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Mathematical Analysis of Corneal Oxygenation

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Abstract

Purpose: To develop a quasi steady state model for the time course concentration profile describing the oxygen diffusion and consumption in a multilayered corneal tissue and investigate the effect of various model parameters on the oxygen concentration for open and closed eyes.

Method: A simple mathematical model for the oxygen transport in multilayered corneal tissue was developed using Fick's law of diffusion and Michaelis-Menten kinetics of metabolism. A Crank-Nicoloson finite difference scheme of the equation describing the oxygen diffusion and consumption was written, in which spatial diffusive terms were approximated by central differences while the temporal terms were approximated by average of forward and backward time differences. A system of linear equations obtained from the Crank-Nicholuson finite differences schemes was solved by the Thomos Algorithm.

Result: The model predict that oxygen tension without contact lens for an open and closed eye increases along the distance from the aqueous side in each of the layers and the partial pressure gradient in the stroma is higher than that in the epithelium and endothelium layers. It is also observed that the oxygen tension with contact lens in the steady and transient states, in case of low oxygen permeability of lens decreases along the distance from the aqueous side to the stroma, whereas, at higher oxygen permeability of the lens it increases along the distance for open and closed eyes.

Conclusion: Oxygen tension as observed in the cornea of an open eye with or without contact lens is higher than that in closed eye. Also at a high oxygen permeability of contact lens enhance the oxygen tension significantly than that of low oxygen permeability.

Keywords: Oxygen transport, finite difference, metabolism, oxygen consumption, pressure gradient.

Ram Avtar

Deepti Tandon

Department of Mathematics,
Harcourt Butler Technological
Institute, Kanpur 208002,
India.

***For Correspondence:**

E-mail:
deepti_hbti@yahoo.co.in

Introduction

The structural integrity of the cornea is maintained by an active fluid transport system, which depends on metabolism. The normal metabolic processes are essential for cell growth and replacement and, in the case of the corneal epithelium and endothelium, for the maintenance of the ionic pump mechanism, which is responsible for maintaining the state of corneal hydration. An increase in water content results in the cornea becoming thicker and cloudy or opaque. The water content of the cornea is determined by the metabolic activity of the epithelium and endothelium. A critical level of oxygen tension in the cornea is required to maintain normal corneal metabolism, which is essential for the growth and development of living and reproducing cells and for the active transport mechanisms of the epithelium and endothelium. Any interference in the metabolic activity of the cornea will cause tissue changes. If there is not enough oxygen available to convert the glucose, primarily sourced from the aqueous humor, by means of glycolysis, into sufficient energy and allow the waste product, lactic acid, to diffuse quickly out of the tissue, then less energy is available for cellular activity. This results in too much lactic acid being produced, which builds up in the stroma and so is implicated in the cause of corneal edema by causing an osmotic imbalance¹. Oxygen tension above a critical level may alter the metabolism and corneal swelling may occur. The oxygen required for essential metabolism of the cornea is primarily derived from the atmosphere via the tears and diffusion across the corneal anterior surface¹. The aqueous humor in the anterior chamber also provides the oxygen to the cornea. All the oxygen supplied to the cornea by the aqueous humor is consumed by the endothelial cells and the keratiocytes in the stroma. This leaves the epithelium dependent solely on oxygen supplied to the anterior cornea surface from the air or palpebral conjunctiva. Each layer of the

cornea consumes oxygen at its own rate. It has been shown¹ that the endothelium, epithelium, and stroma use 21%, 40% and 39%, respectively, of the total oxygen consumption of the cornea.

