



Mathematical Modeling of Flow and Diffusion in the Lens of the Eye

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The present work is concerned with the development of a simple transient mathematical model for the oxygen diffusion-consumption in the eye lens. The model takes into account the transport of oxygen by diffusion and consumption of oxygen is assumed to follow the Michaelis- Menten's kinetics. The partial differential equation governing the partial pressure of oxygen has been solved by using implicit Crank-Nicholson's iteration scheme. The prime objective of the present study is to investigate the effect of model parameters: the Michaelis- Menten's kinetic constant and maximum rate of consumption on the partial pressure of oxygen in the mammalian lens. The computational results of the model have been presented by graphs and effects of model parameters also have been shown through the graphs and discussed. The present mathematical analysis of oxygen diffusion in the lens may contribute to the knowledge of regulation of tissue oxygen in the lens and quantitative understanding achieved through the analysis may facilitate the design of new therapeutic procedures. This analysis may help in regulating the partial pressure of oxygen in the lens.

Keywords: Opacification; spherical lens; differentiating fibre; oxygen diffusion.

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1. INTRODUCTION

A mathematical model for flow and diffusion of oxygen in the lens of the eye has been developed. The model considers the eye lens as a spherical shell, bounded by an epithelium layer and which comprises two functionally different domains of fibre cells: differentiating fibres (DF) near the surface and mature fibres (MF) located in the central region of the tissue.

Opacification of the lens nucleus is a major cause of blindness and is thought to result from oxidation of key cellular components [1]. The marked increase in oxygen consumption that occur when the lens is exposed to increase the oxygen is likely to result in the production of the higher levels of reactive oxygen species and may provide a link between elevated oxygen levels and the risk of nuclear cataract [2]. An increase in oxygen concentration is thought to be responsible for cataract formation [3]. Thus, the knowledge of oxygen concentration and distribution within the lens is of considerable interest clinically.

Few polarographic and optode measurements report oxygen partial pressure from 1 mmHg in the cat lens posterior cortex and nucleus [4 to 10-22 mmHg in the rabbit lens [5] and 0.8-4.0 mmHg in the human anterior cortex [2]. These data indicate that to protect against age-related nuclear cataract formation, oxygen concentration in the lens has to be maintained at very low level.

Eaton [3] and Harding [6] have suggested that partial pressure of oxygen through out the lens is low, if not zero. In vivo, the lens is situated in a relatively low oxygen environment and partial pressure of oxygen could be higher in the core of aged lens. Eaton [3] suggested that the effective exclusion of oxygen from the centre of lens could be one mechanism by which cell in this region preserve their transparency over a prolong period. This hypothesis is supported by the interesting observation that nuclear develop in a remarkable high proportion of patients following hyperbaric therapy [6]. Thus long-term preservation of lens clarity may depend on the maintenance of hypoxia in the lens nucleus [7].

The lens consists of a mass closely packed fibres cells bounded anteriorly by an epithelial monolayer and enveloped by thick basement membrane, the lens capsule. Fibres cells are continuously produced from the adult lens contains two kinds of fibres cells: those located in

the lens core, which are mature and do not contain organelles, and those located in the lens outer layers, which are not yet mature and contains organelles (including mitochondria). Due to steady addition of newly formed fibres, the lens grows throughout life in layers somewhat like an onion. Thus, the lens contains two populations of fibres cells: an outer layer of differentiating fibres (DF) and a core of mature fibres (MF). The relevant difference between MF and DF is that the DF contains mitochondria, which consume oxygen, whereas the MF has no organelles. The schematic diagram of the lens of the eye is shown in image (2).

Mitochondrial respiration account for approximately 90% of oxygen consumption by the lens, which suggests that the outer layer of fibres cells can be responsible for low oxygen concentration in the lens nucleus. Because oxygen is constantly consumed and oxygen consumption reactions are located inside the eye lens [3], it follows that there must be a gradient in oxygen concentration across the fibre cell layers that build the eye lens. Oxygen consumption is necessary to maintain the low oxygen concentration inside the eye lens. Despite numerous experimental studies [5,8-30] the mechanism leading to the opacification is not well understood. The knowledge of many important aspects of lens homeostasis is required. Any therapeutic strategy must be directed towards the long-term preservation of cellular components and to maintain the oldest cells (i.e. cells in the lens core) in a perpetually hypoxic state for maintaining tissue transparency.

