Three-Dimensional Modeling of Metabolic Species Transport in the Cornea With a Hydrogel Intrastromal Inlay

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PURPOSE. Intrastromal inlays for refractive correction of presbyopia are being adopted into clinical practice. An important concern is the effect of the inlay on the long-term health of the cornea due to disturbances in the concentration profiles of metabolic species. A three-dimensional metabolic model for the cornea is employed to investigate oxygen, glucose, and lactate ion transport in the cornea and to estimate changes in species concentrations induced by the introduction of a hydrogel inlay.

METHODS. A reaction-diffusion metabolic model, appropriate for highly oxygen-permeable hydrogel inlays, is used to describe cellular consumption of oxygen and glucose and production of lactic acid. A three-layer corneal geometry (epithelium, stroma, endothelium) is employed with a hydrogel inlay placed under a lamellar flap. The model is solved numerically by the finite element method.

RESULTS. For a commercially available hydrogel material with a relative inlay diffusivity of 43.5%, maximum glucose depletion and lactate ion accumulation occur anterior to the inlay and both are less than 3%. Below 20% relative diffusivity, glucose depletion and lactate ion accumulation increase exponentially. Glucose depletion increases slightly with increasing depth of inlay placement.

CONCLUSIONS. The flux of metabolic species is modified by an inlay, depending on the inlay relative diffusivity. For commercially available hydrogel materials and a typical inlay design, predicted changes in species concentrations are small when compared to the variation of concentrations across the normal cornea. In general, glucose depletion and lactate ion accumulation are highly sensitive to inlay diffusivity and somewhat insensitive to inlay depth.

Keywords: corneal metabolism, intrastromal inlay, presbyopia, oxygen transport, glucose transport

Various designs of intrastromal inlays are currently being adopted into clinical practice for treatment of presbyopia and other refractive conditions.1–5 Compared with alternative refractive surgical options, the use of intrastromal inlays for the improvement of near and intermediate vision in presbyopes has the advantage that the removal of tissue is not required. Experience has shown that inlays can be safely removed at any time, should that become necessary.4 They also appear to preserve the patient’s ability to undergo future ophthalmic procedures, including cataract surgery and retinal imaging. The current generation of intrastromal inlays includes three mechanisms of action: corneal reshaping inlays provide an additive volume that reshapes the central anterior curvature, producing a cornea with a gradual focal gradient; refractive optic inlays employ a bifocal optic with a refractive index that differs from the stroma; and small aperture opaque inlays, which have a small central aperture that increases depth of field through the pinhole optical principle. All three inlay designs are typically implanted in the nondominant eye, concentric with the visual axis or pupil center, and under a lamellar flap or in a pocket created by a mechanical or femtosecond laser platform.

In this study, we consider corneal reshaping inlays. A design that illustrates current technology for these inlays is provided by the Raindrop Near Vision Inlay5 (ReVision Optics, Lake Forest, CA, USA). This hydrogel polymer-based inlay is permeable to metabolic species (including oxygen and glucose) and has high light transmissibility with a refractive index close to that of the cornea. The inlay has a meniscus lens-like shape that after implantation alters the corneal anterior surface curvature above the inlay. Current approximate dimensions for this implant are a diameter of 2 mm with a thickness that varies from 14 μm at the periphery to 34 μm at the center. These dimensions may be compared with the diameter of the corneal limbus, which is approximately 11.5 mm, and to the corneal central thickness of approximately 0.5 mm.

Because the cornea is avascular, the metabolic requirements of corneal cells must be met by the diffusive transport of glucose from the aqueous humor and oxygen primarily from the air, or from the palpebral conjunctiva in the closed eye condition.6 Anaerobic breakdown of glucose in glycolysis produces lactic acid that must also diffuse out of the cornea through the endothelium and into the aqueous chamber. Early experience with impermeable or low-permeable inlays showed that anterior stromal thinning and keratolysis can result.
suggesting the importance of maintaining the transport of glucose, oxygen, and metabolic products such as lactic acid. It is also necessary that the mobility of stromal salt ions be maintained since these ions, in concert with the fixed charges of the glycosaminoglycans, produce the electrolyte character of the stroma and are crucial to the creation of an osmotic pressure and optimal tissue hydration. Thus, a significant barrier to flow can produce both cell stress and hydration imbalance.

The lateral dimension of the cornea is much greater than its thickness and therefore oxygen and glucose will transport directly across the cornea in opposite directions, driven by concentration gradients in an essentially one-dimensional (1D) manner. Introduction of an intrastromal inlay will modify metabolic species concentrations in the surrounding tissue by three principal mechanisms. Flux directions of metabolic species in the stroma will change in the vicinity of the inlay due to diffusivity mismatch; for example, if the inlay has relatively lower diffusivity than the stroma, species flux vectors in the stroma will tend to develop tangential components as species flow around the obstacle. Further, cellular metabolic reactions will be suspended within the implant volume (assuming cells do not migrate into the implant), and the length of the diffusion path across the cornea-inlay system will have been changed by the introduction of the implant. Although current inlay diameters are small compared with the limbal diameter, they lie directly in the path of metabolic species transporting across the central cornea. For the reasons noted above, modeling of metabolic species transport in the cornea with an intrastromal inlay must be treated as a three-dimensional (3D) problem.

