COMPUTATIONAL ANALYSIS OF THE FLUID DYNAMICS AND DRUG DELIVERY INSIDE THE POSTERIOR CHAMBER OF THE EYE IN CASE OF SACCADIC MOVEMENTS

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Introduction

One of the main ocular diseases related to aging is the **age-related macular degeneration** (AMD), which is treated with a **drug injection** inside the eye. The aim of the work is to study the influence of the **saccadic movements** and the physiological boundary conditions on the drug distribution inside the vitreous humour in a patient affected by AMD and treated with an injection of anti-VEGF (*Vascular Endothelial Growth Factor*). This problem has been faced with different approaches: Stay et al, 2003 [1] consider the influence of the tissues around the posterior chamber on the drug delivery, but neglect rotations of the eye; on the other side, Modareszadeh et al., 2013 [2] correctly implement the saccadic movements but they don't take into account neither the presence of the anterior chamber nor the Retina-Choroid-Sclera (RCS) complex. The aim of this work is to propose a complete model of the posterior chamber that overcomes the limits of the works in literature and analyse the real impact of the saccadic motions onto the fluid dynamic and drug delivery mechanisms.

Materials and methods

The saccadic movements

The saccade is an involuntary and imperceptible movement performed by the eye during the focusing of an object. The rotation is caused by the external muscles of the eye. The single saccade has been defined by Repetto et al., 2005 [3] as a **fifth-grade polynomial**:

$$\theta(t) = c_0 + c_1 t + c_2 t^2 + c_3 t^3 + c_4 t^4 + c_5 t^5$$

where the coefficients can be found imposing the following conditions: $\theta(0) = 0, \theta(D) = A, \dot{\theta}(0) = 0$, $\dot{\theta}(t_p) = \Omega_p$, $\dot{\theta}(D) = 0$ and $\ddot{\theta}(t_p) = 0$, where D is the period of a single saccade, A is the amplitude, t_p is the instant of maximum acceleration and Ω_p is the peak angular velocity. The saccade can have **different amplitudes** and frequencies: in this work the movements of **10°**, **30°** and **50°** have been analysed. In order to study different frequencies, a **rest time** of *5D* after each saccade has been added to the complete cycle. The computational analysis has been developed with the software **COMSOL Multiphysics®**.

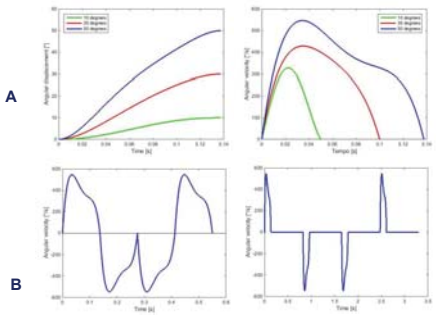

Fig.1 *A) Saccadic angular displacement and velocity with different amplitudes. B) Complete cycles of the saccadic movements without and with the rest time.*

Fluid dynamic analysis

The geometry of the posterior chamber is like an **hemisphere** with an indentation caused by the presence of the lens. The vitreous humor inside the eye is modeled as **water**, due to the liquefaction occurring in old people. The equations solved in the fluid dynamic model are the incompressible **Navier-Stokes** ones. The boundary conditions imposed are explained in table (1). In particular, the pressure on the membrane is due to the presence of the anterior chamber and the Darcy's law describes the outflow of fluid from the RCS complex. The time-dependent study has been extended till the fifth complete cycle of saccadic movement, when the solution reaches an equilibrium condition in the motion field.

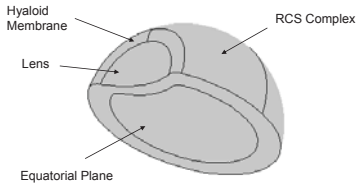

Fig.2 *The geometry used for the fluid dynamic model*

Boundary	Boundary condition
Lens	*Sliding wall* $\mathbf{u} = \dot{\theta}(t) \cdot \boldsymbol{R}$
Equatorial Plane	*Symmetry*
Hyaloid Membrane	*Normal Stress* $p = 2000\ Pa$
Hyaloid Membrane	*Velocity* $\mathbf{u} = \dot{\theta}(t) \cdot \boldsymbol{R}$
RCS Complex	*Velocity* $\mathbf{u} = K_p \cdot (\mathbf{p} - p_v) + \dot{\theta}(t) \cdot \boldsymbol{R}$

Table 1 *The boundary conditions implemented in the fluid dynamic model, where K_p is the normalized permeability of the RCS complex ($5 \cdot 10^{-10}$ cm/(Pa·s)) and p_v is the venous pressure (1200 Pa)*

Drug delivery analysis

In order to analyse the influence of the saccadic movements on the delivery of anti-VEGF after the **intravitreal injection**, the bolus has been considered as a sphere of a known concentration inside the posterior chamber. For this problem, the saccade of amplitude of **50°** and **without rest time** has been chosen. A parametric study on the **location of the bolus** is presented. The equations, solved and properly coupled in the models, are related to the **mass conservation law**, the **Fick's law** and the **Navier-Stokes** equations. The boundary conditions related to the drug delivery are listed in table (2) and they have been added to the fluid dynamics ones in table (1). In particular, the clearance of the drug has been implemented as an outflow from the RCS complex proportional to the concentration on this boundary.

