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Virtual pharmacokinetic model of human eye

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ABSTRACT

A virtual pharmacokinetic 3D model of the human eye is built using Comsol Multiphysics® software, which is based on the Finite Element Method (FEM). The model considers drug release from a polymer patch placed on sclera. The model concentrates on the posterior part of the eye, retina being the target tissue, and comprises the choroidal blood flow, partitioning of the drug between different tissues and active transport at the retina pigment epithelium (RPE)–choroid boundary. Although most straightforward, in order to check the mass balance, no protein binding or metabolism is yet included. It appeared that the most important issue in obtaining reliable simulation results is the finite element mesh, while time stepping has hardly any significance. Simulations were extended to 100,000 s. The concentration of a drug is shown as a function of time at various points of retina, as well as its average value, varying several parameters in the model. This work demonstrates how anybody with basic knowledge of calculus is able to build physically meaningful models of quite complex biological systems.

1. Introduction

Drugs are the essential means in treating eye diseases, and the optimal route of drug delivery depends on the target tissue and disease. Diseases of the anterior eye can usually be treated with eye drops, although less than 5% of the dose is actually absorbed. Most of the dose is absorbed into the systemic circulation via eyelids (via conjunctiva, see Fig. 1 below), or the nasal mucosa where the drops are flown after their administration. Diseases of the anterior eye include glaucoma, inflammations and infections. Eye drops cannot be, however, used in treating diseases of the posterior eye, because the achievable drug concentration in these tissues remains too low. Yet, there is a great need for an effective drug treatment of the posterior eye, as the major reason for visual disability in industrial countries is age related macular degeneration (AMD); in USA alone, there are almost 2 million people affected by AMD [1]. Other diseases in retina include diabetic retinopathy and ganglion cell damage due to glaucoma [2]. AMD also causes growth of new blood veins in choroid, which is a dangerous complication for vision [3]. This is treated ever more frequently by direct injections to the vitreous humor. Other possibilities to drug administration into the posterior eye are systemic delivery (systemic blood circulation) or sub-conjunctival delivery. In systemic delivery, quite high doses must be used in order to reach sufficient effect, and from the dose injected below conjunctiva a sufficient amount of drug is necessarily not partitioned and transported to retina.

New drug delivery systems are subject to a growing interest, since they can facilitate the access of a drug into its target, or prolong its time of action. These delivery systems are based, e.g., on polymers or lipids, which release a drug in a controlled manner, but they cannot be designed without taking the physiology and pharmacokinetics of an eye into account. There are several membranes, tissues and fluid flows in an eye, but the quantitative estimation of their effect on drug delivery is rather difficult. Means to determine ADME (Administration, Distribution, Metabolism, Excretion) properties of a drug in an eye would thus be valuable for drug development.

Pharmacokinetic modeling is typically carried out with Stella® software [4], where different organs are described as dummy boxes, and relations between boxes are defined by simple reaction or transport equations. Using Stella® the values of pharmacokinetic parameters of a few molecules have already been determined in, e.g., rabbit cornea [5], in retinal pigment epithelium [6] and bovine sclera [7]. The limitation of Stella® is that it assumes each organ or computational unit to be homogeneous, i.e. it models interplay between 'ideally stirred tank reactors', ignoring the spatial distribution of concentrations and the geometry of the domains under study. The spatial distribution becomes important when some physical dimension of a tissue or an organ is so large that chemical processes are under mass transfer control.

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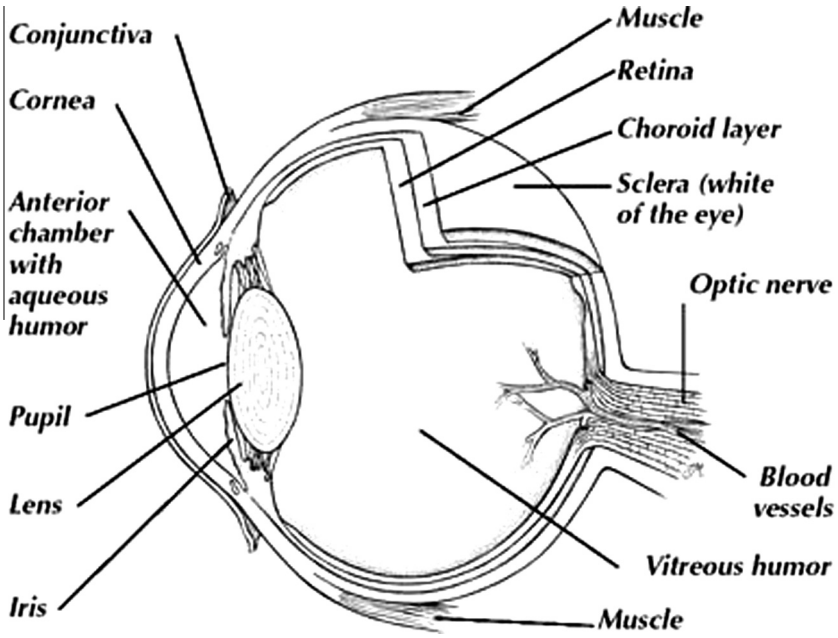

Fig. 1. Structure of an eye [20].