Because it is difficult to measure metabolic processes experimentally, a numerical modeling approach can be useful. The oxygen distribution across the thickness of the cornea has been modeled as a reaction-diffusion problem using experimental data primarily derived from in vitro rabbit cornea. Corneal lactate production, glucose consumption rates reported by Zurawski et al.13 Following that analysis, we extend the model to the case of a cornea with an implanted hydrogel inlay and analyze changes in oxygen tension and glucose and lactate ion concentrations induced by the presence of the inlay.

### Materials and Methods

#### Corneal Metabolism Model

Metabolic consumption of glucose by cells in the corneal layers occurs through aerobic respiration and anaerobic fermentation. Aerobic respiration comprises the three metabolic processes of glycolysis, the Krebs cycle (also called the tricarboxylic acid cycle or citric acid cycle), and oxidative phosphorylation. Glycolysis is a purely anaerobic reaction and while it can occur in the presence of oxygen, oxygen is not involved in the reaction. In glycolysis, one mole of 6-carbon glucose is converted to two moles of 3-carbon pyruvate (pyruvic acid). The Embden-Meyerhof-Parnas pathway is the primary glycolytic pathway in the normal cornea. The pyruvate resulting from glycolysis is converted to acetyl-CoA, enters the Krebs cycle, and is oxidized to carbon dioxide. Finally, oxidative phosphorylation via the electron transport chain produces water by electron acceptance by oxygen atoms. Aerobic respiration may be summarized by the following simplified reaction formula:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + \text{energy}.$$  

Equation 1 implies that 1 mole of glucose is consumed with 6 moles of oxygen to produce 6 moles of carbon dioxide, 6 moles of water and 36 net moles (theoretical upper limit) of adenosine triphosphate (ATP).

In the absence of oxygen, respiration occurs by anaerobic fermentation consisting of the two metabolic pathways of glycolysis and fermentation. In this case, the pyruvate produced by glycolysis is converted by fermentation to lactate (lactic acid) and hydrogen ions. This is described by the following reaction formula:

$$C_6H_{12}O_6 \rightarrow 2C_3H_5O_3^- + 2H^+ + \text{energy}.$$  

In this case, the anaerobic conversion of 1 mole of glucose produces 2 moles of lactate ions, 2 moles of hydrogen ions, and 2 moles of ATP.

#### Metabolic Species Transport

A general 3D reaction-diffusion model for coupled oxygen, glucose, and lactate ion transport in the cornea-inlay system is provided by the following system of reaction-diffusion equations,
where \( \mathbf{x} = \{x_1, x_2, x_3\} \) is the position of a typical point in the cornea-implant domain, \( p_0 \) is the oxygen tension (equilibrium partial pressure), and related to the oxygen concentration \( c_0 \) by Henry’s constant \( k_0 \) such that \( c_0 = k_0 p_0 \). Glucose and lactate ion concentrations are denoted \( c_G \) and \( c_L \), respectively.

In Equations 3 through 5, the diffusivity of all metabolic species is assumed to be isotropic in all layers. The oxygen permeability \( D_{O_2} k_0 \) and glucose and lactate diffusivity \( D_G \) and \( D_L \), respectively, vary by layer as indicated by the dependence on position \( \mathbf{x} \). Likewise, the oxygen and glucose reaction (consumption) rates, \( Q_O \) and \( Q_G \), respectively, and lactate reaction (production) rate, \( Q_L \), must be positive functions that vary, in general, by corneal layer and depend on the concentrations of all three metabolic species. To reduce the complexity of the model, Descemet’s and Bowman’s membranes are modeled as having the same transport (reaction and diffusion) properties as the stroma.\(^{9,15} \) Thus the cornea is represented by the epithelial, stromal, and endothelial layers alone.

Observing the metabolic consumption of glucose described in Equations 1 and 2, and assuming that all glucose is consumed during the Krebs cycle or in reduction to lactate, it follows that the oxygen, glucose and lactate reaction terms in Equations 3 through 5 must be related as follows:

\[
Q_G = \frac{Q_O}{6} + \frac{Q_L}{2}
\]  

(6)

Because the reaction terms are not independent by virtue of this constraint, any two can be modeled, and the third may then be determined from Equation 6. In the Chhabra et al.\(^{18} \) model, reaction functions are written for oxygen and lactate, \( Q_O \) and \( Q_L \), respectively, and the glucose consumption rate is then found by use of Equation 6. If \( Q_O \) and \( Q_L \) are assumed to depend on \( p_0 \) and \( c_G \) only, Equations 3 through 6—specialized for steady-state conditions—reduce to

\[
\sum_{i=1}^{3} \frac{\partial}{\partial x_i} \left( D_{O_2} k_0(\mathbf{x}) \frac{\partial p_0}{\partial x_i} \right) = Q_O(\mathbf{x}, p_0, c_G, c_L) = k_0 \frac{\partial p_0}{\partial t}
\]  

(3)

\[
\sum_{i=1}^{3} \frac{\partial}{\partial x_i} \left( D_G(\mathbf{x}) \frac{\partial c_G}{\partial x_i} \right) - \frac{1}{6} Q_O(\mathbf{x}, p_0, c_G) - \frac{1}{2} Q_L(\mathbf{x}, p_0, c_G) = 0
\]  

