GSMMC 2019:
Contact Lens Drug Delivery Report

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June 15 2019

1 Introduction

Chronic or degenerative diseases of the eye have been historically difficult to medicate properly [1]. For many such diseases, medicated eye drops must be administered both frequently and accurately to ensure successful treatment. Failure to adhere to such guidelines results in significantly decreased effectiveness [2]. For this reason, researchers continue to explore medicated contact lenses as an alternative to eye drops [1][3][4]. We present a simple model to help understand the effectiveness of drug delivery to the cornea by medicated hydrogel contact lenses. This type of targeted medication has significant applications for the treatment of glaucoma, an eye disease that can cause permanent blindness[1].

The tear film is a three-layered film that sits on top of the ocular surface and serves to protect the eye and promote clear vision. The outermost layer is made up of lipids, the middle and thickest layer is comprised mostly of water, and the innermost layer is formed by mucins [5]. We ignore the outer and inner layers and consider only the tear film (TF) and the inserted contact lens (CL).

For this treatment, the contact lens is saturated with some drug, and when inserted into the eye, the drug diffuses into the surrounding tear films. Figure 1 shows the anatomy of the eye with an inserted contact lens. Note that the contact lens divides the tear film into two parts: the pre-lens tear film (PrLTF), which is exposed to the environment, and the post-lens tear film (PoTF), which borders the cornea.

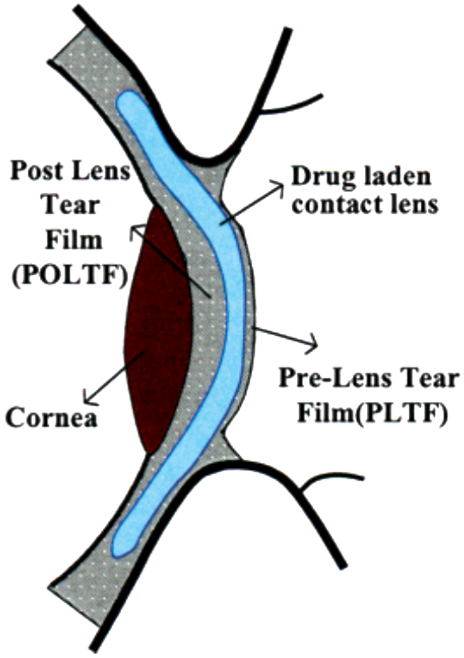

Figure 1: Anatomy of the eye with an inserted contact lens (not to scale).

By solving a diffusion equation along with boundary conditions for the PrLTF and PoLTF thresholds, we derive an analytical solution describing the concentration of the drug in the CL in space and time. MATLAB 2017a is used to solve the problem numerically along with equations for the thickness and drug concentration in the PrLTF and PoLTF. We then visualize the solution with varying parameter values. From these results, we are able to predict the amount of the drug that reaches the cornea and the amount that is lost to lateral flow or other factors.

2 Models

We begin with some simple assumptions to build a framework of the model. During CL wear the drug can diffuse from the CL into the PrLTF and into the PoLTF as well as within the CL. Both the PrLTF and PoLTF thicknesses can change over time; this affects the drug concentration in those compartments. The drug can be lost from the PrLTF or PoLTF laterally and from the PoLTF to the cornea; we assume the drug cannot return from these escape routes. The following schematic captures these assumptions:

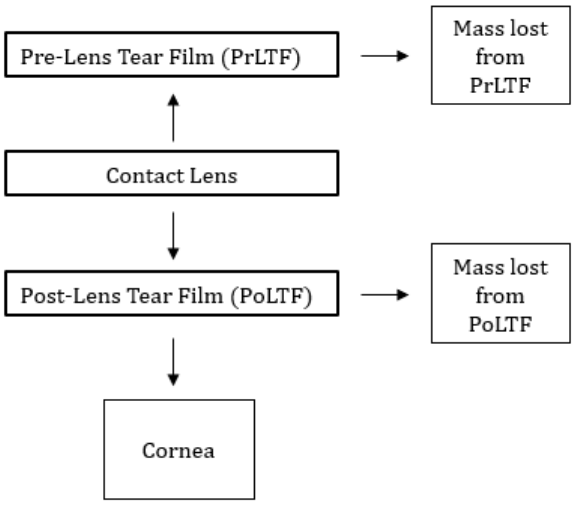

Figure 2: Schematic model of the contact lens system. Arrows indicate direction of diffusion. Concentration values C_i are found for the bolded boxes.

We construct a compartment model consisting of a system of partial and ordinary differential equations to describe the dynamics of the drug concentration. The three concentration variables to be considered are:

C, drug concentration in the contact lens
C_{pre}, drug concentration in PrLTF
C_{post}, drug concentration in PoLTF

We also build ordinary differential equations for the thickness of the PrLTF and PoLTF over time.

The following subsections describe the dynamics of drug flow between the three regions.

2.1 Assumptions

We now discuss more complex assumptions that we will build into our model. We consider factors that will change the thickness or concentration of a compartment during a single blink and across many blink cycles.

Evaporation of the PrLTF removes water, increasing the concentration of the drug in the PrLTF between blinks. During a blink, the fluid in the PrLTF is replenished and some portion of the drug is swept away during the blink. During a blink,

the contact lens moves due to lid motion in both the lateral (along the cornea) and transverse (towards/away from the cornea) directions. This creates a squeezing effect in the PoLTF that removes fluid at the periphery of the contact lens. We assume there is no deformation of the contact lens shape from blinking or PrLTF or PoLTF motion.

Initially the contact lens is uniformly saturated with a drug at concentration C_{init}. The contact lens thickness (200 μm) is much smaller than its lateral extent $\mathcal{O}(\text{cm})$ and so diffusion in the lateral direction is neglected. The pre- and post-lens films each have thicknesses on the order of 5μm and as such are much thinner than the contact lens. An estimate for the diffusion coefficient in the pre- and post-lens tear films is $D_{\text{film}} = 5 \times 10^{-10}\text{m}^2$ /s. Using the thickness $h_{\text{film}} = 5\mu$m gives an estimate for the time scale of diffusion across the thickness of the contact lens as $h_{\text{film}}^2/D_{\text{film}} = 0.05$s. In the contact lens the effective diffusion coefficient is $D_{\text{eff}} = 5 \times 10^{-12}\text{m}^2\ \text{s}^{-1}$. The corresponding time scale for diffusion across the lens is $H^2/D_{\text{eff}} = 8000$s. Given the time scale estimates above, we assume that the pre- and post-lens tear films are uniformly mixed and have concentrations $C_{\text{pre}}(t)$ and $C_{\text{post}}(t)$ that depend only on time. The diffusion problem in the contact lens neglects diffusion in the lateral direction (along the cornea) and addresses only diffusion in the transverse direction. Osmosis adds water to the PoLTF from the cornea, diluting the concentration of the drug in the PoLTF (although we do not directly include this effect). A restoring term (that could be driven by osmosis and/or by elastic rebound of the lens after a blink) will be included to allow the post lens tear film to, on average over multiple blink cycles, maintain a steady thickness. The drug cannot come around the CL from the PrLTF and get to the PoLTF.

2.2 The Contact Lens Solution

If we begin by ignoring the PrLTF and PoLTF, we can focus on the CL itself and create a simple model for the dynamics of the drug concentration. The simplest possible is a basic diffusion model:

$$\partial_t C = D\partial_z^2 C, \quad -L < z < L \tag{1}$$

with $C(z,0) = 1$ for $-L < z < L$ and $C(z,0) = 0$ else, with a symmetry condition $\partial_z C(0,t) = 0$. This assumes an infinite bath of fluid for the drug to diffuse outward through. If we assume instead that $\partial_z C(\pm L, t) = 0$, we are assuming no drug concentration escapes through the top or bottom of the lens.