There are a few simulation studies of ocular drug delivery which consider the geometry of an eye. In the models of Tojo et al. [8,9] the eye was modeled as a cylinder and the partial differential equations were solved with the method of lines. Wyatt modeled drug transport from the anterior chamber [10], using a self-made finite element algorithm. Transscleral drug delivery has been considered by Balachandran and Barocas [11] and Narasimhan and Vishnampet [12]. In the former study computations were done with a Finite Element Method, while in the latter one the commercial software Fluent® based on the finite volume method was applied. Both papers considered also the loss of drug via the choroidal blood flow. Friedrich et al. [13] and later Haghjou et al. [14] modeled the drug distribution in rabbit eye after an intravitreous injection using the Finite Element Method and Fluent software, respectively. Quite recently also the GastroPlus® software, which is based on the finite difference method, is being extended to human eye simulations [15].

Our purpose is to widen and improve the modeling methodology with Finite Element Method (FEM) to 'laymen' in calculus. In this first communication, we present a 3D pharmacokinetic model of the posterior part of human eye, thus ignoring the cornea, anterior chamber and lens. Drug is delivered from a patch placed on sclera, and the amount of drug reaching retina is computed as a function of time. In order to make sure that mass balance is fulfilled at all times, no metabolism or protein binding is yet included, but that is most straightforward to implement in the model.

2. Method

The model is built using Comsol Multiphysics© software [16], version 4.3b. It has mainly been applied to engineering problems, such as in reactor design, statics or electromagnetism, but lately it (or its predecessor Femlab) has been applied ever more frequently in biological systems, such as in modeling the distribution of oxygen in human heart tissues [17], transdermal drug delivery [18] and distribution of heat in the human eye [19]. The gist of using Comsol is that a user does not need to be a computing expert, because the user interface is graphical, and neither equations nor boundary conditions need to be explicitly written but they are chosen from pertinent menus in plain language. The solution of the problem is usually obtained with the default settings of the solver, although some knowledge of numerical solvers naturally helps. Comsol Multiphysics makes simulations to a scientist with basic calculus knowledge feasible, and one can concentrate on creating a model instead of pondering technical issues of FEM or solution algorithms.

As can be seen in Fig. 1 [20], an eye is quite complex an organ, for which building a comprehensive model is very challenging. Therefore, the approach is modular, based on different modes of drug delivery. In this paper we consider a polymer implant below the conjunctiva, hence residing on sclera. Our simplified Comsol drawing is shown in Figs. 2 and 3. It has to be emphasized that

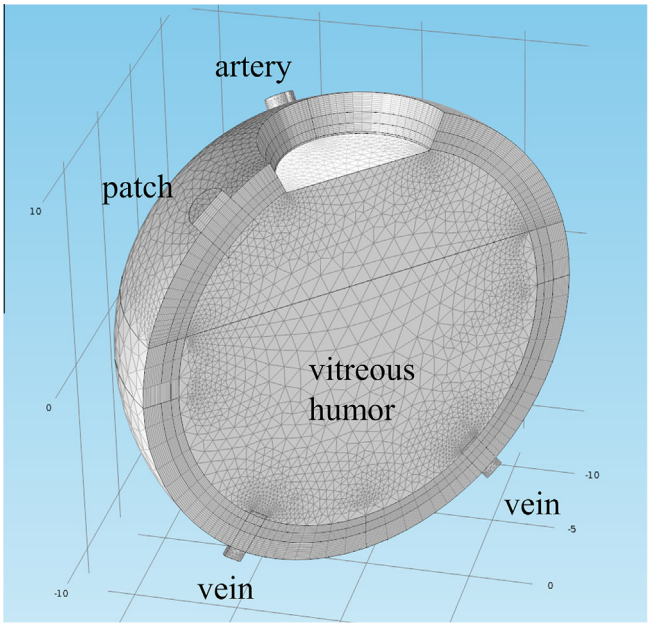

Fig. 2. Comsol drawing of the cross section of an eye, showing also the calculation mesh.