A contact lens effectively occludes the cornea from its surrounding environment of oxygen, tears, and ocular secretions. It impedes the movement of oxygen from the atmosphere. But the oxygen tension at the anterior cornea surface must remain above a critical level, otherwise epithelial metabolism will be altered resulting in corneal swelling. The contact lens may reduce the oxygen tension below the critical level and if this occurs, corneal edema, formation of vertical striae, and epithelial cell loss may result². Thus, adequate oxygen tension and oxygen flux is required in the cornea to maintain normal metabolic processes in both open and closed eyes. Regulation of oxygen tension in the cornea without contact lens and that under a contact lens and oxygen flux into the cornea must be studied in order to investigate the factors influencing the oxygen –level (oxygen tension) in different layers of the cornea.

In addition to numerous experimental studies^{3,4,5,6,7}, the steady state oxygen tension has been calculated using a simplified oxygen consumption rate expression^{4,5,8}. Takahashi et al.⁷, Fatt and Bieber⁴, and Fatt⁵ estimated the oxygen tension in the cornea of an open or closed eye by assuming a constant oxygen consumption rate. Later on, the oxygen consumption was taken as a function of oxygen tension in several studies^{7,8}. In 1976, Lin⁹ developed a steady state mathematical model for the oxygen tension distribution in the cornea. The model takes into account molecular diffusion and nonlinear oxygen consumption rate equation of the Michaelis-Menten type for the metabolic process. The oxygen tension was estimated for open and closed eyes with or without contact lens. In 1977, Barr et al.³ constructed a mathematical model based on the

experimental studies. They estimated the steady state oxygen tension by using constant oxygen consumption rate.

The present work is concerned with the development of transient state mathematical model for the oxygen tension distribution in the cornea. Oxygen diffusion and consumption are assumed to occur in different layers of the cornea: the endothelium layer, stroma layer, and epithelium layer. The oxygen consumption rates in different layers are assumed to follow the Michaelis-Menten kinetics and the numerical solution to the model was estimated using the Crank-Nicholson finite difference implicit iterative scheme. Computational results of the model have been presented in this paper.

Formulation of mathematical model

Transversely, the cornea consists of three distinct cell layers, important to the physiology of the cornea: the outer epithelium, central stroma, and inner endothelium (Figure 1). The epithelium lies the outer aspect of the cornea and the stroma, comprising 90% of the total corneal thickness, is an extracellular matrix. In contrast to the epithelium, the endothelium is a thin monolayer of cells covering the posterior surface of the cornea. For the purpose of modeling the transient oxygen transport phenomenon, the cornea (which can be regarded as hemispherical shell) is treated as a one dimensional tissue in the posterior to anterior direction. The oxygen transport in different layers of the cornea occurs, by diffusion, and the oxygen consumption due to the metabolic reactions occurring in the corneal layers, follows the Michaelis-Menten kinetics^{7,8,10}.

Governing equations: According to Fick's law of diffusion and Michaelis-Menten equation^{7,10,11} for oxygen consumption, differential equation of oxygen tension in each layer of the cornea can be represented by:

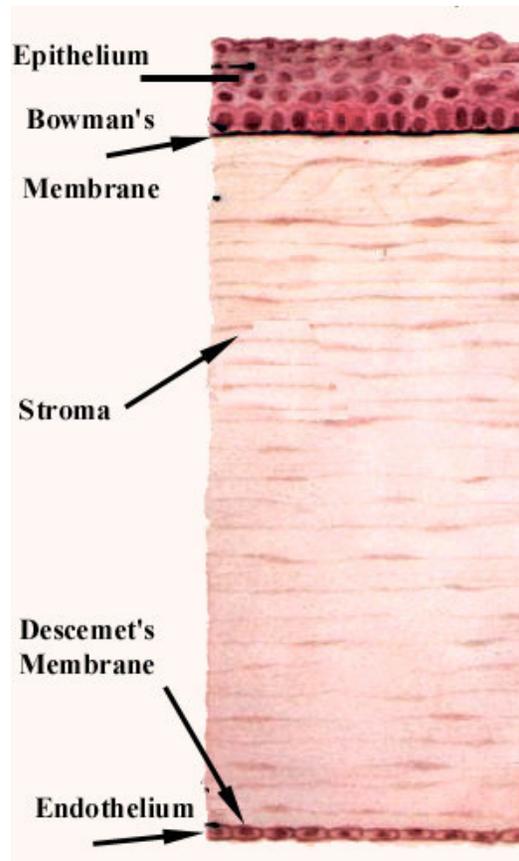


Figure 1: Layers of the Cornea

$$k_i \frac{\partial p_i}{\partial t} = D_i k_i \frac{\partial^2 p_i}{\partial x^2} - \frac{V_i p_i}{p_i + k_m} \quad (1)$$