In order to prolong the lens transparency and to get nuclear cataract delayed as long as possible there is a need to investigate physiological factors affecting the oxygen diffusion, consumption, and oxidation processes within the lens. For the purpose, the understanding of oxygen diffusion and consumption in the lens should be promoted. A mathematical analysis of oxygen diffusion and consumption in the lens may contribute to the knowledge of regulation of tissue oxygen in the lens and quantitative understanding achieved through the analysis may facilitate the design of new therapeutic procedures. McNutty *et al.* [29] developed a simple steady-state diffusion-consumption model for the partial pressure of oxygen in the lens and used it to calculate time constants for oxygen consumption in various regions of the lens and oxygen diffusion coefficient. This model may be

generalized and some more relevant predictions can be made.

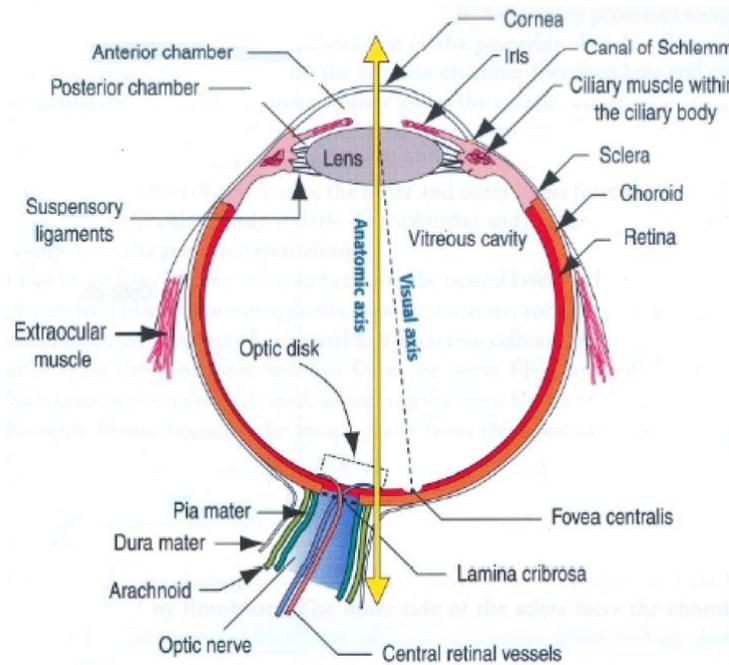


Image 1. Main components of the eye [9]

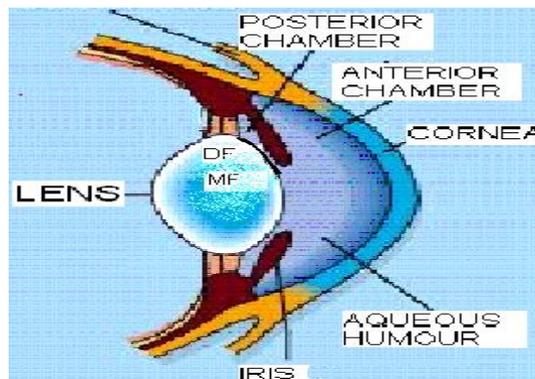


Image 2. Diagram of eye showing inter-relationship between lens, cornea, posterior and anterior chambers [9]

The present work is concerned with the development of a simple transient mathematical model for the oxygen diffusion-consumption in the eye lens. The lens is modeled as a spherical shell, bounded by an epithelium layer and which comprises two functionally different domains of fibre cells: differentiating fibres (DF) near the surface and mature fibres (MF) located in the central region of the tissue. The model takes into account the transport of oxygen by diffusion and consumption of oxygen is assumed to follow the Michaelis- Menten’s kinetics. The partial differential equation governing the partial pressure of oxygen has been solved by using

implicit Crank-Nicholson’s iteration scheme. The prime objective of the present study is to investigate the effect of model parameters: the Michaelis- Menten’s kinetic constant and maximum rate of consumption on the partial pressure of oxygen in the mammalian lens.

