Proceedings of the 15th International Conference
on Computational and Mathematical Methods
in Science and Engineering, CMMSE 2015
3–7July, 2015.

A mathematical model of controlled drug release in a completely detached vitreous

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Abstract

A model represented by four coupled systems of partial differential equations describing the transport of drug in the posterior segment of the eye is presented. The case of drug release to the retina through an aging eye and where a vitreous chamber detachment has already occurred is analyzed. Numerical simulations lead to a better understanding of in vitro results and suggest new research paths.

Key words: Partial differential equations, pharmacokinetics, posterior vitreous detachment

1 Introduction

The posterior part of the eye, the vitreous chamber, is filled with a clear gel called the vitreous humor (VH), or simply vitreous. After birth vitreous gel is composed of 99% water and the other 1% is composed of collagen and hyaluronic acid. The vitreous gel-like consistency is given by these two last components. In healthy conditions the posterior surface of the vitreous is normally in direct contact with the retina (Figure 1 - left).

 ISBN: 978-84-617-2230-3

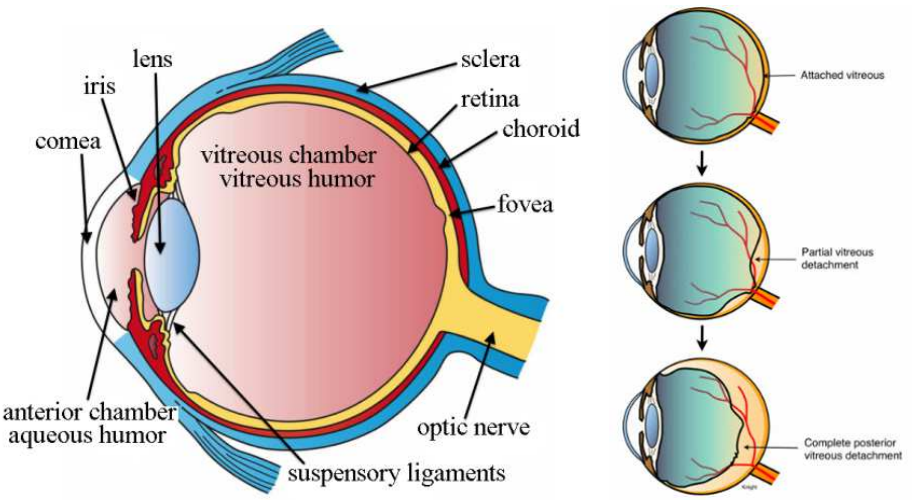

Figure 1: Left: Anatomy of the eye - the vitreous humor is in direct contact with the retina (http://upload.wikimedia.org/wikipedia/commons/). Right: Posterior vitreous detachment - in the top a vitreous completely attached is represented; in the middle a partially detached vitreous is exhibited and in the bottom a complete posterior vitreous detachment is shown ($http$: $//images.netdoctor.co.uk/ukcuk892000000_vitreous-detachment.jp$).

This clear, stagnant and homogeneous gel becomes more fluid with aging: the vitreous liquefies and its adhesion to the retina decreases. It is a normal aging process which can cause a posterior vitreous detachment (PVD), that generally begins at the forth decade of life and near 60% of people has PVD. In Figure 1 (right) we exhibit a vitreous detachment process. In the top a vitreous completely attached is represented. In the middle a partially detached vitreous is exhibited and in the bottom a complete PVD is shown. The void space created by the PVD is filled with aqueous humor. In diseases of the posterior segment of the eye, intraocular drug delivery systems are a gold standard treatment because eye drops and systemic administration cannot release drug continuously and for long periods of time into the vitreoretinal tissue. Intraocular biodegradable or non-biodegradable implants, loaded with drug, are currently used as slow release devices delivering locally drug for an extended period of time. While in a healthy situation the vitreous chamber is completely filled with the homogeneous vitreous gel, in case of a PVD, the void space created by the detachment is occupied by aqueous humor (AH). The different distribution of pressure gradients caused by this new pattern can alter the pharmacokinetics of the drug, raising concern about the drug delivery trend.

