Simulation of the drug delivery to the posterior segment of the eye

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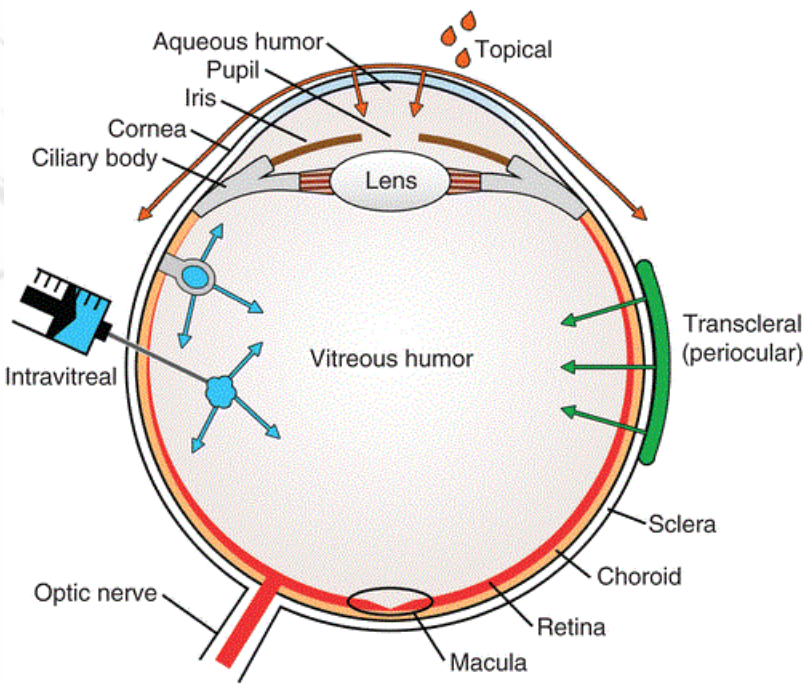
Anatomy of the eye and drug delivery techniques

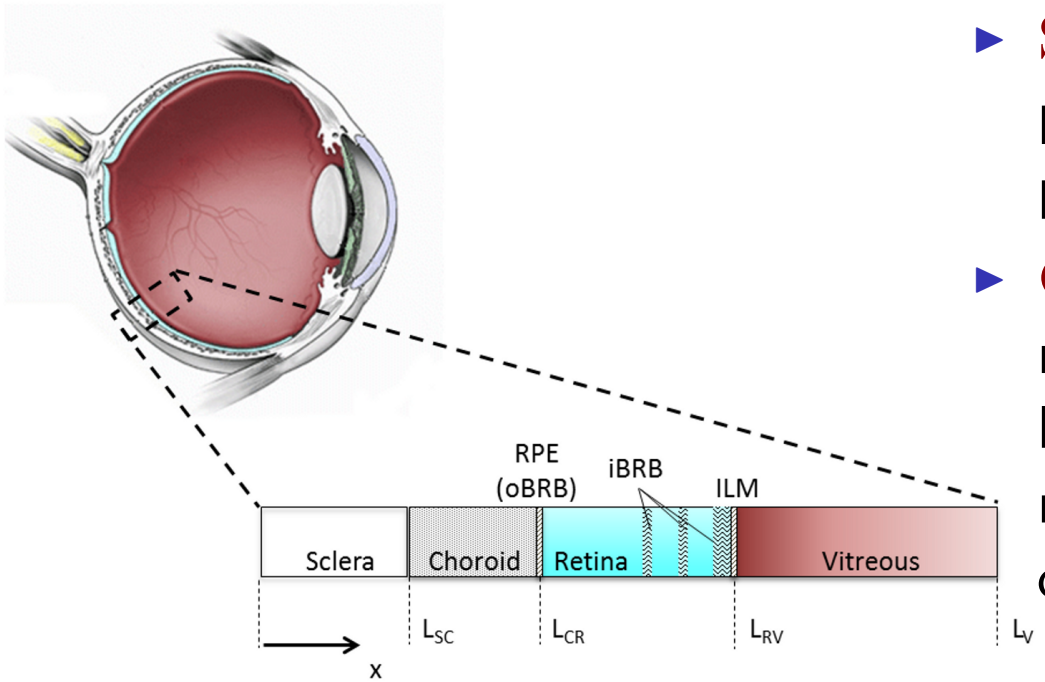


DISEASES affecting the posterior segment of the eye

- age related macular degeneration (AMD) and
- diabetic retinopathy

are the main CAUSES OF BLINDNESS in developed countries.