Equation (2) does not have oxygen consumption term since no oxygen is consumed in the contact lens¹².

$$k_4 \frac{\partial p_4}{\partial t} = D_4 k_4 \frac{\partial^2 p_4}{\partial x^2} \quad (2)$$

The parameters with subscripts $i=1,2,3$, respectively, represent the properties of the endothelium, stroma and epithelium. The above equation represents the oxygen tension in the cornea for an open or closed eye without contact lens. D_i is the diffusion coefficient of oxygen in tissue, k_i the

solubility of oxygen in tissue, V_i , the maximum oxygen consumption rate, and k_{m_i} , the Michaelis-Menten constant.

Initial conditions: The steady state solutions to equation (1) and (2) (subject to appropriate boundary and interface conditions in different layers) are considered to be the initial conditions for the transient problem.

Boundary and interface conditions: The physiologically relevant and mathematically consistent boundary and interface conditions are presented below:

$$p_1(0, t) = p_a \quad (3)$$

$$p_2(x_1, t) = p_1(x_1, t) \quad D_2 k_2 \left(\frac{\partial p_2}{\partial x} \right)_{x=x_1} = D_1 k_1 \left(\frac{\partial p_1}{\partial x} \right)_{x=x_1} \quad (4)$$

$$p_3(x_2, t) = p_2(x_2, t) \quad D_3 k_3 \left(\frac{\partial p_3}{\partial x} \right)_{x=x_2} = D_2 k_2 \left(\frac{\partial p_2}{\partial x} \right)_{x=x_2} \quad (5)$$

$$p_3(x_3, t) = p_b \quad (6)$$

For an open or closed eye with contact lens, boundary condition (6) is replaced by:

$$p_4(x_3, t) = p_3(x_3, t) \quad D_4 k_4 \left(\frac{\partial p_4}{\partial x} \right)_{x=x_3} = D_3 k_3 \left(\frac{\partial p_3}{\partial x} \right)_{x=x_3} \quad (7)$$

$$p_4(x_4, t) = p_b \quad (8)$$

In the above equations, x is the distance measured from the interface between the aqueous humor and the endothelium. At $x=0$, the partial pressure (tension) of oxygen becomes the aqueous humor oxygen tension. Equation (4) and (5) indicate that there must be, at all times, the continuity of oxygen tension and flux at the interface between any two layers. Equation (6) indicates that at the anterior surface of epithelial layer, oxygen tension is constant and is equal to the oxygen tension at the posterior endothelial surface of the cornea. That the flux into the cornea (epithelium) must be equal to the flux of oxygen that is leaving the contact lens when the anterior surface of the cornea is covered with a contact lens is depicted in equation (7). Equation (8) indicates that the oxygen

tension at the surface of contact lens must be equal to that at the posterior endothelial surface.

Numerical solution to the model

The analytical solution to the nonlinear equations (1)-(2), subject to the boundary and interface conditions (3)-(8) in different corneal layers, seems to be a difficult task. Hence, we solved nonlinear partial differential equations numerically to find the oxygen tension distribution in different corneal layers. First, we solved the steady state nonlinear ordinary differential equation for each layer by using the Runge-Kutta Nystrom's method¹¹ to obtain a steady-state solution which was then used as initial condition for the solution of nonlinear partial differential equation. The Crank-Nicholson implicit iterative scheme¹² was used to find the approximate solution of partial differential equation for each layer. By this method, each partial differential equation of the mathematical model was replaced by a system of simultaneous algebraic equations relating values $p(m, n+1)$ at space x_m for all points at a certain time $t=n+1$.