The purpose of this paper is to study numerically how the occurrence of a PVD influences such pharmacokinetics. A better understanding of the impact of these differences is necessary to develop more effective therapies so that drug concentration can be maintained

 ISBN: 978-84-617-2230-3

within the therapeutic window at the target site. In previous papers, some of the authors ([7, 8]), the pharmacokinetics of a drug released from a biodegradable implant was studied in the case of a homogeneous vitreous, completely attached to the anterior face of the retina.

In the last years there has been a certain controversy in the medical literature regarding the causes of the differences between the pharmacokinetics of a drug in a healthy and a vitrectomized ([1, 2, 3]) eye or an eye with a vitreous detachment. The model proposed in this paper follows the arguments in [3] concerning the convection dominated nature of the flow. It is represented by four coupled systems of partial differential equations describing the transport of drug in the implant, the vitreous humor, the space filled with aqueous humor, which has been created by the detachment, and the retina (Figure 2). We analyze the influence of a PVD and compare the pharmacokinetics of a drug in this situation with the pharmacokinetics in the case of a complete attached vitreous.eye.

In Section 2 we propose a coupled model to describe the evolution of drug concentration in the implant, the vitreous, the detachment zone and the retina. In Section 3 we present some numerical simulations to illustrate the alterations that occur in the pharmacokinetics of a drug in case of a PVD. Finally in Section 4 we draw some conclusions.

2 Mathematical model

In Section 2 we present a mathematical model that describes the release of drug from a biodegradable implant, inserted into the vitreous chamber of the eye, through the vitreous humor, a region resulting from the detachment of the vitreous (detachment region) and that is filled with aqueous humor and the retina. In 2.1 an accurate geometry of the model is described. In 2.2 the model equations are presented. To every region of interest are assigned meaningful properties, boundary and interface conditions that enable the model to provide realistic solutions.

2.1 Geometry

The two-dimensional geometric model of the human eye adopted in the present study is shown in Figure 2 and is based on physiological dimensions ([4, 5]).

The vitreous chamber, $\Omega_2 \cup \Omega_3$, is mainly composed by vitreous humor and it occupies about two-thirds of the eye. The lens is modeled here as an ellipsoid. The hyaloid membrane and the lens separate the anterior chamber and the posterior chamber of the eye from the vitreous chamber. The retina forms the boundary of the vitreous on the posterior surface and is modeled as the volume between two spherical surfaces with radius differing of 11 mm. In the retina we assume the pressure is 1200Pa; in the interface that represents the hyaloid membrane, $\partial\Omega_{in}$, we consider a pressure of 2000 Pa. The pressure gradient is responsible for the convection flow between the anterior part of the vitreous chamber and its posterior part. The pressure in $\partial\Omega_{in}$ corresponds to a normal intraocular pressure in the anterior chamber

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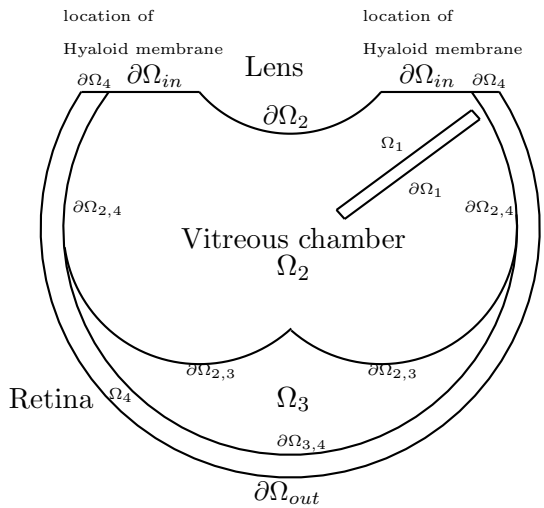

Figure 2: Geometry of the posterior segment of the eye: an implant, Ω_1, inside the vitreous chamber; the vitreous humor Ω_2, occupying part of the vitreous chamber; region, Ω_3 caused by the detachment of the vitreous humor; the retina, Ω_4, and its boundary ($\partial\Omega_{out}$).

of the eye (Figure 1 (left)); the pressure in $\partial\Omega_{2,4}$ and $\partial\Omega_{3,4}$ corresponds to a normal mean blood pressure.