Under this simple model, the amount of drug released up to time t, denoted M_t

is (counting both sides)

$$M_t \;=\; -2\int_0^t D\frac{\partial C}{\partial z}(x=L,t)dt$$

The problem listed above has an exact solution and the fractional drug release can be expressed as

$$\frac{M_t}{M_\infty} \;=\; 1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left[-\frac{(2n+1)^2\pi^2}{4}\frac{Dt}{L^2}\right]$$

In the contact lens, we must account for the different layers. We assign the PoLTF-cornea boundary the value $z=0$. Let $h_{\text{post}}(t)$ be the width of the PoLTF, H be the width of the contact lens and h_{pre} the width of the PrLTF. Then if C_{post} and C_{pre} are the concentrations in PoLTF and PrLTF, respectively, then we impose a new boundary condition for the concentration C on the contact lens. This boundary condition couples the contact lens concentration to that of the PrLFT and PoLFT.

Thus we obtain the model shown below. Here, k is the partition coefficient of the lens-tearfilm boundary. See Figure 3 for a visual representation of the model with boundary conditions.

$$\begin{array}{ll} C(h_{\text{post}},t)=kC_{\text{pre}}(t) & t>0 \\ \partial_t C = D\partial_z^2 C, & h_{\text{post}}<z<h_{\text{post}}+H \\ C(h_{\text{post}},t)=kC_{\text{post}}(t) & t>0 \end{array} \tag{2}$$

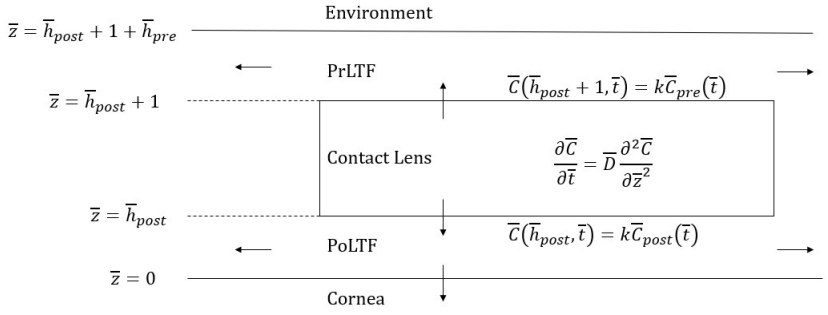

Figure 3: The concentration $\overline{C}$ of drug on the contact lens satisfies the PDE and boundary conditions displayed. Direction of flow is indicated by arrows.

2.3 Pre-Lens Tear Film Equations

We develop the model in the PrLTF by considering the physical aspects of blinking and evaporation. The height of the tear film layer h_{pre} will decrease depending on the evaporation J, only to be replenished by blinking. We choose the simplest possible expression for J and let it be constant. We model a blink by a repeated Gaussian $G(t)$; this restores the height of the fluid. Thus we get a differential equation for h_{pre}.

$$\frac{dh_{\text{pre}}}{dt} = -J + J \cdot G(t) \tag{3}$$

Next we consider how the mass m_{pre} of drug in the PrLTF fluctuates due to diffusion from the contact lens and washing away by blinking. We find the mass by its physical definition. Here, A is the cross-sectional area of the TF.

$$m_{\text{pre}}(t) = A \cdot h_{\text{pre}} \cdot C_{\text{pre}} \tag{4}$$

The influx of mass from the contact lens will be the spatial derivative of the CL solution C evaluated at the CL-PrLTF boundary. During a blink, fresh fluid wipes away some proportion r_{pre} of the amount of mass m_{pre} present. This removal happens in a wave similar to the rise of h_{pre}. Thus we get a differential equation of the form

$$\frac{d}{dt}(m_{\text{pre}}) = A\left(-r_{\text{pre}} h_{\text{pre}} C_{\text{pre}} G(t) - D\left.\frac{\partial C}{\partial z}\right|_{z=H+h_{\text{post}}}\right) \tag{5}$$

Writing in terms of C_{pre}, and canceling the common term A, we obtain our system for PrLTF.

$$\begin{aligned} &\frac{dh_{\text{pre}}}{dt} = -J + J \cdot G(t) && t > 0 \\ &\frac{d}{dt}(h_{\text{pre}} C_{\text{pre}}) = -r_{\text{pre}} h_{\text{pre}} C_{\text{pre}} G(t) - D\left.\frac{\partial C}{\partial z}\right|_{z=H+h_{\text{post}}} \end{aligned} \tag{6}$$

2.4 Post-Lens Tear Film Model

For the PoLTF, we have

$$\frac{dh_{\text{post}}}{dt} = Q_B^{\text{post}} + Q_{\text{rebound}}^{\text{post}} \tag{7}$$

$$\frac{d}{dt}(h_{\text{post}} C_{\text{post}}) = D\left.\frac{\partial C}{\partial z}\right|_{z=H} - k_C C_{\text{post}} - Q_B^{\text{post, C}} + Q_{\text{rebound}}^{\text{post, C}} \tag{8}$$

Each of the terms is described in the table below:

Q_B^{post}	compression of the PoLFT during the blinking phase
$Q_{\text{rebound}}^{\text{post}}$	the return of h_{post} to the initial maximum height $h_{\text{post}}^{\text{init}}$
$D\,\frac{\partial C}{\partial z}\big\vert_{z=H}$	influx due to diffusion from the contact lens
$-k_C C_{\text{post}}$	outflux from PoLFT into the cornea
$Q_B^{\text{post, C}}$	mass flux leaving the system due to squeezing of the PoLFT during blinking
$Q_{\text{rebound}}^{\text{post, C}}$	mass flux reentering the system during rebound

2.4.1 Blink force

We first consider the fluxes in the PoLTF resulting from the blink. We can model the situation as a classic fluid mechanics problem of a force applied to a flat plate sitting on top of a thin film; see [6] for further details on starting assumptions and consequences. The film is assumed to have thickness $h(t)$. Let the coordinate horizontally along the film be x and vertically through the film be z. We will think of the CL as applying a downward force F to the PoLTF, where the CL has its edges at $x = \pm W$. The thin film approximation of the Navier-Stokes equations in 2D is

$$0 = -\partial_z p, \tag{9}$$

$$0 = -\partial_x p + \mu \partial_z^2 u, \tag{10}$$

$$0 = \partial_x u + \partial_z v, \tag{11}$$

where the first two equations are conservation of momentum in the $z-$ and $x-$ directions, respectively, and the last is the continuity equation. The boundary conditions are no slip and no flux at $z = 0$: $u = 0, v = 0$, no slip on the plate at $z = h$: $v = \frac{dh}{dt}$, and we allow for tangential movement of the fluid along the bottom of the plate: $u = U_0(t)$ at $z = h$. We also have a pressure boundary condition: $p = 0$ at $x = \pm W$. Here, we are letting $p = p' - p_0$, where p' is the actual pressure and p_0 is atmospheric pressure.

