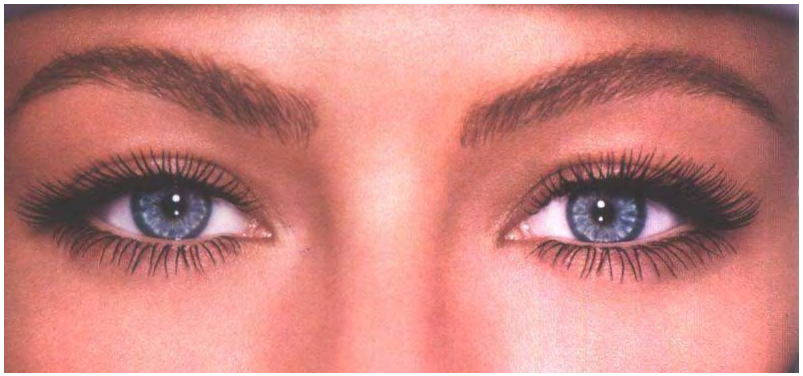
Presented at the COMSOL Conference 2010 Paris

A Virtual Pharmacokinetic Model of a Human Eye



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Motivation

Increasing standard of living:
→ increasing life expectancy
→ increasing number of posterior eye diseases:

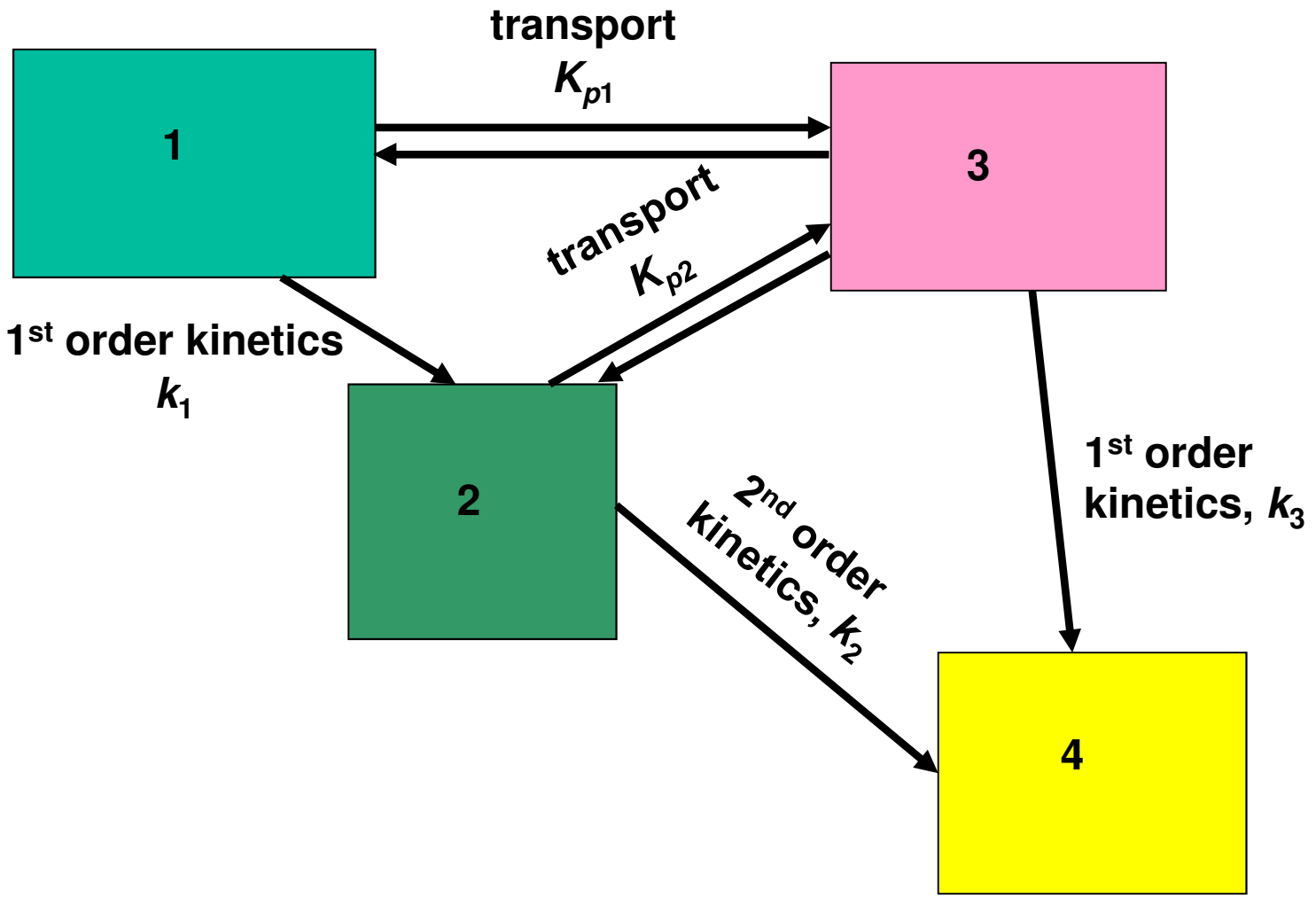
- age related macular degeneration; in USA 2 million
- diabetic retinopathy
- ganglion cell damage due to glaucoma

