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Analytical and numerical study of a coupled cardiovascular drug delivery model

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ABSTRACT

A two dimensional coupled model of drug delivery in the cardiovascular tissue using biodegradable drug eluting stents is developed. Qualitative behavior, stability analysis as well as simulations of the model have been presented. Numerical results computed with an implicit–explicit finite element method show a complete agreement with the expected physical behavior.

1. Introduction

A stent is a metallic scaffold that is inserted in a restricted part of a narrowed blood vessel. A drug eluting stent (DES) consists of a stent coated with a polymeric layer that encapsulates a therapeutic drug to reduce smooth muscle cell growth and to prevent an inflammatory response (see Fig. 1). These are the predominant causes of neointimal proliferation and in-stent restenosis that is the re-narrowing of blood vessels after stent implantation. Application of DES for prevention of restenosis is a promising technology which combines the mechanical support of the vessel with local drug delivery.

Drug release depends on many factors, such as the geometry and location of the vessel, the geometry of the stent, the coating properties as its chemical composition and porosity, and drug characteristics as for example its diffusivity. Due to the involvement of so many factors, prediction of drug release represents an important issue and mathematical models are a useful tool to design an appropriate drug delivery system [1,2]. The use of mathematical models and numerical simulation can give further insight on the pharmacokinetics of cardiovascular drug release leading to optimized clinical results.

During the last years, a number of studies have proposed mathematical models to describe drug delivery in the cardiovascular tissues. We refer without being exhaustive [1,3–12] and also [2] as a review paper. Most of these studies address the release of drug and its numerical behavior in one dimension, while the behavior of the biodegradable materials is disregarded.

Pontrelli and de Monte [6–8] developed a mathematical model for drug release through a drug eluting stent in contact with the vessel wall as a coupled cardiovascular drug delivery system. They analyzed numerically and analytically the drug release from the coating into both a homogeneous mono-layer wall [6] and a heterogeneous multi-layered wall [8] in one dimension. Despite their interesting results, the biodegradation process of the carrier polymer, the penetration of the biological fluid into the coating and the egression of materials from the coating have not been taken into account.

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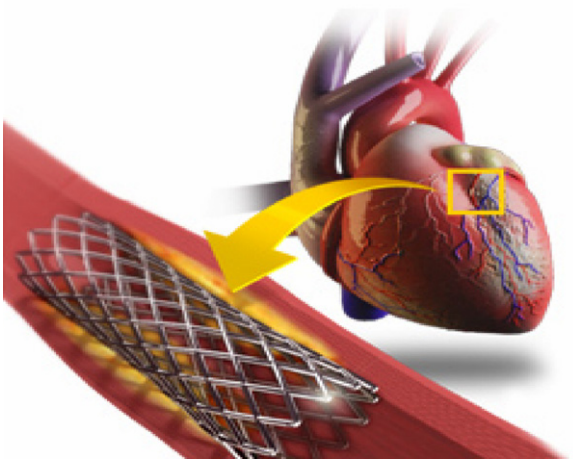

Fig. 1. Drug Eluting Stent (DES) implanted in the blood artery, http://www.michaelrowecardiologist.com.au/coronary-stenting-michael-rowe.html.

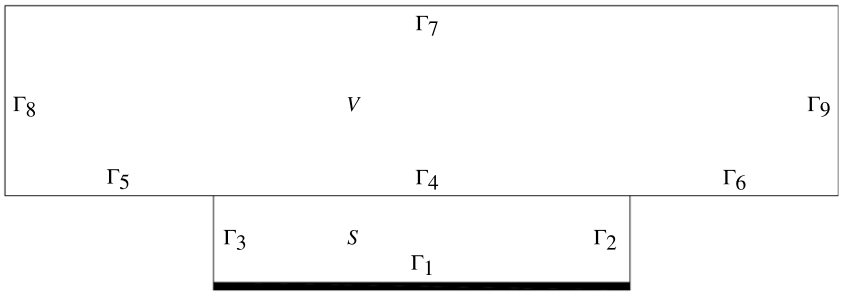

Fig. 2. Polymeric stent S in contact with the vessel wall V.

Prabhu and Hossainy [9] developed a mathematical model to predict the transport of drug with simultaneous degradation of the biodegradable polymer in the aqueous media. These authors use a simplified wall-free condition, in which the influence of the arterial wall is modeled through the coupling with a *Robin* boundary condition. An important feature of this model, which differentiates it from other models, are the conditions used to represent the polymer degradation. It is assumed that a set of oligomers can be identified as one compartment, characterized by a certain molecular weight range, whose diffusion characteristics and degradation kinetics can be considered to be identical. Furthermore, the model in [9] takes into account the underlying chemical reactions responsible for degradation in a more detailed form than the models presented by other researchers. It also accounts for the increase of diffusivity of the different species involved as time evolves. In this paper, while following the approach in [9], we have completed the model with the dynamics of the drug in the arterial vessel.

The geometrical and mechanical effects of the metallic part of the stent in degradation and drug release as well as the penetration of the oligomer and lactic acid into the vessel wall are considered negligible. As the transport properties through the glycocalyx (the coverage of endothelium) are unknown, we have considered the values of the parameters in the endothelium layer. A perfect sink condition at the interface between the vascular wall and the vascular lumen are considered.

The paper is organized as follows. Section 2 is devoted to the description of the model and its initial, boundary and interface conditions. In Section 3 we briefly explain the mass behavior of the materials. In Section 4 we present a variational formulation and we establish a stability result for the continuous model and in Section 5, using an implicit–explicit finite element method, we establish a discrete variational form of the problem. Numerical simulations are discussed in Section 6.

2. Description of the model

We consider a stent S coated with polylactic acid (PLA) containing the drug and in contact with the vessel wall V (Fig. 2). In the stent S, Γ_1 is the boundary between the coated stent and the metallic part of the stent that is stent structure while Γ_2 and Γ_3 are the boundaries which separate the coated stent and the lumen. Γ_4 is an interface boundary which separates the coated stent from the arterial wall. In the vessel wall V, Γ_5 and Γ_6 are the boundaries between the vessel wall and the lumen while Γ_7 is the boundary between the vessel wall and the tissue (outer part of the vessel wall). Finally Γ_8 and Γ_9 are virtual boundaries where symmetry conditions are imposed to simplify the model.