We begin by noting that Eqn. (9) implies p is independent of z, and thus we may integrate Eqn. (10) twice in z to find that

$$u(x, z, t) = \frac{1}{2\mu}\partial_x p(z^2 - hz) + \frac{U_0(t)z}{h}, \tag{12}$$

where we have implemented the boundary conditions. Next, using the continuity equation, we see that

$$v = -\frac{1}{2\mu}\partial_x^2 p \int_0^z (s^2 - sh)\ ds = -\frac{1}{\mu}\partial_x^2 p \left(\frac{z^3}{6} - \frac{z^2 h}{4}\right). \tag{13}$$

Evaluating v at the film/plate interface gives

$$\frac{dh}{dt} = \frac{\partial_x^2 p}{12\mu} h^3. \tag{14}$$

Rearranging for an equation for p, integrating twice in x and applying boundary conditions gives

$$p = \frac{6\mu}{h^3}\frac{dh}{dt}(x^2 - W^2). \tag{15}$$

We now note that the force applied to the fluid by the CL should balance the total pressure across the lens:

$$0 = F + \int_{-W}^{W} p\ dx. \tag{16}$$

Thus, integrating pressure along the lens, we find

$$F = -\frac{6\mu}{h^3}\frac{dh}{dt}\int_{-W}^{W}(x^2 - W^2)dx = \frac{8\mu}{h^3}\frac{dh}{dt}W^3. \tag{17}$$

This suggests a form for Q_B^{post} given below:

$$Q_B^{\text{post}} = \frac{F h_{\text{post}}^3}{8\mu W^3}. \tag{18}$$

It is worth noting that $h(t) \ll W$ for all times. Thus, this force applied by the lens must be very large in order to change the thickness of the PoLTF. We will choose this expression for dh/dt for Q_B^{post}, and at least initially choose Q_E (elastic flux) so that it restores the fluid lost by Q_B^{post}.

Another way we could arrive at Q_B^{post} is by computing

$$Q_B^{\text{post}} = \int_0^h u\ dz \tag{19}$$

at both edges of the lens. Here, we are assuming this is the flux of fluid that escapes laterally beyond the lens. Then we will choose $Q_B^{\text{post},C}$ to be $C_{\text{post}} Q_B^{\text{post}}$. To this end,

$$\int_0^h u|_{x=W} dz = \frac{1}{2\mu}\partial_x p \int_0^h (z^2 - zh)\ dz + \frac{U_0}{h}\int_0^h z\ dz = -\frac{h^3}{12\mu}\partial_x p|_{x=W} + \frac{U_0 h}{2}. \tag{20}$$

Differentiating Eqn. (15) in x and subtituting this into Eqn. (20), after cancelation we have

$$-\frac{dh}{dt}w + \frac{U_0 h}{2}. \tag{21}$$

Note that this is the outward flux at $x = W$, where the outward normal vector points in the same direction. The outward flux at $x = -W$ points opposite the outward normal vector, so that we will choose

$$Q_B^{\text{post},C} = -C_{\text{post}}\frac{dh_{\text{post}}}{dt} \tag{22}$$

for the total concentration flux if $dh/dt < 0$, and $Q_B^{c,\text{post}} = 0$ if $dh/dt > 0$.

2.4.2 Other fluxes

We choose the quantity $Q_{\text{rebound}}^{\text{post}}$ to reflect the relatively slow bounce-back of h_{post} to $h_{\text{post}}^{\text{init}}$. According to Maki and Ross [7] the eye can take up to 5 second after a blink to return to the equilibrium length $h_{\text{post}}^{\text{init}}$. Thus we choose $Q_{\text{rebound}}^{\text{post}}$ so that the resultant h_{post} behaves like a hill function: we want rapid initial rebound, then a slow-down as h_{post} rises. Thus we choose

$$Q_{\text{rebound}}^{\text{post}} = K_R(h_{\text{post}}^{\text{init}} - h_{\text{post}}), \tag{23}$$

with K_R chosen to ensure the correct qualitative behavior of h_{post}.

Furthermore, we assume that during rebound, none of the escaped drug returns to the system. Therefore we set $Q_{\text{rebound}}^{\text{post},C} = 0$. Combining, we get the following equations for PoLTF:

$$\frac{dh_{\text{post}}}{dt} = -\frac{Fh_{\text{post}}^3}{8\mu W^3}G(t) + K_R(h_{\text{post}}^{\text{init}} - h_{\text{post}}), \tag{24}$$

$$\frac{d}{dt}(h_{\text{post}}C_{\text{post}}) = C_{\text{post}}\left(\frac{dh_{\text{post}}}{dt}\right)^{-} G(t) + D\partial_z C|_{z=h_{\text{post}}} - k_c C_{\text{post}}(t), \tag{25}$$

where k_c is the partition coefficient of the cornea-PoLTF boundary and

$$\left(\frac{dh_{\text{post}}}{dt}\right)^{-} = \min\left\{\frac{dh_{\text{post}}}{dt}, 0\right\}.$$

perhaps $G_R = \kappa(1 - G(t))$ so that the restoring force acts only between blinks. This might need to be, in total on a blink cycle, around $h_{\text{post}} - h_{\text{eq}}$ so that the PoLTF thickness never goes to zero.

3 Analytical Solution to the Contact Lens Layer

Here we show our analysis of an explicit solution to the diffusion equation governing the concentration $C(t)$ of the drug within the contact lens. This is based on [8], although we believe their solution to be erroneous. We provide our analysis of their solution, ignoring errors. We also include our own, corrected solution in Section 3.6.

The system we wish to solve is:

$$\begin{cases} C(h_{\text{post}} + H, t) & = k \cdot C_{\text{pre}}(t) \\ \frac{\partial C}{\partial t} & = D\frac{\partial^2 C}{\partial z^2} \\ C(h_{\text{post}}, t) & = k \cdot C_{\text{post}}(t) \end{cases} \tag{26}$$

We incorporate the PrLTF and PoLTF boundary conditions separately by making substitutions of $z = s$ and $z = H - s$ into the solution from [8]. This yields two independent solutions which we can add to find $C(t)$:

3.1 Li-Chauhan Solution

Li et al started with a system similar to ours:

$$\begin{cases} C(z = H, t) = k \cdot C_{\text{pre}}(t) \\ \frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial z^2} \\ C(z = 0, t) = 0 \\ C(z, t = 0) = C_{\text{init}} \end{cases} \tag{27}$$

$$\begin{aligned} C(z,t) \;=\; & C_i \sum_{n=0}^{\infty} \frac{4}{(2n+1)\pi} \sin\left(\frac{(2n+1)\pi z}{H}\right) e^{\frac{-(2n+1)^2\pi^2}{H^2} D \cdot t} \\ & + KC_{\text{pre}}(t)\left[\frac{z}{H} + \sum_{n=1}^{\infty} \frac{2(-1)^n}{n\pi} \sin(\frac{n\pi z}{H})\right] \\ & - K\int_0^t C_{\text{pre}}(\tau) \sum_{n=1}^{\infty} 2(-1)^n \frac{n\pi D}{H^2} \sin\left(\frac{n\pi z}{H}\right) e^{\frac{(-n^2\pi^2)D(t-\tau)}{H^2}} d\tau \end{aligned} \tag{28}$$

We adapt this solution for our diffusion system in two separate parts as below:

3.2 System 1

By substituting $(H - z)$ for z we obtain a solution for diffusion system with zero concentration within the PrLTF and drug diffusion to only to the PoLTF; call this

the PoLFT solution.