(7)

\[
\sum_{i=1}^{3} \frac{\partial}{\partial x_i} \left( D_L(\mathbf{x}) \frac{\partial c_L}{\partial x_i} \right) + Q_L(\mathbf{x}, p_0, c_G) = 0
\]  

(9)

At the interfaces between the corneal layers and between stroma and implant, the three metabolic species must satisfy continuity conditions on concentration and flux. In the absence of data to the contrary, it is assumed that the partition coefficient governing concentration jumps across all interfaces—including the stroma-inlay interface—is unity. This assumption implies simple continuity of all concentrations across all interfaces. Conservation of mass requires continuity of normal fluxes. Letting the interface between any two regions be arbitrarily designated with + and – faces, the following conditions must be satisfied across that interface:

\[
(k_0 p_0)_{+} = (k_0 p_0)_{-}
\]  

(10)

\[
(c_G)_{+} = (c_G)_{-}
\]  

(11)

\[
(c_L)_{+} = (c_L)_{-}
\]  

(12)

All terms contained in a parenthesis are taken to be evaluated at the parenthesis subscript face (\( n_i \)) and (\( n_i \)), are the \( i \)-th components of the unit vectors \( \mathbf{n}_+ \) and \( \mathbf{n}_- \) normal to the interface and pointing out from the + and – faces, respectively, such that \( \mathbf{n}_+ = -\mathbf{n}_- \).

Boundary conditions on the epithelial-air interface \( \Gamma_{AE} \) and endothelial-aqueous chamber interface \( \Gamma_{AC} \) are specified as follows:

\[
p_0|_{\Gamma_{AE}} = p_{0_{air}}, \quad p_0|_{\Gamma_{AC}} = p_{0_{ac}},
\]  

(13)

\[
\left( \sum_{i=1}^{3} D_G(\mathbf{x}) \frac{\partial c_G}{\partial x_i} n_i \right)_{air} = 0, \quad c_G|_{\Gamma_{AE}} = c_{G_{ac}}
\]  

(14)

\[
\left( \sum_{i=1}^{3} D_L(\mathbf{x}) \frac{\partial c_L}{\partial x_i} n_i \right)_{air} = 0, \quad c_L|_{\Gamma_{AC}} = c_{L_{ac}}
\]  

(15)

where \( p_{0_{air}} \) and \( p_{0_{ac}} \) correspond to constant values of oxygen tension at the cornea-air and cornea-aqueous humor interfaces, respectively. For glucose, a zero normal flux at the epithelium-air interface is assumed and at the endothelium-aqueous interface glucose concentration is assumed to be constant with a value denoted by \( c_{G_{ac}} \). For lactate ion, a zero normal flux at the epithelium-air interface is also assumed and \( c_{L_{ac}} \) corresponds to an assumed constant value at the endothelium-aqueous humor interface. The values used for the above-noted physical constants are given in Table 1.

**Reaction Model**

Because both aerobic and anaerobic reactions are catalyzed by enzymes, the oxygen reaction term \( Q_O \) in Equation 7 and the lactate reaction term \( Q_L \) in Equation 9 can be expressed using nonlinear Monod kinetics in the form,\(^{18} \)
tension of \( p_O = 20 \) mm Hg, the lactate ion production rate is 10% above the minimum value. Finally, \( K_D^O \) is the Monod dissociation equilibrium constant for glucose, which is assumed to have the same value as \( K_D^L \). As for the case of oxygen consumption, the lactate ion production rate constants \( K_D^L \) and \( K_G^L \) are assumed to be the same in all layers, whereas \( Q^{\text{min}}_L \) varies by layer; see Tables 1 and 2.

Because of lack of experimental data, we have assumed values for the four reaction constants such that \( K_D^L = K_G^L = K_G^O \) and \( K_D^L = K_G^L = K_O \), reducing the number of reaction constants to two. In this case (but not generally), the glucose consumption rate may be found from Equations 6, 16, and 17 as:

\[
Q_G(p_O, c_G) = \left( \frac{Q^{\text{max}}_O}{6} \frac{p_O}{K_O + p_O} + \frac{Q^{\text{min}}_L}{2} \left[ \frac{c_G}{K_G + c_G} \right] \right)
\]

This rate expression describes the consumption of glucose by aerobic and anaerobic respiration. The glucose consumption rate is zero when glucose concentration is zero. In the absence of oxygen, respiration occurs by glycolysis and fermentation and glucose is then consumed at a rate given by:

\[
Q^{\text{anaerobic}}_G(c_G) = \frac{Q^{\text{min}}_L}{2} \left[ \frac{c_G}{K_G + c_G} \right].
\]

At high levels of oxygen tension and glucose concentration, the glucose consumption rate tends to \( Q^{\text{max}}_O/6 + Q^{\text{min}}_L/2 \), as required.

**Geometric Model and Numerical Solution**

The assumed spherical geometry of the three-layer normal cornea comprises a 5-\( \mu \)m thick endothelium, a 500-\( \mu \)m thick stroma, and a 50-\( \mu \)m thick epithelium; total corneal thickness is 0.555 mm. The anterior radius of the cornea is taken to be 7.53 mm. Solution of the metabolic model for the normal cornea provides the baseline for the study of the effects of the inlay. The metabolic model comprises solution of Equations 7 through 9, implemented with axisymmetry and subject to boundary and interface conditions (Equations 10–15). The nonlinear and coupled system of equations was solved by the finite element method using COMSOL Multiphysics 4.3a (2012), version 4.3.1.161. The mesh employed approximately 80,000 triangular elements that fully resolve the solution in all layers.