The Structure of the Eye – PSE



- Sclera (S) – the white part of the eye, relatively permeable to molecules.
- Choroid (C) – a dense network of large and small blood vessels with a relatively sparse population of cells.
- Retina (R) – a layer tissue containing neural cells.
- Vitreous (V) – clear, jelly-like substance that fills the middle of the eye.

Therapeutic Treatments

Possible therapeutic treatments

- topical ocular eye drops
  Problem: *Most of the drug is cleared by tears and therapeutic levels near the retina may not be reached!*
- high drug doses given intravenously or by intravitreal administration (intravitreal injections).
- drugs release from an implant in the vitreous.

Goal

- maximize the therapeutic benefits
- minimize potential adverse effects such as possible tissue damage caused by excessively high concentration of drugs

Barriers in the drug delivery

- Static barriers such as physical obstacles to drug diffusion such as the sclera itself, the retinal pigment epithelium and the retinal vessels.
- Dynamic barriers include drug clearance mechanisms through blood and lymphatic vessels and degradation processes.
  - Drug solubility,
  - charge,
  - degree of ionization,
  - molecular size and shape
  - ...

  affect the penetration rate of the drug across the various barriers.

Mathematical model of the drug release to the posterior segment of the eye

Model of PSE

$$\frac{\partial C_j}{\partial t} - D_j \frac{\partial^2 C_j}{\partial z^2} + \beta_j \frac{\partial C_j}{\partial z} = Q(C_j), \quad j = S, C, R, V$$

$C_j = C_j(t, x)[g/cm^3]$ ... the drug concentration in layer j,

$D_j \equiv D\ [cm^2/s]$ ... drug diffusivity rate,

$\beta\ \ [cm/s]$ ... advection parameter,

$$Q(C_j) = \begin{cases} -k_j\, C_j,\ k > 0 \\ \bar{Q} = constant \end{cases} \quad \text{... reaction term}$$

Spatial discretization: finite elements

EXAMPLE:

$$\begin{aligned} u''(x) &= f(x) \text{ in } (0,1), \\ u(0) &= 0, \\ u(1) &= 0. \end{aligned}$$

WEAK FORMULATION:

$$\begin{aligned} \int_0^1 u''(x)v(x)\mathrm{d}x &= u'(x)v(x)|_0^1 - \int_0^1 u'(x)v'(x)\mathrm{d}x \\ &= -\phi(u,v). \end{aligned}$$

Spatial discretization: finite elements

We divide the interval $(0, 1)$ such that

$$0 = x_0 < x_1 < ... < x_n < x_{n+1} = 1$$

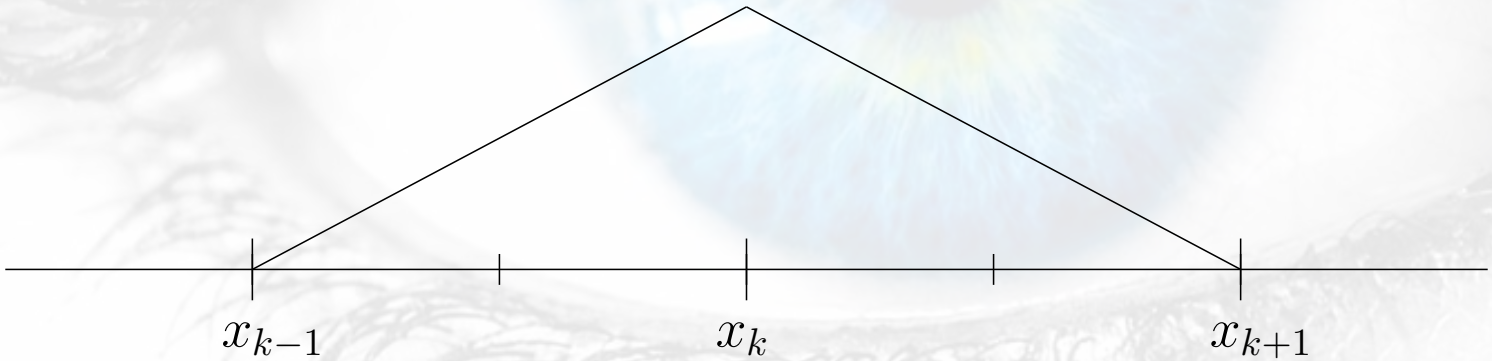


Figure: Possible form of test function v

$$u(x) \approx \sum_{k=1}^{n} u_k v_k(x), \qquad f(x) \approx \sum_{k=1}^{n} f_k v_k(x)$$

