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COMPUTATIONAL MODELING OF INTRAOCULAR DRUG TRANSPORT

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Abstract:

In this work we present computational model for intraocular drug transport using coupled convective-diffusive equations. Model can simulate drug transport using either injection or by state of the art implant devices. We are using Navier-Stokes equation for fluid flow in vitreous humor, and composite smeared finite element (CSFE) for convection in rest of the eye and also for diffusion within the whole model. CSFE takes into account blood vessel properties, such as hydraulic and diffusive components. User interface tool CAD for pre- and post- processing is constructed which enables generation of geometries for patient specific purposes. Computational model provides results in a form convenient for investigation of effects of the drugs on different diseases, such as diabetic macular edema, uveitis, etc. This computational platform has potentials to become a powerful tool for optimization of therapies and simulation of different drugs.

Key words: intraocular drug transport, computational model, finite element analysis, CSFE, Kojic Transport Model.

1. Introduction

Eye is very complex organ and various numerical methods were applied in the past to investigate the intraocular drug transport. It is known that the effective drug delivery to internal ocular tissues must overcome significant barriers [1], and this knowledge is very important for understanding of different diseases, such as diabetic macular edema, uveitis, etc. [2]. Among the first models used in this area were classical pharmacokinetic (PK) models which are then replaced with physiologic-based pharmacokinetic (PBPK) models. Use of the computational fluid dynamics within PBPK models is proved to be powerful technic and can help in establishing safe and efficient drug delivery systems [2]. Abilities of this approach were shown by different authors in the past [1,2,3]. Since many additional aspects have to be explored there is a need for additional research in this area. There is also a need to develop simplified and robust computational approaches that adequately incorporate the main parameters of transport processes. In [4] we introduced a smeared modeling concept for gradient-driven mass transport and formulate a new composite smeared finite element (CSFE). For mass transport within tissue as a porous continuum filled with fluid, the governing laws are the Darcy velocity-pressure relationship for convection and Fick's law for diffusion [4]. Therefore, CSFE is composed of two volumetric parts - capillary and tissue domains, and has four nodal degrees of freedom (DOF): pressure and concentration for each of the two domains. The domains are coupled by connectivity elements at

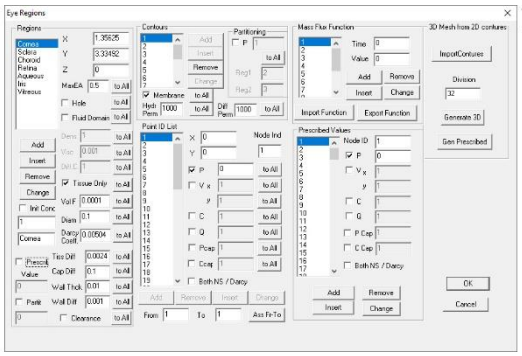
each node. A smeared modeling approach for large domains can effectively be used for transport in the capillary system and tissue. CSFE takes into account blood vessel properties, such as hydraulic and diffusive components, which are fundamental for transport within the cardiovascular system, and organs such as eye.

In this work we present computational model where convection in vitreous humor is modeled using Navier-Stokes equations, while convection in the rest of the eye and diffusion in whole eye is modeled using Kojic Transport Model (KTM) which incorporates CSFE methodology. Additionally, we generated corresponding geometric model of the eye with physiological material properties and boundary conditions according to [3].