We consider the case in which the vitreous is detached from the retina, a condition defined as a posterior vitreous detachment (PVD). If this condition is accompanied by a retinopathy, one of the gold standard treatments is controlled release from an intravitreal implant, Ω_1, that can be bioerodible or non bioerodible. In the model presented in this paper the implant is considered bioerodible[1]. This intravitreal implant containing dispersed drug is placed in the vitreous, near the retina (Figure 2). It is geometrically represented by a cylinder with radius 0.023 mm and height 0.6 mm. The drug is released in a controlled manner into the vitreous which is a porous media, and its target is the retina affected by an inflammatory process.

The detachment zone created by the PVD is naturally filled with aqueous humor. In Figure 2 that zone is represented by Ω_3.

[1]Some of the data used to characterize the implant was gathered from technique informations of Allergan, a pharmaceutical company, that develops intravitreal implants.

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2.2 Equations

An initial amount of drug is dispersed in the polymeric implant. We suppose that when in contact with the vitreous humor an instantaneous swelling occurs. The drug then dissolves and is transported through the implant, the vitreous, the detachment zone and the retina. The model presented in this paper results from the coupling of four systems of partial differential equations each one representing the transport of drug in those isotropic regions.

- Transport in the implant

Assuming that only passive transport takes place in the biodegradable polymeric implant, the concentration of drug C_1 and the molecular weight M of the polymer are described by

$$\begin{cases} \dfrac{\partial C_1}{\partial t} = \nabla \cdot (D_1(M)\nabla C_1) \ \texttt{in} \ \Omega_1 \times (0,T], \\ \dfrac{\partial M}{\partial t} + \beta_1 M = \beta_2 C_1 \ \texttt{in} \ \Omega_1 \times (0,T], \end{cases} \tag{1}$$

where $D1$ stands for the diffusion coefficient of the drug in the polymeric implant, depending on M, and β_1, β_2 are physical constants that characterize the degradation properties of the material ([6]). It is expected that as the polymer erodes, the molecular weight M decreases and the diffusion coefficient of the drug increases. To describe this behavior we define

$$D_1(M) = D_0 e^{\overline{k}\frac{M_0 - M}{M_0}}, \tag{2}$$

where D_0 is the diffusion coefficient of the drug in the non hydrolyzed polymer, $\overline{k}$ is a positive constant and M_0 is the initial molecular weight of the polymeric matrix.

- Transport in the vitreous

The liquid movement through the vitreous body has been a controversial topic for many years. Nowadays it is commonly accepted that there is a movement of aqueous humor in the vitreous chamber leading to a convection dominated flow ([3]). The vitreous has a porous structure and the drug is transported by diffusion, with a coefficient D_2, and by convection with a velocity $\mathbf{v}_2$ induced by the difference of pressure p_2 between the hyaloid membrane ($\partial\Omega_{in}$) and the interface with the detachment zone ($\partial\Omega_{2,3}$). The behavior of the concentration is described by the equations

$$\frac{\partial C_2}{\partial t} + \nabla \cdot (C_2 \mathbf{v}_2) - \nabla \cdot (D_2 \nabla C_2) = 0 \, \texttt{in} \ \Omega_2 \times (0,T], \tag{3}$$

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and

$$\begin{cases} \mathbf{v}_2 = -\dfrac{K}{\mu_1}\nabla p_2 \,\texttt{in}\, \Omega_2 \times (0,T] \\ \nabla \cdot \mathbf{v}_2 = 0 \,\texttt{in}\, \Omega_2 \times (0,T] \end{cases}. \tag{4}$$

In equation (3) C_2 represents the concentration of the drug in the vitreous, D_2 is the diffusion coefficient of the drug in the vitreous and $\mathbf{v}_2$ is the velocity of aqueous humor permeation given by (4). In this last system K is the permeability of the vitreous and μ_1 is the viscosity of the permeating aqueous humour ([5]).