(i) Numerical model

Consider a uniform grid for the flow in the direction $n-1 \rightarrow n \rightarrow n+1$. In the Crank-Nicholson scheme, the space derivative,

$\frac{\partial^2 p_i}{\partial x^2}$, is replaced by the average of its finite

difference approximations on the backward time line (n^{th} step) and the forward time line ($n+1^{\text{st}}$ step). Thus,

$$D_i \left(\frac{\partial^2 p_i}{\partial x^2} \right)_{(m, n+\frac{1}{2})} = D_i \left[\frac{p_i(m-1, n) + p_i(m-1, n+1)}{2(\Delta x_i)^2} - \frac{p_i(m, n) + p_i(m, n+1)}{(\Delta x_i)^2} + \frac{p_i(m+1, n) + p_i(m+1, n+1)}{2(\Delta x_i)^2} \right] \quad (9)$$

The time derivative in this iterative scheme is approximated by a central difference:

$$\left(\frac{\partial p_i}{\partial t}\right)_{(m,n+\frac{1}{2})} = \left[\frac{p_i(m,n+1) - p_i(m,n)}{\Delta t}\right] \quad (10)$$

Equation (1) governing the oxygen diffusion and consumption in the endothelium layer can be replaced by the following finite difference analogue:

$$\begin{aligned} -D_1 r_1 p_1(m-1, n+1) + (2D_1 r_1 + 1) p_1(m, n+1) - D_1 r_1 p_1(m+1, n+1) &= D_1 r_1 p_1(m-1, n) + (1-2D_1 r_1) p_1(m, n) \\ + D_1 r_1 p_1(m+1, n) - \left(\frac{V_1 p_1(m, n)}{p_1(m, n) + k_{m1}}\right) \frac{1}{k_1} \Delta t \end{aligned} \quad (11)$$

The finite difference approximation of equation (1) governing oxygen diffusion and consumption in the stromal layer is as follows:

$$\begin{aligned} -D_2 r_2 p_2(m+1, n+1) + (2D_2 r_2 + 1) p_2(m+2, n+1) \\ - D_2 r_2 p_2(m+3, n+1) = D_2 r_2 * p_2(m+1, n) + (1-2D_2 r_2) p_2(m+2, n) \\ + D_2 r_2 p_2(m+3, n) - \left(\frac{V_2 p_2(m+2, n)}{p_2(m+2, n) + k_{m2}}\right) \frac{1}{k_2} \Delta t \end{aligned} \quad (12)$$

The equation (1) defining the oxygen diffusion and consumption in the epithelium layer can be replaced by the finite difference analogue as follows:

$$\begin{aligned} -D_3 r_3 p_3(m+3, n+1) + (2D_3 r_3 + 1) p_3(m+4, n+1) \\ - D_3 r_3 p_3(m+5, n+1) = D_3 r_3 * p_3(m+3, n) + (1-2D_3 r_3) p_3(m+4, n) \\ + D_3 r_3 p_3(m+5, n) - \left(\frac{V_3 p_3(m+4, n)}{p_3(m+4, n) + k_{m3}}\right) \frac{1}{k_3} \Delta t \end{aligned} \quad (13)$$

The finite difference approximation of equation (2) representing the oxygen diffusion and consumption is given by:

$$\begin{aligned} -D_4 k_4 r_4 p_4(m+5, n+1) + (2D_4 k_4 r_4 + 1) p_4(m+6, n+1) \\ - D_4 r_4 p_4(m+7, n+1) = D_4 * k_4 r_4 p_4(m+5, n) \\ + (1-2D_4 k_4 r_4) p_4(m+6, n) + D_4 k_4 r_4 p_4(m+7, n) \end{aligned} \quad (14)$$

where $r_1 = \frac{\Delta t}{2[(\Delta x_1)]^2}$, $r_2 = \frac{\Delta t}{2[(\Delta x_2)]^2}$,

