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Oxygen-deficient metabolism and corneal edema

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Abstract

Wear of low-oxygen-transmissible soft contact lenses swells the cornea significantly, even during open eye. Although oxygen-deficient corneal edema is well-documented, a self-consistent quantitative prediction based on the underlying metabolic reactions is not available. We present a biochemical description of the human cornea that quantifies hypoxic swelling through the coupled transport of water, salt, and respiratory metabolites. Aerobic and anaerobic consumption of glucose, as well as acidosis and pH buffering, are incorporated in a seven-layer corneal model (anterior chamber, endothelium, stroma, epithelium, postlens tear film, contact lens, and prelens tear film). Corneal swelling is predicted from coupled transport of water, dissolved salts, and especially metabolites, along with membrane-transport resistances at the endothelium and epithelium. At the endothelium, the Na⁺/K⁺ - ATPase electrogenic channel actively transports bicarbonate ion from the stroma into the anterior chamber. As captured by the Kedem–Katchalsky membrane-transport formalism, the active bicarbonate-ion flux provides the driving force for corneal fluid pump-out needed to match the leak-in tendency of the stroma. Increased lactate-ion production during hypoxia osmotically lowers the pump-out rate requiring the stroma to swell to higher water content. Concentration profiles are predicted for glucose, water, oxygen, carbon dioxide, and hydronium, lactate, bicarbonate, sodium, and chloride ions, along with electrostatic potential and pressure profiles. Although the active bicarbonate-ion pump at the endothelium drives bicarbonate into the aqueous humor, we find a net flux of bicarbonate ion into the cornea that safeguards against acidosis. For the first time, we predict corneal swelling upon soft-contact-lens wear from fundamental biophysico-chemical principles. We also successfully predict that hypertonic tear alleviates contact-lens-induced edema.

Keywords

Corneal edema; Oxygen deficiency; Endothelial-bicarbonate active ion pump; Pump-leak swelling; Aerobic and anaerobic respiration; Metabolite transport; Soft-contact-lens oxygen transmissibility

1. Introduction

Human corneal health relies on avascular oxygen supply. Under normal conditions, oxygenation of the anterior cornea is achieved by exposure to the atmosphere when the eye is open, and by exposure to the palpebral conjunctiva when the eye is closed. Upon eye closure, corneal oxygenation is reduced because the palpebral conjunctiva has roughly one-third of the atmospheric concentration (Chhabra et al., 2009). Low-oxygen-transmissible soft contact lenses (SCL) further impede oxygen flow to the cornea with possible loss of corneal transparency upon overwear (Fatt and Weissman, 1992). In exceptional cases, keratitis, microcysts, and acidosis can result (Fatt et al., 1969; Graham et al., 2001; Sweeney, 2003). Consequently, the role of SCL oxygen permeability ($=Dk$, where D is the diffusion coefficient and k is the partition coefficient of oxygen in the lens material) in corneal hypoxia has been extensively studied (Takahashi and Fatt, 1965; Fatt, 1968; Fatt and Bieber, 1968; Fatt and St. Helen, 1971; Fatt et al., 1974, 1998; Weissman and Fazio, 1982; Fatt and Lin, 1985; Harvitt and Bonanno, 1999; Brennan, 2005a, 2005b; Alvord et al., 2007; Chhabra et al., 2009). To assess the critical oxygen requirement (Efron and Brennan, 1987b), these efforts all consider molecular diffusion of oxygen into the cornea with reactive loss.

Clinical diagnosis of corneal hypoxia, however, relies primarily on the observation of increased corneal thickness when the eye is exposed to a hypoxic environment (Polse and Mandell, 1970). Holden and Mertz (1984) showed that SCL wear also swells the cornea. The smaller is the lens oxygen transmissibility ($=Dk/L$ where L is the lens harmonic-mean thickness), the larger is the measured corneal swelling. These observations spurred extensive study of the mechanisms for corneal-thickness control.

Pioneering studies of Maurice (1972, 1984) suggested a “pump-pleak” process at the endothelium to explain corneal thickness (Klyce and Russell, 1979; Bryant and McDonnell, 1998). Corneal swelling is attributed to imbibition or leak-in of water from the anterior chamber across the endothelium. Water flux across the epithelium is assumed unimportant due to the tight junctions and consequent high flow resistance of that layer (Fatt and Weissman, 1992). Water flow across the endothelium and into the cornea is driven by intraocular pressure (IOP) and, more importantly, by the tendency of the stroma to uptake water. Comprised of collagen fibrils with interspersed anionic glycosaminoglycans (Fatt and Weissman, 1992; Ruberti and Klyce, 2002), the human stroma behaves like a hydrogel. Water imbibes until swelling is prevented by a confining stress and is quantified by a swelling-pressure isotherm (Hedbys and Dohlman, 1963; Hedbys and Mishima, 1966). Without confining stress, the stroma swells to large hydrations (Fatt and Weissman, 1992). Excess swelling increases the distance between collagen fibrils and leads to corneal opacity (Fatt and Weissman, 1992).

To maintain a transparent cornea, Maurice (1972, 1984) argued that the swelling-pressure-driven water leak into the stroma is matched by a pump-out process located at the endothelium. Since the stromal swelling-pressure isotherm is uninfluenced by dissolved oxygen, the processes by which hypoxia controls corneal thickness reside primarily at the endothelium. Maurice (1972) suggested the presence of an active ion pump that lowers the

osmolarity at the basolateral endothelium relative to that in the aqueous humor. The resulting osmotic-pressure difference across the endothelium drives fluid from the stroma into the aqueous humor. Hodson and Miller (1976) suggested bicarbonate ion as a source of the active ion pump. Neither Maurice (1972) nor Hodson and Miller (1976), however, examined the influence of hypoxia on fluid pump-out rates. Indeed, a detailed biochemical description of the endothelial pump-out process remains elusive (Bonanno, 2003; Fischbarg and Diecke, 2005).

A mathematical model of the pump-leak mechanism was first devised by Klyce and Russell (1979). They considered a single neutral aqueous solute (i.e., undissociated aqueous NaCl), and endothelial and epithelial sodium-chloride-ion pumps. They adopted the Kedem and Katchalsky (1958) formalism of membrane transport (KK) across the entire cornea including the endothelium, stroma, and epithelium. An alternate three-phase pump-leak model, including a Donnan description of the corneal stroma, was later proposed by Bryant and McDonnell (1998). More recently, the Klyce-Russell model was extended by Li et al. (2004) and Li and Tighe (2006) to include dissolved ionic species. None of these modeling efforts, however, address how hypoxia at the anterior corneal surface might lead to edema.

In 1981, Klyce demonstrated both experimentally and theoretically that corneal swelling is produced through an osmotic imbalance resulting from increased production of lactate ions during hypoxia. Klyce (1981) extended the earlier theoretical model of Klyce and Russell (1979) to include a neutral aqueous lactate species and showed that the water pump-out rate was reduced by empirically increasing lactate concentration. Corneal edema ensued. Huff and coworkers (Rohde and Huff, 1986; Huff, 1991) provided experimental confirmation for rabbit corneas exposed to a hypoxic environment. Upon inhibiting lactate dehydrogenase, lactic-acid production was stifled, and edema was prevented. Again, none of these studies self-consistently related hypoxia to edema.

In all cases to date, no attempt has been made to quantify corneal edema arising from oxygen deficiency. Researchers who mathematically model oxygen behavior in the cornea make no predictive connection to the clinical measurement of corneal edema. Hence, there is considerable debate as to what constitutes safe oxygen levels in the cornea (Efron and Brennan, 1987ab; Fatt, 1987; Benjamin, 1993; Fatt, 1993; Fatt and Ruben, 1993; Fatt, 1996; Chhabra et al., 2009). Similarly, researchers who investigate corneal edema make no predictive connection to oxygen deprivation. The goal of this work is to provide a self-consistent quantitative model of cornea edema based on oxygen metabolism and transport.

Two clues from previous works provide the foundation. First, Chhabra et al. (2009) considered oxygen diffusion in the cornea, including aerobic and anaerobic glucose-consumption reactions. As oxygen concentration falls, anaerobic production of lactate ions and buffering by bicarbonate ions both increase. Metabolic reactions thus connect transport of oxygen, bicarbonate ions, and lactate ions. Second, the seminal effort of Klyce (1981) and later extensions (Li et al., 2004; Li and Tighe, 2006) addressed corneal swelling based on simultaneous transport of salt, lactate, and water. Chhabra et al. (2009) did not consider the transport of NaCl or water and, hence, could not address corneal edema under conditions of epithelial hypoxia. We combine the approaches of Klyce (1981) and Chhabra et al. (2009) to

predict corneal edema. By reducing oxygen supply to the cornea, soft-contact-lens wear diminishes aerobic respiration of glucose. The cornea resorts to a higher amount of anaerobic respiration for its energy needs. In turn, corneal lactate ion production and bicarbonate-ion influx increase. Basolateral-endothelium osmolarity increases, and the osmotic-driven water-efflux rate into the anterior chamber diminishes. The result is edema because swelling of the stroma lowers the water leak-in rate to match the lower pump-out rate.

We calculate steady-state concentration profiles of oxygen, carbon dioxide, glucose, lactate ion, hydrogen ion, bicarbonate ion, sodium ion, and chloride ion, in addition to water hydration, pressure, and electrostatic potential. The proposed framework explains how epithelial hypoxia induces corneal edema. For the first time, we quantify self-consistently the so-called Holden–Mertz curves of corneal thickness (i.e., hydration) versus Dk/L of SCLs (Holden and Mertz, 1984; Fonn and Bruce, 2005).

2. Biophysical formalism

As illustrated in Fig. 1, we adopt a one-dimensional geometry for the corneal system subdivided into the anterior chamber (AC), endothelium (En), stroma (St), epithelium (Ep), and tear film (TF). With lens wear, a postlens tear film (PoLTF), a soft contact lens (CL), and a prelens tear film (PrLTF) are included. Two layers in the cornea, Bowman's layer and Descemet's membrane, are not treated separately because of their small effect on transport (Ruberti and Klyce, 2002). The aqueous humor and prelens tear film serve as well-mixed bounding chambers. Detailed cellular structure of the various corneal layers is not recognized. The endothelium (5 μm) is approximated as an infinitesimally thin membrane and is described by Kedem and Katchalsky (1958) (KK) theory. The stroma (~450 μm) is considered a continuum. The epithelium, however, is conceptually divided into two parts: a continuum of 50- μm thickness and an infinitesimally thin membrane located at the boundary between the epithelium and the tear film. The epithelial membrane reflects the transport resistance of the plasma membranes, as described by the KK equation. Only the thickness of the stroma changes during swelling. We ignore possible swelling of the endothelium and epithelium. Physical parameters of the corneal system are given in Tables 1–4.

2.1. Corneal metabolism

As illustrated in Fig. 2, corneal metabolic reactions provide the foundation for understanding how oxygen influences edema. Following Chhabra et al. (2009), we adopt the two principal metabolic reactions of aerobic glycolysis through the tricarboxylic acid cycle (TCA or Krebs) and anaerobic glycolysis through the Embden-Meyerhof pathway (Fatt and Weissman, 1992). Minor metabolic reactions include the hexose-monophosphate shunt involving the generation of 5-carbon sugars, as well as a sorbitol pathway producing fructose and sorbitol. For simplicity, both are neglected. Additionally, we assume that all glucose required for metabolism is supplied from the anterior chamber. In actuality, about 10% of corneal glucose supply comes from glycogen and endogenous glucose (Riley, 1969).

Aerobic respiration involves the reaction of 1 mol of glucose and 6 mol of oxygen to produce 6 mol of carbon dioxide and 6 mol of water, along with 36 mol of adenosine triphosphate (ATP)

Anaerobic respiration to produce lactic acid is less energy efficient yielding only 2 mol of ATP per mole of glucose consumed

Because the pK_a of lactic acid is 3.87 at body temperature, lactic acid is almost entirely present as lactate and hydrogen ions at the physiologic pH of 7.6 (Lin et al., 2000). For a healthy cornea, about 85% of the breakdown of corneal glucose occurs via anaerobic glycolysis while the remainder is via aerobic reaction (Riley, 1969; Maurice and Riley, 1970; Freeman, 1972). We assume this same reaction proportion as a baseline for metabolism in the healthy, closed eye. As oxygen concentration falls, anaerobic respiration increases. To quantify this increase, we adopt the observation of Klyce (1981) that anaerobic lactate-acid production doubles in rabbit eyes exposed to epithelial hypoxia as discussed by Chhabra et al. (2009).

