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Diffusion, viscoelasticity and erosion: Analytical study and medical applications

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ABSTRACT

In this paper diffusion through a viscoelastic biodegradable material is studied. The phenomenon is described by a set of three coupled partial differential equations that take into account passive diffusion, stress driven diffusion and the degradation of the material. The stability properties of the model are studied.

Erodible viscoelastic materials, as biodegradable polymers, have a huge range of applications in medicine to make drug eluting implants. Using the mathematical model the behavior of a particular ocular drug eluting implant which describes drug delivery into the vitreous chamber of the eye is presented. The model consists of coupled systems of partial differential equations linked by interface conditions. The chemical structure, the viscoelastic properties and the diffusion in the implant as well as the transport in the vitreous are taken into account to simulate the evolution *in vivo* of released drug. The dependence of the delivery profile on the properties of the material is addressed. Numerical simulations that illustrate the interplay between these phenomena are included.

1. Introduction

In the past few decades diffusion through viscoelastic materials has attracted the attention of many researchers [1–6]. Apart from the mathematical interest of non Fickian diffusion such research focus is also explained by the increasing practical use of polymers in coatings, packaging, membranes for transdermal drug delivery and more generally in controlled drug delivery [3,7].

It is well known that diffusion through a viscoelastic material does not obey Fick's law. In fact the material opposes a resistance to the Brownian motion of molecules that can be quantified by the stress response to the strain induced by these molecules. Several authors [1–5,8–12] have proposed a general model represented by

$$\frac{\partial C_1}{\partial t} = -\nabla \cdot J, \tag{1}$$

where C_1 represents drug concentration and J is a modified flux, with a stress driven diffusion term, defined by

$$J = -D_1 \nabla C_1 - D_v \nabla \sigma, \tag{2}$$

where the stress σ is related with the strain by some mechanistic model [13]. In (2) D_1 represents the diffusion coefficient and D_v a viscoelastic parameter whose meaning will be clarified later.

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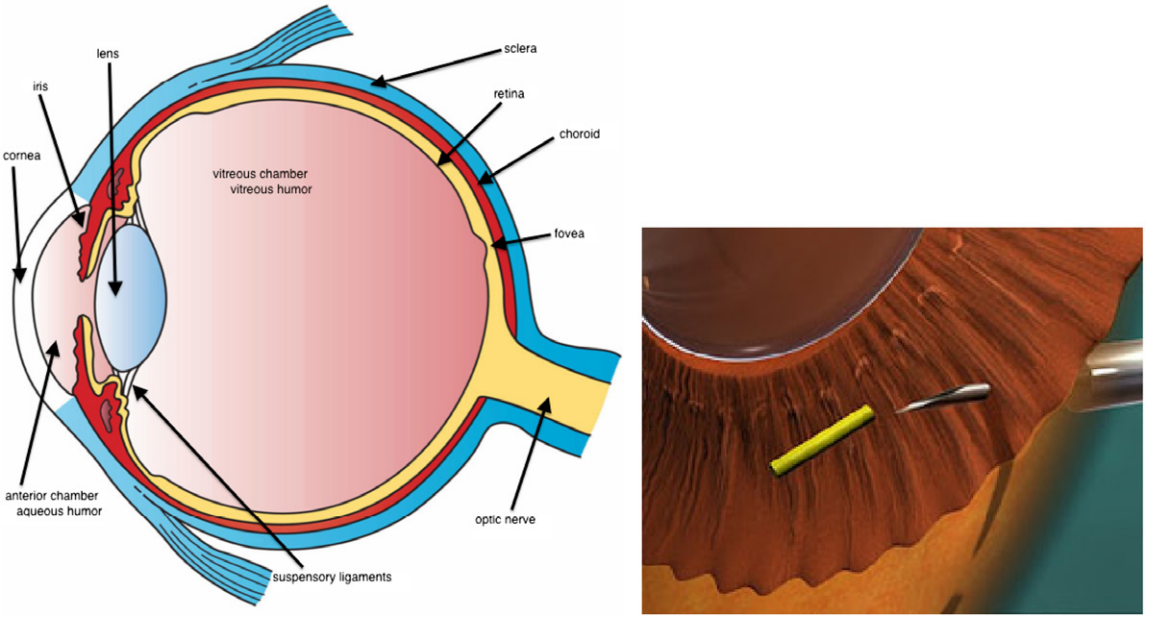

Fig. 1. Anatomy of the human eye (left) and an ocular implant (right) (http://en.wikipedia.org/wiki/ and http://marcelohosoume.blogspot.pt/2010/10/iluvien-and-future-of-ophthalmic-drug.html).

When the polymer matrix is biodegradable the transport of molecules is not well described by (1)–(2) and a more complex system must be considered. As degradation proceeds, the polymer molecular weight decreases and diffusional paths open through the matrix allowing solved drug molecules to leave the polymeric matrix [14]. Because of the increasing permeability of the system upon polymer degradation, the constant diffusion coefficient is replaced by a molecular weight that depends on the diffusion coefficient [15] and a reaction term to describe the degradation of drug inside the polymeric matrix is considered. Eq. (1) is then replaced by

$$\frac{\partial C_1}{\partial t} = \nabla \cdot (D_1(M)\nabla C_1 + D_v \nabla \sigma) - k_1 C_1,$$

where k_1 represents the degradation rate. The model is completed with two other equations: one that describes the mechanistic behavior of the polymer, that is a relation between stress and strain; another equation which represents the evolution of the material molecular weight as drug concentration changes. One of the contributions of this paper is a theoretical study of the model which leads to a stability restriction with a sound physical meaning: if the Fickian diffusion dominates the non Fickian one the mathematical model is stable. As the material where diffusion occurs opposes a barrier to diffusion, the theoretical restriction is also a sound physical condition.

Delivering drugs to the vitreous chamber of the eye assumes a crucial role and is a challenging problem due to the presence of various physiological and anatomical barriers. Classical ocular drug delivery systems for posterior segment diseases is systemic or topical. However none of these drug delivery systems are effective. In fact systemic delivery is not effective because the drug concentration carried by the blood stream is not enough, which means that it does not reach the therapeutic window; with topical delivery just a small fraction of drug reaches the posterior segment of the eye due to physiological barriers. These classical drug delivery systems are being replaced by direct intravitreal injection or intravitreal implants of drug. As vitreal injections imply several treatments and can cause deleterious side effects, intravitreal implants have deserved much attention these last years. Intravitreal implants are being used in different medical delivery systems, as for example in ocular diseases of the vitreous and the retina [16–18]. In fact there are a number of severe diseases that can affect the vitreous and the retina, which must be treated over long periods of time and where drugs must be maintained in their therapeutic windows (Fig. 1).

Many drugs have a narrow concentration window of effectiveness and may be toxic at higher concentration [19], so the ability to predict local drug concentrations is necessary for proper designing of the delivery system. Mathematical models which couple drug delivery from a device with the transport in the living system play a central role because not only they can be used to explain the kinetics of the delivery, by describing the interplay of the different phenomena, as they quantify the effect of physical and physiological parameters in the delivery trend. Several authors have studied Fickian mathematical models to describe transport and elimination of drugs in the vitreous [20–24,19]. However to the best of our knowledge the *in vivo* delivery of drug from a viscoelastic biodegradable implant has not yet been addressed.

In this paper we will propose a model to simulate intravitreal delivery of drug through viscoelastic biodegradable implants. The model consists of coupled systems of partial differential equations linked by interface conditions. The chemical