$$

$$(\frac{dc_T}{dr})_{r=R_2} = 0 \tag{6}$$

$$-D_r(\frac{dc_T}{dr})_{r=R_2} = \beta(c - c_{T1}) \tag{7}$$

Boundary condition (5) states that there will be no concentration at the arteriole end. The boundary condition (6) depicts that, at the capillary end there will no flux. The boundary condition (7) represents that the diffusive flux at the tissue region will be proportional to the diffusive concentration gradient.

5. SOLUTION TO THE PROBLEM

The solution of the Equation (1) corresponding to boundary condition (5) is given by:

$$c(z) = c_{T1}(1 - e^{\alpha z}) \qquad 0 \le z \le L \tag{8}$$

We generalize the Equation (3) as follows:

$$D_r\frac{d^2 c_T}{dr^2} + \frac{D_r a}{r}\frac{dc_T}{dr} - f(c) = 0 \tag{9}$$

subject to

$$(\frac{dc_T}{dr})_{r=R_2} = 0 \tag{10}$$

$$-D_r(\frac{dc_T}{dr})_{r=R_2} = \beta(c - c_{T1}) \tag{11}$$

Equation (9) is written in terms of a constant a, which can be selected to reflect Cartesian ($a = 0$), cylindrical ($a = 1$) or spherical ($a = 2$) geometry.

Equation (9) is relevant for any uptake model $f(c)$ selecting $a = 1$ and $f(c_T) = \frac{Ac_T}{B+c_T}$we recover the original non- dimensional model. Let us select that solution of Equations (9-11) is sufficiently smooth so that it can be explained in Taylor series given by

$$c_T(r) = \sum_{i=0}^{\infty} \frac{r^i}{i!}\frac{d^i c_T}{dr^i} = c_T(r = r_1) + r(\frac{dc_T}{dr})_{r=r_1} + \frac{r^2}{2}(\frac{d^2c_T}{dr^2})_{r=r_1} + \frac{r^3}{6}(\frac{d^3c_T}{dr^3})_{r=r_1} + \cdots \tag{12}$$

To determine the values of the derivative at $r = r_1$, we rewrite the Equation (9) as

$$D_r\frac{d^2c_T}{dr^2} = -\frac{D_r a}{r}\frac{dc_T}{dr} + f(c_T) \tag{13}$$

Let us assume that $f(c_T)$ is sufficiently differentiable, we evaluate derivatives of $c_T(r)$ by recursively differentiating Equation (12) to gives

$$\frac{d^2c_T}{dr^2} = -\frac{a}{r}\frac{dc_T}{dr} + \frac{f(c_T)}{D_r} \tag{14}$$

$$\frac{d^3c_T}{dr^3} = \frac{a}{r^2}\frac{dc_T}{dr} - \frac{a}{r}\frac{d^2c_T}{dr^2} + \frac{1}{D_r}\frac{df(c_T)}{dc_T}\frac{dc_T}{dr} \tag{15}$$

$$\frac{d^4c_T}{dr^4} = -\frac{2a}{r^3}\frac{dc_T}{dr} + \frac{2a}{r^2}\frac{d^2c_T}{dr^2} - \frac{a}{r}\frac{d^3c_T}{dr^3} + \frac{1}{D_r}\frac{df(c_T)}{dc_T}\frac{d^2c_T}{dr^2} \tag{16}$$

We now evaluate the derivative expressions in Equation (16) at the $r = R_1$ by substituting $r = R_1$ in Equation (16) and impose the boundary condition that $(\frac{dc_T}{dr})_{r=R_2} = 0$ at $r = R_1$ we have,

$$(\frac{dc_T}{dr})_{r=R_1} = 0 \tag{17}$$

$$(\frac{d^2c_T}{dr^2})_{r=R_2} = \frac{f(c_{T0})}{D_r} \tag{18}$$

$$(\frac{d^3c_T}{dr^3})_{r=R_2} = -\frac{a}{R_1}\frac{f(c_{T0})}{D_r} \tag{19}$$

$$(\frac{d^4c_T}{dr^4})_{r=R_2} = \frac{2a}{{R_1}^2}\frac{f(c_{T0})}{D_r} + \frac{a^2}{R_1^2}\frac{f(c_{T0})}{D_r} + \frac{f(c_{To})}{{D_r}^2}[\frac{df(c_T)}{dc_T}]_{c=c_{To}} \tag{20}$$

