MODELING AND SIMULATIONS OF DRUG DISTRIBUTION IN THE HUMAN VITREOUS

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Abstract

We develop a mathematical model for the drug distribution in the vitreous body of a human eye. The drug is injected in the vitreous and used for the treatment of retinal diseases. For an optimal effect the drug is supposed to stay as long as possible in a certain area. We model the distribution of the drug with anisotropic diffusion which include the effect of the collagen fibers which have a certain orientation in the vitreous body. In addition to the diffusion we include also the steady permeating flow of the aqueous humor and model it with the Darcy equation driven by a pressure drop. The simulations are performed with the Finite Element method. Therefore, the geometry of the vitreous and a grid is constructed. The discretization is realized by using the Crank-Nicolson scheme in time, the Raviart-Thomas elements for the velocity, discontinous zero-order elements for the pressure and Lagrange elements for the concentration. The position of injection is analyzed by introducing specific output functionals which measure the mean or relative amount of the drug in the vitreous and in the area of action. Our simulations show that the injections should be located in the center of the vitreous body for a more efficient therapy.

Keywords: anisotropic diffusion, darcy equations, finite elements, drug distribution, vitreous

1 Introduction

Intravitreal injections are a common therapy for treating retinal diseases. To achieve a therapeutic concentration drugs have to be delivered to the posterior segment of the eye, the vitreous body. The vitreous is a transparent gel-like, complex, hydrated network, located between the lens and the retina. Due to the meshwork of collagen fibrils that are suspended in the network of hyaluronic acid it behaves like a viscoelastic gel and gives the shape of the eye. A schematic diagram of the structure and the position of the vitreous in the eye is shown in Figure 1. Many drugs, which are used in the intravitreal injection therapy, have a small effective concentration range and higher concentrations may be toxic. Therefore, a better understanding of the drug distribution within the eye is important to improve the treatment process.

In this study, we develop a mathematical model for the drug distribution in the human vitreous and perform simulations by using the finite element method based on a detailed geometry and boundary conditions of the vitreous.

![Figure 1: Structure of the eye (left) and schematic diagram of healthy vitreous ultrastructure (right) [8]](https://doi.org/10.14311/TPFM.2017.013)
2 Modeling

Existing diffusion models of previous investigators [5] and [6] assumed that the vitreous is homogeneous and therefore the drug distribution isotropic. Diffusive and advective mass transport were modeled in [6] as described by the standard advection-diffusion equation. There, the distribution of the drug in the aqueous humor flow inside the vitreous is considered. We extend the simple diffusion to an anisotropic ansatz taking into account the heterogeneous collagen structure of the vitreous which is observed in experiments on autopsy eyes in [9]. The steady permeating flow of aqueous humor through the vitreous is described by Darcy’s law as flow in an incompressible porous media driven by a pressure drop between the anterior and the posterior surfaces. Including the advective term to Fick’s law we obtain the advection diffusion equation. The active transport through the retina is described by the permeability boundary condition.

Let $\Omega \in \mathbb{R}^n$, $n = 2, 3$, be the domain of the vitreous and $\partial \Omega = \Gamma_R \cup \Gamma_L \cup \Gamma_Z$ the boundary with $\Gamma_R$ the part to the retina, $\Gamma_L$ the part to the lens and $\Gamma_Z$ the part to the zonula fibres. We have $\partial \Omega \subset C(\mathbb{R}^{n-1})$. Our model describing the drug distribution in the human vitreous reads:

$$\partial_t C(t, x) + (v(x) \cdot \nabla) C(t, x) - \nabla \cdot (D(x) \nabla C(t, x)) = 0, \quad \text{in } \Omega$$

(1)

$$\nabla \cdot v(x) = 0, \quad \text{in } \Omega$$

(2)

$$\nu K^{-1} v(x) + \nabla p(x) = 0, \quad \text{in } \Omega$$

(3)

with the boundary conditions

$$D(x) \partial_n C(t, x) = g(t, x, C, v) \quad \text{on } \Gamma_R \cup \Gamma_L, \quad p(x) = h(x, v) \quad \text{on } \Gamma_R \cup \Gamma_Z$$

(4)

and the initial conditions

$$C(x, 0) = C_0(x), \quad v(x, 0) = v_0(x) \quad \text{for } x \in \Omega.$$  

(5)

Here $C(t, x)$ is the concentration of the drug, $v(t, x)$ the velocity of the permeating aqueous humor, $p(t, x)$ the pressure, $K$ the permeability (hydraulic conductivity) of the vitreous humor, $\mu$ the viscosity of the aqueous humor, $D(x)$ is the space-dependent diffusion coefficient.