- Transport in the detachment zone

The transport of drug in Ω_3 is described by a convection diffusion equation. As this zone is filled with aqueous humor, which composition is 99% of water, Stokes equation is used to model the velocity. The drug concentration is then described by

$$\frac{\partial C_3}{\partial t} + \nabla \cdot (C_3 \mathbf{v}_3) - \nabla \cdot (D_2 \nabla C_3) = 0 \,\texttt{in}\, \Omega_3 \times (0,T], \tag{5}$$

where the velocity is given by the Stokes equations

$$\begin{cases} -\nabla.\mu_1(\nabla \mathbf{v}_3 + (\nabla \mathbf{v}_3)^T) + \rho(\mathbf{v}_3.\nabla)\mathbf{v}_3 + \nabla p_3 = 0 \,\texttt{in}\, \Omega_3, \\ \nabla.\mathbf{v}_3 = 0 \,\texttt{in}\, \Omega_3. \end{cases} \tag{6}$$

In equation (5), C_3 represents the drug concentration in Ω_3 and D_2 the drug diffusion coefficient in AH. The variables p_3 and $\mathbf{v}_3$ in (6) represent the pressure and the velocity of the AH in Ω_3, respectively.

- Transport in the retina

The target organ for the drug released from the intravitreal implant is the retina. The behavior of the drug concentration in the retina is simulated considering the following equation

$$\frac{\partial C_4}{\partial t} - \nabla \cdot (D_3 \nabla C_4) = 0 \,\texttt{in}\, \Omega_4 \times (0,T], \tag{7}$$

In equation (7) C_4 represents the concentration of drug in the retina Ω_4 and D_3 the diffusion of the drug in the retina.

To complete the model initial, boundary and interface conditions are added.

- Initial conditions

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Initial conditions for the concentrations account for the fact that at $t = 0$ the concentration of drug is zero everywhere except in the implant, that is

$$\begin{cases} C_1(0) = C_0 \,\texttt{in}\, \Omega_1, \\ C_2(0) = 0 \,\texttt{in}\, \Omega_2, \\ C_3(0) = 0 \,\texttt{in}\, \Omega_3, \\ C_4(0) = 0 \,\texttt{in}\, \Omega_4. \end{cases} \tag{8}$$

- Boundary conditions and interface conditions

- For the pressure: $p = 2000 \,\texttt{on}\ \partial\Omega_{in}$ and $\quad p = 1200 \,\texttt{on}\ \partial\Omega_{3,4} \cup \partial\Omega_{2,4}$. We note that $\partial\Omega_{in}$ represents the hyaloid membrane and $\partial\Omega_{3,4} \cup \partial\Omega_{2,4}$ represents the interface of the retina with the vitreous and the detachment zone. These two values of the pressure correspond to the intraocular pressure in the anterior chamber near the lens and the pressure of the blood system, respectively.

- For the velocity: $\mathbf{v} \cdot \eta = 0$ on the boundaries $\partial\Omega_2$, $\partial\Omega_1$, $\partial\Omega_4$ (Figure 2). In this last equation $\mathbf{v}$ and η represent the velocity and the unit exterior normal to each one of those boundaries, respectively.

- Continuity of the velocity and the pressure in the interface $\partial\Omega_{2,3}$.

- Interface conditions for the fluxes of drug defined by $J_1 = -D_1(M)\nabla C_1$, $J_2 = -D_2\nabla C_2 + \mathbf{v}_2 C_2$, $J_3 = -D_2\nabla C_3 + \mathbf{v}_3 C_3$ and $J_4 = -D_3\nabla C_4$.

  Implant - Vitreous: $J_1 \cdot \eta = J_2 \cdot \eta, \quad J_1 \cdot \eta = A_1(C_1 - C_2) \,\texttt{on}\ \partial\Omega_1 \times (0, T]$, where A_1 is the permeability constant and η is the unit exterior normal to Ω_1 on $\partial\Omega_1$;

  Vitreous - Retina: $J_2 \cdot \eta = J_4 \cdot \eta, \quad J_2 \cdot \eta = A_2(C_2 - C_4) \,\texttt{on}\ \partial\Omega_{2,4} \times (0, T]$, where A_2 is the permeability constant and η is the unit exterior normal to Ω_2 on $\partial\Omega_{2,4}$.

  Vitreous - Detachment zone: $J_2 \cdot \eta = J_3 \cdot \eta, \quad C_2 = C_3 \,\texttt{on}\ \partial\Omega_{2,3} \times (0, T]$, where η is the unit exterior normal to Ω_2 on $\partial\Omega_{2,3}$

  Detachment zone - Retina: $J_3 \cdot \eta = J_4 \cdot \eta, \quad J_3 \cdot \eta = A_3(C_3 - C_4) \,\texttt{on}\ \partial\Omega_{3,4} \times (0, T]$, where A_3 is the permeability constant and η is the unit exterior normal to Ω_3 on $\partial\Omega_{3,4}$.