$$(\frac{d^5c_T}{dr^5})_{r=R_2} = -\frac{6a}{{R_1}^3}\frac{f(c_{T0})}{D_r} - \frac{5a^2}{R_1^3}\frac{f(c_{T0})}{D_r} - \frac{2a\,f(c_{To})}{R_1\,{D_r}^2}[\frac{df(c_T)}{dc_T}]_{c=c_{To}} - \frac{a^3 f(c_{To})}{R_1^3\,D_r} \tag{21}$$

where $c_{T0} = (c_T)_{r=R_1}$ these derivatives terms evaluated at $R = R_1$ allow us to express the taylor series solutions as,

$$c_T(r) = (c_T)_{r=R_1} + \frac{r^2}{2}\frac{f(c_{To})}{D_r} - \frac{ar^3}{6R_1}\frac{f(c_{To})}{D_r} + \frac{r^4}{24}\left[\frac{2a}{R_1^2}\frac{f(c_{T0})}{D_r} + \frac{a^2 f(c_{To})}{R_1^2 D_r} + \frac{f(c_{To})}{D_r^2}\left(\frac{df(c_T)}{dc_T}\right)_{c=c_{T0}}\right] + \frac{r^5}{120}\left[\frac{-6a\, f(c_{To})}{R_1^3 D_r} - \frac{5a^2}{R_1^3 D_r} f(c_{To}) - \frac{a^3}{R_1^3 D_r} f(c_{To}) - \frac{2a}{R_1 D_r^2} f(c_{To})\left(\frac{df(c_T)}{dc_T}\right)_{c=cTo}\right] + O(R^6) \quad (22)$$

The i^{th} term in Taylor series is:

$$\frac{R^i}{i}\left(\frac{\partial^{i-2}}{\partial R^{i-2}}\left[-\frac{a}{R}\frac{dc_T}{dr} + f(c)\right]\right)_{R=R_1} \qquad i \geqslant 2 \quad (23)$$

The derivative expansions in Equation (23) can be evaluated at $R = R_1$. The resulting expressions are combinations of derivatives of the functions $c_T(r)$ and $f(c)$ evaluated at $R = r_1$ and $c_{T0} = c_T(r = R_1)$ respectively. Since we have assumed that $c_T(r)$ and $f(c)$ are everywhere sufficiently differentiable applying the ratio test of this series shows that the radius of convergence is infinite. This means that the series will converge for all values of R and this will be true for all standard form of the uptake function $f(c)$ (polynomial functions and certain rational functions such as the Michaelis-Menten model). Therefore, the taylor series is an exact solution that always converges for all practical choices of $f(c)$.Furthermore, we can implement the series solution by truncating the series after a finite number of terms.

6. Boundary Condition at R=1

To implement the series solution for a particular we must determine c0 by applying the remaining boundary condition at $r = R_2$ given by $-D_r(\frac{dc_T}{dr})_{r=R_2} = \beta(c - c_{T1})$To satisfy this condition, we differentiate the general series with respect to r to obtain$\frac{dc_T}{dr}$.After truncating the series expression for $\frac{dc_T}{dr}$. and expression for $c(z)$ we obtain an relationship of the form $c_{T0} = D_r(\frac{dc_T}{dr})e^{-\alpha z} \quad 0 \leq z \leq 2.5 \times 10^{-2}$. This process gives an approximate value of c_{T0}.However,since the series solution is convergent we can arbitrarily increase the accuracy of this approximation by simply retaining more terms in the truncated series and examine the convergence behavior of c_0 as further terms are retained in the series.

7. Results and Discussion:

The values of most of model parameters are not known to the best of our knowledge. We have used appropriately estimated values of the physiological parameters in the computational model results. The computational results of the present model have been obtained from the above approximate solutions by using appropriate values of the physiological parameters listed in Table1.

Table 1.