2.1 Weak Formulation

We define following functional spaces:

$$H_0^{\text{div}}(\Omega) := \{ v | v \in H^1(\Omega), \nabla \cdot v = 0 \text{ on } \Gamma_L \},$$

(velocity)

$$Q := \{ p | p \in L^2(\Omega) \},$$

(pressure)

$$H_0^1(\Omega) := \{ C | C \in H^1(\Omega), C = 0 \text{ on } \Gamma_Z \},$$

(concentration)

$$H^{\text{div}}(\Omega) := \{ v | v \in L^2(\Omega), \nabla \cdot v \in L^2(\Omega) \},$$

Then the weak formulation of problem (1) reads:

We search for $C \in H_0^1(\Omega)$, $v \in H_0^{\text{div}}(\Omega)$ and $p \in Q$ such that

$$\nu K^{-1} v \cdot \varphi - (p, \nabla \cdot \varphi) - (\nabla \cdot v, \xi) + b_v(v, p; \varphi) = 0,$$

(6)

$$\partial_t C(\phi) + ((v \cdot \nabla C), \phi) + (\nabla^2 C, \nabla \phi) + b_C(C, v; \phi) = 0,$$

(7)

for all test functions $(\varphi, \xi) \in H^{\text{div}}(\Omega)$ and $\phi \in H^1(\Omega)$ and the boundary terms $b_v(v, p; \varphi)$ and $b_C(C, v; \phi)$.
3 Numerical Method

Our Model is solved with the Finite Element method [4] using the software deal.ii ([1] and [2]). At first we generate a grid of the vitreous. The geometry of the vitreous is constructed after own in-vivo measurements performed in the Department of Ophthalmology. The size of the domain is about 16mm × 20mm × 20mm. For the discretization we use the Rothe method, first we discretize in time and then in space.

3.1 Discretization

At first we solve the Darcy equation (6). The velocity is discretized with the Raviart-Thomas $RT_0$ elements. For the pressure we use the discontinuous DG(0) elements (see [3]). The discretized equation reads

$$-(p_h, \nabla \cdot \varphi_h) + (\nu K^{-1} v_h, \varphi_h) + b_u(v_h, p_h; \varphi_h) = 0.$$

We need the solution $v_h$ for the diffusion-convection equation (7). Here, the concentration is discretized by bilinear Lagrange elements. For the time discretization we use the Crank-Nicolson scheme and choose a constant timestep. For each time step we solve

$$\left( \frac{C_h^{n+1} - C_h^n}{\Delta t} + 0.5((v_h \cdot \nabla)(C_h^n + C_h^{n+1}), \phi_h) + 0.5(D(x)(\nabla(C_h^n + C_h^{n+1}), \nabla \phi_h) + 0.5b_C((C_h^n + C_h^{n+1}), v_h; \phi_h) \right) = 0.$$

3.2 Results

We simulate the drug distribution in the vitreous in 2D and 3D for a time period of four days. The Figure 2 shows the convective diffusion of the drug and its heterogeneous distribution.

Figure 2: Drug distribution in the vitreous in 2D and 3D. The convective direction is the direction of the injection.