Drug therapy of posterior eye very difficult

- direct injections to eye, for example

Modeling of drug distribution in eye is one way of facilitating the development of eye therapies

Pharmacokinetics with state model



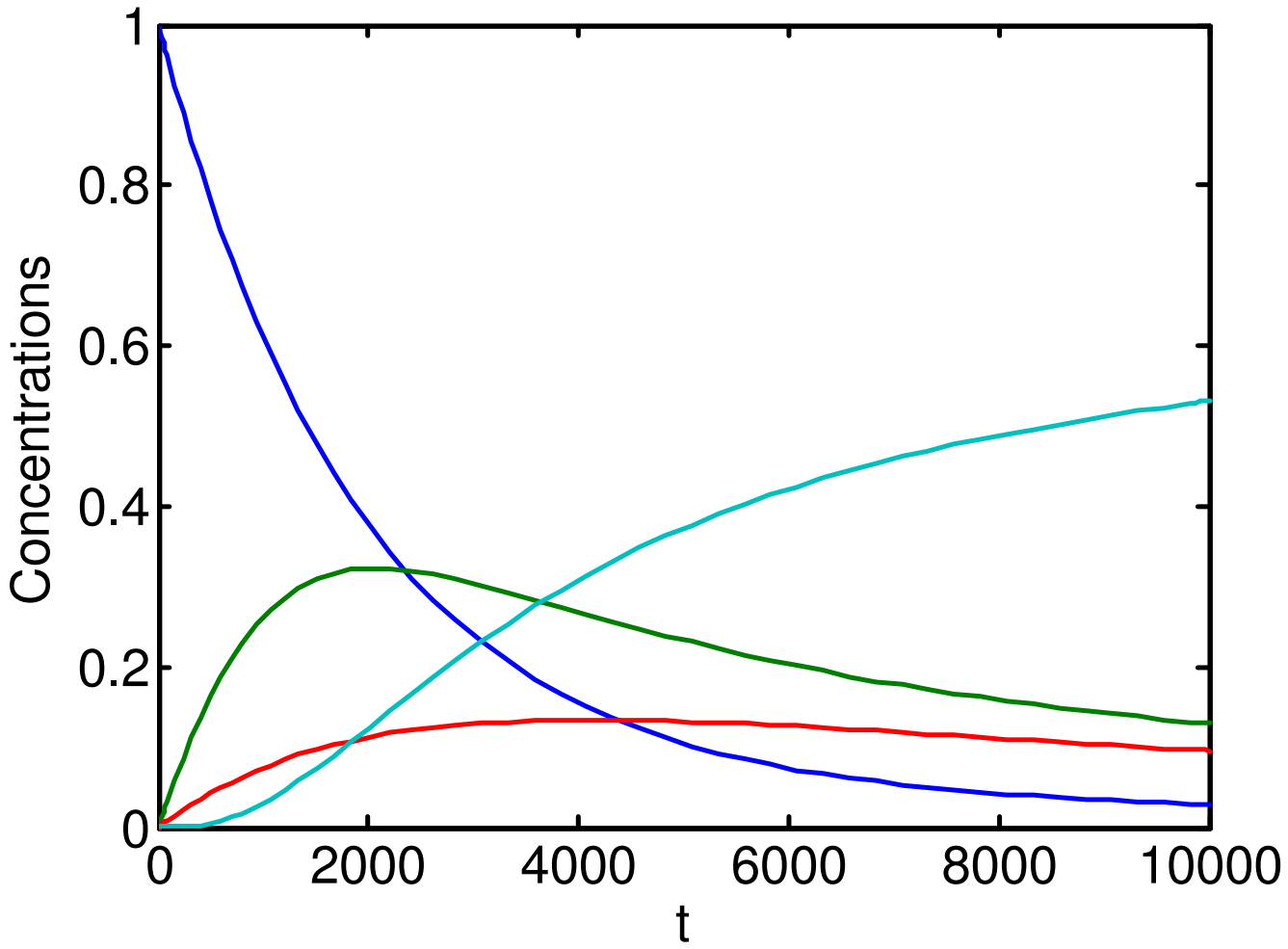
Kinetic equations:

$$\begin{cases} \dfrac{dc_1}{dt} = -K_{p1}(c_1 - c_3) - k_1 c_1 \\ \dfrac{dc_2}{dt} = k_1 c_1 - K_{p2}(c_2 - c_3) - k_2 c_2^2 \\ \dfrac{dc_3}{dt} = K_{p1}(c_1 - c_3) - k_3 c_3 \\ \dfrac{dc_4}{dt} = k_2 c_2^2 + k_3 c_3 \end{cases}$$

$$\frac{d}{dt}\begin{bmatrix} c_1 \\ c_2 \\ c_3 \\ c_4 \end{bmatrix} = \begin{bmatrix} -K_{p1} - k_1 & 0 & K_{p1} & 0 \\ k_1 & -K_{p2} - k_2 c_2 & K_{p2} & 0 \\ K_{p1} & 0 & -K_{p1} - k_3 & 0 \\ 0 & k_2 c_2 & k_3 & 0 \end{bmatrix} \begin{bmatrix} c_1 \\ c_2 \\ c_3 \\ c_4 \end{bmatrix}$$

$$\frac{d\mathbf{c}}{dt} = \mathbf{A}\mathbf{c}$$

This is what e.g. Stella® does

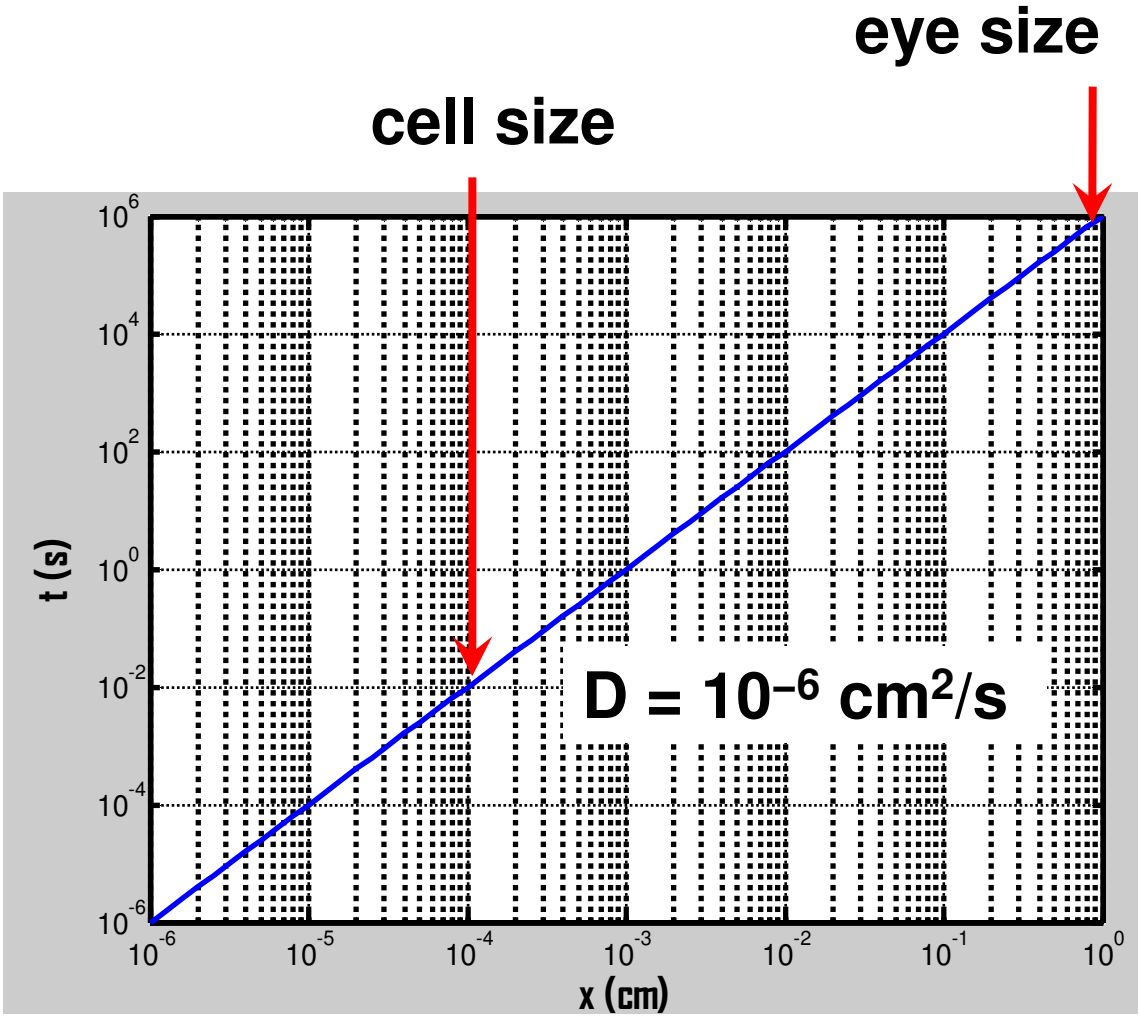


Q: Why COMSOL?
A: Length scale

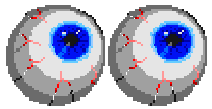
$$x \approx \sqrt{Dt} \quad \Rightarrow \quad t \approx \frac{x^2}{D}$$

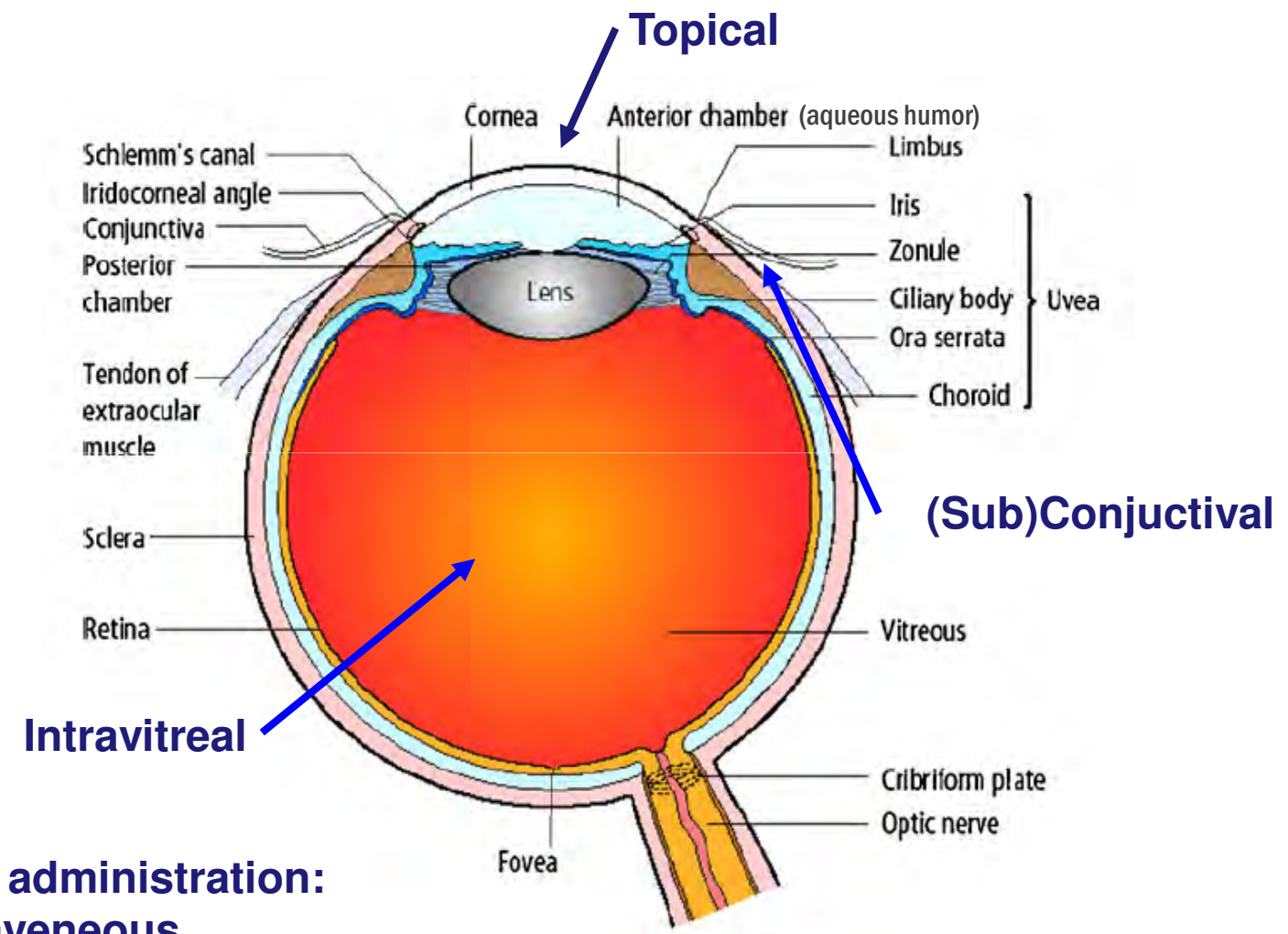
Evolution:

- On cellular level diffusion not an issue.
- Convection due to blood circulation very efficient.



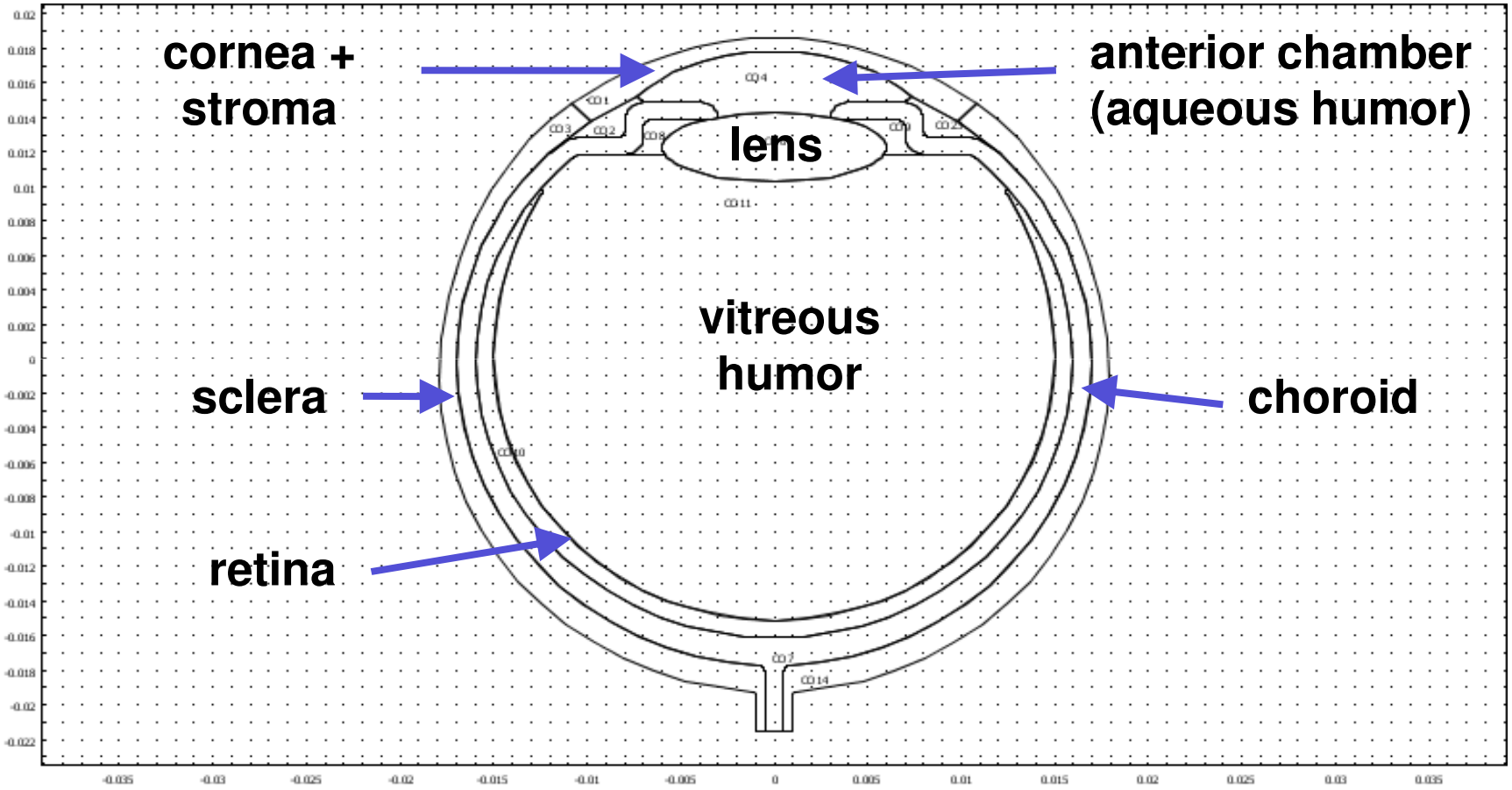
Cross-section of the human eye and administration routes