The cornea model was extended to include a centrally located hydrogel inlay placed under a lamellar flap. The hydrogel polymer-based inlay (ReVision Optics) was selected as a representative inlay device and the dimensions and transport parameters of that inlay (Table 3) have been employed as reference values for the study. In order to facilitate a direct comparison of metabolic species concentrations in the normal cornea and cornea with inlay, it was necessary to introduce a modified normal cornea model.

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### Table 1. Metabolic Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p_{O_{2c}} )</td>
<td>24.0</td>
<td>mm Hg</td>
</tr>
<tr>
<td>( p_{O_{2aw}} )</td>
<td>155.0</td>
<td>mm Hg</td>
</tr>
<tr>
<td>( c_{Gc} )</td>
<td>6.9</td>
<td>mM</td>
</tr>
<tr>
<td>( c_{Gc} )</td>
<td>7.7</td>
<td>mM</td>
</tr>
<tr>
<td>( K_D^O )</td>
<td>2.2</td>
<td>mm Hg</td>
</tr>
<tr>
<td>( K_D^L )</td>
<td>2.2</td>
<td>mm Hg</td>
</tr>
<tr>
<td>( K_G^O )</td>
<td>0.4</td>
<td>mM</td>
</tr>
<tr>
<td>( K_G^L )</td>
<td>0.4</td>
<td>mM</td>
</tr>
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### Table 2. Values of Physical Constants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Endothelium</th>
<th>Stroma</th>
<th>Epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_{k}k_{O} )</td>
<td>Fatt Dk (Barrer)</td>
<td>5.3</td>
<td>29.5</td>
<td>18.8</td>
</tr>
<tr>
<td>( D_{L} )</td>
<td>( 10^{-6} ) cm/s</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>( D_{L} )</td>
<td>( 10^{-6} ) cm/s</td>
<td>4.4</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>( Q^{\text{max}}_O )</td>
<td>( 10^{-3} ) mLO_{2}/ml/s</td>
<td>47.78</td>
<td>2.29</td>
<td>25.9</td>
</tr>
<tr>
<td>( Q^{\text{min}}_L )</td>
<td>( 10^{-3} ) mol/mL/h</td>
<td>4.7</td>
<td>23.4</td>
<td>28.1</td>
</tr>
</tbody>
</table>
model is designed to correspond to the normal cornea solution but displayed on an “expanded” cornea that matches the geometry of the corneal tissue surrounding the inlay. This can be accomplished by solving the cornea-inlay model with the inlay domain modeled with: (1) stromal oxygen permeability and stromal glucose and lactate diffusivities scaled by a factor of 106; and (2) suspending metabolic reactions, so that $Q_O = Q_L = Q_G = 0$. This has the effect of shunting the concentrations across the implant domain at constant values and exactly reproduces the normal cornea concentration profiles on the cornea-implant geometry, thereby facilitating a direct comparison on the two solutions.

RESULTS

Concentration Profiles for Normal Cornea

The solution for the normal cornea is 1D in character, with species gradients in the thickness direction only. Figure 1 illustrates oxygen tension, glucose concentration, and lactate ion concentration profiles across the central corneal thickness (CCT). Note that the thickness coordinate (mm) has its origin at the endothelium–aqueous humor interface and ends at 0.555 mm on the anterior surface of the epithelium. Predicted glucose and lactate ion concentrations at this interface are 4.93 mM and 10.08 mM, respectively. Steady-state consumption rates for oxygen and glucose and production rate for lactate ion were computed from Equations 16, 18, and 17, respectively, and their profiles across the CCT are shown in Figure 2.

Assessment of Metabolic Model for Normal Cornea

In this section, we provide a measure of the accuracy of the metabolic model by comparing predicted glucose consumption rates to direct measurements for rabbit in vitro. Zurawski et al.13 collected and cultured rabbit stromal keratocyte, epithelial, and endothelial cells that were grown to confluence in a gas flow humidified incubator with Krebs-Ringers solution at a pH of 7.2 and with varying initial glucose concentrations. For each of the three cell types, glucose concentration versus time is reported for three initial glucose concentrations of 0.9, 0.6, and 0.3 mM, giving a total of nine trials. Each of the trials comprises five consecutive measurements taken with an interval of 20 minutes. Zurawski et al.13 report the average glucose consumption rate for each cell monolayer of each cell line. If it is assumed, following Zurawski et al.,13 that the average number of cell layers found in the epithelium, stroma, and endothelium are 5, 7.5, and 1, respectively, the glucose consumption rate per unit volume in each corneal layer may be estimated by direct calculation. Zurawski et al.13 labeled the cell monolayer consumption rates with the approximate initial glucose concentration targeted at the start of each trial. We examined the data presented in Zurawski et al.13 and estimated the average glucose concentration during each of the nine individual trials. The average glucose concentrations, converted to mM units by assuming a glucose molar mass $M_G = 0.18016$ kg/mol are given in Table 4 along with the corresponding glucose consumption rates for each of the corneal layers. As might be anticipated by cellular density.