An interesting issue is to analyze the effect of the position of the injection. The drug will be injected around the base of the cornea. We want to achieve that the drug remains in the vitreous as long as possible and that it operates in a specific region. To show this mathematically, we define the following output functionals:

**Definition 1.** With $J_1(t, C) : \mathbb{R}^+ \times H^1_0(\Omega) \to \mathbb{R}^+$ we denote the relative amount of drug which is left in the vitreous at the current time point,

$$J_1(t, C) := \frac{\int_{\Omega} C(t, x) \, dx}{\int_{\Omega} C(0, x) \, dx}.$$
With $J_2(t, C) : \mathbb{R}^+ \times H_0^1(\Omega) \to \mathbb{R}^+$ we denote the total amount of the drug present in the vitreous for all $t \leq T$,

$$J_2(T, C) := \frac{1}{T} \int_0^T \int_{\Omega} C(t, x) \, dx \, dt.$$  

With $J_3(t, C) : \mathbb{R}^+ \times H_0^1(\Omega) \to \mathbb{R}^+$ we denote the amount of the drug present in a sphere around the area of interest $m$ at the current time point,

$$J_3(t, C) := \int_{B_r(m)} C(t, x) \, dx.$$  

Finally, $J_4(t, C) : \mathbb{R}^+ \times H_0^1(\Omega) \to \mathbb{R}^+$ denotes the total amount of the drug present in the area of interest for all times $t \leq T$,

$$J_4(T, C) := \frac{1}{T} \int_0^T \int_{B_r(m)} C(t, x) \, dx \, dt.$$  

We want to investigate the output functionals $J_1, \ldots, J_4$ for three different injection positions. The first calculations are in 2D. The first position which we denote by $p_1$ is located to the right of the lens in the center of the vitreous body and the direction of the injection is always towards the optical nerve (Figure 3a). The second position, $p_2$, is located below, approximately at the same depth and the direction of the injection is again towards the optical nerve (Figure 3c). The third position, $p_3$, is above the lens about 5 cm behind the cornea. It is the location used so far in the practice for such injections (Figure 3d).

(a) Position $p_1$  
(b) Position $p_2$  
(c) Position $p_1$ and $p_2$  
(d) Position $p_3$

Figure 3: Schematic view of the injection positions and directions.
The numerical results are presented in Table 1, 2 and 3.

### Table 1: The amount of drug for the respective output functionals at position $p_1$.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>24</td>
<td>0.63</td>
<td>33.1</td>
<td>0.26</td>
<td>0.13</td>
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<tr>
<td>48</td>
<td>0.28</td>
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<td>0.16</td>
<td>0.17</td>
</tr>
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<td>96</td>
<td>0.053</td>
<td>15.1</td>
<td>0.035</td>
<td>0.13</td>
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<tr>
<td>192</td>
<td>0.0018</td>
<td>7.8</td>
<td>0.0012</td>
<td>0.071</td>
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### Table 2: The amount of drug for the respective output functionals at position $p_2$.

<table>
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<tr>
<td>24</td>
<td>0.46</td>
<td>29.5</td>
<td>0.79</td>
<td>1.46</td>
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<tr>
<td>48</td>
<td>0.18</td>
<td>20.6</td>
<td>2</td>
<td>0.94</td>
</tr>
<tr>
<td>96</td>
<td>0.034</td>
<td>12.1</td>
<td>0.025</td>
<td>0.51</td>
</tr>
<tr>
<td>192</td>
<td>0.0011</td>
<td>6.2</td>
<td>0.0008</td>
<td>0.25</td>
</tr>
</tbody>
</table>

### Table 3: The amount of drug for the respective output functionals at position $p_3$.

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>0.39</td>
<td>23.4</td>
<td>0.069</td>
<td>0.020</td>
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<tr>
<td>48</td>
<td>0.17</td>
<td>16.9</td>
<td>0.082</td>
<td>0.054</td>
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<td>96</td>
<td>0.032</td>
<td>10.0</td>
<td>0.020</td>
<td>0.050</td>
</tr>
<tr>
<td>192</td>
<td>0.0011</td>
<td>5.2</td>
<td>0.00076</td>
<td>0.028</td>
</tr>
</tbody>
</table>