2. Methods

In order to handle the FE model generation and results post-processing in an easy way, we have developed a graphical interface. This in-house graphical interface called CAD also provides a tool to be used in the investigation of different drugs and patient specific analysis. For the purpose of generating axial symmetric 2D eye model, we implemented algorithm for parametric model generation. This module within CAD enables reconstruction of lines from 2D eye images in form of curves and then enables generation of 2D mesh. For each of 7 domains within the eye we can specify physiological material characteristics and boundary conditions using CAD dialog presented in Figure 1b. Data for volumetric fractions of capillaries and diffusion coefficients used in our model is presented in Figure 1b.

a



b

	Vol. Fract. of Capillaries	Diff. Coeff. in Tissue domain [μm²/min]
Cornea	0.0001	10
Aqueous Humour	0	100
Ciliary body and Iris	0.2	1
Sclera	0.0001	10
Choroid	0.5	1
Retina	0.001	1
Vitreous humor	0.0001	100

Fig. 1. a) Dialog of CAD pre-processing tool for setting eye parameters, b) Parameters of volume fractions and diffusion coefficients used in our numerical simulation.

Numerical simulations are performed using finite element method (FEM). Fluid flow in vitreous humor is represented with the continuity equation and differential Navier-Stokes equations [5]:

$$-\mu\nabla^2 v_l+\rho(v_l\cdot\nabla)v_l+\nabla p_l=0 \quad (1)$$

$$\nabla v_l=0 \quad (2)$$

where v_l is the blood flow velocity, p_l is the pressure, μ is the coefficient of dynamic viscosity of blood and ρ is the density of blood.

The CSFE relies on the transformation of the one-dimensional (1D) constitutive relations (for transport within capillaries) into the continuum form expressed by Darcy's and diffusion tensors. The CSFE is composed of two volumetric parts - capillary and tissue domains, and has four nodal degrees of freedom (DOF): pressure and concentration for each of the two domains. The domains are coupled by connectivity elements at each node. The fictitious connectivity elements take into account the surface area of capillary walls which belongs to each node, as well as the wall material properties (permeability and partitioning). The overall FE model contains geometrical and material characteristics of the entire capillary-tissue system, with physiologically measurable parameters assigned to each FE node within the model. The smeared concept is implemented into our implicit-iterative FE scheme and into FE package PAK [6]. Convective and diffusive transport within tissue, which is considered as a porous continuum, can be described by incremental-iterative FE systems of equations, which rely on Darcy's and Fick's laws. Additional details are given in [4]. For each of the domains, the FE incremental-iterative equations of balance, for a time step Δt and iteration *i*, can be written as [5]

$$\left(\frac{1}{\Delta t}\mathbf{M}+\mathbf{K}\right)^{(i-1)}\Delta\mathbf{\Phi}^{(i)}=\mathbf{Q}^{ext}+\mathbf{Q}^{V}-\frac{1}{\Delta t}\mathbf{M}^{(i-1)}\left(\mathbf{\Phi}^{(i-1)}-\mathbf{\Phi}^{t}\right)-\mathbf{K}^{(i-1)}\mathbf{\Phi}^{(i-1)} \quad (3)$$

where the matrices and volumetric nodal vector $\boldsymbol{Q}^{v}$ are given elsewhere (our references [4,5]); $\boldsymbol{Q}^{ext}$ is the external effects nodal vector and $\mathbf{\Phi}^{t}$ corresponds to start of the time step.

3. Results and discussion

Simplified 2D model of the eye is presented in Figure 2. FE mesh is consisted of 7 groups of elements, where each 2D group is connected with 1D connective elements representing membrane between compartments. Drug source can be applied with zone representing either implant or injection domain, where in this example we used implant source denoted as blue. Implant has initial drug concentration, where drug is releasing over time from implant and leaves the eye using clearance mechanism.