Acidification of the cornea due to Reaction (2) is significantly mitigated by buffering with bicarbonate ion to produce dissolved carbon dioxide

In the cornea, Reaction (3) is catalyzed by carbonic anhydrase (Wistrand et al., 1986; Conroy et al., 1992). We assume that the forward and backward reaction rates in Eq. (3) are fast so that local equilibrium is established.

Reactions (1)–(3) are critical to understanding how oxygen influences corneal swelling. During hypoxia, the rate of lactate-ion production from Reaction (2) increases (Klyce, 1981) causing lactate ion concentration to rise throughout the cornea. Since little lactate crosses the tight junctions of the epithelium (Klyce, 1981), there is a corresponding increase in efflux of lactate ion into the anterior chamber. The increased lactate-ion concentration from Reaction (2) is accompanied by increased corneal acidosis. To protect against a significant rise in acid concentration, bicarbonate ions are drawn into the cornea from the anterior chamber by the buffering Reaction (3). CO_2 produced both by aerobic glycolysis in Reaction (1) and by buffering in Reaction (3) leaves the cornea both through the epithelium and through the endothelium (Fatt, 1968; Fatt and Bieber, 1968; Chhabra et al., 2009). Connection to corneal swelling is two-fold. The endothelial-bicarbonate active ion pump lowers the osmolarity at the endothelial/stroma interface and induces water outflow in the pump-leak mechanism. Subsequently, the rise in lactate-ion concentration and resulting increased osmolarity at the endothelium during hypoxia lowers the fluid pump-out rate by reducing the osmotic driving force.

2.2. Fluid pump

The fluid pump refers to an overall process that expels water from the stroma into the anterior chamber. Definitive evidence exists that the machinery for water expulsion originates at the endothelium (Maurice, 1972; Hodson 1974). There is also considerable evidence that bicarbonate ions are involved in the pumping process (Hodson and Miller, 1976; Bonanno, 2003; Fischbarg and Diecke, 2005). Molecular detail of how the pump operates, however, remains clouded. Current thinking (Bonanno, 2003) is summarized in Fig. 3. The $3\text{Na}^+/2\text{K}^+$ - ATPase active electrogenic transporter (labeled as ATP) exports 3 Na^+ ions out of the intracellular matrix for every 2 K^+ ions drawn in, both against their chemical-potential gradients. The net cellular charge-loss contributes to a negative electrostatic potential measured at about -50 mV relative to zero potential at the basolateral/stroma interface (Lim and Fischbarg, 1981; Bonanno, 2003; Fischbarg and Diecke, 2005). To maintain steady state, potassium ions escape through a uniporter. Due to favorable concentration and potential differences, sodium ions enter via the $\text{Na}^+/2\text{HCO}_3^-$ secondary active cotransporter (labeled as NBC1). Bicarbonate ions are co-imported. These catalytically neutralize hydronium ions via carbonic anhydrase (labeled as CA), allowing some HCO_3^- to exit through the apical plasma membrane in the form of CO_2 . Concomitantly, bicarbonate (and chloride) ions directly exit across the apical membrane via passive uniporters (labeled as CaCC and CFTR). The remaining ion channels in Fig. 3 do not strongly impact the transport of bicarbonate ions through the endothelium. Their descriptions and behavior may be found in Bonanno (2003) and Fischbarg and Diecke (2005).

Although molecular detail of the endothelial transporters is not complete (Bonanno, 2003), the net result is an active component of bicarbonate-ion flux directed from the stroma toward the anterior chamber. The resulting efflux of bicarbonate ions across the endothelium lowers the osmolarity at the basolateral/stromal interface relative to that in the aqueous humor. As a consequence of this active ion transport, water is osmotically driven across the endothelium toward the anterior chamber. The driving force for the endothelial-osmotic water outflow arises in the free energy released upon converting ATP to ADP in the Na^+/K^+ active ion pump. Maurice (1972) referred generically to this process as the “fluid pump.” If either the Na^+/K^+ - ATPase ion pump is blocked or all sources of bicarbonate ion (including carbon dioxide) are replaced (Hodson, 1974; Bonanno, 2003), the fluid pump ceases (Hodson, 1974; Bonanno, 2003).

Excess lactate ion is produced in the cornea during epithelial hypoxia. This process raises the osmolarity at the stroma/endothelium interface, thus lowering the endothelial/AC osmotic-pressure difference (Klyce, 1981). Consequently, less water is driven out of the stroma. Corneal swelling ensues to a larger stromal hydration where the lower pump-out rate is compensated by a smaller leak-in rate. Fischbarg and Diecke (2005) present a similar picture of the isolated endothelial fluid pump, except they hypothesize that the water efflux is by electro-osmosis through the tight junctions rather than by aquaporin channels shown in Fig. 3 (labeled as AQP1). Importantly, there is dispute about the mechanism of fluid transport for secretory cells in general. Theories utilizing osmosis or electro-osmosis have both been proposed (Zeuthen, 2002). We adopt an osmotic driving force to describe water

pump-out across the endothelium as embodied in the KK phenomenological membrane-transport formalism.

We emphasize that most cell-biology studies of fluid and ion transport across the corneal endothelium consider isolated cell layers with isotonic solutions bathing both the apical and basolateral membranes. They do not consider how endothelial cells behave in the whole corneal system. Hence, the net directions of the various ion fluxes in Fig. 3 are not necessarily correctly captured when the endothelium is part of a live cornea. For example, although there is an identified active transport of bicarbonate ions toward the anterior chamber, the net transport of bicarbonate ions is toward the stroma, as demanded by Reactions (2) and (3).

We ignore the specific ion channels in Fig. 3 and treat the endothelium as an infinitesimally thin membrane that obeys the KK equations. For bicarbonate ions, however, the KK flux includes an active component (i.e., directed against the chemical-potential gradient). Following others (Klyce and Russell, 1979; Li and Tighe, 2006), we take the active bicarbonate-ion endothelium flux as a constant. To capture measured voltage profiles across the cornea, we similarly include an active pump of chloride ion at the epithelial membrane (Klyce, 1975). The active epithelial chloride-ion efflux, however, is small.

3. Mathematical representation

To predict the degree of stromal swelling due to hypoxia at the cornea anterior surface, all species in the metabolic process must be described. Following Chhabra et al. (2009), these are oxygen, glucose, carbon dioxide, and lactate, hydrogen, and bicarbonate ions. In addition, water and the majority salt species, NaCl, must be included. Minority solutes, potassium and hydroxide ions, for example, are neglected. Since aqueous ion transport is present, the electrostatic potential, ψ , enters the problem. Because the cornea is thin relative to its radius of curvature, and because the corneal limbus makes only a small contribution to the lateral transfer of solutes (Fatt and Weissman, 1992; Takatori and Radke, in press), we adopt a one-dimensional model in which all species transport normal to a flat corneal surface. Foundational equations are summarized briefly below. Detailed equations are available in Appendix A.

3.1. Water flux

In the pump-leak mechanism, water imbibition into the stroma is balanced by the endothelial fluid pump. At steady state, however, it is not necessary that these two flows exactly match. Indeed, in agreement with Klyce and Russell (1979), we predict a small net weeping of water directed from the anterior chamber toward the prelens tear film.

Water transport across the endothelial and epithelial membranes is given by (Kedem and Katchalsky, 1958)

$$J_v = -L_p \left[\Delta P - \sum_{i \neq w} \sigma_i (RT \Delta C_i + z_i \langle C_i \rangle F \Delta \psi) \right] \quad (4)$$

Here, J_v is the volumetric flux or superficial velocity of water in the x -direction of Fig. 1. L_p is the hydraulic transmissibility of the membrane, P is the hydraulic pressure difference across the membrane, σ_i is the reflection coefficient of solute i , R is the ideal gas constant, T is absolute temperature, F is Faraday's constant, z_i is the valence of solute i , and ψ is the electrostatic-potential difference across the membrane. C_i is the i th-solute fluid concentration difference across the membrane, and $\langle C_i \rangle$ is the logarithmic-mean fluid concentration of solute i across the membrane. All concentrations are per unit volume of fluid. The first term in the brackets on the right of Eq. (4) describes the imbibition flow of water driven by the swelling tendency of the stroma (i.e., the leak-in rate). The second term on the right describes the flow of water due to osmotic-pressure and electrostatic-potential differences (i.e., the pump-out rate). The summation in Eq. (4) is overall solute species. A minus sign appears in the front of Eq. (4) since the differences in pressure, concentration, and potential are in the direction of increasing x . Eq. (4) serves as boundary conditions for water at $x = 0$ (the endothelium) and at $x = L_T$ (the epithelium membrane) where L_T is the total thickness of the cornea. Steady mass conservation of water applies in the stroma and epithelium

$$-\frac{dJ_v \rho_f / M_w}{dx} + Q_w = 0 \quad (5)$$

where ρ_f is the fluid mass density, M_w is the molecular weight of water, and Q_w is the net molar production rate of water from Reactions (1) and (3).

To describe fluid flow in the stroma and epithelium, we adopt Darcy's law (Fatt and Goldstick, 1965)

$$J_v = -\frac{K}{\mu} \frac{dP}{dx} \quad (6)$$

where K is the hydraulic permeability of the stroma or epithelium and μ is the fluid viscosity. Water flow conductivities, K/μ , are available from Fatt and Goldstick (1965) for the stroma, and from Mishima and Hedbys (1967) for the epithelium. As outlined in Appendix A, Eq. (6) in the stromal region is supplemented by information on the swelling-pressure isotherm.

Since stromal thickness changes during swelling, a fixed x coordinate cannot be used directly in Eqs. (5) and (6). Thus, for the stromal domain, we utilize a coordinate system based on the dry stromal tissue, first introduced by Fatt and Goldstick (1965). Appendix A gives the details. Since swelling in the epithelium is neglected, we retain the x coordinate in that region.

3.2. Solute fluxes

At the endothelial and epithelial boundaries, KK-flux equations are written for glucose and lactate, bicarbonate, hydrogen, sodium, and chloride ions (Kedem and Katchalsky, 1958)

$$J_i = (1 - \sigma_i) J_v \langle C_i \rangle - \omega_i (RT \Delta C_i + z_i \langle C_i \rangle F \Delta \psi) + J_{ai} \quad (7)$$

where J_i is the molar flux of species i , ω_i is the membrane permeability of solute i , and J_{ai} is an active flux (directed against a chemical- potential gradient). The sign convention in Eq. (7) is the same as that in Eq. (4): all differences are in the direction of increasing x . The first term on the right of Eq. (7) reflects solute transport across the membrane by convection. The second and third terms correspond to molecular diffusion and electrical migration, respectively. Active fluxes are written only for bicarbonate ions at the endothelium membrane ($x = 0$) and for chloride ions at the epithelial membrane ($x = L_T$). By the chosen sign convention, J_{ai} is positive for chloride ions and negative for bicarbonate ions.

Oxygen and carbon dioxide passively diffuse across both the endothelial and epithelial membranes. Their transport behavior at these two membranes is described by the KK equation with zero valence.

In the bulk stromal and epithelial domains, all solute species are conserved

$$-\frac{dJ_i}{dx} + Q_i = 0 \quad (8)$$

where Q_i is the net molar production rate per unit tissue volume for those solute species that react (i.e., oxygen, glucose, carbon dioxide, lactate ions, bicarbonate ions, and hydrogen ions). We utilize the rate expressions pioneered by Chhabra et al. (2009). Implicit in these kinetic expressions is the assumption that keratocytes and epithelial cells are evenly distributed.

The flux of all solute species in the stroma and epithelium obeys the Nernst–Planck equation (Newman and Thomas-Alyea, 2004):

$$J_i = C_i J_v - D_i \frac{dC_i}{dx} - z_i D_i C_i \frac{F}{RT} \frac{d\psi}{dx} \quad (9)$$

The three terms on the right of Eq. (9) correspond, respectively, to convection, molecular diffusion, and electrical migration. Molar concentrations, C_i , appearing in Eq. (9) are per unit volume of fluid. Again, for the stromal region, the x coordinate is abandoned in favor of a constant dry-mass coordinate. Detailed description of the conservation equations for each species is given in Appendix A.

We demand local electroneutrality ($\sum_i z_i C_i = 0$) and enforce continuity of species flux and pressure at the endothelium/stroma and stroma/epithelium boundaries. Zero net current is imposed at the endothelium membrane ($\sum_i z_i J_i = 0$). The epithelial membrane is considered impermeable to glucose and to lactate ion (Chhabra et al., 2009). Diffusive resistance of oxygen is considered in the soft contact lens. However, we do not account for aqueous sodium-chloride (Guan et al., 2011), hydronium ion, and water (Fornasiero et al., 2008; Boushehri et al., 2010) gradient-driven transport resistance in the lens. Water hydraulic flow across the SCL is zero because of the high resistance to pressure-driven flow (Monticelli et al., 2005). Additional detail on the boundary conditions is relegated to Appendix A.