Using

$$\phi(v_i, v_j) = \int_0^1 v_i' v_j' \mathrm{d}x,$$

the approximated equation becomes

$$-\sum_{k=1}^{n} u_k \phi(v_k, v_j) = \sum_{k=1}^{n} f_k \int v_k v_j.$$

This can be written in the **matrix form** -L**u**=M**f**

where

$$\mathbf{u} = (u_1, ..., u_n)' \text{ and } \mathbf{f} = (f_1, ..., f_n)'$$

$$L_{ij} = \phi(v_i, v_j), \qquad M_{ij} = \int v_i v_j$$

Time discretization: Theta method

EXAMPLE:

$$\begin{aligned} \mathbf{y}' &= \mathbf{f}(t, \mathbf{y}) \\ \mathbf{y}(0) &= 0, \end{aligned}$$

where $\mathbf{y}$ and $\mathbf{f}$ are vectors depending on time $t \geq 0$.

To approximate the solution at the next time level $t_{n+1} = t_n + \Delta t$, we use a method of the form

$$y_{n+1} = y_n + \Delta t[\theta f(t_n, y_n) - (1-\theta) f(t_{n+1}, y_{n+1})],$$

where $n = 0, 1, ...$ and $\theta \in [0, 1]$.

Implement the Neumann Boundary Condition

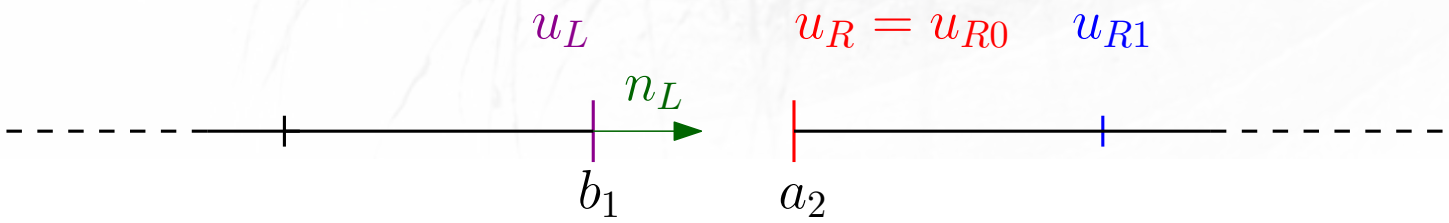
Continuity of fluxes

$$\frac{\partial u_L}{\partial n_L} = \frac{\partial u_R}{\partial n_L},$$

Approximation by

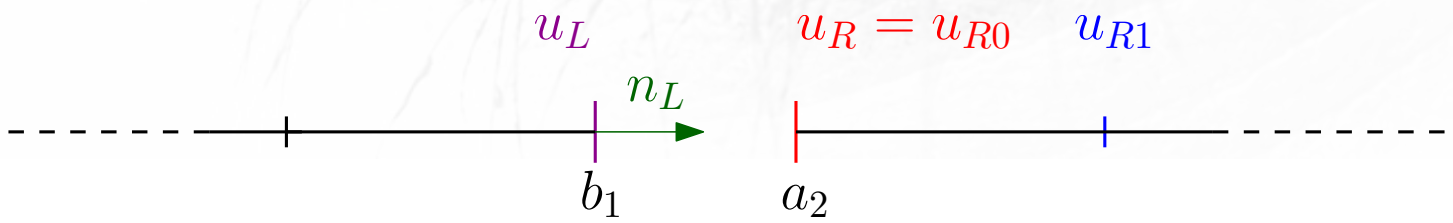
$$\frac{\partial u_R}{\partial n_L} \approx \frac{u_{R1} - u_{R0}}{\Delta x},$$

where $\Delta x = \dfrac{b_2 - a_2}{N_2}$.