$r_3 = \frac{\Delta t}{2[(\Delta x_3)]^2}$, $r_4 = \frac{\Delta t}{2[(\Delta x_4)]^2}$.

and $\Delta x_1, \Delta x_2, \Delta x_3, \Delta x_4$ are the step sizes of mesh in the endothelium, stroma, epithelium layers, and contact lens, respectively. The boundary and continuity conditions at different interfaces are given by:

$$p_1(m-1, n+1) = p_a \quad (15)$$

$$p_2(m, n+1) = p_1(m, n+1) \quad (16)$$

$$p_3(m+1, n+1) = p_2(m+1, n+1) \quad (17)$$

$$p_3(m+2, n+1) = p_b \quad (18)$$

If the cornea is covered by the permeable contact lens, then condition (18) is replaced by:

$$p_4(m+2, n+1) = p_3(m+2, n+1) \quad (19)$$

$$p_4(m+3, n+1) = p_b \quad (20)$$

(ii) Numerical flux continuity condition

The finite difference analogue of the flux continuity condition at any interface is derived by following Fatt et al.¹³. Let D_i represent the diffusion coefficient of oxygen in the i^{th} layer and D_{i+1} represents the diffusion coefficient of oxygen in the $(i+1)^{th}$ layer.

$$Q_i = D_i k_i \left[\frac{p_i(m, n) - p_i(m-1, n)}{\Delta x_i} \right] \quad (21)$$

$$Q_{i+1} = D_{i+1} k_{i+1} \left[\frac{p_i(m+1, n) - p_i(m, n)}{\Delta x_i} \right] \quad (22)$$

$$\frac{Q_{i+1} - Q_i}{\Delta x_i} = \frac{\partial p_i}{\partial t} \quad (23)$$

If this equation is averaged with its counterpart at the forward time line, we obtain the finite difference approximation of the flux continuity condition at the interface in the following form:

the layers and that the partial pressure gradient of oxygen in the stroma layer is higher than that in the epithelium and endothelium layers. The oxygen tension becomes constant at the anterior surface of the epithelium because the cornea can not receive much oxygen from the aqueous humor unless the oxygen tension in the epithelium layer becomes 155 mmHg.

Table 1: Computed oxygen tension distribution in different corneal tissue layers

Symbol	Explanation	Numerical Value			
		Endothelium	Stroma	Epithelium	Lens
x	Thickness (cm)	0.01	0.45	0.04	0.02
V_i	Oxygen consumption rate (ml(O ₂) ml - sec)	11×10^{-4}	1.5×10^{-7}	2.1×10^{-4}	0
k_{m_i}	Michaelis-Menten constant (mmHg)	4.834	4.834	4.834	4.834
P_a	Aqueous humor oxygen tension	55 mm Hg (open and closed eye)	-	-	-
P_b	Posterior endothelial oxygen tension	-	-	155 mm Hg (open eye) 55mm Hg (closed eye)	-

Besides, the oxygen tension in the transient state is higher than that in the steady-state in different layers of the cornea and it increases with time. Under closed eye condition, the oxygen tension profiles in the steady and transient states in the endothelium, stroma and epithelium layers of the cornea are depicted in Figure 3. In this case, the oxygen tension decreases along the distance from the aqueous side in the endothelium layer, whereas, the tension increases along the depth in the stroma and epithelium. The pressure gradient at the stroma–epithelium interface is higher than that at the endothelium–stroma interface. Oxygen

tension becomes constant at the anterior surface of the epithelium.