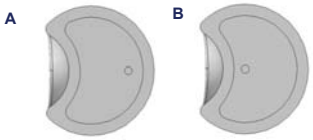

Fig.3 *A) The bolus next to the RCS complex B) The bolus at the center of the posterior chamber*

Boundary	Boundary condition
Vitreous humour	*Initial Value* $c = 0$
Bolus	*Initial Value* $c = 39.5849\ mol/m^3$
Hyaloid Membrane	*Concentration* $c = 0$
RCS Complex	*Flux* $\mathbf{N} = k \cdot c$
Lens	*No Flux* $\mathbf{N} = 0$
Equatorial Plane	*Symmetry*

Table2 *The boundary conditions added to the drug delivery model, where k is equal to 10^{-5} cm/s*

Results

The equatorial velocity maps related to the steady state condition are shown in fig. 4, while the streamlines averaged on the whole cycle are presented in fig. 5. The distribution of the anti-VEGF on the equatorial plane is shown in fig. 6, for both the bolus locations considered. In order to underline the entity of the saccade on both the motion field and the drug distribution, table (3) presents the averaged values of the velocity of the RCS complex and the Péclet number, in case of the saccade of 50° of amplitude and without any rotation. Fig. 7 shows the concentration maps on the equatorial and vertical planes in the motionless case. The exponential decay of the number of moles inside the posterior chamber is presented in fig. 8: the two plots are related to the saccadic movement and to the motionless cases.

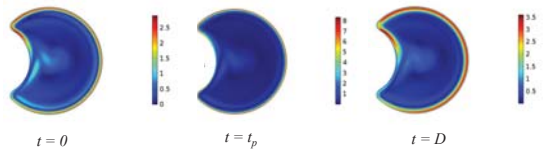

Fig.4 *Equatorial velocity maps generated by the saccade with amplitude of 50° in three important instants of the motion [cm/s]*

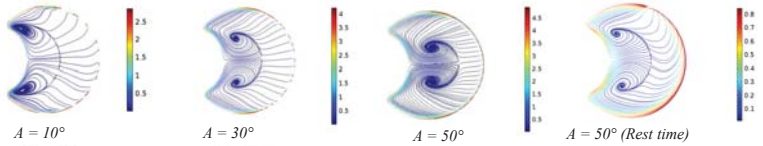

Fig.5 *Streamlines related to all the saccadic movements implemented in the model. [cm/s]. It can be noticed that some vortexes are created, mainly because of the presence of the lens. With higher amplitudes, the value of the velocity increases and the location of the vortexes moves to the center of the eye. The streamlines related to the rest time show lower values of velocity.*

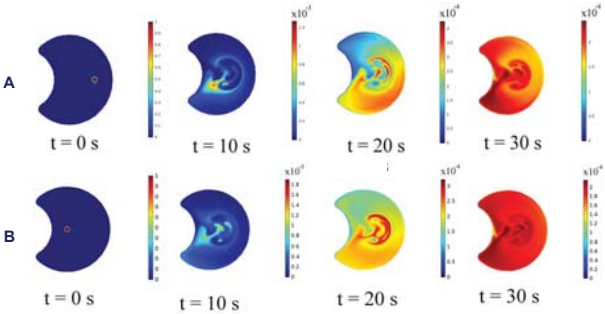

Fig.6 *Equatorial map of the normalized concentration for the two different locations considered. Both when the bolus is next to the RCS complex (A) and when it is in the center of the eye the maps are similar and a uniform distribution is reached after 30 seconds from the intravitreal injection. In particular, in the maps related to t = 30 s, the vortexes underlined by the streamlines (fig. 5) can be seen.*

	Motion (A = 50°)	Motionless
Average velocity on the RCS complex	3.72 cm/s	$3.99 \cdot 10^{-7}$ cm/s
Péclet number	$7.56 \cdot 10^{5}$	1.18

Table 3 *The average velocity on the RCS complex and the Péclet number are shown in order to underline the great influence of the saccadic motion both on the fluid dynamics and the drug delivery. The drug considered in this work are the anti-VEGF, which have a diffusion coefficient of $7.6 \cdot 10^{-11}$ m^2/s but the use of any other molecules don't change the results because the Péclet number due to the saccade is very high .*

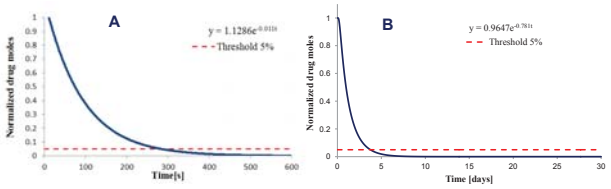

Fig. 8 *Time course of the normalized drug moles inside the posterior chamber with the saccadic movement of 50° (A) and without any motion (B). The threshold of 5% of the initial moles has been set in order to consider the drug cleared from the domain. In the first case, the threshold is reached more or less after 300 seconds after the injection, while in the second case 4 days are needed.*

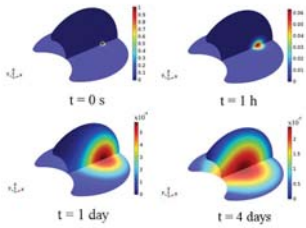

Fig.7 *Equatorial and vertical maps of the normalized concentration for the motionless case. It is clear that the timing clearly increases with respect to the saccadic movement case. In addition to that, the uniform distribution is never reached, because the clearance of the drug is faster than its diffusion.*

Conclusions

This study shows that the saccadic movements cannot be neglected due to their great influence on both the fluid dynamic and the drug delivery mechanism inside the posterior chamber of the eye. A complete characterization of the surrounding tissues is also mandatory in order to consider the changes in permeation across the RCS complex and the specific anti-VEGF consumption nearby the retinal surface.

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References:
[1] M. S. Stay et al., *Pharm. Res*, vol. 20, no. 1, pp. 96–102, *2003*
[2] A. Modareszadeh et al., *Biomech. Model. Mechanobiol.*, vol. 12, no. 2, 2013.
[3] R. Repetto et al., *Phys. Med. Biol.* vol. 50, pp. 4729–4743, *2005*