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# Oxygen-deficient metabolism and corneal edema

B.K. Leung [a], J.A. Bonanno [b], C.J. Radke [a,c,*]

[a] Chemical and Biomolecular Engineering Department, University of California, Berkeley, CA 94720, United States
[b] Indiana University, School of Optometry, Bloomington, IN 4740, United States
[c] Vision Science Group, University of California, Berkeley, CA 94720, United States

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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.



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* Corresponding author. University of California, Chemical and Biomolecular Engineering Department, Berkeley, CA 94720, United States.
*E-mail address:* radke@berkeley.edu (C.J. Radke).

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## 1. Introduction

Human corneal heath 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-leak" 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,