The curves shown in Figure 4 represent the steady and transient states oxygen tension profiles in the endothelium, stroma and epithelium layers of the cornea in open eye with contact lens for high and low oxygen permeabilities of the lens. It is observed from figure that the tension in the steady and

transient states, in case of low oxygen permeability of the lens, decreases along the distance from the aqueous side to the stroma, whereas, at high oxygen permeability of the lens, it increases along the distance. Thus the tension increases with an increase in the oxygen permeability of the contact lens in steady and transient states. It is evident from the curves that the oxygen tension increases along the depth in the stroma and epithelium towards the anterior surface of the cornea.

An increase in the oxygen permeability of the contact lens enhances the oxygen tension in different layers of the cornea. The tension achieves the prescribed value at the anterior surface of the contact lens. It increases with time in different layers of the cornea at high and low oxygen permeabilities of the contact lens.

The curves in Figure 5 represents the steady and transient states oxygen tension profiles in different layers of the cornea in a closed eye with contact lens. Evidently, the oxygen tension decreases along the depth from the aqueous side in the endothelium and stroma. This decrease in the stroma is linear. However, the tension increases along a distance in the epithelium–contact lens layer from the stroma–epithelium interface and it attains a constant value at the anterior surface of the contact lens.

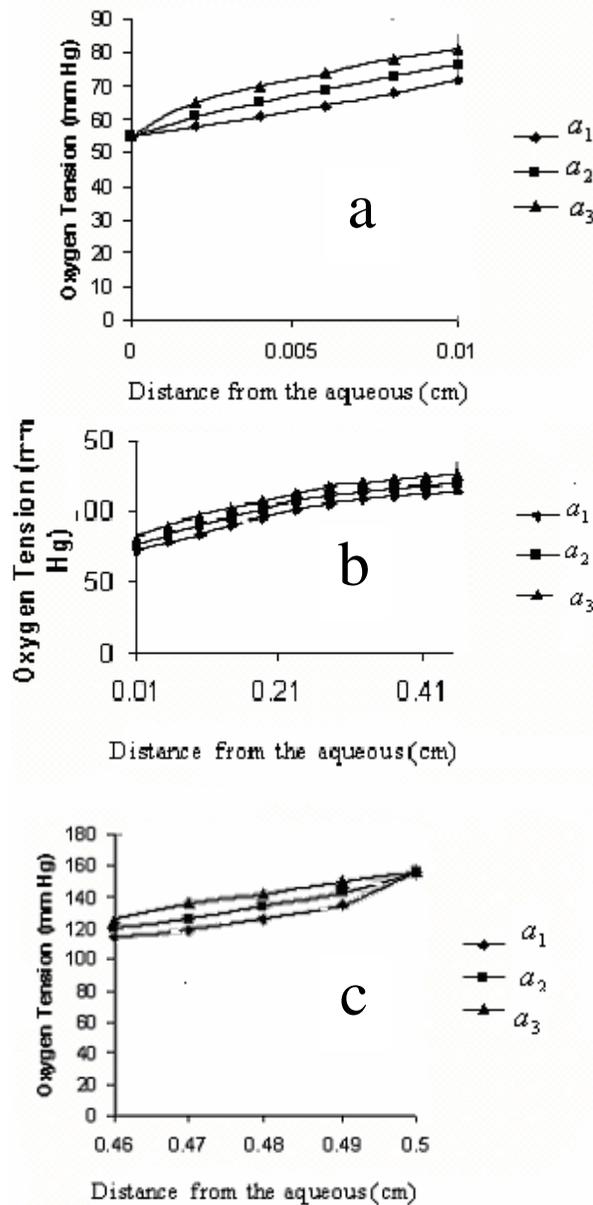


Figure 2: Oxygen tension profiles in the (a) endothelium, stroma (b) and epithelium (b) layers under open eye condition at different times (a_3 :0 sec, a_2 :100 sec, a_1 : 200 sec)