Appendix B outlines the choice of parameters appearing in the model along with the physical constants adopted. All parameters and simulations correspond to physiologic temperature of 35 °C.

Species conservation and flux equations (Eqs. (4)–(9)) with attendant boundary conditions are discretized in space using centered finite differences and solved using Newton iteration. Appendix C outlines the numerics.

4. Results and discussion

To gain insight into hypoxic edema, we present steady concentration profiles of the various species modeled in the system. Open and closed-eye cases are compared with no-lens wear that we approximate by solving with a contact lens in place but with $Dk/L = 10^4$ hBarrer/cm. Truncated vertical lines locate the various domain boundaries. The coordinate system commences at the anterior chamber/endothelium (AC/En) interface, as pictured in Fig. 1. As discussed in Appendix B, the total osmolarity in the open-eye tear is taken as 308 mOsM relative to 300 mOsM in the anterior chamber. The 308 mOsM value accounts for tear evaporation during interblinks (Gilbard and Cohen, 1992).

4.1. Glucose profiles

Calculated glucose profiles across the cornea are shown in Fig.4 for open (dashed line) and closed eye (solid line). Glucose is provided to the eye from the anterior chamber at about 7 mM. It provides the energy needs for corneal health producing ATP in the Krebs cycle of Reaction (1). Some of that energy is consumed in driving the sodium-potassium electrogenic active ion channel in Fig. 3. There is a significant drop in glucose concentration across the endothelium due to the Kedem–Katchalsky (KK) membrane-transport resistance. Glucose then convects and diffuses toward the epithelium while metabolizing according to Reactions (1) and (2). Tight junctions of the epithelium prevent glucose transport into the tear film, enforced here by a zero-flux boundary condition (i.e., zero slope) consistent with the low glucose concentrations found in the tear film. Our model predicts that glucose in the cornea is not in excess (Chhabra et al., 2009).

The smaller concentrations of glucose in the closed eye (solid line) indicate more consumption during sleep. When the eye is closed, more glucose is consumed along the anaerobic pathway. Increased anaerobic production of lactic acid also decreases corneal pH. Accordingly, a higher rate of aerobic glucose consumption is required (Harvitt and Bonanno, 1998). Both effects lead to larger glucose consumption under closed-eye conditions.

Anaerobic glucose consumption is inefficient, since Reaction (2) produces only one-eighteenth as much ATP per mole of glucose compared to aerobic respiration. We do not explicitly account for ATP in the model. However, the lower energy efficiency of Reaction (2) is embodied in the Monod constants of Eqs. (A15) and (A16). Specifically, the highest glucose consumption rate due to anaerobic respiration is larger than that of aerobic respiration. Hence, more glucose is needed during hypoxia to maintain the energy needs of

the cells. Finally, note that the swelling extent of the stroma is larger in closed eye. Even with no-lens wear, the cornea swells during sleep (Mandell and Fatt, 1965).

4.2. Oxygen profiles

Fig. 5 shows oxygen-tension profiles across the cornea for open (dashed line) and closed eye (solid line). As a consequence of consumption, oxygen profiles trend downward from both the TF and AC toward the center of the cornea. During open eye, the slope of the oxygen profile at the epithelium is steep, implying a high amount of oxygen influx from the atmosphere; the slope of the profile near the aqueous humor is shallow in comparison, implying that aqueous-humor oxygen supply is small. During closed eye, oxygen tensions are everywhere lower as a result of the low oxygen content of the palpebral conjunctiva relative to air (61.5 mmHg versus 155 mmHg tension). As a result of Monod kinetics in Eq. (A11) (i.e., zero oxygen consumption in the limit of low oxygen concentration), oxygen tensions never reach zero (Chhabra et al., 2009). Perhaps surprisingly, the closed eye, even with no-lens wear, tends toward zero oxygen tension over a sizable portion of the cornea. Fortunately, both the epithelium and endothelium remain oxygenated due to proximity to the tear film and anterior chamber, respectively. Again, swelling of the stroma is clearly evident in the closed-eye case.

4.3. Carbon-dioxide profiles

Fig. 6 displays the calculated carbon-dioxide tension profiles during open (dashed line) and closed (solid line) eye. In open eye, carbon dioxide is produced by aerobic metabolism (Reaction (1)) and exits into the tear film and anterior chamber. When the eye is closed, tear-film CO_2 tension rises to that in the anterior chamber, about 38 mmHg. Accordingly, the overall level of carbon dioxide rises throughout the cornea. Moreover, there is a definitive maximum in the tension profile near the middle of the cornea. This maximum indicates a net larger production of CO_2 in the closed eye compared to that in the open eye. The reason is understood from Reactions (2) and (3). During closed-eye hypoxia, more glucose reacts to form lactate and hydronium ions. Excess hydrogen ions are buffered by a net input of bicarbonate ions from the anterior chamber. These, in turn, produce carbon dioxide according to the equilibrated Reaction (3). CO_2 product diffuses both toward the endothelium and toward the epithelium emerging across each membrane. A small tension decline in CO_2 concentration is seen at the epithelial membrane due to diffusion resistances in the membrane, SCL, and tear films. Note that buffering against acidosis demands a net input of bicarbonate ion from the AC. This means that the efflux of bicarbonate ion toward the AC pictured in Fig. 3 does not hold when the endothelium acts in consort with the whole live cornea.

4.4. Bicarbonate-ion profiles

Corresponding bicarbonate-ion profiles are presented in Fig. 7. As discussed in Appendix B, the concentration of bicarbonate ion in the aqueous humor is set at 36 mM, whereas that in the TF is 12.4 mM for open-eye conditions (Rismondo et al., 1989). Bicarbonate ion transports from the anterior chamber toward the tear film with only minimal egress. The large concentration drop across the endothelium arises because of the KK-membrane-

transport resistance. Despite the opposing active-flux component due to the bicarbonate-ion pump (i.e., J_{aB}), the net flux of bicarbonate ion is from the anterior chamber into the cornea.

Various components of the endothelium bicarbonate-ion flux are illustrated in the bar graph of Fig. 8. Positive flux indicates transport into the cornea (in the positive x -direction) and *vice versa*. Open bars correspond to open eye while filled bars correspond to closed eye. Labels on the bars designate the corresponding flux contributions in Eq. (7). The active-pump drives bicarbonate ion out of the stroma and into the AC, as portrayed in Fig. 3. Active pumping lowers the bicarbonate-ion concentration at the En/St interface. To overcome the membrane-transport resistance, a large favorable concentration difference and a small electrostatic-potential difference arise to drive bicarbonate ion into the cornea, allowing bicarbonate to buffer against acidosis. Convective flow makes no reportable contribution.

It is generally accepted that the flux of bicarbonate ion across the endothelium is directed from the stroma into the aqueous humor (Hodson and Miller, 1976; Bonanno, 2003; Mergler and Pleyer, 2007). Our results indicate otherwise. We indeed include a bicarbonate-ion efflux into the AC from the active-pump component to flux, as illustrated in Figs. 3 and 8. When the endothelium is placed next to the swelling stroma in a live cornea, however, the net flux of bicarbonate ion is into the cornea. This net inflow is due to buffering against acidosis and to maintenance of electroneutrality, both arising from hypoxic lactic-acid production. Because lactate ion is assumed not to penetrate the epithelial membrane, all produced lactate must exit through the endothelium. To counterbalance the resulting outflow of lactate anions, there must be a net flow of other anions (in excess of cations) into the cornea at the AC. Sodium and chloride ions do not participate in the metabolic reactions, so their contributions to current do not directly respond to hypoxia. Rather, bicarbonate ions are forced to enter the cornea from the AC to maintain overall electroneutrality (i.e., zero net current).

Bicarbonate-ion concentration in Fig. 7 gradually declines through the stroma and epithelium. At the Ep/TF interface, however, another abrupt concentration difference arises due to the epithelial-membrane-transport resistance. The bicarbonate-ion flux remains directed toward the tear film. Fig. 9 gives the driving-force contributions to total HCO_3^- flux at the epithelium membrane. Compared with the total bicarbonate-ion flux across the endothelium, corresponding values at the epithelial membrane/TF interface are about 2 orders of magnitude smaller. The much smaller net flux across the epithelium arises from reactive loss of bicarbonate ion in buffering and from the large transmembrane resistance of the epithelium. At the epithelial membrane, the electrostatic-potential difference drives bicarbonate ion into the cornea, whereas convective water efflux, J_v , and a favorable concentration difference combine to transport bicarbonate ion into the tear film, but at an extremely small rate. Effectively, there is no flux of bicarbonate ion into the tear. As opposed to the endothelium, there is no active pump of bicarbonate ion at the Ep/TF interface.

4.5. Lactate-ion profiles

Fig. 10 shows the predicted lactate-ion profiles across the cornea for open and closed eye. Lactate is produced from anaerobic respiration and must leave the cornea. However, the resistance to cross the epithelial membrane is large. Effectively, lactate ion does not transport into the tear film. Accordingly, we set the flux of lactate ion at the Ep/TF boundary to zero, making the profiles horizontal at that location. Lactate ion then exits into the AC where the concentration is about 8 mM. The large drop in concentration from the stroma across the endothelium is due to membrane-transport resistance.

Lactate-ion concentrations are noticeably higher in the closed eye because of increased anaerobic respiration. As noted above, almost all glucose consumed in the closed eye occurs via the Embden-Meyerhof pathway pictured in Fig. 2. The rise in lactate-ion concentration at the basolateral side of the endothelium during closed eye is larger than the corresponding fall in bicarbonate-ion concentration (see Fig. 7). Compared to basolateral lactate and bicarbonate-ion concentrations, all other solute concentrations change little upon closed-eye hypoxia. Hence, the total osmolarity at the En/St interface rises. Basolateral rise in osmolarity lowers the osmotic-pressure difference across the endothelium and lowers the water pump-out rate in Eq. (4). By swelling the stroma to a lower imbibition pressure, the pressure difference across the endothelium falls and lessens the water leak-in rate in Eq. (4). The corresponding lower leak-in rate matches the lower pump-out rate. We also find that to maintain zero current, lactate-ion efflux at the stroma posterior almost exactly equals the bicarbonate ion influx. This observation provides additional support for the net inward flow of bicarbonate ion from the AC.

There is a noticeable difference between our lactate-ion profiles and those of Chhabra et al. (2009). Specifically, the model of Chhabra et al. (2009) adopts Fickian molecular diffusion to account for the lactate-ion transport across the endothelium. In a Fickian model, the endothelium is too thin to produce a sharp concentration gradient. We, however, treat the endothelium as an infinitesimally thin membrane obeying the Kedem–Katchalsky relation. Consequently, we predict a much larger change in lactate-ion concentration. Giasson and Bonanno (1994b) measured the steady state, space-averaged lactate-ion concentration in the closed eye to be roughly 14 mM, which the model of Chhabra et al. (2009) does not reproduce. Use of the Kedem–Katchalsky expression (Eq. (7)) allows our predictions for lactate ion to be consistent with those measured by Giasson and Bonanno (1994b). For the same reason, the concentration changes of bicarbonate ion across the endothelial and epithelial membranes in Fig. 7 are larger than those of Chhabra et al. (2009).

4.6. pH profiles

Fig. 11 gives the steady pH profiles across the cornea. Anaerobic respiration is high during closed eye due to the lower oxygen levels. Because of the resulting increased generation of hydrogen ions, pH profiles are lowered. In both open and closed-eye conditions, predicted pH values are somewhat lower than measured space-averaged values (Bonanno and Polse, 1987b; Giasson and Bonanno, 1994a), possibly because of uncertainties in model parameters and/or in experimental data. Predicted pH values in the epithelium for open eye are more alkaline than expected. For open eye, the low CO_2 concentration of the environment and

local equilibrium (Eq. (A19)) demand low hydrogen-ion concentrations. In the cornea and tear, however, other buffering solutes not accounted for in our model, such as proteins and polyelectrolytes, contribute to buffering capacity (Carney et al., 1989). We set the tear film pH to 7.6 (Fischer and Wiederholt, 1982) and elsewhere consider buffering only by bicarbonate ion.

Bicarbonate-ion buffering is crucial to corneal health. If buffering in Reaction (3) is inhibited, our model predicts a pH in the cornea of about 3 in both open and closed eye. It is the bicarbonate-ion influx from the AC that prevents such acidic conditions.