### Table 3. Material Parameters for Reference Hydrogel Inlay Material

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen permeability</td>
<td>50.8</td>
<td>Fatt Dk (or Barrer)</td>
</tr>
<tr>
<td>Glucose diffusivity</td>
<td>1.304</td>
<td>$10^{-6}$ cm$^2$/s</td>
</tr>
<tr>
<td>Lactate ion diffusivity</td>
<td>1.913</td>
<td>$10^{-6}$ cm$^2$/s</td>
</tr>
</tbody>
</table>

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**Figure 1.** Predicted metabolic species concentration profiles across central corneal thickness for the normal cornea. (A) Oxygen tension. (B) Glucose concentration. (C) Lactate ion concentration. The endothelium, stroma, and epithelium are 0.005 mm, 0.5 mm, and 0.05 mm thick, respectively. The thickness coordinate (mm) has its origin at the endothelial-aqueous humor interface and ends at the anterior surface of the epithelium with a value of 0.555 mm.
glucose consumption rates in the epithelial and endothelial layers exceed that of the stroma. For example, at a glucose concentration of 5 mM, the epithelial and endothelial glucose consumption rates exceed the stromal rate by factors of 5.0 and 3.7, respectively.

The data in Table 4 can be modeled with reasonable accuracy using the following (dimensionally-dependent) expressions:

\[
Q_{epi}^{G\text{mM/s}} = 0.0023 \frac{c_G^{mM}}{C_{138}} \quad \text{(20)}
\]

\[
Q_{stroma}^{G\text{mM/s}} = 0.0023 \left(1 - \exp\left(-0.5c_G^{mM}\right)\right) \quad \text{(21)}
\]

\[
Q_{endo}^{G\text{mM/s}} = 0.0135 \left(1 - \exp\left(-0.185c_G^{mM}\right)\right) \quad \text{(22)}
\]

Use of these expressions allows mild extrapolation of the data to the range of glucose concentration found in the normal human cornea. Figure 3 shows a comparison of the experimental glucose consumption data summarized in Table 4 with modeling provided by Equations 20 through 22. The agreement of the two sets of curves and the required degree of extrapolation is apparent from the plot.

Using the metabolic model, oxygen tension and glucose and lactate ion concentration profiles were computed for all layers of the cornea as described above. Reaction Equations 16 and 17 were then evaluated, giving predicted oxygen consumption and lactate ion production rate profiles across all corneal layers. These were converted to a predicted glucose consumption rate by use of Equation 6 or 18. Having obtained both the predicted glucose concentration and the glucose consumption rate profiles across the corneal thickness, these two quantities can be directly related at each point through the CCT. The result for the stroma is shown in Figure 4.

Glucose consumption rates estimated from the Zurawski et al.\textsuperscript{13} data, summarized in Table 4, are given for the experimental range of glucose concentration of 1.7 through 5.0 mM. The range of glucose concentration across the normal cornea predicted by the model is 4.93 to 6.9 mM. In order to compare the estimated and predicted rates, the results in Table 3 were mildly extrapolated by employing Equations 20 through 22. A comparison of estimated and predicted glucose consumption rates versus glucose concentration at the center of the three principal corneal layers is given in Table 5.

### Concentration Profiles With Hydrogel Intrastromal Implant

The geometric model of the cornea with the hydrogel polymer-based inlay\textsuperscript{5} (ReVision Optics) is shown in Figure 5. The posterior face of the inlay is curved to conform with the stromal bed. The inlay has thickness which varies from 14 \(\mu\text{m}\) at the periphery to 34 \(\mu\text{m}\) at the center. The 150-\(\mu\text{m}\) thick corneal flap above the inlay lies directly on the inlay and is assumed to conform to the inlay shape, which slightly alters

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**Table 4.** Glucose Consumption Rate \(Q_G^{G\text{mM/s}}\) Versus Glucose Concentration \(c_G^{mM}\) Based on In Vitro Rabbit Data in Zurawski et al.\textsuperscript{13}

<table>
<thead>
<tr>
<th></th>
<th>Epithelium</th>
<th>Stroma</th>
<th>Endothelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>(c_G^{mM})</td>
<td>(Q_G^{G\text{mM/s}})</td>
<td>(c_G^{mM})</td>
<td>(Q_G^{G\text{mM/s}})</td>
</tr>
<tr>
<td>1.49867</td>
<td>0.00262</td>
<td>1.27664</td>
<td>0.00116</td>
</tr>
<tr>
<td>3.16385</td>
<td>0.00756</td>
<td>2.66430</td>
<td>0.00160</td>
</tr>
<tr>
<td>4.44050</td>
<td>0.01035</td>
<td>4.16297</td>
<td>0.00208</td>
</tr>
</tbody>
</table>
FIGURE 3. Glucose consumption rates versus glucose concentration are plotted for the epithelium, stroma, and endothelium. The solid curves are based on the experimentally measured values for in vitro rabbit in Zurawski et al.\textsuperscript{13} Note that the concentration values correspond to the mean concentration during the tests and not the initial (label) concentrations reported in Zurawski et al.\textsuperscript{13} The experimental data is modeled by Equations 20 through 22, which are plotted as dashed curves. These functions are used to extrapolate the experimental data to the range of glucose concentration found in the normal cornea (6.9 mM at the endothelium and 4.93 mM at the epithelium); the extent of the dashed curves indicates the range of extrapolation required.