$$\begin{aligned} &C_1(z = h_{\text{post}} + H, t) = 0 \\ &\frac{\partial C_1}{\partial t} = D\frac{\partial^2 C_1}{\partial z^2} \\ &C_1(z = h_{\text{post}}, t) = k \cdot C_{\text{post}}(t) \\ &C_1(z, t = 0) = \frac{1}{2}C_{\text{init}} \end{aligned} \tag{29}$$

The full analytical solution is found to be:

$$\begin{aligned} C_1(z,t) \;=\; & \frac{1}{2}C_i \sum_{n=0}^{\infty} \frac{4}{(2n+1)\pi} \sin\left(\frac{(2n+1)\pi(H-z)}{H}\right) e^{\frac{-(2n+1)^2\pi^2}{H^2}D\cdot t} \\ & + KC_{\text{post}}(t)\left[\frac{z}{H} + \sum_{n=1}^{\infty} \frac{2(-1)^n}{n\pi}\sin(\frac{n\pi(H-z)}{H})\right] \\ & - K\int_0^t C_{\text{post}}(\tau) \sum_{n=1}^{\infty} 2(-1)^n \frac{n\pi D}{H^2} \sin\left(\frac{n\pi(H-z)}{H}\right) e^{\frac{(-n^2\pi^2)D(t-\tau)}{H^2}} d\tau \end{aligned} \tag{30}$$

3.3 System 2

Equation 27 gives a direct solution for the diffusion system with zero concentration within the PotLTF and drug diffusion only to the PrLTF; call this the PrLFT solution.

$$\begin{aligned} &C_2(z = h_{\text{post}} + H, t) = k \cdot C_{\text{pre}}(t) \\ &\frac{\partial C_2}{\partial t} = D\frac{\partial^2 C_2}{\partial z^2} \\ &C_2(z = h_{\text{post}}, t) = 0 \\ &C_2(Z, t = 0) = \frac{1}{2}C_{\text{init}} \end{aligned} \tag{31}$$

The full analytical solution is as follows:

$$\begin{aligned} C_2(z,t) &= \frac{1}{2}C_i \sum_{n=0}^{\infty} \frac{4}{(2n+1)\pi} \sin\left(\frac{(2n+1)\pi z}{H}\right) e^{\frac{-(2n+1)^2\pi^2}{H^2}D\cdot t} \\ &\quad + KC_{\text{pre}}(t)\left[\frac{z}{H} + \sum_{n=1}^{\infty} \frac{2(-1)^n}{n\pi}\sin(\frac{n\pi z}{H})\right] \\ &\quad - K\int_0^t C_{\text{pre}}(\tau) \sum_{n=1}^{\infty} 2(-1)^n \frac{n\pi D}{H^2} \sin\left(\frac{n\pi z}{H}\right) e^{\frac{(-n^2\pi^2)D(t-\tau)}{H^2}} d\tau \end{aligned} \tag{32}$$

It can be easily verified that

$$C = C_1 + C_2 \tag{33}$$

is a solution for the diffusion system of 26. Also note that the middle term consisting of the product of $KC_{\text{pre}}(t)$ and z/H plus an infinite sum in equation 30 and equation 32 is zero. To evaluate the drug influx quantities from the PoLTF and PrLFT in 8 and 6, we compute:

$$\begin{aligned} \left.\frac{dC_1}{dz}\right|_{z=0} &= \frac{2}{H}C_i \sum_{n=0}^{\infty} e^{\frac{-(2n+1)^2\pi^2}{H^2}D\cdot t} \\ &\quad - K\int_0^t C_{\text{post}}(\tau) \sum_{n=1}^{\infty} 2(-1)^n \frac{n^2\pi^2 D}{H^3} e^{\frac{(-n^2\pi^2)D(t-\tau)}{H^2}} d\tau \end{aligned} \tag{34}$$

$$\begin{aligned} \left.\frac{dC_2}{dz}\right|_{z=0} &= -\frac{1}{H}C_i \sum_{n=0}^{\infty} e^{\frac{-(2n+1)^2\pi^2}{H^2}D\cdot t} \\ &\quad - K\int_0^t C_{\text{post}}(\tau) \sum_{n=1}^{\infty} 2\frac{n^2\pi^2 D}{H^3} e^{\frac{(-n^2\pi^2)D(t-\tau)}{H^2}} d\tau \end{aligned} \tag{35}$$

$$\tag{36}$$

$$\left.\frac{dC_1}{dz}\right|_{z=H} = -\frac{2}{H}C_i\sum_{n=0}^{\infty} e^{\frac{-(2n+1)^2\pi^2}{H^2}D\cdot t} + K\int_0^t C_{\text{pre}}(\tau)\sum_{n=1}^{\infty} 2\frac{n^2\pi^2 D}{H^3} e^{\frac{(-n^2\pi^2)D(t-\tau)}{H^2}} d\tau \quad (37)$$

$$\left.\frac{dC_2}{dz}\right|_{z=H} = -\frac{2}{H}C_i\sum_{n=0}^{\infty} e^{\frac{-(2n+1)^2\pi^2}{H^2}D\cdot t} - K\int_0^t C_{\text{pre}}(\tau)\sum_{n=1}^{\infty} 2\frac{n^2\pi^2 D}{H^3} e^{\frac{(-n^2\pi^2)D(t-\tau)}{H^2}} d\tau \quad (38)$$

3.4 Pre-lens and post-lens flux solutions

We now have enough materials for evaluating $F_{\text{pre}}(t)$:

$$F_{\text{pre}}(t) = \left.\frac{dC}{dy}\right|_{z=y} = \left.\frac{dC_1}{dy}\right|_{y=0} + \left.\frac{dC_2}{dy}\right|_{y=0} \quad (39)$$

By appropriate cancellation and merging terms based on results above, we have:

$$\begin{aligned} F_{\text{pre}}(t) &= \left.\frac{dC}{dy}\right|_{y=0} \\ &= C_i\sum_{n=0}^{\infty} -\frac{4}{H} e^{-\frac{-(2n+1)^2\pi^2}{H^2}D\cdot t} \\ &\quad + K\int_0^t \sum_{n=1}^{\infty} 2(-1)^n (C_{\text{pre}}(\tau)\cos(n\pi) - C_{\text{post}}(\tau))\frac{n^2\pi^2 D}{H^3} e^{\frac{-\pi^2 n^2}{H^2}D\cdot(t-\tau)} d\tau \end{aligned} \quad (40)$$

Similarly, we find $F_{\text{post}}(t)$:

$$F_{\text{pre}}(t) = \left.\frac{dC}{dy}\right|_{y=H} = \left.\frac{dC_1}{dy}\right|_{y=H} + \left.\frac{dC_2}{dy}\right|_{y=H} \quad (41)$$

$$
\begin{aligned}
F_{\text{post}}(t) &= \left.\frac{dC}{dy}\right|_{y=0} \\
&= C_i \sum_{n=0}^{\infty} \frac{4}{H} e^{-\frac{-(2n+1)^2\pi^2}{H^2} D \cdot t} \\
&\quad + K \int_0^t \sum_{n=1}^{\infty} 2(-1)^n (C_{\text{post}}(\tau)\cos(n\pi) - C_{\text{pre}}(\tau)) \frac{n^2\pi^2 D}{H^3} e^{\frac{-\pi^2 n^2}{H^2} D \cdot (t-\tau)} d\tau
\end{aligned}
\tag{42}
$$

We note that we could use numerical techniques with this solution to find the fluxes into the PrLTF and PoLTF by approximating ∂C_z. One option would be to use cubic splines along with boosting to find a discrete prediction of $C_{\text{pre}}(t)$ and $C_{\text{post}}(t)$. Then we could employ an appropriate quadrature rule for numerical integration.