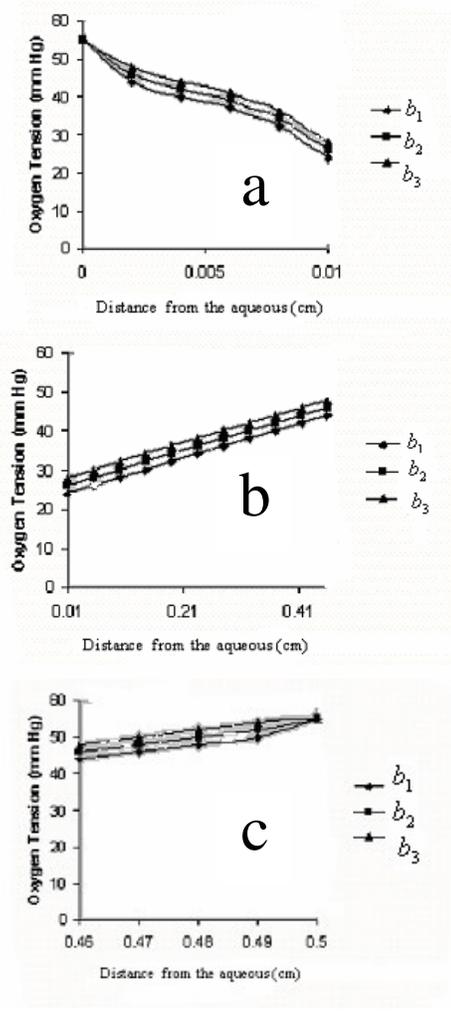


Figure 3: Oxygen tension profiles in the (a) endothelium, stroma (b) and epithelium (b) layers under closed eye condition at different times (b_3 :0 sec, b_2 :100 sec, b_1 : 200 sec)