We conclude that at the first position, $p_1$, the functional value of $J_1$ and as well as of $J_2$ reaches the greatest values for all times and positions considered in the simulations. This means that in this case the drug remains longer in the vitreous than in the other cases. Position $p_1$ has the longest diffusion distance to the retina through which the drug disappears. The values are closer to the retina and the drug can disappear. The values of the functional $J_3(T,C)$ drop from day to day, which is also linked to the fact that the drug disappears through the retina. The values of $J_4(T,C)$ stay relative constant for $p_1$. In all eight days, the same time averaged amount of drug is in the area of interest. However, the simulation of the localization of the injection in the second position reveals the greatest functional values for $J_3$ and $J_4$ in the first two days. This is due to the closeness of the injection position to the area of interest. Thereafter, the values are lower than in the other positions, the drug dissapears quicker because the position is closer to the retina where the drug penetrates. After approximately eight days $J_3$ reaches the greatest value for the first injection position. The highest time averaged amount of $J_4$ is found for the second injection position $p_2$ at the starting time point (Table 2). Also all other values are much greater than in the other positions due to this high starting value. At the beginning we have a large overspill of drug in the area of interest such that not all of it can act. With time it vanishes quicker due the closeness to the retina. The aim of the therapy is to gain a long effect such that the value of the functional $J_3$ is more important for us. So, in contrast to the injection in the second position in the first one the drug operates for a comparatively long time in the area of interest. And at the third position, all functional values are small. According to our simulation we recommend to inject the drug around the center of the vitreous and to locate the injection at position $p_1$. Then, the functionals $J_1$, $J_2$ and $J_3$ have the maximal values and the maximal amount of drug is found in the area of interest for the considered time period.
4 Viscoelasticity

Beside the diffusion of the drug, the influence of the aqueous humor flow and the inhomogeneity of the vitreous body the viscoelasticity due to the collagen hyaluronic acid network influences the drug distribution in the vitreous. In [7] measurements to study the rheological behavior of the vitreous were performed and showed that the human vitreous is a viscoelastic material with significant differences within three regions, the anterior, the central and the posterior vitreous. Besides these space differences, there are even much larger differences in viscosities of different old vitreous bodies or pathological ones. Thus, we will include space dependent viscoleasticity to the presented model.

Preliminary work about viscoelastic flow problems was done in [10] where new finite element approaches were developed and completed with numerical analysis. The developed theory was tested on a 2D benchmark problem and the accuracy of the solution was controlled with reference values in the literature for the drag and lift forces which are significant quantities of the flow depending on the characteristic velocity and geometry. In Figure 4 we can see the influence of different viscosities on the velocity profile and therefore the drug distribution which is coupled by the convection term to the aqueous humor flow. The higher the viscosity of the vitreous the lower is the velocity. In Figure 5 we see the influence of the viscosities on the pressure.

Figure 4: Influence of different viscosities on the velocity profile [10]
But the hyperbolic nature of viscoelastic models results in numerical instabilities for increasing elasticity due to high stress gradients which can be handled variously with different viscoelastic constitutive relations. With increasing Weissenberg number $We$, a dimensionless number which compares the viscous forces to the elastic forces, the error to the reference value in the literature for the drag force grows depending on the choice of the viscoelastic model, see Table 4 for the Oldroyd-B and the Giesekus model. Thus, depending on the concrete model parameters, the correct model for the viscoelasticity must be chosen.

<table>
<thead>
<tr>
<th>$We$</th>
<th>Oldroyd-B error[%]</th>
<th>Giesekus error[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.002</td>
<td>5.59504 -0.21</td>
<td>5.59665 0.27</td>
</tr>
<tr>
<td>0.02</td>
<td>5.56486 -0.88</td>
<td>5.55987 -0.83</td>
</tr>
<tr>
<td>0.2</td>
<td>5.16305 -12.16</td>
<td>5.08641 2.08</td>
</tr>
<tr>
<td>1.0</td>
<td>25.1712 99.95</td>
<td>5.11118 7.03</td>
</tr>
</tbody>
</table>

Table 4: Drag force error for various Weissenberg numbers [10]

5 Conclusion, Remarks & Outlook

Our model and the simulations showed that the course of the collagen fibers and the injection location has a great influence on the distribution of the drug. Up to now, only homogeneous diffusion was realized and thus, the former models were not realistic. Our next step is to include the viscoelasticity to the here presented vitreous model and to calibrate the parameters to measured data. Thus, another step is taken towards a more realistic model for drug distribution in the human vitreous.

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References