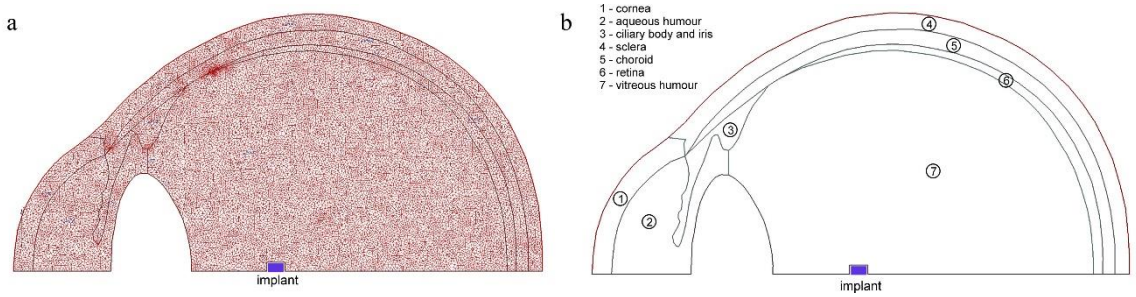


Fig. 2. a) Two-dimensional FE mesh of eye model with drug implant in the middle of the eye, b) Eye model with compartments

In Figure 3a we showed vectors of velocities while in Figure 3b we showed field of pressures. Field of drug concentrations for tissue and capillary domain of composite smeared finite element are shown in Figures 4a and 4b, respectively.

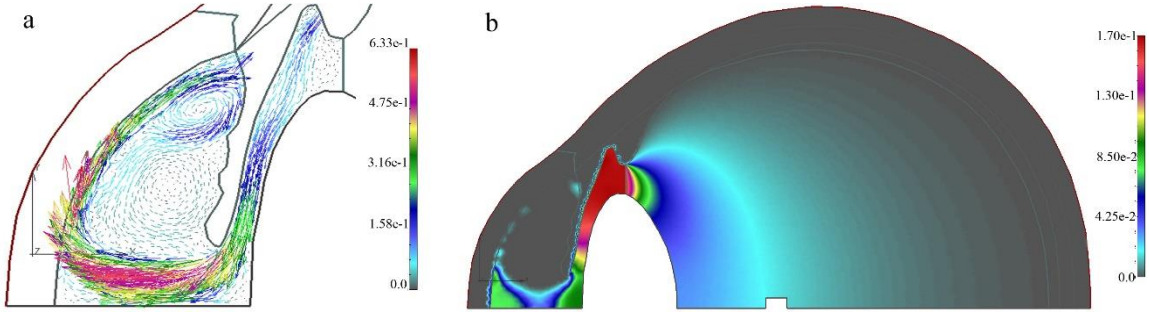


Fig. 3. Results of FE simulation: a) velocity vectors [mm/min] and b) pressure field [mmHg] after 24h.

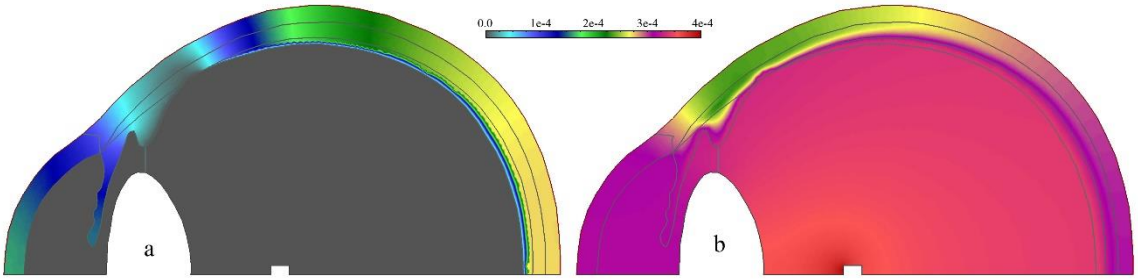


Fig. 4 Concentration field after t = 140 min in a) tissue and b) capillary domain

4. Conclusions

In this paper we presented computational tool for modeling intraocular drug transport. Our computational tool consists of in-house pre- and post-processing tool CAD, and finite element code PAK which is used for solving fluid flow and drug transport within the eye model. Finite element procedure consists of coupled fluid flow and drug transport, where drug transport is modeled using Kojic Transport model. This computational model has potential to be used in the future for investigation of clearance barriers and for improvement of drug therapies in the eye.

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