3.5 Issues with Li-Chauhan Solution

We end this section by commenting on the solution in [9]. It is repeated below for consideration.

$$
\begin{aligned}
C_1(z,t) &= \frac{1}{2} C_i \sum_{n=0}^{\infty} \frac{4}{(2n+1)\pi} \sin\left(\frac{(2n+1)\pi(H-z)}{H}\right) e^{\frac{-(2n+1)^2\pi^2}{H^2} D \cdot t} \\
&\quad + K C_{\text{post}}(t) \left[\frac{z}{H} + \sum_{n=1}^{\infty} \frac{2(-1)^n}{n\pi} \sin\left(\frac{n\pi(H-z)}{H}\right)\right] \\
&\quad - K \int_0^t C_{\text{post}}(\tau) \sum_{n=1}^{\infty} 2(-1)^n \frac{n\pi D}{H^2} \sin\left(\frac{n\pi(H-z)}{H}\right) e^{\frac{(-n^2\pi^2)D(t-\tau)}{H^2}} d\tau
\end{aligned}
$$

If one attempts to verify that it is a solution to the heat equation, then one must be careful in passing the derivative under the infinite summations. In fact, when we take the derivatives with respect to t of the second and third terms, we run into major issues. In both terms, we find that the putative derivative is not uniformly convergent–not convergent at all in this case! Thus we cannot pass the derivative under the summations.

We note that the Fourier series in the second term, with coefficients $\frac{2(-1)^n}{n\pi}$, is the Fourier series for $-\frac{z}{H}$, and thus the second term is actually 0. The third term is not

so easily dispatched, as far as we can tell, and attempts to take its t derivative will be unsuccessful for the above reasons.

This solution is still quite close to the one we obtain below, and perhaps a formal integration by parts would bridge the gap between the two.

3.6 Analytic Solution to the Diffusion Equation in the Lens

The diffusion equation within the lens for our model is a homogeneous heat equation with non-constant boundary conditions, C_{pre} and C_{post}. It is coupled with the compartments generating these boundary conditions as well. We write our solution using Fourier Series, and so we take an approach using Duhamel's Principle.

The problem is to find $C(z,t)$ satisfying the conditions below.

$$\begin{cases} \dfrac{dC}{dt} = D\dfrac{d^2C}{dz^2} & 0 < z < H, 0 < t \\ C(z,0) = C_i = 1 & 0 < z < H \\ C(0,t) = C_{\text{post}}(t) & 0 < t \\ C(H,t) = C_{\text{pre}}(t) & 0 < t \end{cases}$$

We approach this problem by first dealing with the two boundary conditions. We define two simple functions, f_{pre} and f_{post}, to account for the respective boundary conditions. We define

$$f_{\text{pre}}(y,t) = C_{\text{pre}}(t)\frac{y}{H} \tag{43}$$

$$f_{\text{post}}(y,t) = C_{\text{post}}(t)\frac{H-y}{H} \tag{44}$$

These solve the following systems of equations. We recall that C_{pre} and C_{post} are both 0 when $t = 0$.

$$\begin{cases} \dfrac{df_{\text{pre}}}{dt} = D\dfrac{d^2f_{\text{pre}}}{dz^2} + C'_{\text{pre}}\dfrac{y}{H} & 0 < z < H, 0 < t \\ f_{\text{pre}}(z,0) = 0 & 0 < z < H \\ f_{\text{pre}}(0,t) = 0 & 0 < t \\ f_{\text{pre}}(H,t) = C_{\text{pre}}(t) & 0 < t \end{cases} \quad \begin{cases} \dfrac{df_{\text{post}}}{dt} = D\dfrac{d^2f_{\text{post}}}{dz^2} + C'_{\text{post}}\dfrac{y}{H} & 0 < z < H, 0 < t \\ f_{\text{post}}(z,0) = 0 & 0 < z < H \\ f_{\text{post}}(0,t) = C_{\text{post}}(t) & 0 < t \\ f_{\text{post}}(H,t) = 0 & 0 < t \end{cases}$$

We will construct our solution $C = f_{\text{pre}} + f_{\text{post}} + u$, where u solves the inhomogeneous system below.

$$\begin{cases} \dfrac{du}{dt} = D\dfrac{d^2u}{dz^2} + C'_{\text{pre}}\dfrac{y}{H} + C'_{\text{post}}\dfrac{H-y}{H} & 0 < z < H, 0 < t \\ u(z,0) = C_i = 1 & 0 < z < H \\ u(0,t) = 0 & 0 < t \\ u(H,t) = 0 & 0 < t \end{cases}$$

This system is solved through the use of a sin Fourier series expansion of the initial condition. The boundary conditions are accounted for using Duhamel's principle, and this gives us the following formula for the concentration.

$$\begin{aligned} &C(y,t) = \\ &C_i \sum_{n=0}^{\infty} \frac{4}{(2n+1)\pi} \sin\left(\frac{(2n+1)\pi}{H} z\right) e^{\dfrac{-(2n+1)^2\pi^2}{H^2} Dt} \\ &+ \frac{1}{H}\left[C_{\text{pre}}(t)z + C_{\text{post}}(t)(H-z)\right] \\ &+ \frac{1}{H} \sum_{n=1}^{\infty} \int_0^t \left(\frac{2(-1)^n}{n\pi}\right) \left[C'_{\text{pre}}(\tau) \sin\left(\frac{n\pi}{H} z\right) + C'_{\text{post}} \sin\left(\frac{n\pi}{H}(H-z)\right)\right] \\ &e^{-D\left(\frac{n\pi}{H}\right)^2 (t-\tau)} \, d\tau \end{aligned}$$

We invite the reader to verify that this does solve the system 3.6. The first term of $C(y,t)$ is itself a solution of the homogeneous heat equation with Dirichlet boundary conditions. The second term clearly satisfies the nonzero boundary conditions, but upon derivation with respect to t, new terms appear. Careful differentiation of the third term using Leibniz rule yields a term which cancels with this one.

To check the initial and boundary conditions, it is important to note that the first term contains the sine series for the constant 1, and that the third term contains the sign series for $-z$, used twice.

We note that the solution given in [9, eq.A2-15] is very similar to ours. They take a Laplace transform approach. However, careful examination shows that their formula is incorrect, and in fact not differentiable. The second term in their equation is actually zero–although this is hidden behind a sine series–and the third term is not differentiable in time, if one pays attention to the convergence rate of the derivative.

However, if one naively differentiates through the summation sign, without respect to appropriate convergence, then you can verify that their formula "formally" solves the problem. Our solution is very close to theirs, and may only differ by a formal integration by parts.

4 Nondimensionalization

We now move towards a numerical solution of the full problem. In doing so we will discretize even the diffusion problem discussed above, although as mentioned it has an analytic solution. Whether solved analytically or numerically, nondimensionalization is required to identify dominant parameters and to make the problem physically relevant. In order to nondimensionalize the system, we must pick essential quantities in several different units used in our problem. We choose the height of the contact lens in meters, H, as our characteristic length, the time of one blink cycle in seconds, t_B, and the initial concentration of the drug in the contact lens C_{init} as our base variable for concentration. All other variables are nondimensionalized in terms of these.

4.1 Justification of 1D diffusion model

Note that if we look again at the problem just in the CL, we could begin with a two dimensional version of the diffusion equation and argue that due to our scalings, the problem may be reduced to one in a single spatial variable.