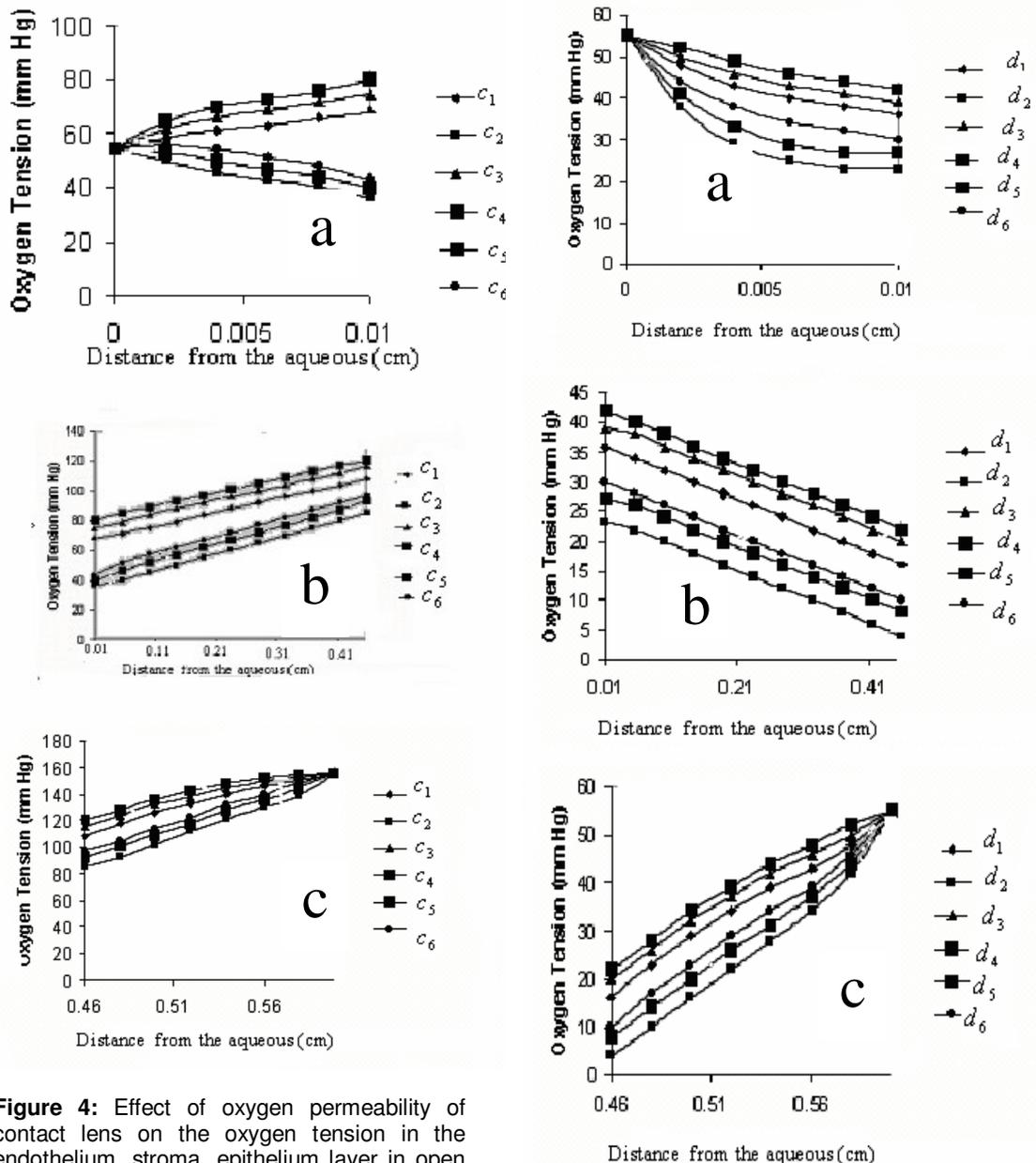


Figure 4: Effect of oxygen permeability of contact lens on the oxygen tension in the endothelium, stroma, epithelium layer in open eye ($c_3, c_2, c_1 : D_4k_4 = 500 \times 10^{-11} \text{ ml}(O_2) - \text{cm}_2 / \text{ml}(\text{tissue}) - \text{mmHg} - \text{sec}$ at $t=0 \text{ sec}, 100 \text{ sec}, 200 \text{ sec}$; $c_6, c_5, c_4 : D_4k_4 = 13.1 \times 10^{-11} \text{ ml}(O_2) - \text{cm}_2 / \text{ml}(\text{tissue}) - \text{mmHg} - \text{sec}$ at $t=0 \text{ sec}, 100 \text{ sec}, 200 \text{ sec}$, respectively)

Figure 5: Effect of oxygen permeability of contact lens on the oxygen tension in the endothelium stroma, epithelium layer in closed eye ($c_3, c_2, c_1 : D_4k_4 = 500 \times 10^{-11} \text{ ml}(O_2) - \text{cm}_2 / \text{ml}(\text{tissue}) - \text{mmHg} - \text{sec}$ at $t=0 \text{ sec}, 100 \text{ sec}, 200 \text{ sec}$; $c_6, c_5, c_4 : D_4k_4 = 13.1 \times 10^{-11} \text{ ml}(O_2) - \text{cm}_2 / \text{ml}(\text{tissue}) - \text{mmHg} - \text{sec}$ at $t=0 \text{ sec}, 100 \text{ sec}, 200 \text{ sec}$, respectively)

Transient oxygen tension in the cornea with contact lens is higher than steady state oxygen tension. The effect of oxygen permeability of the contact lens on the oxygen tension in different layers of the cornea has also been depicted. It is observed from the figures that the oxygen tension in the endothelium, stroma and epithelium increases with an increase in the oxygen permeability of the contact lens in the steady and transient state. This observation is supported from that fact that more oxygen enters into the cornea at higher oxygen permeability of the contact lens increasing the oxygen tension in the cornea.

Conclusion

The computational results of the model predict that the oxygen tension in the cornea of an open eye with or without contact lens is higher than that in closed eye. Also, at a high oxygen permeability of the contact lens, the transient oxygen tension increases significantly comparative that at to the low oxygen permeability. The understanding achieved through present study may be useful in the design of contact lens.

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