- As the retina is a permeable membrane, the following boundary condition for the flux is assumed $J_4 \cdot \eta = A_4 C_4$, where η is the unit outward normal to Ω_4 on $\partial\Omega_{out}$ and A_4 is a positive constant.

- As the lens and the hyaloid membrane are not permeable to the drug then $J_2 \cdot \eta = 0 \,\texttt{on}\ \partial\Omega_2 \times (0, T]$, and $J_4 \cdot \eta = 0 \,\texttt{on}\ \partial\Omega_4 \times (0, T]$, where η is the unit outward normal to Ω_2 on $\partial\Omega_2 \cup \partial\Omega_4$.

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3 Simulations

The mathematical model described in Section 2 is numerically simulated using the following strategy: firstly equations (4) and (6) are solved for the pressure and the velocity of the AH in the domains Ω_2 and Ω_3; secondly the evolution of drug concentrations given by (1), (3), (5) and (7) is computed. The numerical results were obtained with *COMSOL Multiphysics* version 4.2, using a piecewise finite element method, linear for the velocity and the pressure and quadratic for the concentrations. A triangulation automatically generated is used with 4980 elements. To integrate in time, adaptive Backward Differentiation Formulae with order between 1 and 2 and adaptive time step, have been used.

The numerical simulations have been obtained with $C_0 = 1.7887 \times 10^{-6}$ (mol/mm^3) and $M_0 = 1 \times 10^{-6}$ (Da), which represent the initial drug concentration and the initial molecular weight in the implant, respectively. All the media are considered isotropic. The diffusion of the drug in the implant is defined considering $D_0 = 1 \times 10^{-12}$; its diffusion coefficient in the vitreous is defined by $D_2 = 2.7778 \times 10^{-10}$ (m^2/s) and in the retina by $D_3 = D_2/2$. We recall that the diffusion coefficient in the polymer will increase as the molecular weight decreases that is as degradation occurs.

The following values for the parameters have been considered in the simulations: $K = 0.7{\times}8.4{\times}10^{-10}$ (cm^2), $\mu_1 = 0.7$ $(Pa.s)$, $\beta_1 = 1{\times}10^{-7}$ $(1/s)$, $\beta_2 = 1{\times}10^{-10}$ $(Dam^3/(mol.s))$, $\overline{k} = 1$, $A_1 = 1 \times 10^{-10}$, $A_2 = A_3 = A_4 = 1 \times 10^{-9}$, (m/s), and $\rho = 970$ (kg/m^3).

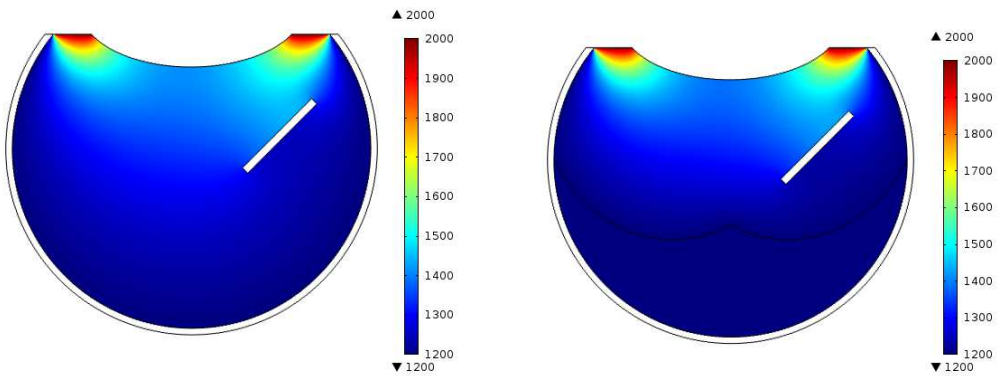

Figure 3: Pressure in the vitreous for two different situations: a completely attached vitreous (left) and a completely detached vitreous (right).