Defining scalings for our variables in terms of characteristic units:

$$\bar{x} = \frac{x}{W}, \quad \bar{z} = \frac{z}{H}, \quad \bar{t} = \frac{t}{t_B}, \bar{C} = \frac{C}{C_{\text{init}}},$$

we let bars denote dimensionless variables and $W \gg H$. Here, we are modeling the TF-CL system so that the z-axis is aligned perpendicular to the lens and the x-axis is aligned along the lens. Inserting this into the 2D diffusion equation gives

$$\frac{C_{\text{init}}}{t_B}\partial_t C = \frac{C_{\text{init}} D}{H^2}\left(\partial_z^2 C + \left(\frac{H}{W}\right)^2 \partial_x^2 C\right) \tag{45}$$

Letting $H/W = \epsilon$, we see that at leading order in ϵ, the above equation becomes

$$\partial_t C = \frac{t_B D}{H^2}\partial_z^2 C. \tag{46}$$

This suggests that in a lubrication theory setting like the TF, a one-dimensional model in space is sufficient to capture the dynamics of the system.

4.2 Variables

We list variables that are now non-dimensionalized:

$$\bar{t} = \frac{t}{t_B} \tag{47}$$

$$\overline{z} = \frac{d}{H} \tag{48}$$

$$\overline{h}_{\,\mathrm{pre}} = \frac{h_{\mathrm{pre}}}{H} \tag{49}$$

$$\overline{h}_{\,\mathrm{post}} = \frac{h_{\mathrm{post}}}{H} \tag{50}$$

$$\overline{C} = \frac{C}{C_{\mathrm{init}}} \tag{51}$$

$$\overline{C}_{\,\mathrm{pre}} = \frac{C_{\mathrm{pre}}}{C_{\mathrm{init}}} \tag{52}$$

$$\overline{C}_{\,\mathrm{post}} = \frac{C_{\mathrm{post}}}{C_{\mathrm{init}}} \tag{53}$$

$$\overline{G}\,(\,\bar{t}\,) = t_B G(t) \tag{54}$$

$$\overline{W} = \frac{W}{H} \tag{55}$$

$$\overline{J} = \frac{t_B}{H} J \tag{56}$$

$$\overline{D} = \frac{t_B}{H^2} D \tag{57}$$

$$\overline{F} = \frac{t_B F_{\mathrm{blink}}}{8\mu H\,\overline{W}^{\,3}} \tag{58}$$

$$\overline{K}_{\,L} = \frac{K_L t_B}{H} \tag{59}$$

$$\overline{\sigma} = \frac{\sigma}{t_B} \tag{60}$$

Many of these are standard substitutions, but we highlight the function $G(t)$. We have chosen $G(t)$ to be an approximation of the Dirac delta function. (Several such substitutions might be made, with various levels of accuracy in correctly approximating the motion and effect of an eye blink.) However, this necessitates $G(t)$ have the units $1/s$, and so even this must be nondimensionalized.

We also remark on the variables $\overline{W}$, $\overline{J}$, $\overline{D}$, $\overline{F}$, and $\overline{K_L}$ as they are governing parameters for the system. These are the parameters that affect the behavior and outcome of the system, such as total drug absorbed into the cornea, or lost into the rest of the eye.

4.3 Numerical Parameter Values

Parameter values k, K_c and D were obtained from the paper by Li & Chauhan [9]. Estimates for the blink force were from papers by Chauhan & Radke (2002) and Martin & Holden (1986). From a study involving 42 healthy TF subjects, the average blink rate was measured at 11 blinks/min [10]. Consider moving this to the results section: The drug diffuses out of the contact lens after approximately $\frac{(2\times10^{-4}m)^2}{5\times10^{-12}m^2}s$, or about 2 hours. This corresponds to about 1600 blinks, assuming the subject blinks

every 5 seconds. For the post- and pre- lens, the drug diffuses through these regions in about 0.05 seconds. add citation

Many of our parameter values were taken from [11], whose authors used a similar model framework. We list these values below, along with their corresponding dimensionless parameters.

4.3.1 Table of Variables and Parameters

t_B	length of blink cycle	5 s	$\bar{t}_B$	1
H	CL height	2^{-4} m	$\overline{H}$	1
J	PrLTF evaporation rate	$\frac{1}{6} \times 10^{-7} m/s$	$\overline{J}$	4.167×10^{-4}
$h_{\text{pre}}^{\text{init}}$	PrLTF initial height	5×10^{-6} m	$\overline{h}_{\text{pre}}^{\text{init}}$	2.5×10^{-2}
$h_{\text{post}}^{\text{init}}$	PoLTF initial height	5×10^{-6} m	$\overline{h}_{\text{post}}^{\text{init}}$	7.5×10^{-2}
W	CL width	7×10^{-3} m	$\overline{W}$	35
D	CL diffusion constant	5×10^{-12} m^2/s	$\overline{D}$	6.25×10^{-4}
	CL-TF boundary diffusion coefficient		k	5
K_c	PoLFT-cornea boundary diffusion coefficient	1.5×10^{-7}m/s	$\overline{K}_c$	3.75×10^{-3}
K_R	PoLFT rebound coefficient	5	$\overline{K}_R$	1
μ	TF viscosity	1.3×10^{-3}Pa$\cdot$ s		
F	force exerted by CL on PoLTF	1-10 N/m	$\overline{F}$	5.61×10^2

4.4 Equations in Nondimensional Form

We now write out our system of equations in these new variables, beginning with the ordinary differential equations, followed by the partial differential equation governing the diffusion of the drug through the hydrogel lens. In the upcoming section, we compute a numerical solution to this system of differential equations.

$$\frac{d\,\overline{h}_{\text{pre}}}{d\,\overline{t}} = -\,\overline{J} + \overline{J}\,\overline{G}\,(\,\overline{t}\,) \tag{61}$$

$$\frac{d\,\overline{h}_{\text{pre}}\,\overline{C}_{\text{pre}}}{d\,\overline{t}} = r_{\text{pre}}\,\overline{C}_{\text{pre}}\,\overline{h}_{\text{pre}}\,\overline{G}\,(\,\overline{t}\,) - \overline{D}\,\frac{d\,\overline{C}}{d\,\overline{z}}\bigg|_{\overline{z}=1+\overline{h}_{\text{post}}} \tag{62}$$

$$\frac{d\,\overline{h}_{\text{post}}}{d\,\overline{t}} = \overline{F}\;\overline{h}_{\text{post}}\,\overline{G}\,(\,\overline{t}\,) + \overline{K}_R(\,\overline{h}_{\text{post}}^{\text{init}} - \overline{h}_{\text{post}}) \tag{63}$$

$$\frac{d\,\overline{h}_{\text{post}}\,\overline{C}_{\text{post}}}{d\,\overline{t}} = \overline{C}_{\text{post}}\left(\frac{d\,\overline{h}_{\text{post}}}{d\,\overline{t}}\right)^{-} + \overline{D}\,\frac{d\,\overline{C}}{d\,\overline{z}}\bigg|_{\overline{z}=\overline{h}_{\text{post}}} - \overline{K}_L\,\overline{C}_{\text{post}} \tag{64}$$

$$\begin{cases} \dfrac{d\,\overline{C}}{d\,\overline{t}} = \overline{D}\,\dfrac{d^2\,\overline{C}}{d\,\overline{z}^{\,2}} & z \in (\,\overline{h}_{\,\text{post}},\, \overline{h}_{\,\text{post}} + 1) \\ \overline{C} = k\,\overline{C}_{\,\text{pre}} & \overline{z} = \overline{h_{\text{post}}} + 1 \\ \overline{C} = k\,\overline{C}_{\,\text{post}} & \overline{z} = \overline{h}_{\,\text{post}} \end{cases}$$

5 Results

The following solutions are obtained numerically. We begin by discretizing the spatial domain of the CL using the Chebyshev spectral collocation method [12]; the resulting system of ODEs at the Chebyshev points along with the ODEs for the thickness of the PrLTF, drug mass in the PrLTF, thickness of the PoLTF, and drug mass in the PoLTF is solved in Matlab 2017a via `ode15s`.