2. MATHEMATICAL FORMULATION

The almost spherical ocular lens contains two populations of fibre cell: an outer layer of differentiating fibres (DF) which contains organelles and a core of mature fibres (MF), which do not. The oxygen enters the lens by

diffusion from the surrounding humors and crosses many thousands of fibre cell plasma membrane readily. Some of the oxygen is consumed by mitochondria and non-mitochondrial elements and the remaining reaches/diffuses readily into the centre of the lens. The illustration of physical model relevant to the present study is shown in Image (3).

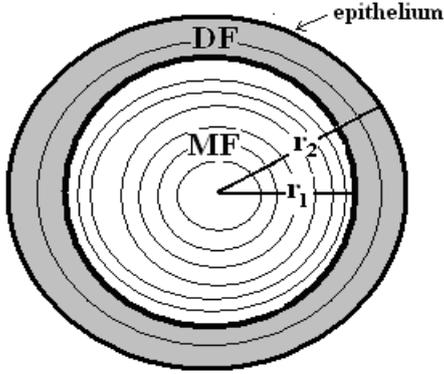


Image 3. Schematic diagram of lens of the eye

The model treats the lens as a sphere with radius r_2 . If r is the radial distance from the lens centre, the outer shell of differentiating fibre (DF) is located at $r_1 \leq r \leq r_2$, where $r_1 = 0.8r_2$. Thus mature fibre (MF) is at $0 \leq r \leq r_1$. The border between DF and MF is located at a distance r_1 from the centre.

2.1 Governing Equation

The Fick's law of diffusion and Michaelis-Menten's kinetics of consumption result in following P.D.E. describing the partial pressure of oxygen in the lens:

$$\frac{\partial P}{\partial t} = D \left(\frac{\partial^2 P}{\partial r^2} + \frac{2}{r} \frac{\partial P}{\partial r} \right) - \frac{V_{\max} P}{P+K}, \quad r > 0 \quad (1)$$

$$\frac{\partial P}{\partial t} = 3D \left(\frac{\partial^2 P}{\partial r^2} \right) - \frac{V_{\max} P}{P+K}, \quad r = 0 \quad (2)$$

where P is the partial pressure of oxygen, V_{\max} is the maximum rate of consumption, K the Michaelis-Menten's Kinetic constant for the reaction and D the diffusion coefficient.

2.2 Boundary and Interface Conditions

In order to formulate a physiologically consistent and mathematically tractable model, boundary and interface conditions relevant to present model are described below:

$$P(r_2, t) = P(bath) \quad (3)$$

$$P(r_1^+) = P(r_1^-), \quad \left(\frac{\partial P}{\partial r} \right)_{r=r_1^+} = \left(\frac{\partial P}{\partial r} \right)_{r=r_1^-}, \quad t \geq 0 \quad 4(a,b)$$

$$\left(\frac{\partial P}{\partial r} \right)_{r=0} = 0 \quad (5)$$

Eq. (3) shows that, the partial pressure of oxygen at the surface of the lens is same as that in the bathing solution i.e., $P(bath)$. Eq.4 (a,b) represents that, there must be, all times, the continuity of oxygen concentration and flux at the interface between two adjacent layers. Eq. (5) depicts that at the centre of the lens there is no flux.