4.7. Electrostatic-potential profiles

Fig. 12 shows the potential profile across the cornea based on a zero reference in the tear. Relative to the tear and the AC, the cornea is positive migrating anions inward and cations outward. The voltage gradient is small across the stroma resulting in small migration fluxes. The endothelium voltage drop is also small, on the order of tenths of mV, in agreement with the low electrical resistance of the endothelium and with experiment (Bonanno, 2003). The epithelial membrane, however, is a high-resistance barrier. The predicted voltage difference between the epithelial membrane and tear is larger, about 5 mV.

Klyce (1975) measured voltage profiles across the cornea, being careful to differentiate between the different types of cells present in the corneal epithelium. Because we model the epithelium as a 50- μm thick continuous medium capped by a single infinitesimally thin membrane, we cannot reproduce the abrupt voltage jumps observed experimentally when transitioning between specific epithelial cell layers. Our model attributes the potential drop across the epithelium completely to the infinitesimally thin membrane at the Ep/TF interface.

As reported by Klyce (1975), an active chloride-ion pump is included at the epithelial membrane, directed from the epithelium to the tear. Thus, a positive chloride-ion flux, J_{aCl} , is included in the Kedem–Katchalsky epithelial-membrane equation. Omission of the chloride-ion active pump produces a negative corneal voltage relative to the tear, in disagreement with experiment Klyce (1975). Fortunately, the active chloride-ion pump rate is small and has little impact on swelling behavior.

4.8. Sodium and chloride-ion profiles

Figs. 13 and 14 display calculated sodium and chloride-ion profiles, respectively, across the cornea for the open (dashed lines) and closed eye (solid lines) with no-lens wear. Compared to the reactive ion species, sodium and chloride ions are at considerably higher concentrations, and their changes in concentration across the stroma and epithelium are smaller. Sodium ions transport from the AC toward the TF. Conversely, Fig. 14 suggests that chloride ion transports toward the AC. However, the net flux of chloride ion is toward the TF at a small value of about 10^{-11} mol/cm²/s. For chloride ion, the rise in positive electrostatic potential (see Fig. 12) in the cornea and epithelium conducts anions toward the TF. When combined with the small convective flux in that direction, electrical migration over-compensates the opposing concentration gradient. For sodium ion, the flux is also

positive, but the driving-force contribution of electrostatics is oppositely directed. Electrical migration transports cations toward the AC, but the diffusive concentration gradient augmented by the small positive convective flux over-compensate to give a small net positive flux toward the TF. Only minor changes in the sodium and chloride-ion profiles are evident when the cornea is hypoxic in closed eye relative to open eye.

Large concentration jumps are seen at the endothelial and epithelial membranes in Figs. 13 and 14 due to significant transport resistances embodied in the KK equations. Sodium ion has an adverse concentration gradient at the epithelial membrane, whereas chloride ion must overcome adverse concentration gradients at both the endothelial and epithelial membranes.

Figs. 15 and 16 give flux contributions for aqueous Na^+ and Cl^- at the endothelium. Here, sodium ion enters into the cornea from the AC by diffusion and against an adverse electrostatic gradient. Conversely, chloride ion enters via a favorable electric-potential gradient and against a concentration gradient.

Figs. 17 and 18 give the corresponding flux contributions for aqueous Na^+ and Cl^- at the epithelial membrane. Although the net flux of sodium and chloride ions is the same as that at the endothelium (and as that in the stroma and epithelium), the contributions to those fluxes are much smaller and differently distributed. This is because salt permeability of the epithelial membrane is much smaller than that of the endothelium by a factor of about 100 (Klyce and Russell, 1979). Epithelial-membrane sodium ions are carried into the TF by convection and migration. The large adverse concentration gradient has less influence because of the large diffusive resistance of apical epithelial cells. Likewise, the adverse concentration gradient for chloride-ion transport across the epithelial membrane makes little contribution to Cl^- flux. Rather, convection and the active ion pump move chloride ion from the epithelium into the TF.

4.9. Water-hydration profiles

Fig. 19 shows water-hydration profiles across the stroma for no-lens open and closed eye. Our model predicts a small, linearly decreasing water-hydration profile across the stroma. This decline is consistent with experiments showing that the anterior stroma exhibits lower water content than that of the posterior stroma (Turss et al., 1971; Edelhauser, 2006). The negative slope of the hydration profiles indicates a net flow of water from the AC to the TF. Clearly, the stroma extends farther along the x -axis in closed eye confirming corneal swelling during sleep, as seen in all profiles presented above. Due to evaporation, tear-film osmolarity in the open eye is higher than that in the closed eye, drawing more water through the cornea.

Fig. 20 displays the corresponding pressure profiles across the cornea in open and closed eye. There is a large pressure drop for water transport across the endothelium, and an even larger one for flow across the high-resistance epithelial membrane. By comparison, flow through the stroma is relatively unimpeded.

Fig. 21 accentuates the differing components of the volume flux at the endothelium along with the total water flow. As with Figs. 8 and 9, a positive flux indicates transport toward

the TF, whereas a negative flux indicates travel toward the AC. Labels on the bars designate the three driving-force terms in the KK equation for water flow (Eq. (4)). Thus, stromal swelling pressure (P), and to some extent, the electrostatic potential (ψ) pull water into the cornea (leak-in), whereas osmotic pressure (π) forces water into the AC (pump-out). Leak-in and pump-out rates do not balance exactly. A small, net water flux of about $1 \mu\text{L}/\text{cm}^2/\text{h}$ is predicted in the direction of the aqueous humor to the tear film. This value is in agreement with that calculated by Fatt and Weissman (1992). It is about 20% of normal subjects' tear-evaporation rate, or $5.5 \mu\text{L}/\text{cm}^2/\text{h}$ at 40% relative humidity (Mathers, 2004; Tomlinson et al., 2009). From Fig. 21, a pump-out rate of about $12 \mu\text{L}/\text{cm}^2/\text{h}$ is required to balance the fluid leak-in flux. Typical values cited for the isolated endothelial pump-out rates of rabbit cornea are $6\text{--}10 \mu\text{L}/\text{cm}^2/\text{h}$ (Fischbarg et al., 1977; Baum et al., 1984; O'Neal and Polse, 1985). The main component of the pump-out rate is the osmotic-pressure difference across the endothelium. Because of the active bicarbonate-ion pump, the osmolarity at the basolateral side of the endothelium is lower than that at the apical side. This difference draws water into the AC to balance closely the outflow due to the suction pressure of the stroma.

In closed eye (filled bars), the osmotic pump-out rate decreases compared to that in open eye (open bars). Increased lactate-ion concentration at the endothelium/stroma interface (see Fig. 10) relative to the corresponding decrease in bicarbonate-ion concentration (see Fig. 7) increases the osmolarity adjacent to the basolateral plasma of the endothelium. The resulting smaller osmotic-pressure difference across the endothelium reduces the osmotic pump-out rate.

Fig. 22 shows the corresponding water-flux components at the epithelium. Since aerobic respiration and bicarbonate buffering generate a small amount of water, the total flux from the epithelium into the TF is slightly greater than that from the AC into the stroma in Fig. 21. Compared to the endothelium, however, magnitudes are different for the various driving-force contributions. Stromal swelling pressure and electrostatic potential in Fig. 22 imbibe water across the epithelial membrane into the cornea. Conversely, osmotic-pressure drives water out of the cornea. The osmotic-driven efflux at the epithelial membrane is slightly larger than the pressure-driven influx, confirming a small net water flow into the tear.

4.10. Contact-lens oxygen transmissibility

Fig. 23 compares oxygen profiles for no-lens and lens wear in open (dashed lines) and closed eye (solid lines). Lens transmissibility is $Dk/L = 10 \text{ hBarrer}/\text{cm}$, typical of a HEMA soft contact lens. Oxygen profiles for higher values of Dk/L are similar to those of Chhabra et al. (2009). For the low- Dk lens in Fig. 23, a significant portion of the cornea experiences complete oxygen starvation, most apparent in closed eye. Especially important is the lowering of oxygen tension at the epithelium during contact-lens wear. Only the endothelium remains normoxic due to its proximity to the AC. With contact-lens wear, the stroma swells more than without lens wear, as seen by comparing the vertical-line markers at end of the stroma in Fig. 23. We do not display remaining solute concentration profiles for differing values of lens transmissibility because general behavior is as expected. For example, carbon dioxide and lactate-ion profiles in Figs. 6 and 10, respectively, shift upward

with decreasing Dk/L values, whereas profiles for oxygen in Fig. 23 and bicarbonate ion in Fig. 7 shift downward.

The predicted role of Dk/L in corneal swelling is portrayed in Figs. 24 and 25 for open and closed eye, respectively. Circles in these figures correspond to the experimental data of Holden and Mertz (1984). Solid lines give the model predictions using the parameters in Tables 1–4. Agreement between theory and experiment for corneal swelling is acceptable in view of the intricacy of the model, unavailability of measured values for some of the membrane coefficients appearing in the Kedem–Katchalsky equations, and human-subject variability (Efron, 1986; Hutchings et al., 2010). According to the model, the open-eye cornea is fully oxygenated above a Dk/L of about 40 hBarrer/cm. Experiment suggests that a lower value is sufficient.

For the closed eye in Fig. 25, the model suggests full oxygenation for a lens transmissibility above about 100–120 hBarrer/cm. Few lenses with these high values were available to Holden and Mertz (1984) so experimental confirmation is lacking. About 5% swelling is predicted for the closed eye with no-lens wear. This result is in reasonable agreement with the deswelling experiments of Mandell and Fatt (1965).

Some of the thickness change in Fig. 25 is due to the increased osmolarity of the open-eye tear film relative to that in the AC (Chan and Mandell, 1975; Ruberti and Klyce, 2002). During an interblink, some tear evaporates, increasing tear osmolarity (Gilbard and Cohen, 1992) and deswelling the cornea (Mandell and Fatt, 1965). Because evaporation ceases in the closed eye, we assume little to no osmolarity difference between the tear film and the anterior chamber and, therefore, no evaporation-induced osmotic deswelling. Hence, total swelling in the closed eye must be corrected for the natural-occurring osmotic swelling due to the closed-eye tear-film osmolarity falling from that of open eye to that in the AC.

To evaluate this effect in our model, we set the open-eye tear-film osmolarity to 308 mOsM compared to 300 mOsM in the AC. The dot-dashed line in Fig. 25 predicts about 2% osmotic swelling from an open eye (with osmotic deswelling) to a closed eye (with equal osmolarity at the anterior chamber and tear film). Swelling above this line is attributed to epithelial hypoxia.

Fig. 26 graphs as open circles measured oxygen tension in the PoLTF as a function of lens transmissibility (Benjamin, 1993). The solid line gives our model prediction with no further adjusted parameters. Agreement between theory and data is excellent.

4.11. Tear osmolarity

Increasing the tear salt concentration, such as with evaporative dry eye or artificial tear, leads to more corneal deswelling. Fig. 27 predicts the magnitude of this effect. When the osmolarity of tear in open eye with no lens is increased from 300 to 330 mOsM, the cornea shrinks by nearly 50 μm . Thus, tear hypertonicity reduces hypoxic swelling.

4.12. Parameter sensitivity

The proposed corneal-hydration model embodies a number of parameters including those describing the endothelial and epithelial membranes and those characterizing the stroma and epithelium (see Tables 2 and 3). Since the epithelium is highly resistant to species transport, hypoxic edema arises primarily from osmotic differences across the endothelium (Klyce, 1981). Hence, we find that endothelial KK parameters play important roles in model predictions.

With decreased lens transmissibility in the Holden–Mertz graphs of Figs. 24 and 25, we predict an osmotic-concentration buildup at the stroma/endothelium interface that leads to swelling. The increase in lactate-ion concentration at the stroma/endothelium interface due to increased hypoxic lactate generation exceeds the decrease in the summed bicarbonate ion and glucose concentrations demanded by the hypoxic increase in bicarbonate ion and glucose consumption. The overall result in the pump/leak mechanism is stromal swelling. Although trans-endothelial gradients of the other species, such as sodium and chloride ions, also change in hypoxic environment, their summed contribution to the endothelial-osmotic imbalance is small.