FIGURE 4. Predicted glucose consumption rate versus glucose concentration in the normal corneal stroma.
the corneal anterior surface above the inlay. The stroma–inlay interfaces are assumed to be tightly contacting boundaries for species transport and continuity conditions described by Equations 10 through 12 are assumed to hold. The oxygen permeability and glucose diffusivity of the hydrogel inlay were measured by the manufacturer but lactate diffusivity for the hydrogel is unknown. This value was chosen by requiring the inlay glucose-lactate ion diffusivity ratio to match the value for the stroma; from Table 2, the ratio is $D_G/D_L = 0.682$. Values of the inlay transport parameters used in the study are summarized in Table 3.

Oxygen tension and glucose and lactate ion concentration profiles across the CCT for the normal cornea and cornea with inlay are shown in Figure 6. Percentage changes in concentration for each species due to the introduction of the inlay was computed by evaluating $(c_{\text{inlay}} - c_{\text{normal}}) * 100/c_{\text{normal}}$ pointwise over the entire corneal longitudinal cross-section. Fringe plots showing areas of depletion and accumulation for oxygen, glucose and lactate ion are shown in Figure 7. Changes in concentrations remote from the inlay are zero. Maximum glucose depletion was 2.5% in the tissue anterior to the inlay and maximum glucose accumulation was 0.6% in the tissue posterior to the inlay (Fig. 7B). Maximum lactate accumulation was 1.4% anterior to the inlay (Fig. 7C). Maximum oxygen depletion was 3.5% at mid-stroma and maximum oxygen accumulation was 3.3% and occurs immediately anterior to the inlay (Fig. 7A).

Sensitivity to Inlay Glucose and Lactate Ion Diffusivity

In the long-term use of hydrogel inlays it is possible that the transport properties of the hydrogel could change with time as pore structure and organization become modified by chemical or other processes. For this reason, it is useful to analyze the sensitivity of metabolic species transport to variations in the properties of the inlay. Since the molecular size of oxygen is less than that of glucose by an order, it is probable that glucose

<table>
<thead>
<tr>
<th>Layer and Glucose Concentration</th>
<th>Current Model</th>
<th>Zurawski et al. $^{13}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-epithelium $c_G = 4.9$ mM</td>
<td>0.00564</td>
<td>0.0113</td>
</tr>
<tr>
<td>Mid-stroma $c_G = 5.6$ mM</td>
<td>0.00332</td>
<td>0.0022</td>
</tr>
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<td>Mid-endothelium $c_G = 6.9$ mM</td>
<td>0.00381</td>
<td>0.0095</td>
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**FIGURE 5.** Geometry of the cornea and reference hydrogel inlay used in calculations. All dimensions are in mm. (A) Shows the inlay placed within the cornea extended to the limbus. (B) A detailed view of the cornea and inlay with dimensions used in the model. Note that the stromal thicknesses is preserved, which requires the shape of the stroma and epithelium anterior to the inlay to be slightly modified to accommodate the volume of the inlay, and which produces changes in the anterior surface curvature.
FIGURE 6. Metabolic species concentration profiles across the central corneal thickness with and without inlay illustrating regions of depletion (concentration reduction) and accumulation (concentration increase). (A) Oxygen tension. (B) Glucose. (C) Lactate ion. The profile for the cornea without inlay (blue) has a horizontal segment in which the concentrations are constant across the inlay thickness (see “Methods”). The profile for the cornea with inlay is shown in red.

FIGURE 7. Species concentration percent change were determined from \((c_{\text{inlay}} - c_{\text{normal}}) \times 100/c_{\text{normal}}\) (accumulation is positive and depletion is negative). The percent changes are plotted as fringes in the corneal region containing the inlay. (A) Oxygen tension. (B) Glucose. (C) Lactate ion.
and lactate ion transport modification would occur well before oxygen transport modification. To model this condition, we introduce the inlay relative diffusivity defined as $C_p = (D_p)_\text{inlay} / (D_p)_\text{stroma}$. From Tables 2 and 3, the hydrogel inlay material used in the present study corresponds to $C_p = 0.435$. Lactate ion and glucose inlay relative diffusivities will have the same value by virtue of our assumption on inlay lactate ion diffusivity. We now consider the situation in which glucose (and lactate ion) transport properties of the implant are varied over the range $C_p > [0.01, 1.0]$ while oxygen permeability is maintained at the value of $D_p k_{O_2} = 50.8$ Fatt Dk units, where 1 Fatt Dk unit $= [10^{-11} \text{cm}^2/\text{s}](\text{mL/O}_2 \text{at STP/mL \text{mm Hg}})$. At $C_p = 1.0$, the inlay glucose diffusivity exactly matches the corneal diffusivity (for all layers), $C_p = 0.435$ corresponds to the reference hydrogel material, and at $C_p = 0.01$ the inlay glucose diffusivity is reduced to 1% of the corneal diffusivity.