Algorithm

1. set a tolerance $TOL = 10^{-4}$
2. use u^0_{R0} and u^0_{R1} from initial condition and compute derivative
3. set $u^k_{R0} = u^0_{R0}$, $u^k_{R1} = u^0_{R1}$ and $k = 0$
4. set $u^{k+1} = pu^0 + (1-p)u^k$, with $p \in (0,1)$,
5. compute difference $diff = \left\| u^{k+1} - u^k \right\|_\infty$
6. *if* $diff < TOL$, accept result
7. *else*, set $u^k_{R0} = u^{k+1}_{R0}$, $u^k_{R1} = u^{k+1}_{R1}$ and $k = k+1$ and go to 4.



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Sclera

$$\frac{\partial C_S}{\partial t} - D_S \frac{\partial^2 C_S}{\partial z^2} = -\kappa_S C_S,$$

κ_S ... decay coefficient

Boundary and interface conditions

Dirichlet: $C_S = c(t)$

Neumann condition – Continuity of fluxes

$$D_S \frac{\partial C_S}{\partial z} \cdot n_S = D_C \frac{\partial C_C}{\partial z} \cdot n_S$$

Choroid

$$\frac{\partial C_C}{\partial t} - D_C \frac{\partial^2 C_C}{\partial z^2} = -\kappa_C C_C,$$

κ_C ... decay coefficient

Interface conditions:

Robin condition – Permeability law

$$-D_C \frac{\partial C_C}{\partial z} \cdot n_C = L_p(C_C - C_S)$$

$L_p\ [cm/s]$ ... membrane permeability coefficient

Neumann condition – Continuity of fluxes

$$D_C \frac{\partial C_C}{\partial z} \cdot n_C = D_R \frac{\partial C_R}{\partial z} \cdot n_C$$

Retina

$$\frac{\partial C_R}{\partial t} - D_R \frac{\partial^2 C_R}{\partial z^2} + \beta_R \frac{\partial C_R}{\partial z} = -\kappa_R C_R,$$

κ_R ... decay coefficient
β_R ... pumping velocity

Interface conditions:

Robin condition – Permeability law

$$-D_R \frac{C_R}{\partial z} \cdot n_R = L_p(C_R - C_C)$$

Neumann condition – Continuity of fluxes

$$D_R \frac{\partial C_R}{\partial z} \cdot n_R = D_V \frac{\partial C_V}{\partial z} \cdot n_R$$

Vitreous

$$\frac{\partial C_V}{\partial t} - D_V \frac{\partial^2 C_V}{\partial z^2} = -\kappa_V C_V,$$

κ_V ... decay coefficient

Interface and boundary conditions:

Robin condition – Permeability law

$$-D_V \frac{C_V}{\partial z} \cdot n_v = L_p(C_V - C_R)$$

Neumann condition $\frac{\partial C_V}{\partial z} = 0$

Table of parameters

Description	Par.	Unit	Value
Sclera thickness	l_S	μm	600
Choroid thickness	l_C	μm	300
Retina thickness	l_R	μm	246
Vitreous thickness	l_V	μm	15000
Drug Diffusivity coefficient	D	cm^2/s	10^{-6}
Permeability coefficient	L_p	cm/s	10^{-5}
Advection coefficient	β_R	cm/s	$-2.44 \cdot 10^{-5}$
Decay coefficient in sclera	k_S	$1/s$	$3 \cdot 10^{-4}$
Decay coefficient in choroid	k_C	$1/s$	$3 \cdot 10^{-4}$
Decay coefficient in retina	k_R	$1/s$	$3 \cdot 10^{-4}$
Decay coefficient in vitreous	k_C	$1/s$	$8 \cdot 10^{-5}$

- We focused on the one dimensional problem;
- At the sclera external boundary we impose a concentration exponentially decreasing in time fitting the trend obtained from a model of drug release in posterior eye gel implants (see [1]);
- Initial concentration is zero on all the domains;
- The problem is convection dominated.


Michail E. Kavousanakis, Nikolaos G. Kalogeropoulos, and Dimitrios T. Hatziavramidis. *Computational modeling of drug delivery to the posterior eye*. Chemical Engineering Science 108 (2014): 203-212.


Causin P., Malgaroli F. *Mathematical assessment of drug build–up in the posterior eye following transscleral delivery*. submitted to Journal of Mathematics in Industry, (2016).