Accordingly, model sensitivity to endothelial KK parameters is anticipated for glucose, and bicarbonate and lactate ions. During closed eye with no-lens wear, for example, decreasing ω_L in Table 2 by 30% increases corneal thickness by 20% at $Dk/L = 140$ hBarrer/cm and by 60% at $Dk/L = 10$ hBarrer/cm while keeping all other parameters constant. Similar variations in stromal thickness exist for parameter variations of ω_B and J_{aB} , as well as for σ_B and σ_L . These observations confirm the competing effects contributing to endothelial osmotic-concentration differences. Variations in the parameters ω_G and σ_G produce smaller changes in corneal thickness, while variations in the other endothelial-membrane parameters are responsible for still smaller changes in hypoxic corneal swelling.

Not all parameter choices give physically correct results. For example, we found particular sets of parameters that, contrary to the trend observed in our predictions of the Holden–Mertz plots, yield corneal deswelling upon increasing osmotic buildup at the endothelium/stroma interface over some ranges of Dk/L . To predict hypoxic swelling quantitatively demands constraints on endothelial-membrane coefficients so that osmotic buildup occurs at the endothelium/stroma interface upon increasing Dk/L . Lactate permeability (ω_L) at the endothelium must be smaller than the bicarbonate permeability (ω_O), and the bicarbonate reflection coefficient (σ_B) must be lower than the lactate reflection coefficient (σ_L). The model of Klyce (1981) is not so constrained because no metabolic reactions are explicitly considered and because zero current is not enforced. Sensitivity of model results to the KK-membrane parameters highlights the need for a more detailed molecular understanding of ion and fluid movement across the endothelium.

5. Conclusions and future directions

We present, for the first time, a self-consistent quantitative explanation for how oxygen deprivation causes human corneal edema. The Na^+/K^+ - ATPase electrogenic ion pump of the endothelium engenders active transport of bicarbonate ion from the stroma into the

anterior chamber. The bicarbonate-ion active flux lowers the osmolarity at the endothelium/stroma interface relative to that in the anterior chamber. The resulting osmotic-pressure difference drives water out of the cornea across the endothelium. The pump-out rate is closely balanced by a water leak-in rate into the stroma caused by the tendency of the stroma to swell. Hypoxia disturbs this balance because corneal respiration increases anaerobic production of lactate ion. The additional lactate production raises the osmolarity at the endothelium/stroma interface relative to that during normoxia. The resulting smaller osmotic-driven pump-out rate is matched by a lower leak-in rate caused by the stroma swelling to higher water content.

We describe this process by Darcy's law for water flow and by the Nernst–Planck convective-diffusion equations in the stroma and epithelium. Endothelial and epithelial membranes are represented by Kedem–Katchalsky transport. Nine species are included in the model: water, oxygen, glucose, carbon dioxide, and sodium, chloride, lactate, bicarbonate, and hydronium ions. Anaerobic glucose metabolism generates lactic acid and provides the connection between oxygen deficiency and lactate-ion production.

Several features of the model warrant attention. First, although bicarbonate ions are actively pumped from the stroma into the anterior chamber, the net flux of bicarbonate ion is inward from the AC toward the stroma. The reason for the net reversal of direction is to countermand acid production. Bicarbonate ions enter the cornea from the AC to minimize acidosis accompanying lactic-acid production. To maintain electroneutrality in the cornea, lactate ions lost to the anterior chamber from the cornea must be replaced by anions. Bicarbonate ions also serve that purpose.

Second, increased osmolarity of the open-eye tear arising from evaporation draws water from the cornea across the epithelial membrane. Thus, some of the swelling observed in closed eye can be attributed to loss of evaporative-driven increased tear-film osmolarity. Gain of the open-eye osmotic deswelling is about half of the total swelling observed in closed eye. The remainder of is due to oxygen deficiency at the epithelium.

We successfully predict water hydration and electrostatic-potential profiles, in addition to glucose, oxygen, carbon dioxide, and hydronium, lactate, bicarbonate, sodium, and chloride-ion concentration profiles across the cornea at steady state. Parameters in the model are taken almost exclusively from the literature and yield good agreement with expected values, such as for the corneal voltages, endothelium pump rates, tightness of the epithelial membrane, and magnitudes and directions of water and ion fluxes. In addition, the proposed metabolic model provides insight into the flux contributions of the various species arising from diffusion, osmotic and hydraulic flow, electrical migration, and active ion pumping.

With minimal parameter adjustment, Holden and Mertz (1984) experimental curves are well-represented for cornea swelling versus contact-lens Dk/L in both open and closed eye. Likewise, excellent agreement is obtained for measured PoLTF oxygen partial pressure as a function of contact-lens Dk/L .

Our analysis considers only the steady state. Future studies should be directed toward a deeper understanding hypoxic-swelling dynamics. Although work has been done on

transient modeling of corneal swelling (Klyce and Russell, 1979; Li et al., 2004; Li and Tighe, 2006) and on transient oxygen transport neglecting swelling (Chhabra et al., 2009), no studies self-consistently predict corneal edema driven by metabolic kinetics. We have analyzed the coupled passive and active transporters of the corneal endothelium/epithelium using the Kedem–Katchalsky formalism. This approach does not account for the detailed molecular mechanisms by which these transporters operate (Fischbarg and Diecke, 2005). As more transporters are identified and their kinetic rates are understood, a more detailed treatment of the endothelial and epithelial membranes is warranted.

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Appendix A. Detailed species balances

Before introducing the detailed species balances, we indicate how stromal swelling is taken into account.

A.1. Swelling coordinate ξ

Because the stroma swells, we introduce a coordinate, ξ , based on the thickness of dry polymer (Fatt and Goldstick, 1965). Non-swelling regions retain the x coordinate. Following Fatt and Goldstick (1965), let $d\xi = \phi_d dx$ where ϕ_d is the local volume fraction of dry material in the stroma. Since the density of dry material, ρ_d , is fixed, the volume of dry tissue is conserved. It is convenient to relate the volume fraction ϕ_d to the hydration of fluid in the stroma, H_f , or the mass of fluid per mass of dry tissue

$$H_f = \frac{\rho_f \phi_f}{\rho_d \phi_d} \quad (\text{A1})$$

where ϕ_f and ϕ_d denote the volume fractions of the fluid and dry phases in the corneal stroma, respectively, and ρ_f and ρ_d denote the mass densities of the fluid and dry tissue. Since $1 = \phi_d + \phi_f$, Eq. (A1) is rewritten as

$$1 = \left(1 + \frac{H_f \rho_d}{\rho_f} \right) \phi_d \quad (\text{A2})$$

Substitution of this result into the definition of $d\xi$ allows stromal conservation statements to be rewritten in the ξ -coordinate

$$dx = \left(1 + \frac{H_f \rho_d}{\rho_f} \right) d\xi \quad (\text{A3})$$

Because the dissolved species in the fluid are dilute, the ratio of fluid hydration to fluid density is replaced by the ratio of water hydration to water density, H_w/ρ_w , where ρ_w is the

mass density of pure water. Once the water hydration profile is known as a function of ξ , the thickness of the wet stroma, L_{St} , can be calculated

$$L_{St} = \int_0^{\xi_{St}} \left(1 + \frac{H_w \rho_d}{\rho_w} \right) d\xi \quad (A4)$$

where ξ_{St} is the dry-volume thickness of the stroma estimated from the known density of dry polymer in the stroma (Li and Tighe, 2006) and from the wet stromal thickness of Chhabra et al. (2009). In this manner, swelling of the cornea is established under differing hypoxic environments. All stromal calculations are based on the ξ coordinate system while conservation equations in the remaining layers are based on the x -coordinate system. We assume that all swelling occurs because of stromal expansion. Endothelial and epithelial swelling are negligible in comparison (Klyce, 1981; Hutchings et al., 2010).

A.2. Water

In the ξ -coordinate, mass conservation for water in the stroma is rewritten from Eq. (5) as

$$-\frac{dJ_v \rho_f / M_w}{d\xi} + Q_0 + Q_B = 0 \quad (A5)$$

where Q_0 corresponds to the water production rate from aerobic respiration in Reaction (1), and Q_B reflects the water production rate from acid reaction with bicarbonate according to Reaction (3). The expression for Q_0 is given below in the discussion of oxygen-consumption kinetics. To quantify Q_B , we utilize conservation of bicarbonate ion in Eq. (A18), as discussed below. Total water production rate in Eq. (A5) is the sum of that from aerobic respiration and from acid buffering, $Q_w = Q_0 + Q_B$.

Similar to the models of Li et al. (2004) and Li and Tighe (2006), we base water conservation on mass conservation rather than on volume conservation as adopted by Klyce and Russell (1979). However, we account for water generation associated with aerobic respiration and with bicarbonate buffering. Fluid mass density in Eq. (A5) is approximated as

$$\rho_f = \rho_w \left(1 + \frac{\sum_{i \neq w} C_i M_i}{C_w M_w} \right) \quad (A6)$$

where C_i and M_i denote the molar concentration and molar mass of solute i , and C_w and M_w denote the concentration and molar mass of water. Water volumetric flux, J_v , in Eq. (A5) follows Darcy's law (Eq. (6)) where P is the hydrostatic pressure. In the stroma, P is a unique function of water hydration

$$P = IOP - \gamma e^{-H_w} \quad (A7)$$

where $IOP = 2670$ Pa is the intraocular pressure acting on the endothelium and γ is a fitting constant (Hedbys and Dohlman, 1963). Eq. (A7) is an empirical fit (Fatt and Goldstick,

1965) to the stromal swelling-pressure data of Hedbys and Dohlman (1963). This expression represents an average over the whole stroma. Anterior collagen fibrils are more strongly interwoven compared to posterior fibrils (Morishige et al., 2011) and may exhibit different swelling behavior.

In the constant-mass coordinate system, Darcy's law becomes

$$J_V = - \frac{K}{\mu} \left[\frac{dP}{dH_w} \right] \left[\frac{d\xi}{dx} \right] \frac{dH_w}{d\xi} \quad (\text{A8})$$

where the first bracketed term on the right follows from Eq. (A7) and the second follows from Eq. (A3). Eq. (A8) is combined with Eqs. (A5) and (A6) to establish the steady water-hydration profile in the stroma: $H_w(\xi)$. There is no need to change coordinates in the nonswelling epithelium. Here, Eqs. (5) and (6) hold directly.

Boundary conditions for the water-conservation equation at the endothelium/stroma and the epithelium membrane/postlens tear film interfaces are given by Eq. (4). In the postlens tear film, the pressure is zero. Whereas in the anterior chamber, hydraulic pressure is taken as the intraocular pressure. When Eq. (4) is written at the epithelial membrane, values used for the pressure and concentrations belong to the epithelium and the postlens tear film. It is assumed that the water volume flux calculated in this way is constant throughout the postlens tear film. At the Ep/St interface, pressure is continuous.

For all remaining solutes in the stroma, Eqs. (8) and (9) are rewritten in the ξ -coordinate using the chain rule and Eq. (A3). Reaction rates in the stroma must be specified in terms of the molar production per volume of dry material. We utilize stromal reaction rates per unit volume of wet stromal tissue from Chhabra et al. (2009) and convert those rate laws into the ξ -coordinate as follows. From Eq. (A3) the volume of wet stromal tissue per volume of dry tissue is $1 + H_w \rho_d / \rho_f$. Multiplication of the rate expressions of Chhabra et al. (2009) by this factor gives the reaction rate per unit volume of dry material. Chhabra et al. (2009) assume a stromal water mass percentage of about 78% or a hydration of $H_w = 3.45$ g water/g dry tissue. We utilize this value for H_w in the coordinate-conversion factor. In the epithelial domain, reaction-rate expressions and parameters are taken directly from Chhabra et al. (2009). We now outline the conservation equations for each solute species.

A.3. Sodium and chloride ions

In the swelling stroma, conservation equations of Na^+ and Cl^- ions follow the expressions

$$\frac{dJ_{Cl}}{d\xi} = \frac{dJ_{Na}}{d\xi} = 0 \quad (\text{A9})$$

where the fluxes J_{Cl} and J_{Na} are given by the Nernst–Planck expression (Eq. (9)) written in the dry-mass coordinate. In the no-swelling epithelium, we retain the x coordinate

$$\frac{dJ_{Cl}}{dx} = \frac{dJ_{Na}}{dx} = 0 \quad (\text{A10})$$

where the fluxes are again given by Eq. (7). As before, boundary conditions are required at the endothelium/stroma and epithelium/postlens tear film interfaces. These are prescribed by the irreversible-thermodynamic KK expression (Eq. (7)) written for each ion. At the epithelial membrane, however, there is an identified active chloride pump that drives chloride ions into the postlens tear (Klyce, 1975). Consequently, we include a small active chloride pump rate, J_{aCl} (positive), when writing Eq. (7) at the epithelium/postlens tear-film interface.