We begin by making a general remark that characterizes the flow of AH, transporting drug molecules, in the vitreous chamber of the eye: its convection dominated character. The pressure in the vitreous chamber is represented in the Figure 3 for two different situations: a completely attached vitreous (left) and a completely detached vitreous (right). Observing this figure we conclude that the difference of pressure between $\partial\Omega_2$ and $\partial\Omega_{23}$ is

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more significant in the case of a PVD. As the velocity in a porous media is proportional to the gradient of pressure it is expected that this fact will influence the velocity field as we can see in the Figure 4. In this figure we represent the AH vector field in a vitreous

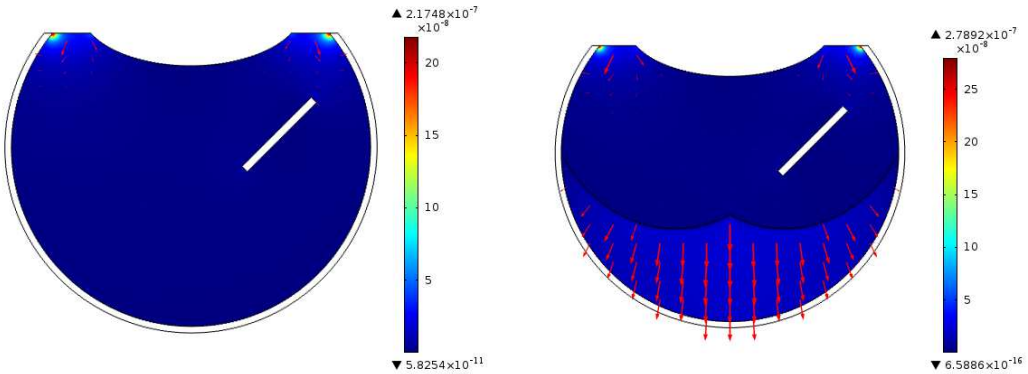

Figure 4: Velocity fields: a completely attached vitreous (left) and a completely detached vitreous (right).

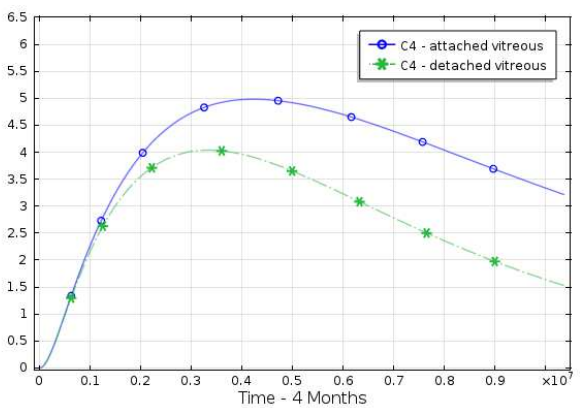

Figure 5: Evolution on time of the drug mean concentration in the retina: a completely attached vitreous and a vitreous with detachment.

completely attached (left) and a vitreous with a detachment zone (right). We observe that the scales are different in the left and right pictures. The mean value for the magnitude of the velocity in a completely attached vitreous (left) is 2.9×10^{-9} and in a completely detached vitreous (right) the mean velocity is 4.1×10^{-9} in the vitreous humor.The velocity is larger in the vitreous humor in the case of a PVD than in the case of a completely attached vitreous. This means that the drug approaches faster the retina. Considering that

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the diffusion coefficient of the drug in the vitreous is 2.7778×10^{-10}, we conclude that the transport of drug molecules is convection dominated ([3]).

In Figure 5 we exhibit the evolution of drug concentration in the retina during 4 months, in a complete attached vitreous and when a complete vitreous detachment has occurred. We observe a peak of drug concentration is attained after two months of release in the case of a completely attached vitreous. This result is in agreement with the data in the technical literature concerning the bioerodible implant of Allergan simulated in this work (see for example [10]). In the case of a detached vitreous the maximum value of concentration is achieved immediately after the first month and lower concentrations are observed in the retina, except for an initial period of time. This behaviour can be predicted from the nature of the convective field. In fact the convective field drags the drug molecules to the proximity of the optical nerve, which implies that the retina surface available for sorption, in the case of a PVD, is mainly $\partial\Omega_{2,3}$.

