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Bifurcation analysis of a model for atherosclerotic plaque evolution

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HIGHLIGHTS

- We perform a codimension-two bifurcation analysis for a model of atherosclerosis.
- The bifurcation diagram was found to be organized by a Bogdanov–Takens point.
- We predict that there is threshold for the cholesterol intake parameter that marks growth or stability of plaques.
- Oscillations in the macrophage, monocyte and LDL concentration are precursors for plaque growth.
- There is slow–fast dynamics in atherosclerosis which we study by geometric singular perturbation theory.

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ABSTRACT

We analyze two ordinary differential equation (ODE) models for atherosclerosis. The ODE models describe long time evolution of plaques in arteries. We show how the dynamics of the first atherosclerosis model (model A) can be understood using codimension-two bifurcation analysis. The Low-Density Lipoprotein (LDL) intake parameter (d) is the first control parameter and the second control parameter is either taken to be the conversion rate of macrophages (b) or the wall shear stress (σ). Our analysis reveals that in both cases a Bogdanov–Takens (BT) point acts as an organizing center. The bifurcation diagrams are calculated partly analytically and to a large extent numerically using AUTO07 and MATCONT. The bifurcation curves show that the concentration of LDL in the plaque as well as the monocyte and the macrophage concentrations exhibit oscillations for a certain range of values of the control parameters. Moreover, we find that there are threshold values for both the cholesterol intake rate d_{crit} and the conversion rate of the macrophages b_{crit}, which depend on the values of other parameters, above which the plaque volume increases with time. It is found that larger conversion rates of macrophages lower the threshold value of cholesterol intake and vice versa. We further argue that the dynamics for model A can still be discerned in the second model (model B) in which the slow evolution of the radius of the artery is coupled self-consistently to changes in the plaque volume. The very slow evolution of the radius of the artery compared to the other processes makes it possible to use a slow manifold approximation to study the dynamics in this case. We find that in this case the model predicts that the concentrations of the plaque constituents may go through a period of oscillations before the radius of the artery will start to decrease. These oscillations hence act as a precursor for the reduction of the artery radius by plaque growth.

1. Introduction

Atherosclerosis is a chronic inflammation of the layers of the artery wall, which gives rise to plaque formation. The plaque is covered with a fibrous cap that may ultimately rupture and lead to a myocardial event. The subject of how atherosclerotic plaques grow and how they may eventually rupture has been investigated for a long time. One mechanism that is responsible for the onset of atherosclerosis is endothelial injury after which subsequent biochemical phenomena take place that trigger the formation of plaques in arteries. The

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evolution of atherosclerotic plaques is characterized by accumulation of so-called lipid-laden foam cells over time [1] in a part of the arterial wall that is called the intima. The evolution of plaques involves a number of different substances, some of which are carried with the blood flow and others reside in the layers of the artery. Important constituents include LDL-cholesterol, monocytes, macrophages, cytokines and smooth muscle cells. Besides, the biochemical reactions that occur within the plaque mechanical stimuli were shown to play an important role in the development of atherosclerosis [2,3]. The shear stress that is exerted by the blood on the endothelial layer is especially crucial. It was found that high wall shear stress leads to a reduced plaque growth. The growth of a plaque region is therefore anisotropic: the plaque grows predominantly in the downstream direction where the shear stress is much lower than upstream [4]. Also during later stages in which smooth muscle cells proliferate and a fibrous cap covering the plaque is constructed, biomechanical factors become important for the stability and elasticity of the cap [5]. Mathematical models describing the elasticity of the arterial wall were developed by [6].

Although beneficial effects of high wall shear stress on plaque evolution have been demonstrated in experiments [3,2], hardly any mathematical model has been developed that takes biomechanical effects into account. In a recent paper [7], we put forward an ODE model for the progression of atherosclerosis which includes wall shear stress effects. This model was inspired by a model of Zohdi et al. [8], who introduced a phenomenological model to describe plaque evolution by focusing on particle adhesion rather than wall shear stress. Another ODE model was developed by Ougrinovskaia et al. [9] for the initiation of the disease. Even though ODE models can never capture all aspects that are relevant for atherosclerosis, ODE models can give qualitative results that can serve as guidelines for clinical experiments. Moreover, ODEs are relevant limiting cases for partial differential equation (PDE) models. These PDE-models usually contain parameters whose values are not always known from experiments. Bifurcation analysis can provide clues for the parameter values and the correctness of the model.