A.4. Oxygen

In the stroma, conservation of oxygen is given by Eq. (8) in the form

$$-\frac{dJ_O}{d\xi} - Q_O^{\max} \left[1 + 0.8 \frac{7.6 - \text{pH}}{K_{\text{pH}} + 7.6 - \text{pH}} \right] \left[\frac{C_G}{K_G^O + C_G} \right] \left[\frac{P_O}{K_O^O + P_O} \right] = 0 \quad (\text{A11})$$

where J_O is the molar flux of oxygen and P_O is the partial pressure of oxygen. The second term on the left corresponds to the oxygen consumption rate, i.e., the negative of Q_O , following Chhabra et al. (2009). All symbols in the Monod rate expression (Blanch and Clark, 1996) for oxygen, and in all rate expressions to follow, have the same meanings as in Chhabra et al. (2009). The first bracketed factor in the reaction term of Eq. (A11) empirically describes the dependence of oxygen consumption on pH (Harvitt and Bonanno, 1998; Chhabra et al., 2009). The second factor represents a Monod glucose dependency. At high glucose concentration, the reaction saturates, whereas at low glucose concentration, the reaction ceases. Similar arguments hold for the oxygen Monod dependence in the third bracketed factor of the rate expression. At high oxygen tension, the concentration of oxygen–enzyme complexes saturates. Oxygen consumption is then independent of oxygen partial pressure. $Q_O^{\max}$, the maximum oxygen reaction rate, is from Chhabra et al. (2009) after correction for the dry-mass coordinate, as described above. Eq. (9) quantifies the oxygen flux, except that because the aqueous dissolved oxygen is dilute, Henry's law applies. It is, therefore, convenient to recast oxygen concentrations in Eq. (9) in terms of oxygen partial pressures (Chhabra et al., 2009).

In the epithelial domain, the x -coordinate system is used in all conservation equations.

Hence, Eq. (A11) applies, but with ξ replaced by x ; $Q_O^{\max}$ has the same value as in Chhabra et al. (2009).

In the soft contact lens, oxygen consumption is zero, so the oxygen conservation equation reduces to

$$-\frac{dJ_O}{dx} = 0 \quad (\text{A12})$$

Eqs. (A11) and (A12) are supplemented by Eq. (9) with appropriate transformation into the dry coordinate in the stroma. Convection is absent in the soft contact lens, and all concentrations are written in terms of partial pressures (see Chhabra et al., 2009). Diffusion resistances in the postlens and prelens tear films are accounted for by the permeability of

oxygen in water and the thicknesses of these two films (Fatt, 1989). The boundary condition at the end of the prelens tear film fixes the oxygen tension at 155 mmHg for the open eye and at 61.5 mmHg for the closed eye (Brennan, 2005a, b; Chhabra et al., 2009). Oxygen tension in the aqueous humor is fixed at 24 mmHg. Because the convective flux of oxygen is small, molecular diffusion transports oxygen across the endothelium.

A.5. Lactate ion

The conservation equation for lactate ions in the swelling stroma is

$$-\frac{dJ_L}{d\xi} + Q_L^{\min} \left[1 + \frac{K_O^L}{K_O^L + P_O} \right] \left[\frac{C_G}{K_G^L + C_G} \right] = 0 \quad (\text{A13})$$

and in the nonswelling epithelium it reads

$$-\frac{dJ_L}{dx} + Q_L^{\min} \left[1 + \frac{K_O^L}{K_O^L + P_O} \right] \left[\frac{C_G}{K_G^L + C_G} \right] = 0 \quad (\text{A14})$$

where the lactate flux, J_L , is given by the Nernst–Planck expression in Eq. (9). Monod kinetics is used for the rate of lactate production in Eqs. (A13) and (A14). The first bracketed term accounts for the dependence of the lactate production rate on oxygen tension: low oxygen tension promotes lactate production. Klyce (1981) noticed that below an oxygen tension of 7 mmHg the lactate production rate roughly doubled. The first factor quantifies this observation empirically (Chhabra et al., 2009): at zero oxygen tension, for example, the bracketed factor is 2, whereas at high oxygen tension, it is unity. A Monod dependence of the lactate reaction rate on glucose concentration is adopted in the second bracket factor similar to that for oxygen consumption. The Monod glucose equilibrium constant, K_G^L is assumed to be the same as that for oxygen. Values of the reaction-rate scaling factor, $Q_L^{\min}$, for the stroma and epithelium are from Chhabra et al. (2009) except that correction is made to dry-tissue volume in the stroma. Values chosen give an overall 85% anaerobic oxygen consumption under open-eye conditions. Again, J_L in Eqs. (A13) and A14 is given by the Nernst–Planck fluxes (Eq. (9)) appropriately corrected in the stroma for the dry-coordinate system.

At the endothelium/stroma interface, the boundary condition states that the Nernst–Planck flux (Eq. (9)) equals the KK flux (Eq. (7)) with parameter values specific to lactate ion. This means that the passive basolateral and apical endothelial transporters for lactate ion pictured in Fig. 3 are lumped into the KK-membrane model. Overall electrical neutrality across the endothelium is imposed by a zero-current condition, as discussed below. Aqueous-humor concentration of lactate ion is fixed at 7.7 mM.

At the Ep/PoLTF interface, lactate-ion flux is zero, consistent with the observation that lactate concentration in the tear film is negligible. Lactate concentration in the soft contact lens is also set to zero.

A.6. Glucose

Conservation of glucose in the stroma is given by

$$-\frac{dJ_G}{d\xi} - \frac{Q_L^{\min}}{2} \left[1 + \frac{K_O^L}{K_O^L + P_O} \right] \left[\frac{C_G}{K_G^L + C_G} \right] - \frac{Q_O^{\max}}{6} \left[1 + 0.8 \frac{7.6 - pH}{K_{pH} + 7.6 - pH} \right] \left[\frac{C_G}{K_G^O + C_G} \right] \left[\frac{P_O}{K_O^O + P_O} \right] = 0 \quad (A15)$$

and for the epithelium, we write that

$$-\frac{dJ_G}{dx} - \frac{Q_L^{\min}}{2} \left[1 + \frac{K_O^L}{K_O^L + P_O} \right] \left[\frac{C_G}{K_G^L + C_G} \right] - \frac{Q_O^{\max}}{6} \left[1 + 0.8 \frac{7.6 - pH}{K_{pH} + 7.6 - pH} \right] \left[\frac{C_G}{K_G^O + C_G} \right] \left[\frac{P_O}{K_O^O + P_O} \right] = 0 \quad (A16)$$

where J_G is the glucose flux. The two reaction terms in Eqs. (A15) and (A16) indicate that glucose is consumed both aerobically and anaerobically, as illustrated in Fig. 2.

Stoichiometry of Reactions (1) and (2) demands that 1 mol of glucose reacts with 6 mol of oxygen in aerobic respiration, whereas in anaerobic respiration, 2 mol of lactate are produced for every mole of glucose consumed. This observation explains the constant factors of 1/2 and 1/6 multiplying the scaling coefficients $Q_L^{\min}$ and $Q_O^{\max}$. Appropriate forms of the Nernst–Planck equation describe the flux of glucose in the both the stroma (rewritten in the ξ -coordinate) and the epithelium (in the x coordinate).

The boundary condition at the endothelium/stroma interface is given by Eq. (7) with coefficients pertinent to glucose, while the boundary condition at the Ep/PolTF interface forces the glucose flux to be zero, again consistent with the observation of small glucose concentrations in the tear film. In the anterior chamber, the glucose concentration is 6.9 mM (Fatt and Weissman, 1992). As with lactate ion, glucose concentration in the postlens tear film, soft contact lens, and prelens tear film is zero based on the observation that it tends to be 40 times less than that in the aqueous humor (Fatt and Weissman, 1992).

A.7. Hydrogen and bicarbonate ions

Conservation of hydrogen ion in the stroma and epithelium is given by

$$-\frac{dJ_H}{dx} + Q_L^{\min} \left[1 + \frac{K_O^L}{K_O^L + P_O} \right] \left[\frac{C_G}{K_G^L + C_G} \right] - Q_B = 0 \quad (A17)$$

where J_H is the hydrogen-ion flux and Q_B is the consumption rate of bicarbonate ion in Reaction (3). The second term on the left of Eq. (A17) specifies production of hydrogen ion from anaerobic glycolysis, as described above in Eq. (A14), and the second reaction term in Eq. (A17) gives the consumption rate of hydrogen ion due to bicarbonate buffering.

Similarly, conservation of bicarbonate ion reads

$$-\frac{dJ_B}{dx} - Q_B = 0 \quad (A18)$$

where J_B is the bicarbonate-ion flux. In the presence of carbonicanhydrase enzyme, the forward and reverse rates of Reaction (3) are large so that Q_B is close to zero. Consequently, local buffering equilibrium is imposed (Chhabra et al., 2009)

$$K_B = \frac{C_B C_H}{s_C P_C} \quad (\text{A19})$$

Here, K_B is the buffering equilibrium constant, s_C is the solubility of carbon dioxide in water (Bonanno and Polse, 1987a), and C_H and P_C are the concentration of hydrogen ion and the carbon-dioxide partial pressure, respectively. Since concentrations appearing in Eq. (A19) are per unit volume fluid, the constants K_B and s_C hold in both the stroma and the epithelium.

Q_B is unspecified in Eqs. (A17) and (A18) and is eliminated to give

$$-\frac{dJ_H}{dx} + \frac{dJ_B}{dx} + Q_L^{\min} \left[1 + \frac{K_O^L}{K_O^L + P_O} \right] \left[\frac{C_G}{K_G^L + C_G} \right] = 0 \quad (\text{A20})$$

Thus, rather than solving separate species balances for hydronium and bicarbonate ions, we solve the combined fluxes in Eq. (A20) along with local equilibrium in Eq. (A19). J_H and J_B in Eq. (A20) each obey the Nernst–Planck relation. In the stroma, Eqs. (A20) and (9) are transformed into the ξ coordinate, and $Q_L^{\min}$ is scaled according to dry-tissue volume. Since Q_B is not explicitly calculated, we also eliminate it from Eq. (A5) using Eq. (A18).

A.8. Carbon dioxide

Local carbon-dioxide conservation demands that

$$-\frac{dJ_C}{dx} + Q_O^{\max} \left[1 + 0.8 \frac{7.6 - pH}{K_{pH} + 7.6 - pH} \right] \left[\frac{C_G}{K_G^O + C_G} \right] \left[\frac{P_O}{K_O^O + P_O} \right] + Q_B = 0 \quad (\text{A21})$$

where J_C is the molar flux of carbon dioxide. The second term in Eq. (A21) accounts for carbon-dioxide production in aerobic respiration. Q_B is the net production rate of CO_2 due to buffering (i.e., equivalent to the net consumption rate of HCO_3^- in Reaction (3)). Since the forward and reverse rates of the catalyzed buffering reaction are fast, Q_B is close to zero so we impose local equilibrium in Eq. (A19). Consequently, Eqs. (A18) and (A21) are combined to eliminate Q_B

$$-\frac{dJ_C}{dx} - \frac{dJ_B}{dx} + Q_O^{\max} \left[1 + 0.8 \frac{7.6 - pH}{K_{pH} + 7.6 - pH} \right] \left[\frac{C_G}{K_G^O + C_G} \right] \left[\frac{P_O}{K_O^O + P_O} \right] = 0 \quad (\text{A22})$$

In the stroma, Eq. (A22) is rewritten in the ξ coordinate and the parameter $Q_O^{\max}$ is scaled to dry-volume units. Both carbon dioxide and bicarbonate-ion fluxes obey Eq. (9) appropriately transformed in the stroma to the ξ coordinate. For carbon dioxide, however, concentration is expressed in partial-pressure units (Chhabra et al., 2009).

At the endothelium/stroma interface, bicarbonate ion flows from the stroma into the aqueous humor via a secondary active transporter (Bonanno, 2003; Fischbarg and Diecke, 2005). Consequently, we include a constant (negative) active flux of bicarbonate, J_{aB} , when writing Eq. (7) for the endothelium. Further, at the endothelium/AC and Ep/PoLTF interfaces, we include bicarbonate-ion buffering. In this case, Reaction (3) occurs at the interface. To account for buffering in the endothelial and epithelial membranes, we include a heterogeneous reaction rate in the flux-continuity condition of carbon dioxide, bicarbonate ion, and hydrogen ion. As noted above, the buffering reaction rate is fast, so following the procedure in Eq. (A22), we eliminate this rate from the flux-continuity condition for carbon dioxide, bicarbonate ion, and hydrogen ion, respectively: $J_B + J_C = 0$ for carbon dioxide and $J_B - J_H = 0$ for bicarbonate ion where Δ stands for the difference across each membrane in the positive direction. In the flux difference, KK (Eq. (7)) and Nernst–Planck (Eq. (9)) flux expressions are applied. The equilibrium constraint in Eq. (A19) completes the membrane equation set.