Figure 8 depicts maximum glucose and lactate ion percent concentration depletion and accumulation versus inlay relative diffusivity. For each value of the inlay relative diffusivity, the depletion and accumulation values reported are taken from those positions in the cornea where they achieve maximum values; in general, these positions change with the relative diffusivity. Thus, for any relative diffusivity, the plot shows the maximum glucose depletion that occurs anywhere over the entire cornea; similarly with the lactate ion accumulation.

![Figure 8. Maximum glucose and lactate ion percent concentration depletion and accumulation versus inlay relative diffusivity. For each value of the inlay relative diffusivity, the depletion and accumulation values reported are taken from those positions in the cornea where they achieve maximum values; in general, these positions change with the relative diffusivity. Thus, for any relative diffusivity, the plot shows the maximum glucose depletion that occurs anywhere over the entire cornea; similarly with the lactate ion accumulation.](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932989/)

Sensitivity to Depth of Placement, Corneal Thickness, and Inlay Dimensions

**Depth of Placement.** In order to characterize sensitivity to depth of placement, three geometric models for the cornea-inlay system corresponding to lamellar flap thicknesses of 100 μm, 150 μm, and 250 μm were analyzed. The dimensions of the inlay were maintained at their reference values (Fig. 5B) and the inlay oxygen permeability was taken to be constant at $D_p k_{O_2} = 50.8$ Fatt Dk units. For each flap thickness, maximum species concentration percentage change was determined for inlay relative diffusivities $C_p$ of 43.5% (hydrogel reference value), 20%, and 5%. The results for glucose, lactate ion, and oxygen tension are summarized in Figures 11A through 11C.
Glucose depletion and lactate ion accumulation both increase with: (1) an increase in inlay depth of placement, and (2) a reduction in inlay relative diffusivity. Further, sensitivity to depth of placement increases for lower values of the inlay relative diffusivity.

Central Corneal Thickness. Three modified models of the cornea-inlay system were analyzed corresponding to CCT of 450 μm, 555 μm, and 650 μm, in order to characterize sensitivity to CCT. The inlay was modeled under a 150-μm-thick lamellar flap in all cases and the changes in CCT were modeled as changes in the thickness of the stroma only. The metabolic model was solved using the inlay oxygen permeability of $D_O k_O = 50.8$ Fatt Dk units and two values of inlay relative diffusivity $\Gamma_G$ of 43.5% (hydrogel reference value), and 20%. The results for maximum glucose depletion and maximum lactate ion accumulation are summarized in Tables 6 and indicate that a small increase in glucose depletion occurs with increasing CCT.

Inlay Dimensions. The inlay reference dimensions (Fig. 5B) were systematically varied to characterize sensitivity to inlay dimensions. Four new inlay shapes were created: half-thickness, half-diameter; half-thickness, double-diameter; double-thickness, half-diameter; and double-thickness, double-diameter. The metabolic model was solved for these geometric cases with all inlays placed under a 150-μm lamellar flap. The inlay oxygen permeability of $D_O k_O = 50.8$ Fatt Dk units was used with two values of inlay relative diffusivity $\Gamma_G$ of 43.5% (hydrogel reference value), and 20%. The results for maximum glucose depletion and maximum lactate ion accumulation are summarized in Table 7. Not surprisingly, the double-thickness, double-diameter condition produced the greatest glucose depletion of around 6% and 13% for $\Gamma_G$ of 43.5% and 20%, respectively.
DISCUSSION

A contact lens placed on the eye impedes the flow of oxygen from the atmosphere into the cornea. An intrastromal hydrogel inlay typically provides oxygen permeability that is equal to or greater than that of the stroma. In the normal cornea, glucose is not significantly transported out of the epithelium into the tear film (as modeled by condition Equation 14A) and a contact lens will therefore not directly modify the glucose state at the cornea–lens interface. In contrast, a hydrogel inlay placed within the stroma could impede the flow of glucose and lactic acid as they move across the cornea following their concentration gradients. In the analysis of the safety and metabolic impact of contact lenses, oxygen is of prime interest, whereas for intrastromal inlays, glucose is of prime interest.

Reduction in the flow of metabolic species resulting from the inlay may cause changes in the tissue and cells. An extreme example is provided by the early intrastromal inlays which used materials that were impermeable to water and metabolic species. These implants caused anterior stromal necrosis followed by implant extrusion. Modern hydrogel materials, such as that analyzed in this study, have oxygen permeability that is very close to that of the stroma, or even exceeding it. However, the glucose diffusivity of these materials is inferior to the stroma and small changes in glucose concentration in adjacent stroma will certainly be generated, generally as depletion anterior to the inlay and accumulation posterior to the inlay. In this study we have analyzed these changes as a function of the inlay relative diffusivity and, as discussed below, for currently available inlay materials, the changes in glucose concentration are small. However, there exists the theoretical possibility that the pores of the hydrogel material may become obstructed in time with a concomitant reduction in diffusivity. As far as we know, no explanted hydrogel inlay has been tested for changes in diffusivity. As shown in this study, if the inlay material is reduced to relative diffusivities below 20%, there is an exponential increase in glucose depletion. An earlier theoretical study by Larrea et al. drew a similar conclusion when the relative diffusivity approached 10%.