Parameter	Value
Arterial blood oxygen concentration $C_A(cm^3O_2/cm^3\text{blood})$	3.2×10^{-3}
Oxygen diffusivity	2×10^{-5}
Oxygen capacity of the blood at 100% saturation	6×10^{-5}
$\bar{N}(cm^3O_2/cm^3\text{blood})$ oxygen consumption rate	0.204
M $(cm^3O_2/cm^3$ tissue sec)	8.5×10^{-4}
Capillary length L	200
Capillary radius R_c (μm)	3
Tissue radius R_t (μm)	30

The effect of diffusion coefficient on the oxygen concentration distribution for different value of radial co-ordinate have been shown in Figure 2 curves .As is evident from the graphs in Figure 2 an increase in the diffusion coefficient increases oxygen concentration in the retinal tissue.

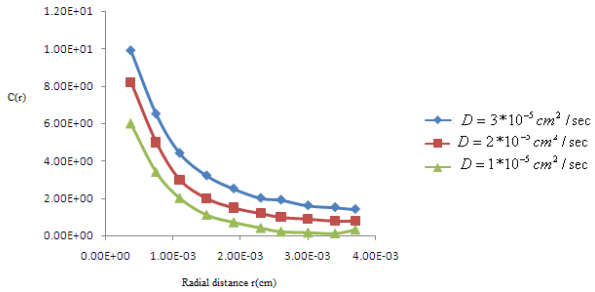

Figure 2. The effect of diffusion coefficient on the tissue oxygen concentration .

It is obvious from the graphs in Figure 2 that the retinal layer/cells near the retinal capillary receive more oxygen and the layers/cells far from the capillary receive less oxygen.The maximum concentration of oxygen occurs at the entry point of the tissue on the arterial Side. Thus, owing to excessive accumulation of oxygen in the tissue, the toxic effects, (if any) will be first felt in the region close to arterial end of the tissue.

The curve in Figure 3 represents the effect of change in metabolic rate relative to data shown in Table 1. These curves illustrate when the metabolic rate is increased, the value of oxygen concentration will decreased. Thus, oxygen is delivered to the retinal tissue in excess of that necessary to meet its metabolic needs.

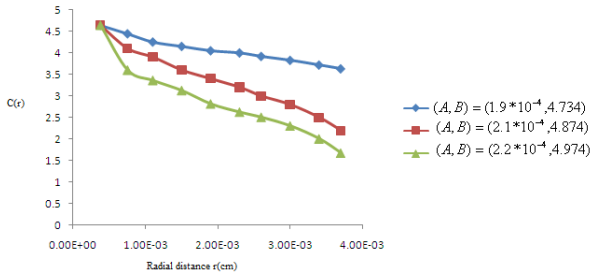

Figure 3. The effect of metabolic rate constant on the tissue oxygen concentration .

The various curves in Figure 4 depicts the effect of arterial oxygen concentration on the tissue concentration. It is observed that when the arterial concentration increases the tissue concentration will increase. Thus when the arterial concentration increases a more amount of oxygen will move from artery end to tissue end.

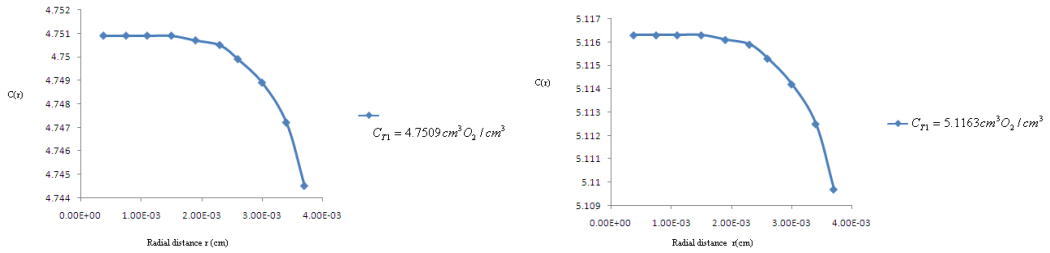

Figure 4. Effect of arterial oxygen concentration on the retinal tissue.

It is therefore, concluded that, the rate of capillary blood flow affects the oxygen transport significantly.

8. Conclusion

The computational results of the model presented here predict that the oxygen concentration in the retinal tissue decreases along the capillary axis from the arteriolar end to venular end. It also decreases along the depth (radial distance) of retinal tissue. The sites in the retinal tissue at the greatest depth in the tissue from the venous end of the capillary would be most vulnerable to oxygen lack under the conditions of normal capillary oxygen levels. Thus it has been suggested that manipulation of the retinal oxygen environment may be therapeutic tool in the management of retinal diseases.

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