During open-eye conditions, the concentrations of bicarbonate ion in the aqueous humor and tear film are 36 mM and 12.4 mM, respectively. Hydrogen-ion concentrations in the anterior chamber and the tear follow from buffering equilibrium and solution electroneutrality. In the tear film, however, bicarbonate-ion buffering is thought to account for only a portion of the total buffering capacity (Carney et al., 1989; Chen and Maurice, 1990). For simplicity, we assume that the pH at the epithelium/tear film interface is determined by the equilibrium expression (A19).

Reaction rates are zero in the contact lens, and the conservation equation simplifies to

$$-\frac{dJ_C}{dx} = 0 \quad (\text{A23})$$

In the prelens tear film, the tension of carbon dioxide is fixed at 38 mm Hg or at 0.3 mm Hg for closed and open eye, respectively. For the endothelium/aqueous humor interface, carbon-dioxide tension is also fixed at 38 mm Hg (Bonanno and Polse, 1987b).

A.9. Electric potential

Electroneutrality is imposed everywhere

$$\sum_i z_i C_i = 0 \quad (\text{A24})$$

Eq. (A24) allows calculation of the electrostatic-potential profile. Additionally, we demand zero current throughout the cornea

$$\sum_i z_i J_i = 0 \quad (\text{A25})$$

However, Eq. (A25) can be applied independently at only one location. We enforce zero current at the En/AC boundary, thereby guaranteeing zero current throughout all domains. We take the voltage in the tear film to be zero as the reference potential.

Appendix B. Parameters

Tables 1–4 give the model parameters and physical constants adopted in this work, all at physiologic temperature.

B.1. Anterior-chamber and tear compositions

Table 1 gives the AC and TF electrolyte concentrations. These serve as boundary conditions for the model equations. During closed eye, both the tear and aqueous humor exhibit a total osmolarity of 300 mOsM, although each has a different composition. During open-eye conditions, we assume a total osmolarity of 308 mOsM in the tear film and obtain the individual component concentrations by scaling from the closed-eye values in Table 1. Glucose and lactate-ion concentrations are small in the tear film and are thus taken as zero. Consequently, the only solutes present in the TF are oxygen, carbon dioxide, and sodium, chloride, and bicarbonate ions. Because hydrogen-ion concentration is small in tear (pH ~7.6; Fischer and Wiederholt, 1982) and because tear is electrically neutral, the sodium-ion concentration is set at 150 mOsM for closed-eye conditions. Rismondo et al. (1989) measured the bicarbonate-ion concentration in tear to be 12.4 mOsM under open-eye conditions. We estimate the closed-eye bicarbonate-ion concentration as 12.1 mOsM. Using this value and solution electroneutrality, we calculate the chloride-ion concentration in Table 1 as 137.9 mOsM for the closed eye. We adopt these concentration values in the pre and postlens tear films.

In the AC, lactate-ion concentration is set to 7.7mM(Imre,1977). Glucose concentration is 6.9mM(Fatt and Weissman, 1992) and pH is 7.6 (Giasson and Bonanno, 1994a). Carbon-dioxide tension is set at 38 mm Hg (Bonanno and Polse, 1987b), while oxygen tension is fixed at 24 mm Hg (Brennan, 2005a, b). Bicarbonate-ion concentration is then computed from the equilibrium expression of Reaction (3) at about 36 mOsM given the above pH and carbon-dioxide tension (Fischbarg and Diecke, 2005; Giasson and Bonanno, 1994a; Li and Tighe, 2006) Sodium and chloride-ion concentrations listed in Table 1 are then determined from electroneutrality and a total salt content of 300 mOsM during closed eye and 308 mOsM during open eye. Hydraulic pressure in the AC is 2670 Pa relative to atmospheric pressure in the TF. Partial pressures in the AC and TF are listed for oxygen and carbon dioxide in both open and closed eye where appropriate.

B.2. Endothelium and epithelium parameters

Table 2 reports KK coefficients at the endothelium and epithelial membranes. Hydraulic transmissibilities, L_p , of the two membranes are from Klyce and Russell (1979). To our knowledge, no attempt has been made to measure the KK coefficients for the solutes of interest at the limiting membranes. Kedem–Katchalsky expressions for oxygen and carbon dioxide reduce essentially to Fickian diffusion since convective fluxes for these neutral

species are small. Accordingly, we estimate permeability coefficients, ω_i , of oxygen and carbon dioxide at the endothelium from endothelial diffusion coefficients of these gases (Chhabra et al., 2009) upon division by the thickness of the endothelium. At the epithelium, we similarly use permeability coefficients for carbon dioxide and oxygen that are consistent with measured Fickian diffusion coefficients (Chhabra et al., 2009).

At the epithelial membrane, permeabilities, ω_i , and reflection coefficients, σ_i , of all solutes are those of Klyce and Russell (1979) for NaCl, with the exception of lactate ion and glucose. The near absence of lactate and glucose in the tear film demands epithelial-membrane reflection coefficients of unity and permeabilities of zero. This choice guarantees zero flux of these two species across the epithelial membrane.

Likewise, except for lactate and bicarbonate ions, permeabilities and reflection coefficients of all solutes at the endothelium are equal to those of NaCl from Klyce and Russell (1979). Reflection and permeability coefficients for lactate and bicarbonate ions are constrained at the endothelium. Lactate-ion permeability is set lower than that of bicarbonate ion. Conversely, the lactate-ion reflection coefficient is set higher than that of bicarbonate ion. If these constraints are not imposed, we do not predict hypoxic swelling because the depletion of bicarbonate-ion concentration associated with oxygen starvation outweighs lactate accumulation at the En/St interface. This observation implies that osmotic buildup at the En/St interface is requisite to predict edema during hypoxia.

Active bicarbonate-ion flux at the endothelium is $J_{aB} \sim -10^{-9}$ mol/cm²/s giving fluid pump-out rates that are consistent with literature (i.e., ca. 10 μ L/cm²/h from Fischbarg et al. (1977), Baum et al. (1984), and O'Neal and Polse (1985)). Our estimate of the epithelial active flux of chloride ion, $J_{aCl} \sim +10^{-11}$ mol/cm²/s is slightly larger than that of Klyce and Russell (1979). Too small a value for the chloride-ion pump flux results in negative corneal electrostatic potentials relative to that in the tear film, which is not consistent with experiment (Klyce, 1975). Because the model of Klyce and Russell did not account for electrostatics in the cornea, their estimate of J_{aCl} may not be quantitative.

B.3. Diffusion, flow, and reaction parameters

Stromal and epithelial diffusion coefficients for every species except sodium and chloride ion are taken from Chhabra et al. (2009). Because Chhabra et al. (2009) did not feature aqueous NaCl, we obtain these two ionic diffusion coefficients from Klyce and Russell (1979).

Hydraulic conductivities, K/μ , must be specified in the stromal and epithelial domains. For the stroma, we employ the expression of Fatt and Goldstick (1965) who demonstrated that K/μ is proportional to the fourth power of hydration. In the epithelial domain, we obtain K/μ from Mishima and Hedbys (1967). Monod constants, $Q_L^{\min}$ and $Q_O^{\max}$, for the stroma and epithelium are from Chhabra et al. (2009). In the stroma, however, correction is made for swelling, as discussed in Section A.2.

Aerobic and anaerobic baseline oxygen reaction rates, and the equilibrium constant for the bicarbonate reaction are those of Chhabra et al. (2009) along with stromal and epithelial diffusion coefficients for every species except sodium and chloride ions. Unavailable values for epithelial solute diffusion coefficients were assumed identical to the measured stromal diffusion coefficients listed in Table 3. Following Chhabra et al. (2009), we scale the lactate reaction rate so that 85% of glucose fed to the cornea reacts through anaerobic respiration under no-lens closed-eye conditions.

B.4. Physical constants

The value of the dry stromal density in Table 4 is from Li and Tighe (2006). Remaining physical constants in Table 4 are from Chhabra et al. (2009).

Appendix C. Numerical solution

Conservation equations and electroneutrality conditions are discretized in x -space and ξ -space using centered finite differences and solved using Newton–Raphson iteration. We illustrate the technique with the example of carbon dioxide in Eq. (A22). At mesh point j , we write a center difference approximate about half mesh points $j - 1/2$ and $j + 1/2$ so that Eq. (A22) reads

$$J_{C,j-1/2} - J_{C,j+1/2} + J_{B,j-1/2} - J_{B,j+1/2} + Q_O^{\max} \left[1 + 0.8 \frac{7.6 - \text{pH}_j}{K_{\text{pH}} + 7.6 - \text{pH}_j} \right] \left[\frac{P_{o,j}}{K_o^o + P_{o,j}} \right] \left[\frac{C_{G,j}}{K_{G,j}^o + C_{G,j}} \right] \Delta x = 0 \quad (\text{C1})$$

where Δx is the mesh size. To evaluate the carbon dioxide and bicarbonate-ion fluxes in Eq. (C1), we adopt the Nernst–Planck relation of Eq. (9). At the half interval $j - 1/2$, for example, we write that

$$J_{i,j-1/2} = C_i J_{\nu}|_{j-1/2} - D_i \frac{dC_i}{dx}|_{j-1/2} - z_i D_i C_i \frac{F}{RT} \frac{d\psi}{dx}|_{j-1/2} \quad (\text{C2})$$

Species i flux at $j + 1/2$ is similarly written. All first-order derivatives in Eq. (C2) are expressed as a central difference. For example, the concentration gradient at $j - 1/2$ is

$$\frac{dC_i}{dx}|_{j-1/2} = \frac{C_{i,j} - C_{i,j-1}}{\Delta x} + O(\Delta x^2) \quad (\text{C3})$$

and likewise for the electrostatic-potential gradient. Similar expressions are written for the half interval $j + 1/2$. For carbon dioxide (and for oxygen), concentrations appearing in Eqs. (C1)–(C3) are written in terms of partial pressure: $C_C = k_C P_C$ where k_C is the carbon-dioxide partition coefficient in water or the inverse Henry's constant (Chhabra et al., 2009). Eqs. (C2) and (C3) and their counterparts at $j + 1/2$ are substituted into Eq. (C1) to give a set of nonlinear algebraic equations over the mesh points $j - 1$, j , and $j + 1$. These are solved by linearization and iteration according to the Newton–Raphson algorithm.

The mesh index j runs from 1 to $N_{\max}$ ($= N_{St} + N_{Ep} + N_{PoLTF} + N_{CL} + N_{PrLTF}$). Kedem–Katchalsky equations are written at $j = 2$ and $j = N_{St} + N_{Ep}$ corresponding to the endothelial

and epithelial membranes, respectively. An internal boundary occurs at the St/Ep interface located at $j = N_{St}$ (i.e., at $x = L_{St}$). We treat mesh points to the left of this location in the dry-polymer ξ -coordinate system. Mesh points to the right of $j = N_{St}$ are treated in the unadjusted x -coordinate system. Because the unknown variables are assigned to specific j -values, and not to specific x -values, no special adjustment is required at the internal St/Ep boundary. Equilibrium and continuity conditions join the two regions.

Mesh point $j = 1$ corresponds to the AC. Mesh points $N_{St} + N_{Ep} < j < N_{St} + N_{Ep} + N_{PoLTF}$ correspond to the postlens tear film. We write Eqs. (C1)–(C3) and their analogs for the different species throughout the stroma, epithelium, and contact-lens domains including the internal boundaries. In the post and prelens tear films, as well as in the contact lens, only conservation equations for oxygen and carbon dioxide are solved. Reaction rates are zero in the tear film and contact lens.

Centered differencing produces a block tridiagonal, banded matrix solved using BAND and MATINV subroutines (Newman and Thomas-Alyea, 2004) that extend the Thomas algorithm for tridiagonal matrices. Table 5 provides a finite-difference map displaying more clearly the equations to be solved at each mesh point. The Fortran code used to solve the equation set is available from the authors upon request.