Systemic administration: oral, intraveneous

Our COMSOL drawing of an eye



Equations

- Incompressible Navier-Stokes, laminar flow in steady-state, in anterior chamber and choroid
- Transient convective diffusion in anterior chamber and choroid
- Transient diffusion elsewhere

Homogeneous reactions, usually 1st order or Michaelis-Menten kinetics

Mobility in various tissues:

- blood ≈ water
- vitreous humor ≈ hydrogel, $\eta \approx 4000$ cP (experiments with FRAP)

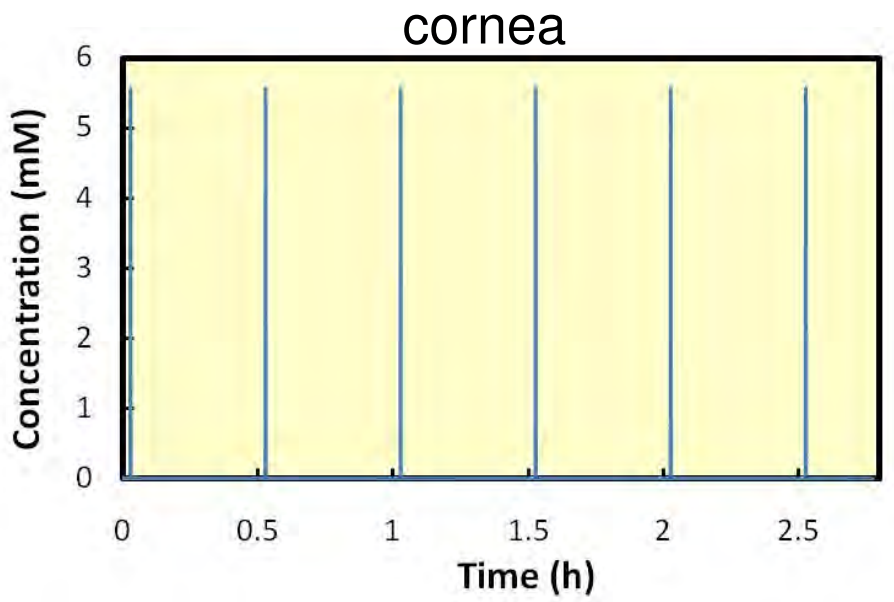
Pulsed boundary condition

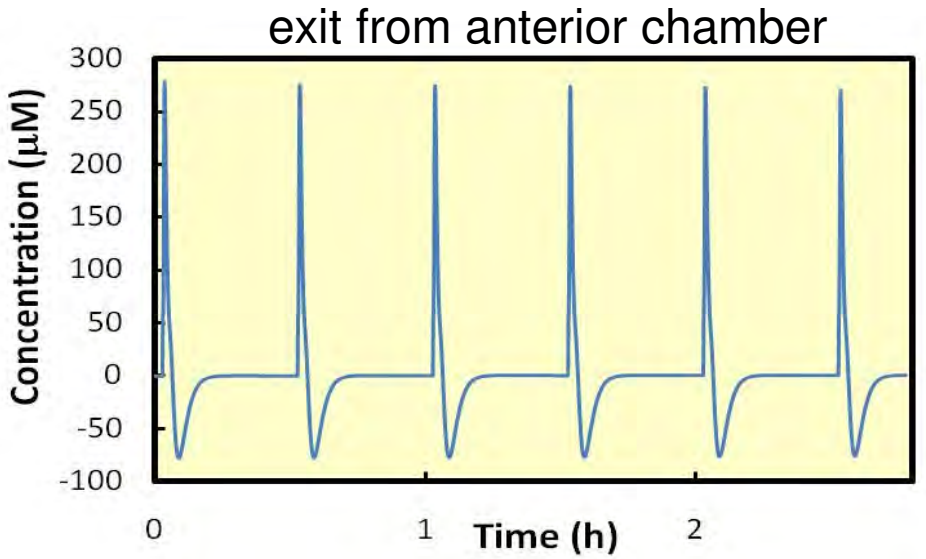
$$y = H_s\left\{\sin\left[\frac{2\pi(t+t_1-\tau)}{T}\right]-A\right\}$$