Complications associated with hydrogel inlays for presbyopic correction have included intracorneal deposits, corneal haze, epithelial perilenticular opacity, and vision-related effects such as irregular astigmatism. Some of the complications have been identified with the surgical implant procedure and some with an immunological or inflammatory response to the hydrogel material. It is probable that the latter, mediated by macrophages or activated keratocytes, does not result from low levels of oxygen or glucose. It is currently not clear to what extent small changes in metabolic species concentrations, such as seen in the current study, contribute to the development of complications. However, if an inlay exhibits progressive reduction in diffusivity, the resulting glucose depletion will likely become an important factor in the long-term health of the tissue.

In this work, we have employed the metabolic model proposed by Chhabra et al. but restricted by the assumption that the corneal pH is maintained at a normal and constant value of 7.6. To provide an assessment of the model, we have computed the glucose consumption rate versus glucose concentration in the normal cornea and compared the results to estimates based on rabbit data presented by Zurawski et al. The agreement is considered fair for the stroma (Table 5). While the predicted glucose consumption rates in the epithelium and endothelium exceed the predicted glucose consumption rate in the stroma, agreeing with the trend in the experimental data, the predicted consumption rates are nevertheless underestimated by approximately 50% and 60%.

<table>
<thead>
<tr>
<th>Thickness, μm</th>
<th>Maximum Glucose Depletion, %</th>
<th>Maximum Lactate Ion Accumulation, %</th>
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<tr>
<td>450</td>
<td>2.29</td>
<td>1.60</td>
</tr>
<tr>
<td>555</td>
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</tr>
<tr>
<td>650</td>
<td>2.84</td>
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**Table 6. Sensitivity to CCT**

**FIGURE 11.** Maximum metabolic species percent concentration change when depth of inlay placement (flap thickness) and inlay relative diffusivity (RD) is varied. (A) Glucose depletion. (B) Lactate ion accumulation. (C) Oxygen depletion. The inlay glucose (and lactate ion) relative diffusivity were varied while the inlay oxygen permeability is maintained constant.
respectively. (It may be noted that because the bounding cellular layers are thin compared to the stroma, the total glucose consumed in those layers will be less than the total glucose consumed in the stroma.) These results are influenced by the values assigned to the epithelial and endothelial maximum oxygen consumption rate $Q_{O_{2}}^{\text{max}}$ and minimum lactate production rate $Q_{L}^{\text{min}}$. The data summarized in Table 5 could be employed to revise these values, although we have not pursued such a study in the present work. Because glucose is the only reactant in glycolysis, it is also suggested that that the glucose consumption rate data provided by Zurawski et al.\textsuperscript{13} could be directly modeled using simple Monod or Michaelis-Menten kinetics. The oxygen consumption rate would retain the form of Equation 16 and the lactate ion production rate would be derived from Equation 6.

The current model has assumed isotropic diffusion in all corneal layers. The corneal stroma has a lamella structure that suggests that anisotropic diffusion of metabolic species might be important. No experimental measurement of anisotropy in stromal tissue is available. Stromal lamellae contain parallel arrays of collagen fibrils in a regular lattice arrangement with an average fibril diameter of approximately 25 nm and center-to-center spacing of approximately 53 nm. The question for isotropy is whether diffusive transport across the fibril direction is significantly hindered by the fibril "obstacles" compared with transport along the fibril direction. However, the clear distance between adjacent fibril faces of approximately 28 nm relative to the molecule diameter (which is on the order of 1 nm for glucose), seems to suggest that isotropy will hold to first order and that transport is governed primarily by the properties of the interstitial fluid of the extracellular matrix.

A further assumption in the model is that the transport and reaction properties of Descemet’s and Bowman’s layers are the same as the stroma. Descemet’s and Bowman’s have collagen fibril arrangement and density that is comparable with the stroma and both exhibit elasticity. In the absence of experimental measurements, we have taken their diffusive transport and metabolic reaction properties to be similar to the stroma and the model simply combines their volumes with that of the stroma.

With regard to accuracy of the model for application to the hydrogel inlay, it is noted that the principal results are given as the difference of two solutions; the cornea with inlay and the cornea without inlay. The differences in glucose concentration anterior to the inlay are set up (Fig. 10B), but these are not adequate to generate sufficient lateral mass transport. The latter point is further illustrated in Figure 9, which depicts glucose and lactate ion concentration profiles when the inlay has a relative diffusivity of 5%.

Finally, it is remarked that our analysis indicates that glucose depletion always increases with increasing depth of placement and that this sensitivity increases as the inlay relative diffusivity is reduced (in our study from 43.5% to 5%; see Fig. 11). Larrea et al.\textsuperscript{20} have performed an analogous sensitivity study in which the relative diffusivities are varied over a lower range from 10% to 0%. Results for 5% inlay relative diffusivity are common to both studies and our findings agree, namely that glucose depletion increases with depth of inlay placement. That is, shallow placement is always favored with respect to glucose concentration. However, at inlay diffusivities lower than 0.1%, Larrea et al.\textsuperscript{20} show a reversal in the trend whereby glucose depletion reduces with depth of placement. Although we have not reported results for such low values of inlay diffusivity here—our analyses at these low values do not support that finding—we find that glucose depletion always increases slightly with depth of placement for any value of inlay diffusivity. From a practical point of view, and for commercially available hydrogel materials, Figure 11A shows that glucose depletion is essentially insensitive to depth of inlay placement.

**Acknowledgments**

Disclosure: P.M. Pinsky, ReVision Optics (C)

**References**