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List of Symbols

AC	anterior chamber
$\langle C_i \rangle$	log-mean concentration of species <i>i</i> (mol/cm ³)
C_i	concentration of species <i>i</i> (mol/cm ³)
D	diffusion coefficient for oxygen (cm ² /s)
D_i	diffusion coefficient of species <i>i</i> (cm ² /s)
En	endothelium
Ep	epithelium
F	Faraday's constant (C/mol)
H_w	stromal hydration (g water/g dry polymer)
IOP	intraocular pressure (Pa)
J_{ai}	active flux of species <i>i</i> at a limiting membrane (mol/cm ² s)
J_i	molar flux of species <i>i</i> (mol/cm ² s)
J_v	volumetric flux of water (cm ³ /cm ² /s)
k	inverse Henry's constant of oxygen in SCL (mL/(mL mm Hg))
k_i	inverse Henry's constant of species <i>i</i> (mL/(mL mm Hg))
K	hydraulic permeability of stroma and epithelium (cm ²)
K_i^L	Monod constant of species <i>i</i> in the anaerobic reaction (mM or mm Hg)
K_i^o	Monod constant of species <i>i</i> in the aerobic reaction (mM or mm Hg)
K_{pH}	Monod constant of hydrogen in the aerobic reaction
L	harmonic-mean lens thickness of SCL (μm)
L_p	membrane hydraulic conductivity (cm ³ /(s dyne))
L_{St}	stromal thickness (μm)
L_T	total cornea thickness (μm)
M_i	molecular weight of species <i>i</i> (g/mol)
P	hydraulic pressure (Pa)
P_i	partial pressure of species <i>i</i> (mm Hg)
pH	negative base-10 logarithm of hydrogen-ion concentration
pK_B	negative base-ten logarithm of the bicarbonate equilibrium constant
PoLTF	postlens tear film

PrLTF	prelens tear film
Q_i	volumetric production rate of species <i>i</i> (mol/cm ³ /s)
Q_L^{min}	minimum baseline lactate reaction rate (μL/cm ³ /h)
Q_O^{max}	maximum baseline oxygen reaction rate (mL/cm ³ s)
R	ideal gas constant (J/(K mol))
s_c	solubility of carbon dioxide in water (mM/mm Hg)
St	stroma
T	absolute temperature (K)
TF	pre-corneal tear film
x	position in the domain relative to the aqueous humor (cm)
z_i	valence of species <i>i</i>

Greek letters

γ	empirical constant in Eq. (A7) (Pa)
Δ	difference across a membrane
φ_i	volume fraction of component <i>i</i>
ρ_i	mass density of species <i>i</i> (g/cm ³)
σ_i	reflection coefficient of species <i>i</i>
ω_i	membrane permeability of species <i>i</i> (cm/s)
ξ	dry polymer coordinate (cm)
ψ	electric-potential relative to the tear film (mV)
μ	fluid viscosity (mPa s)

Subscripts

AC	anterior chamber
B	bicarbonate ion
C	carbon dioxide
Cl	chloride ion
d	dry
En	endothelium
Ep	epithelium
f	fluid

G	glucose
H	hydrogen ion
i	species <i>i</i>
L	lactate ion
Na	sodium ion
O	oxygen
PoLTF	postlens tear film
PrLTF	prelens tear film
St	stroma
T	total
w	water

Fig. 1.
Schematic of cornea and contact-lens system (after Chhabra et al., 2009 with permission).

Fig. 2.
Glucose metabolic pathways in the cornea.

Fig. 3. Ion transporters across an isolated endothelium (from Bonanno with permission). Circles, ellipses, and squares along the plasma membrane correspond to named ion channels (Bonanno, 2003). CA corresponds to carbonic anhydrase enzyme.

Fig. 4.
Glucose profiles in open and closed eye.

Fig. 5.
Oxygen profiles for open and closed eye.

Fig. 6.
Carbon-dioxide profiles for open and closed eye.

Fig. 7.
Bicarbonate-ion profiles for open and closed eye.

Fig. 8.
Contributions to bicarbonate-ion flux at the endothelium for open and closed eye.

Fig. 9.
Contributions to bicarbonate-ion flux at the epithelium for open and closed eye.

Fig. 10.
Lactate-ion profiles for open and closed eye.

Fig. 11.
pH profiles for open and closed eye.

Fig. 12.
Electrostatic-potential profiles for open and closed eye.

Fig. 13.
Sodium-ion profiles for open and closed eye.

Fig. 14.
Chloride-ion profiles for open and closed eye.

Fig. 15.
Contributions to sodium-ion flux at the endothelium for open and closed eye.

Fig. 16.
Contributions to chloride-ion flux at the endothelium for open and closed eye.

Fig. 17.
Contributions to sodium-ion flux at the epithelium for open and closed eye.

Fig. 18.
Contributions to chloride-ion flux at the epithelium for open and closed eye.

Fig. 19.
Water-hydration profiles for open and closed eye.

Fig. 20.
Pressure profiles for open and closed eye.

Fig. 21.
Contributions to water flux, J_v , at the endothelium for open and closed eye.

Fig. 22.
Contributions to water flux, J_v , at the epithelium for open and closed eye.

Fig. 23.
Comparison of oxygen profiles for open and closed eye with a low oxygen transmissibility lens of $Dk/L = 10$ hBarrer/cm.

Fig. 24. Corneal swelling as a function of lens transmissibility for open eye. Open circles are the data of Holden and Mertz (1984).

Fig. 25.

Corneal swelling as a function of lens transmissibility for closed eye. Filled circles are the data of Holden and Mertz (1984). The long dashed line indicates no-lens wear. The dot-dashed line gives the contribution to swelling resulting from the neglect of the osmolarity change between the open (308 mOsM) and closed eye (300 mOsM).

Fig. 26.
Oxygen tension at the post-lens tear film as a function of lens transmissibility (Benjamin, 1993).

Fig. 27.
Deswelling of the cornea due to tear osmolarity.

Table 1

Tear film and anterior-chamber parameters.

	AC	PoLTF (open/closed)	PrLTF
C_{Na} (mM)	*146.55	*150/154	–
C_{Cl} (mM)	*102.85	*137.9/141.6	–
C_L (mM)	$a_{7.7}$	$b_{0/0}$	–
C_B (mM)	*36	$c_{12.1/12.4}$	–
pH	$d_{7.6}$	$e_{7.6}$	–
C_G (mM)	$f_{6.9}$	f_0	–
Total osmolarity (mM)	300	300/308	–
Pressure (Pa)	$g_{2,670}$	0	0
P_O (mm Hg)	h_{24}	(solved for)	h_{155} (open eye) $h_{61.5}$ (closed eye)
P_C (mm Hg)	i_{38}	(solved for)	$f_{0.5}$ (open eye) i_{38} (closed eye)

* derived, see text.

 a_{Imre} (1977). b_{Klyce} (1981). $c_{Rismondo}$ et al. (1989). $d_{Giasson}$ and Bonanno (1994a). $e_{Fischer}$ and Weiderholt (1982). f_{Fatt} and Weissman (1992). g_{Klyce} and Russell (1979). $h_{Brennan}$ (2005a, b) $i_{Bonanno}$ and Polse (1987a).

Table 2

Endothelial and epithelial membrane coefficients.

Coefficient	Endothelium	Epithelium
$L_p \times 10^{12}$ (cm ³ /(dyne s))	42	6.1
σ_{Na}	0.45	0.79
σ_{Cl}	0.45	0.79
σ_L	0.45	a_1
σ_B	$b_{0.38}$	0.79
σ_O	0.45	0.79
σ_C	0.45	0.79
σ_H	0.45	0.79
σ_G	0.45	a_1
$\omega_{Na}RT \times 10^5$ (cm/s)	8	0.019
$\omega_{Cl}RT \times 10^5$ (cm/s)	8	0.019
$\omega_LRT \times 10^5$ (cm/s)	b_3	a_0
$\omega_BRT \times 10^5$ (cm/s)	8	0.019
$\omega_HRT \times 10^5$ (cm/s)	8	0.019
$\omega_GRT \times 10^5$ (cm/s)	8	a_0
$\omega_O k_O RT$ (mol O ₂ cm/(s mm Hg cm ³))	$c_{15.8 \times 10^{-12}}$	$d_{D_O k_O / x}$
$\omega_C k_C RT$ (mol CO ₂ cm/(s mm Hg cm ³))	$c_{316 \times 10^{-12}}$	$d_{D_C k_C / x}$
$J_a \times 10^{10}$ (mol/(cm ² s))	$b_{-9.4}$ (bicarbonate)	$b_{0.16}$ (chloride)

Unless otherwise noted, all values are from Klyce and Russell (1979).

^aConsistent with zero flux.^bAdjusted. Minus sign indicates the negative x -direction.^cCalculated from Chhabra et al. (2009). $\omega k RT$ is set as Dk divided by the measured endothelial thickness (see Table 3).^dCalculated from Chhabra et al. (2009). $\omega k RT$ is set as Dk divided by the mesh size in the epithelial continuum (see Table 3).

Table 3

Diffusion and reaction parameters.

	Endothelium	Dry stroma	Epithelium	PolTF	PrLTF
Length (μm)	<i>a</i> _{1.5}	[*] <i>a</i> ₇₈	<i>a</i> ₅₀	<i>a</i> ₃	<i>a</i> ₃
<i>D</i> _{O₂O} (Barrer)	<i>a</i> _{5.3}	<i>a</i> _{29.5}	<i>a</i> _{18.8}	<i>a</i> ₉₀	<i>a</i> ₉₀
<i>D</i> _{C₆C} (Barrer)	<i>a</i> ₁₀₆	<i>a</i> ₅₉₀	<i>a</i> ₃₇₆	<i>a</i> ₉₀₀	<i>a</i> ₉₀₀
<i>D</i> _L × 10 ⁶ (cm ² /s)	–	<i>a</i> _{4.4}	<i>a</i> _{4.4}	–	–
<i>D</i> _G × 10 ⁶ (cm ² /s)	–	<i>a</i> ₃	<i>a</i> ₃	–	–
<i>D</i> _H × 10 ⁵ (cm ² /s)	–	<i>a</i> _{1.18}	<i>a</i> _{0.19}	–	–
<i>D</i> _B × 10 ⁶ (cm ² /s)	–	<i>a</i> _{1.5}	<i>a</i> _{0.22}	–	–
<i>D</i> _{Na} × 10 ⁶ (cm ² /s)	–	<i>b</i> ₉	<i>b</i> ₉	–	–
<i>D</i> _{Cl} × 10 ⁶ (cm ² /s)	–	<i>b</i> ₉	<i>b</i> ₉	–	–
<i>K</i> /μ × 10 ¹⁵ (cm ² /(dyne s))	–	<i>b</i> _{8.63} <i>H</i> _w ⁴	<i>c</i> ₂₇	–	–
<i>Q</i> ₀ ^{max} × 10 ⁹ (mol/(cm ³ s))	–	[*] <i>a</i> _{6.28}	<i>a</i> _{11.6}	–	–
<i>Q</i> ₀ ^{min} × 10 ⁹ (mol/(cm ³ s))	–	[*] <i>#</i> _{24.7}	<i>#</i> _{4.83}	–	–

^{*} Value in dry stromal coordinates obtained from *H_w* = 3.45 g water/g dry tissue.

[#] Scaled to achieve 85:15 anaerobic:aerobic glucose consumption at no-lens closed-eye conditions (Chhabra et al., 2009).

^aChhabra et al. (2009).

^bKlyce and Russell (1979).

^cMishima and Hedbys (1967)

Table 4

Physical constants.

Parameter	Value
ρ_d (dry stromal density, g/cm ³)	$a_{1.49}$
γ (Pa)	2.41×10^6
K_0^0 (mm Hg)	2.2
K_0^L (mm Hg)	2.2
K_G^0 (mM)	0.4
K_G^L (mM)	0.4
K_{pH}	0.1
pK_B	6.04
s_c (mM/mm Hg)	0.0258

Unless otherwise noted, values are from Chhabra et al. (2009).

^aLi and Tighe (2006).

Table 5

Finite-difference map.

	AC	En/St Interface	St; Ep	Ep/PoLTF Interface	PoLTF; SCL; PrLTF	PrLTF/Air Interface
Sodium	Fixed concentration	Continuity of Kedem-Katchalsky and Nernst-Planck fluxes	Material balance	Continuity of Kedem-Katchalsky and Nernst-Planck fluxes	Fixed concentration	Fixed concentration
Chloride						
Lactate						
Bicarbonate					Material balance	
Oxygen						
Carbon Dioxide						
Glucose					Fixed concentration	
Hydrogen						
Voltage	Bicarbonate equilibrium				Fixed voltage	Fixed voltage
Water	Fixed intraocular pressure	Continuity of Kedem-Katchalsky and Darcy fluxes	Material balance	Continuity of Kedem-Katchalsky and Darcy fluxes	Fixed pressure	Fixed pressure