In this paper we analyze the dynamics associated with the progression of atherosclerosis by performing a codimension-two bifurcation analysis of the two models proposed in [7]. These models referred to as models A and B, respectively, consider the evolution of the plaque in two cases. In model A the dynamics of plaque constituents is modeled without taking into account biomechanical effects. In model B, these effects were included by presuming a wall shear stress dependent recruitment of monocytes. The assumption of a constant throughput of the blood through the artery leads then to a self-consistent model, in the sense that a smaller radius gives rise to larger flow velocity which implies on its turn an increased wall shear stress in a consistent way. The importance of such coupling of the blood flow to the plaque is essential in predicting how the radius of the artery behaves and how the total volume of the plaque evolves.

We organize this paper as follows: In Section 2 we present the models A and B. In Section 3 we focus on the codimension-two bifurcation diagram with two different sets of control parameters. We first consider the dynamics in the case that the LDL-intake rate and the ingestion rate of (oxidized) LDL are the control parameters and later we replace the ingestion rate by the wall shear stress. In both cases, we obtain similar bifurcation diagrams which have a Bogdanov–Takens (BT) point as an organizing center. This allows us to unfold the dynamics for a wide range of parameters. For model B which has a trivial bifurcation diagram, we perform a slow–fast analysis in Section 4 as the radius of the artery evolves on a much longer time scale than the typical time scale associated with the biochemical responses of the plaque constituents. We calculate the slow-manifold and determine the evolution of the artery radius. In Section 5, we discuss the physical interpretation of our bifurcation studies and finally in Section 6 we present the conclusions.

2. Introduction of models A and B

2.1. Model A

The evolution equations for model A are given as:

$$\dot{m} = \left(\frac{aL}{(1+\sigma)(1+L)} - \epsilon - c\right) m, \tag{2.1a}$$

$$\dot{M} = cm - \frac{bML}{1+L}, \tag{2.1b}$$

$$\dot{L} = \frac{dm}{f+m} - eLM - L, \tag{2.1c}$$

$$\dot{F} = \frac{bLM}{1+L}. \tag{2.1d}$$

All parameters and variables in the model (2.1) are dimensionless and nonnegative and the dot denotes the time derivative. The physical interpretation of this coupled system of plaque constituents is described in detail in [7]. Here we will only give a brief explanation of the terms and parameters of the model.

Eq. (2.1a) describes the evolution of the monocytes (m) which enter the arterial wall after a signaling response transmitted by monocytes that are involved in oxidizing LDL molecules [7]. We assume that the monocytes are converted into macrophages at a dimensionless rate c and may diffuse through the endothelial layer into the blood at a rate ϵ. The macrophage concentration (M) is governed by Eq. (2.1b). The macrophages ingest ox-LDL and are next converted into so-called foam cells (F) at a rate b. Since macrophages are much larger than monocytes they will typically diffuse much slower and therefore no diffusion term was included in Eq. (2.1b). Finally, the ox-LDL (L) concentration, whose dynamics is governed by Eq. (2.1c), decreases due to the ingestion of ox-LDL by macrophages, at a rate e, and increases at a rate d due to the oxidation by monocytes of unoxidized LDL molecules present in the arterial wall. The saturation of this process is taken into account by the parameter f. The *unoxidized*-LDL in the blood penetrates the endothelial layer, which gives rise to a concentration of *oxidized*-LDL in the arterial wall that we denote by d. We assume that the value of d is proportional to the actual intake of cholesterol and therefore we consider d to be a control parameter. Dependence of the dynamics on b and e will also be studied as these parameters influence the 'life time' of the ox-LDL in the plaque, which is a determining factor in the development of atherosclerosis.