5.1 Numerical solutions

For the plots that follow, we use a decay rate of $r = 10$ to control the mass of the drug leaving the PrLTF and $k_r = 5$ to control the restoring rate at which the PrLTF thickness returns to its initial value. Our nondimensional CL domain is represented by a unit length, where $z = 0$ is the CL/PoLTF boundary, and $z = 1$ is the CL/PrLTF boundary.

There is a distinct difference in the qualitative nature of solutions at short times versus long times. The following two plots highlight the slowness of diffusion in the CL. Each curve represents a different time level measured in number of blink cycles completed. We note that at short times, the middle of the CL remains near initial concentration, while more drug is diffused to the PrLTF than the PoLTF. At long times, the drug has diffused away from the middle of the CL and the concentration is approaching zero at the PrLTF and PoLTF boundaries. We remind the reader that a rough estimate of the time it would take all drug concentration to leave the CL is 1600 blinks; Fig. 5 shows this.

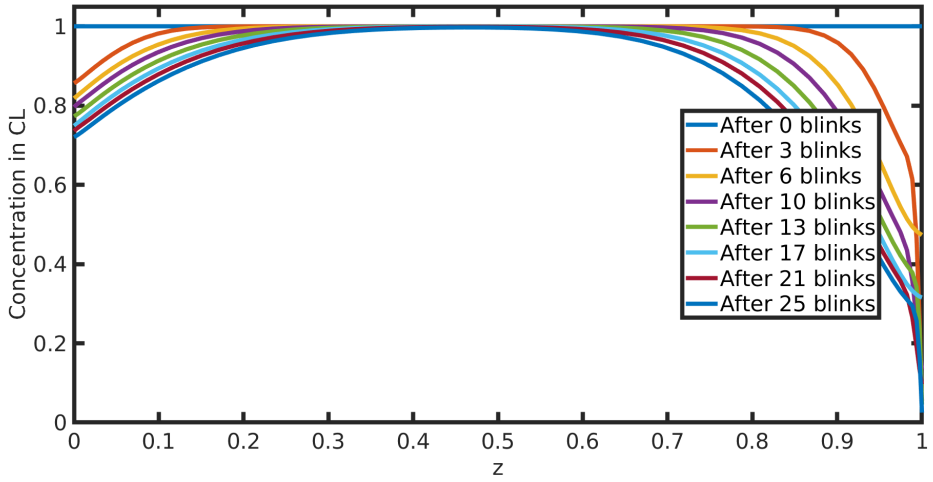

Figure 4: Drug concentration in the CL from the PrLTF ($z = 0$) to the PoLTF ($z = 1$) over 25 blink cycles.

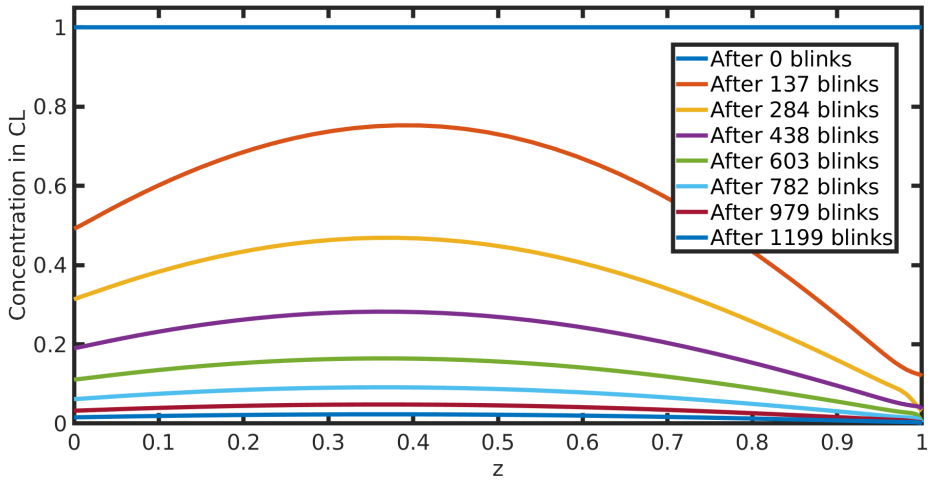

Figure 5: Drug concentration in the CL from the PrLTF to the PoLTF.

Figure Fig. 6 looks at the dynamics in the PrLTF and PoLTF for short times. We recall our assumption that these layers are thin enough relative to the CL that we treat them as point quantities in space that vary over time. The PrLTF over time is changed slightly by evaporation; we expect this tiny oscillation due to the blink

action $G(t)$ and our small evaporation force J. The action of the blink on the PrLTF concentration can be seen by the periodic spikes in the lower left corner plot of Fig. 6. The PoLTF thickness has a greater oscillation than that of the PrLTF due to the downward force from the CL (discussed in section 2.4.1). However, just like the blink action on the PrLTF, there is a restorative force that acts to bring the PoLTF thickness closer to its starting value after each blink. The drug concentration in the PoLTF is not affected by the blink cycle and thus is non-oscillatory, but ultimately decreases over time due to the drug mass lost to the cornea and laterally beyond the CL. The dynamics shown in Fig. 6 are shown only at short times, but their trends continue if we increase the number of blink cycles.

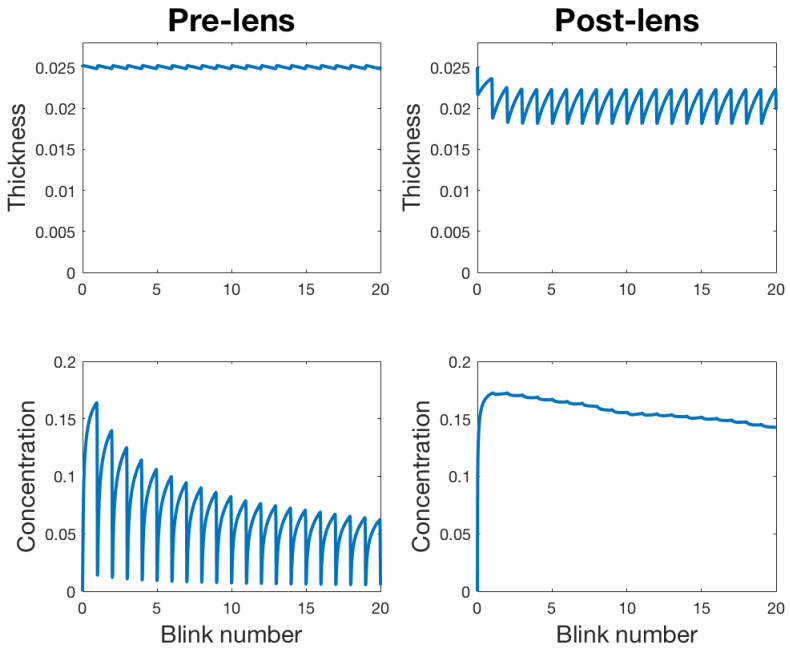

Figure 6: PrLTF and PoLTF thickness and concentration dynamics over 20 blink cycles.