2.3 Initial Condition

A study state solution [1] to the governing Eqs. (1)- (2) subject to the boundary and interface conditions (3), 4(a,b), and (5) and the case $P \ll K$, which serves as an initial condition for our transient state problem, is given by:

$$P(r, t = 0) = P_1 \begin{cases} \frac{\lambda_{MF} r_2 \sinh\left(\frac{r}{\lambda_{MF}}\right)}{\lambda_{DF} r \cosh\left(\frac{r_1}{\lambda_{MF}}\right)}, & 0 < r \leq r_1 \\ \frac{r_2 \sinh\left(\frac{r-r_1}{\lambda_{DF}}\right)}{r} + \left(\tanh\left(\frac{r_1}{\lambda_{MF}}\right) \right) \frac{\lambda_{MF} r_2 \cosh\left(\frac{r-r_1}{\lambda_{DF}}\right)}{\lambda_{DF} r}, & r_1 < r \leq r_2 \end{cases} \quad (6)$$

where P_1 is the common term of the solution of Eqs. (1) – (2) is given by:

$$P_1 = \frac{P_{Bath}}{\cosh\left(\frac{r_2 - r_1}{\lambda_{DF}}\right) \left[\tanh\left(\frac{r_2 - r_1}{\lambda_{DF}}\right) + \frac{\lambda_{MF}}{\lambda_{DF}} \tanh\left(\frac{r_1}{\lambda_{MF}}\right) \right]}$$

Here be λ_{DF} and λ_{MF} are length constant for DF and MF regions

3. SOLUTION TO THE PROBLEM

3.1 General Consideration

Finite difference Crank Nicholson implicit scheme require discretisation of the spatial and temporal domains and they may vary according to requirements of each particular problem. For the purpose of this model, the spatial domain 'r' has been discretised into 25 equidistant points. The distance between any two points is given by $\Delta r = 0.02\text{cm}$ so that $r_j = j\Delta r$, $j=1, 2, \dots, 25$. The time domain has been discretised using Δt as a constant time step so that $t = k\Delta t$, be $k \in N$. The

value of $P(r, t)$ in discretised domain is thus represented by $P_{j, k}$.

This method ensures that the equation to be solved is satisfied at the mid-point between the solution at time $t = k\Delta t$ and the time that $t = (k+1)\Delta t$. Central finite difference are employed to find the temporal derivative at $(j\Delta r, (k+1)\Delta t)$ and the average between the spatial derivative evaluated at the points $(j\Delta r, k\Delta t)$ and $(j\Delta r, (k+1)\Delta t)$. Hence finite difference approximation of equations (1) and (2) representing the oxygen diffusion and consumption are given by

$$a_i P_{j-1, k+1} + b_i P_{j, k+1} + c_i P_{j+1, k+1} = f_i(P_{j, k}) \quad (7)$$

Where $f_i(P_{j, k})$ denote the term corresponding to the equation for location j in the grid and is given by:

$$a_1 P_{j, k+1} + b_1 P_{j-1, k+1} + c_1 P_{j, k} + P_{j+1, k+1} = f_1(P_{j, k}) \quad (8)$$

$$a_2 P_{j, k+1} + b_2 P_{j-1, k+1} + c_2 P_{j, k} + P_{j+1, k+1} = f_2(P_{j, k}) \quad (9)$$

where

$$a_1 = (P_{j, k} + K + 2\alpha), \quad b_1 = (-\alpha + \beta), \quad c_1 = -(\alpha + \beta),$$

$$a_2 = (P_{j, k} + K + 6\alpha), \quad b_2 = -3\alpha, \quad c_1 = -3\alpha,$$

$$f_1(P_{j, k}) = P_{j, k}^2 + (K - 2\alpha - V_{\max} \Delta t) P_{j, k} + (\alpha - \beta) P_{j-1, k} + (\alpha + \beta) P_{j+1, k},$$

$$f_2(P_{j, k}) = P_{j, k}^2 + (K - 6\alpha - V_{\max} \Delta t) P_{j, k} + 3\alpha P_{j-1, k} + 3\alpha P_{j+1, k},$$

$$\alpha = \frac{D}{2} \frac{\Delta t}{(\Delta r)^2} (P_{j, k} + K) \quad \text{and} \quad \beta = \frac{D}{2r} \frac{\Delta t}{\Delta r} (P_{j, k} + K), \quad \text{for } r > 0$$

The finite difference analogues of the boundary and interface conditions are given by:

$$P_{j-1, k+1} = P_{j+1, k+1}, \quad j=1, 21 \quad (10)$$

$$P_{j, k+1} = P(\text{bath}), \quad j=26 \quad (11)$$

$$P_{j+2, k+1} - 2P_{j, k+1} + P_{j-2, k+1} = -P_{j+2, k} + 2P_{j, k} - P_{j-2, k}, \quad j=21 \quad (12)$$

Here $j=1$, $j=21$ and $j=26$ in equations (10), (11), (12) are respectively centre of the lens, border of MF and DF region and the outer surface of DF region.