$$a = \sin\left(\frac{2\pi\Delta t}{T}\right) \quad ; \quad b = \cos\left(\frac{2\pi\Delta t}{T}\right)$$

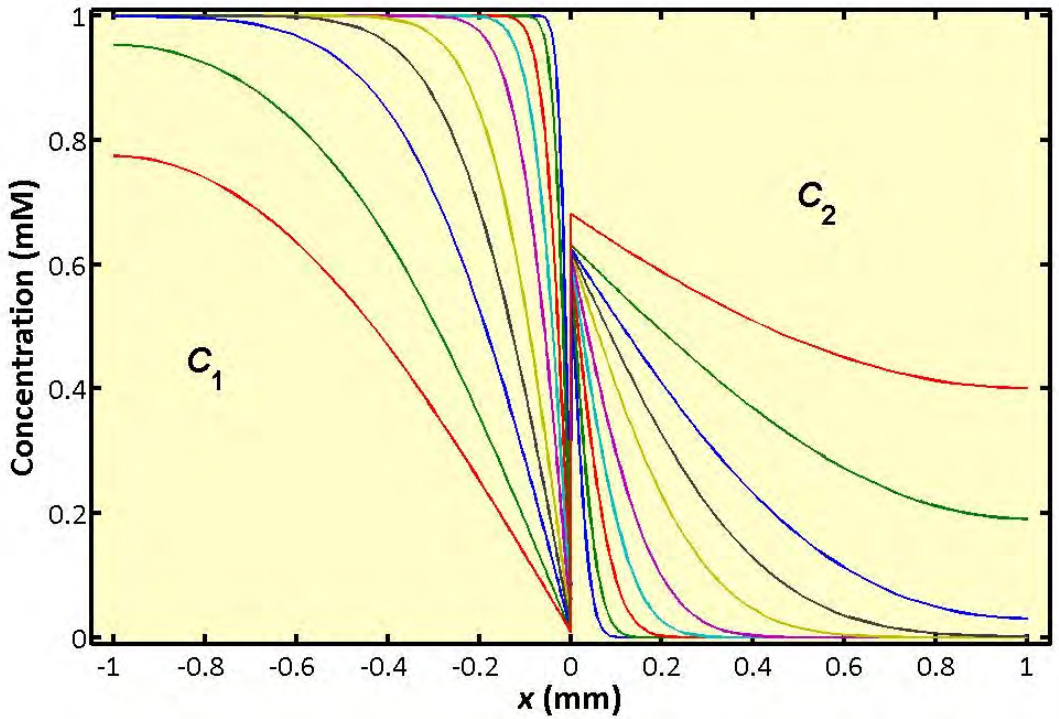
$$A = \frac{a}{\sqrt{2(1-b)}} \quad ; \quad t_1 = \arcsin(A)$$

H_s = Heaviside step function (flc2hs)
τ = pulse delay
T = pulse period
Δt = pulse width
t_1 makes the first pulse start at $t = 0$





Boundary condition between phases



Permeability (K_p) and partition (P) must be taken into account at the phase boundaries

$$\text{Flux} = -K_p(Pc_1 - c_2) \quad | \quad \text{Flux} = K_p(Pc_1 - c_2)$$

Conclusions:

- Project goals achievable
- 64 bit PC required for 3D modeling
- Drawing preferably with CAD

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THANK YOU