Figures 7, 8, and 9 track the mass of the drug over time as well as how much of the drug has been delivered to the cornea. The force acting on the PoLTF is an order of magnitude greater for the case plotted in Figure 7 than for the case in Figure 8. The lower force case delivers approximately 18% of the initial drug to the cornea, while the higher drug case delivers approximately 25% of the initial drug to the cornea.

In Figure 9, the value of r_{pre} (which controls how much drug is lost during blinking) has been lowered in addition to the force on the PoLTF. As expected, the resulting amount of drug delivered to the cornea is higher than in either of the previous two cases, with approximately 27% of the drug being delivered to the cornea.

In all cases, the drug leaves the system at a decreasing rate, and the proportion of the drug leaving the system that goes to the cornea appears to approach a constant after hundreds of blinks. Moving most of the mass out of the system appears to require around 1200 blinks, which corresponds to one to two hours.

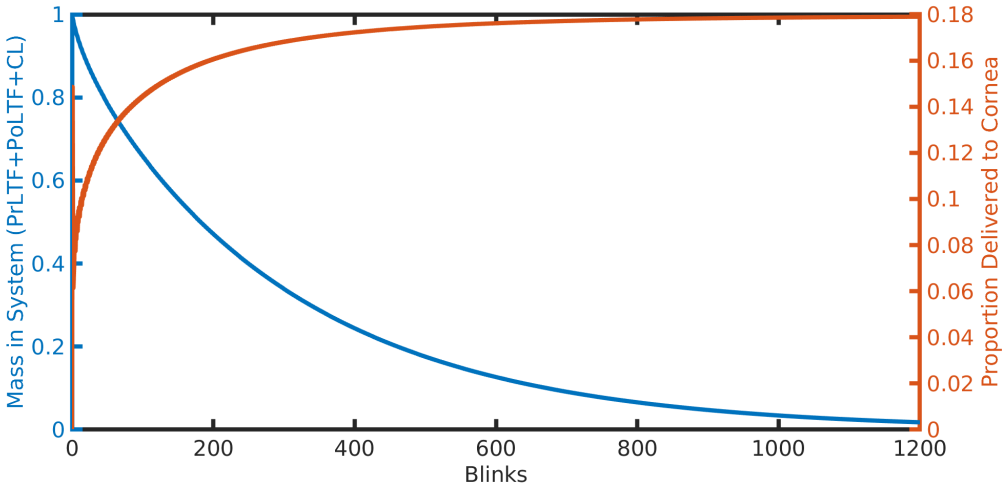

Figure 7: Mass tracked over time.

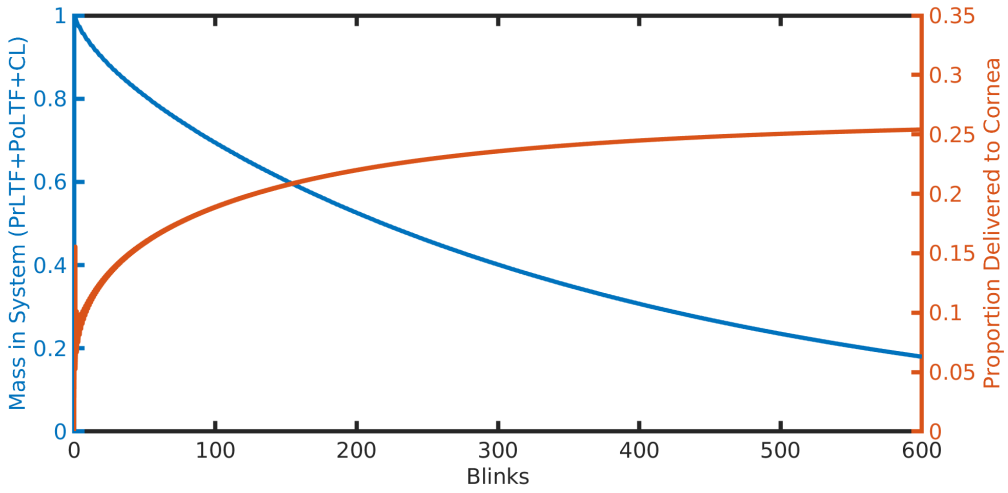

Figure 8: Mass tracked over time with a lower force acting on the PoLTF.

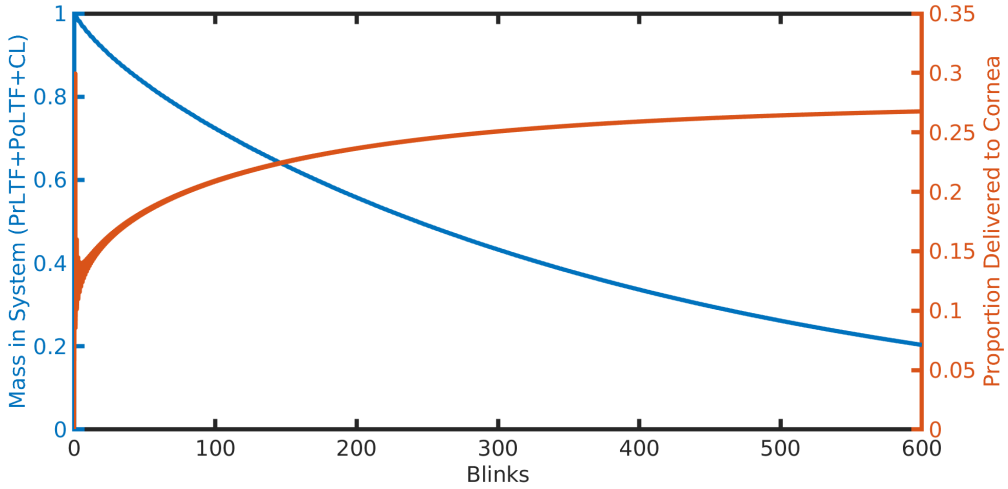

Figure 9: Mass tracked over time with a lower force acting on the PoLTF.

6 Summary

Starting from a very simple diffusion model for the contact lens, we have introduced a framework to incorporate the PrLTF and PoLTF and explored both analytic and

numerical solutions in our quest for a model for the diffusion of a drug from a contact lens into the cornea. Our model involves ODEs for the PrLTF and PoLTF and keeps the diffusion equation for the CL. By coupling these models together at the boundaries, we have found a system of ordinary differential equations and solved that system numerically for various values of the governing parameters.

Exact values for the governing parameters are unknown, but using reasonable estimates from the literature has given results that are consistent with other findings. Specifically, the main result is that approximately 20% of the drug is eventually delivered to the cornea, while 80% is lost to non-targeted areas. The actual amount delivered to the cornea depends on the specific parameters chosen to model what happens to the drug during the blink, such as the force on the PoLTF and the factor capturing how much fluid is washed away from the PoLTF during a blink, k_{pre}.

Avenues for future work include:

- Incorporating the analytical solution to the diffusion equation for the contact lens with time-varying boundary conditions discussed in this paper into the numerical scheme.
- Including the lateral motion of the contact lens in the model.
- Modeling the spatial dependence of the concentration in the PrLTF and PoLTF.
- Considering more complicated expressions for the evaporation function J, perhaps involving an van der Waals term, such as $J = 1 - \left(\frac{h_{\text{eq}}}{h}\right)^3$, that further serve to prevent the film from thinning to zero.

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