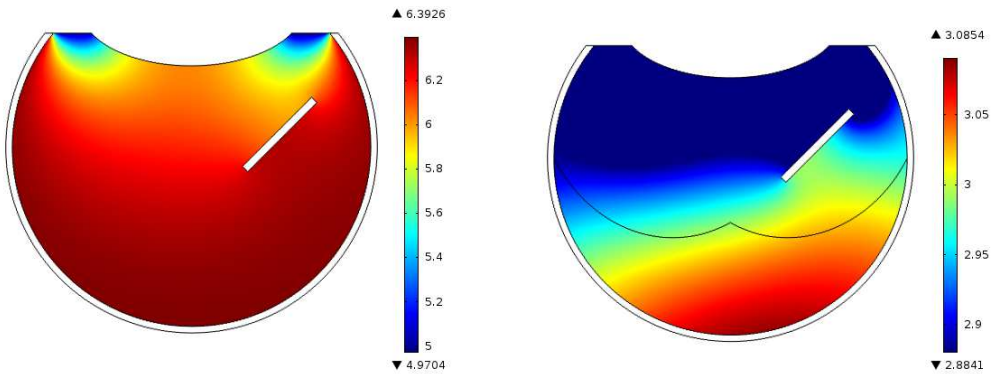

Figure 6: Drug distribution in a vitreous without PVD (left) and with a PVD (right) after four months of release.

To support the previous comments we illustrate in what follows the concentration distributions after 4 months of release in the vitreous chamber and in the retina. Figure 6 illustrates the drug distribution in a completely attached vitreous (left) and in a vitreous chamber where a PVD has occurred (right). We note that the two scales in the figure are different. As expected from the plot in Figure 5, in a complete attached vitreous it is observed higher levels of concentration than in a vitreous with a PVD. Moreover in the first case the drug is homogeneously distributed, while in the vitreous chamber with a PVD the drug accumulates in the proximity of the optical nerve, permeates the retina and is washed out.

The distribution of the drug concentration in the retina after four months of release is represented in Figure 7, for a vitreous completely attached (left) and when the vitreous is detached (right). We note that the two scales are different. It can be observed that the

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drug concentration in the retina is two times lower in the case of a PVD.

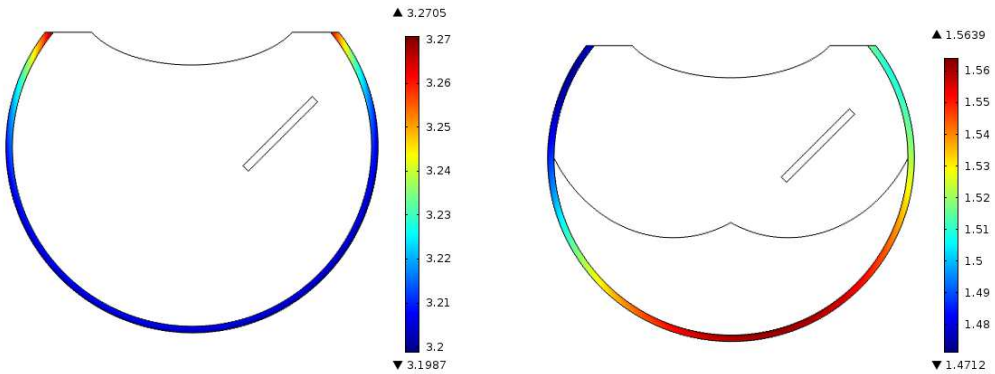

Figure 7: Drug concentration in the retina after four months of release in two different situations: a completely attached vitreous (left) and a detached vitreous (right).

4 Conclusions

The comparison of the pharmacokinetics of a drug released from a bioerodible implant in the cases of a completely attached vitreous and a completely detached vitreous was modeled and simulated. The results obtained suggest that, in the case of a completely attached vitreous, the peak of the concentration is higher, occurs after two months of drug release, and the residence time of drug within a predefined therapeutic window is larger. In the case of a posterior vitreous detachment the peak is attained after one month of release and the residence time within a predefined therapeutic windrow is shorter. Further numerical simulations are needed, with larger data sets for the parameters, in order to have a global picture of the behavior of drug concentration in the retina.

Acknowledgements

This work was partially supported by the Centro de Matemática da Universidade de Coimbra (CMUC), funded by the European Regional Development Fund through the program COMPETE.

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