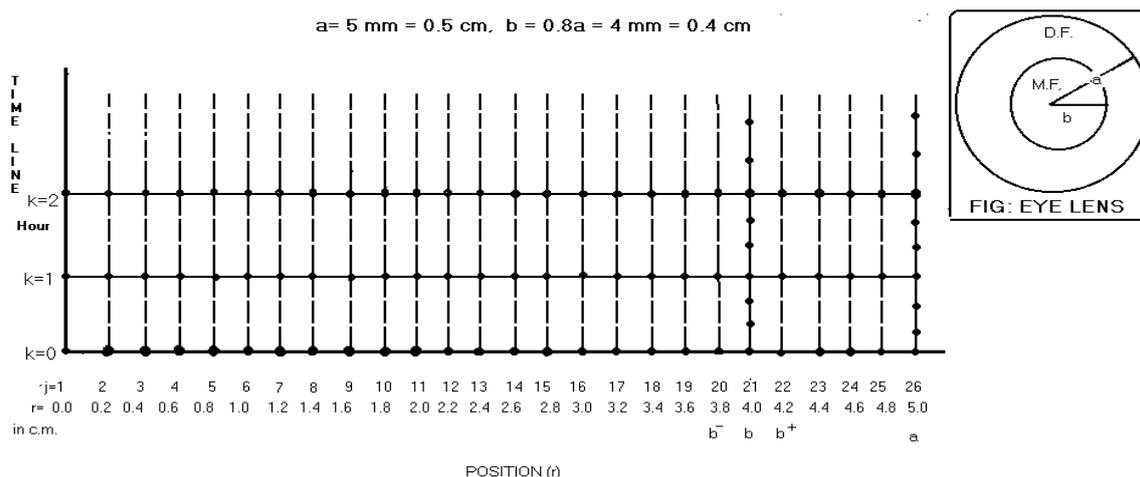


Image 4. Crank Nicholson implicit scheme

Table 1. Input parameters for our model

Constant	Symbol	Numerical value
Partial pressure of oxygen in bathing solution	$P(bath)$	36 mmHg
Michaelis- Menten's Kinetic constant	K	4.834
Diffusion coefficient	D	$3 \times 10^{-5} \text{ cm}^2\text{s}^{-1}$
Maximum rate of consumption	V_{max}	$9.9 \mu\text{l}\cdot\text{h}^{-1}$
Length constant for DF region	λ_{DF}	0.8 mm
Length constant for MF region	λ_{MF}	0.9 mm
Radius of lens	r_2	5.0 mm

3.2 Solution to the Algebraic Equation

The implicit iterative scheme given by Eq.(7,8) is simplified in light of the finite difference analogues of the initial, boundary and interface conditions and the resulting system of algebraic equation written in the trigonal matrix form $AP_{j,k+1} = f(P_{j,k})$ was solved by using Thomas algorithm.

These parameter values are supported by [9,1].

4. RESULT AND DISCUSION

The computational results to the model are obtained by using the physiological values of the parameters listed in Table 1 and discussed through the graphs:

Figs. 1. and 2 shows that from centre of lens to outward, the partial pressure of oxygen increases with increase in Michaelis- Menten's Kinetic constant K at different time.

Fig. 7 and 8 shows that from centre of lens to outward, the partial pressure of oxygen increases

with increase in maximum rate of consumption at different time.

