Mathematical Modeling of Intraocular Drug Delivery

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Introduction

Human eye is prone to different conditions that need treatment with different medications, delivery methods, concentrations, and time windows. Some of such common condition include age-related macular degeneration (AMD) in older adults that damage retina, glaucoma which is caused by damaged optic nerve and manifested by increased fluid pressure in the anterior chamber of the eye, and diabetic retinopathy, in which the retina is gradually worn due to damage in blood vessels due to diabetes. Figure 1 shows a schematic view of human eye.

Treatment through medication depends on the type of condition and other factors, but they can be broadly classified as systemic and topical. In systemic drug delivery, medication is administered into the bloodstream through injection or soluble pills. In topical delivery, drug is usually administered through drops onto the outer surface of the eye. When the target of the drug is the posterior segment of the eye, these classical methods fall short because of drug dissipation in the bloodstream or incomplete reach from the exterior membrane through drops.

Intravitreal injection or implants are viable alternatives to classical drug delivery method inside the eye in which a therapeutic agent is released from a (non)biodegradable implant in a controlled manner. Because the efficacy of the drug is time critical, it is very important to predict local drug concentration in the eye so that the treatment and follow-ups are administered properly. Mathematical modeling used the chemical, physical, and dynamical properties and phenomena of the implant, the drug, and the eye to predict the diffusion and concentration of drug.

Mathematical Model

Because the main mathematical tool in modeling drug delivery in the eye consists of differential equations with boundaries, our first step is to designate boundaries in the eye that constrain the differential equations. Figure 2 below shows a geometric view of the eye along the boundaries δΩ.

In this study, the purpose is to model the diffusion of the drug starting at the implant through to the target, which is the retina. Therefore, the entire dynamics occur both inside the implant and inside the vitreous, giving two dynamical sub-models that can be coupled. So, we divide the dynamics into two sub-models as drug dynamics inside the implant and drug dynamics inside the vitreous, which are then coupled to form the complete model.

Drug dynamics in the polymer is modeled by the diffusion-reaction PDE’s as follow:

\[
\begin{aligned}
\frac{\partial C_1}{\partial t} &= \nabla (D_1(M) \nabla C_1) + D_v \Delta \sigma - k_1 C_1 \quad \text{in } \Omega_1 \times (0, T) \\
\frac{\partial \sigma}{\partial t} + \frac{\beta}{E} \sigma &= E C_1 \quad \text{in } \Omega_1 \times (0, T) \\
\frac{\partial M}{\partial t} + \beta_1 M &= \beta_2 C_1 \quad \text{in } \Omega_1 \times (0, T)
\end{aligned}
\]

where Ω₁ stands for the implant (a cylindrical device with dispersed drug), C₁ is the drug concentration in the polymer, σ is the stress exerted by the polymer and M represents the polymer molecular weight. The diffusion coefficient of the drug in the polymer, D₁, is a function of the molecular weight, the parameter D_v stands for a stress-driven diffusion coefficient and k₁ is the degradation rate of the drug.

The second equation in the system above relates the stress with the strain ϵ where E is the Young modulus of the polymer.
and \( \mu \) is the polymer viscosity. The third equation in the system shows the degradation of the polymer which governs the diffusion of drug concentration in a decay process:

\[
D_1(M) = \lambda e^{\frac{M_0}{M}}
\]

Where \( M_0 \) is the initial molecular weight.

**Drug dynamics in the vitreous** Once drug is released from the implant, it travels towards the target through the vitreous through convection. Therefore, we need to model both convection and diffusion this compartment of the model by the mass transport equation characterized by diffusion and convection as follows. The velocity of the permeation is governed by Darcy’s law in \( \Omega_2 \).

\[
\frac{\partial C_2}{\partial t} + \mathbf{v} \cdot \nabla C_2 - D_2 \Delta C_2 = 0 \quad \text{in} \quad \Omega_2 \times (0, T]
\]

\[
\mathbf{v} = -\frac{K}{\mu_1} \nabla p \quad \text{in} \quad \Omega_2 \times (0, T]
\]

\[
\nabla \cdot \mathbf{v} = 0 \quad \text{in} \quad \Omega_2 \times (0, T]
\]

where \( C_2 \) represents the concentration of the drug in the vitreous, \( D_2 \) is the diffusion coefficient of the drug in the vitreous and \( \mathbf{v} \) the velocity of aqueous permeation given by second system. In this last system \( K \) is the permeability of the vitreous and \( \mu_1 \) is the viscosity of the vitreous. The term \( \frac{K}{\mu_1} \) is referred to as the hydraulic conductivity.

The initial and boundary conditions used for the system of PDE’s are as follows:

**Initial conditions:**

\[
\begin{align*}
C_1 &= c_0, \quad \text{in} \quad \Omega_1, \ t = 0 \\
\sigma &= \sigma_0, \quad \text{in} \quad \Omega_1, \ t = 0 \\
M &= M_0, \quad \text{in} \quad \Omega_1, \ t = 0 \\
C_2 &= 0, \quad \text{in} \quad \Omega_2, \ t = 0 \\
\mathbf{v} &= 0, \quad \text{in} \quad \Omega_2, \ t = 0 \\
p &= 2000, \quad \text{in} \quad \Omega_2, \ t = 0 
\end{align*}
\]

**Boundary conditions for the pressure:**

\[
p = 2000, \quad \text{in} \quad \partial \Omega_2 \cup \partial \Omega_3 t > 0 = 1200, \quad \text{in} \quad \partial \Omega_5, t > 0
\]

**Interface boundary conditions for the flux of drug concentration:**

\[
D \nabla C_1 \cdot \eta = A (C_1 - C_2), \quad \text{in} \partial \Omega_4, t > 0.
\]

**Wall conditions for the velocity:**

\[
V = 0 \quad \text{in} \quad \partial n \Omega_4
\]

**Results**

We used the 2D Crank-Nicolson (CN) numerical method to solve the system of PDE’s both in the implant and in the vitreous. This method is an implicit–explicit (IMEX) scheme which is used to solve second-order diffusion PDE’s implicit in time. One advantage of the Crank-Nicolson is that it is unconditionally stable and has error \( O(h^2) + O(k^2) \). The CN method uses backward-difference formula for the time derivative and an evenly weighted combination of forward-difference and backward-difference approximations for the remainder of the equation. We ran the simulation in Matlab. The following two plots show concentration of the drug over time in the implant and inside the eye vitreous chamber, respectively.

![Figure 3: Concentration of drug over time.](image-url)
Future Directions

The current model can be extended in the future research in several ways. Because with aging the structure of the vitreous changes, we can add an additional stochastic term to these PDE’s to account for the inhomogeneity of the vitreous structure in the eye in older adults. In addition, since the implant is positioned in the eye with a certain angle, it would be interesting to know the effect of the implant angle on the diffusion of the drug. In other words, what angle would make the diffusion optimal.

References