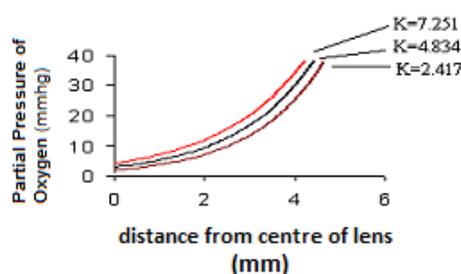


Fig. 1. Partial pressure of oxygen profile for different values K at 1 hour

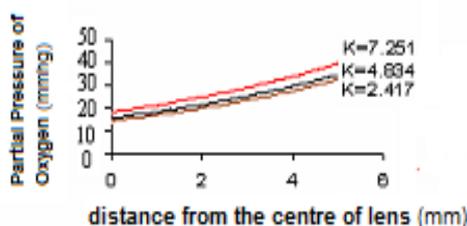


Fig. 2. Partial pressure of oxygen profile for different values K at 2 hour

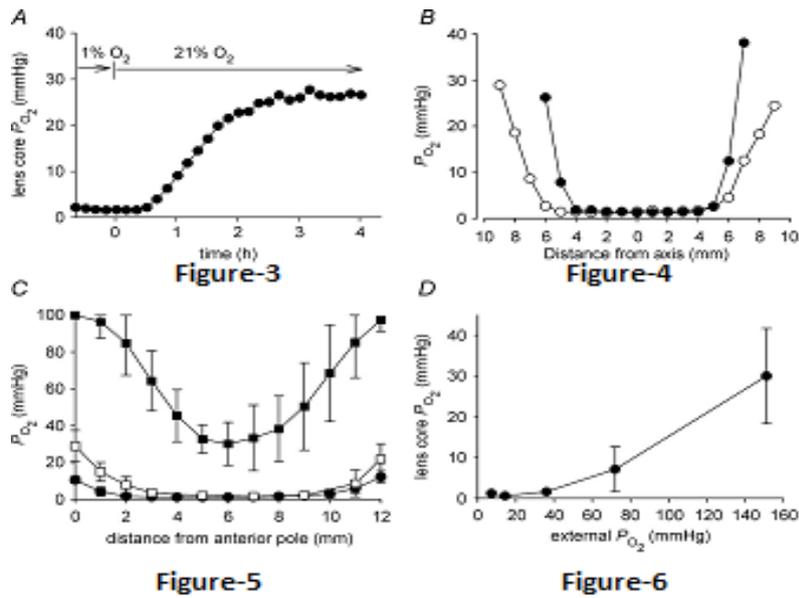


Fig. 3-6. Distribution of partial pressure of oxygen in lens of the eye

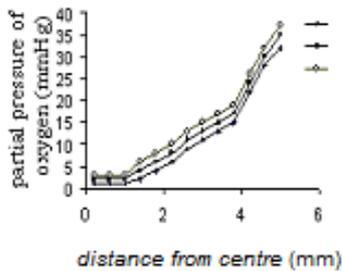


Fig. 7. Partial pressure of oxygen profile for different values of maximum rate of consumption at 1 hour

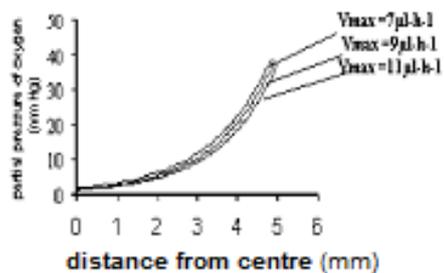


Fig. 8. Effect of maximum rate of consumption on pressure distribution along radius at hour

These graphs show that partial pressure of oxygen increases with increase of 'K' and decreases with increase of V_{max} . Therefore Partial Pressure can be regulate by regulating 'K'.

5. CONCLUSION

The present mathematical analysis of oxygen diffusion in the lens may contribute to the knowledge of regulation of tissue oxygen in the lens and quantitative understanding achieved through the analysis may facilitate the design of new therapeutic procedures. This analysis may help in regulating the partial pressure of oxygen in the lens. Simple mathematical models developed for flow and diffusion phenomena in the lens of the eye may encourage academicians to develop more generalized mathematical models by incorporating non-linearities involved

and observed in the flow systems and oxygen diffusion in future models. Many scientific problems involved in the developing realistic, tractable models and in interpreting, the results of mathematical analysis may be reduced, thus facilitating theoretical research in the area.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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