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Analysis of control for a free boundary problem of steady plaques in the artery

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ABSTRACT

In the earlier paper of Friedman et al. a simplified model of plaque growth involving LDL and HDL cholesterols, macrophages and foam cells is considered and they satisfy a coupled system of PDEs with a free boundary. The paper adds some control function to that model, allowing the controlled growth of LDL, HDL and plaque. Next, the new dual dynamic programming approach for free boundary problem is developed to formulate sufficient optimality conditions for the optimal steering of drugs. Finally an approximate optimality and numerical calculations are presented.

1. Introduction

The atherosclerosis disease is the leading cause of death over the world. It originates from a plaque which builds up in the arteries and may eventually trigger a heart attack or a stroke. There are several mathematical models that describe the growth of a plaque in the artery, see e.g., [1–6]. All these models recognise the critical role of the "bad" cholesterols – LDL and the "good" cholesterols – HDL, in determining whether a plaque, once formed, will grow or shrink. The most recent and most comprehensive model, in [7,8], including smooth muscle cells, **T** cells and various cytokines is described by a system of 17 PDEs. In turn in [9] significant simplification of the model from [7] is investigated and finally the system of four equations is considered. It is determined in [9], by rigorous mathematical analysis, whether small steady state plaques exist and whether they are stable, which in the case of 17 PDEs is a difficult challenge. We will concentrate on this simplified model due to the fact that our aim is to study some type of an optimal control drug model and show that such simplification is still interesting from biological point of view and simultaneously allows to be more rigorous mathematically. Following [9], we present simplified model with the following variables: L = LDL − concentration in g/cm^3, H = HDL − concentration in g/cm^3, F = foam cells density in g/cm^3. The artery is assumed to be a long circular cylinder, its diameter $2B$, will be taken to be 2 cm, and all variables are functions of (t, r) only where r is measured in units of cm, and t is measured in units of days. The plaque is given by $R(t) < r < 1$ and parameters λ, δ relate to the simplification of the model. The variables L, H, F satisfy the following equations in the region $\{(t, r);\ R(t) < r < 1,\ t > 0\}$,

$$\frac{\partial L}{\partial t} - \Delta L = -k_1 \frac{(M_0 - F)L}{K_1 + L} - r_1 L, \quad \frac{\partial H}{\partial t} - \Delta H = -k_2 \frac{HF}{K_2 + F} - r_2 H, \tag{1}$$

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$$\frac{\partial F}{\partial t} - D\Delta F + F_r v = k_1 \frac{(M_0 - F)L}{K_1 + L} - k_2 \frac{HF}{K_2 + F} \tag{2}$$
$$-\lambda \frac{F(M_0 - F)L}{M_0(\delta + H)} + \frac{\mu_1}{M_0}(M_0 - F)F - \frac{\mu_2}{M_0}(M_0 - F),$$

$$\frac{dR(t)}{dt} = v(t, R(t)), \tag{3}$$

where r_1 and r_2 are reaction rates of oxidization, k_1 is a rate of ox-LDL ingestion by macrophages, k_2 denotes the reaction rate of HDL removing ox-LDL from foam cells, μ_1 is a death rate of macrophages, μ_2 is a death rate of the foam cell, M_0 is the density of macrophages in the blood, F_r means the derivative with respect to r and v is the radial velocity satisfying

$$M_0 v_r = \lambda \frac{(M_0 - F)L}{\delta + H} - \mu_1(M_0 - F) - \mu_2 F, \quad v(t, 1) = 0, \ t > 0. \tag{4}$$

Δ denotes the Laplace operator with respect to the space variable r. In the next sections, if a function will depend on more than two variables to underline that the Laplace operator is with respect to r, we write Δ_r. The boundary conditions on the free boundary $r = R(t)$ are following:

$$\frac{\partial L}{\partial n} + \alpha(L - L_0) = 0, \ \frac{\partial H}{\partial n} + \alpha(H - H_0) = 0, \ \frac{\partial F}{\partial n} + \beta F = 0, \tag{5}$$

L_0, H_0 are concentrations of L, H in the blood, and on the blood vessel wall $r = 1$

$$\frac{\partial L}{\partial n} = \frac{\partial H}{\partial n} = \frac{\partial F}{\partial n} = 0. \tag{6}$$

It was demonstrated in [9] that there a unique, radially symmetric, stationary plaque exists in a small ring-region $1 - \varepsilon < r < 1$ and the linear asymptotic behaviour of the stationary solution. In the conclusion of Friedman and Hao [9], it has been suggested that if we denote by $R(t, L_0, H_0)$ the free boundary $r = R(t)$ corresponding to (L_0, H_0), then it is increasing if L_0 increases and H_0 decreases. The aim of this paper is to investigate the application of some drugs and/or injections in fixed time $[0, T]$ to patient with $R(0) = r_0$, $0 < r_0 < 1$, to control quantities of L, H, F and to obtain minimal value of $1 - R(T)$. Since we want to be near practice, we assume some simplification in the number of control functions in system (1)–(5) i.e., we assume only one measurable control $\varphi(t)$, $0 \le \varphi(t) \le K$, $t \in [0, T]$, T and K given, fixed. This simplification relates to the fact that nowadays research is carried out on mice and drugs given them are described only by φ. Namely, we will study the following optimal control problem for the system (1)–(6):

$$\textit{minimize } 1 - R(T) \tag{7}$$

subject, in the region $\{(t, r);\ R(t) < r < 1,\ 0 < t < T\}$, to

$$\frac{\partial L}{\partial t} - \Delta L = -k_1 \frac{(M_0 - F)L}{K_1 + L} - r_1 L, \ \frac{\partial H}{\partial t} - \Delta H = -(\varphi(t) + k_2) \frac{HF}{K_2 + F} - r_2 H, \tag{8}$$

$$\frac{\partial F}{\partial t} - D\Delta F + F_r v = k_1 \frac{(M_0 - F)L}{K_1 + L} - (\varphi(t) + k_2) \frac{HF}{K_2 + F} \tag{9}$$
$$-\lambda \frac{F(M_0 - F)L}{M_0(\delta + H)} + \frac{\mu_1}{M_0}(M_0 - F)F - \frac{\mu_2}{M_0}(M_0 - F),$$

$$\frac{dR(t)}{dt} = v(t, R(t)), \tag{10}$$

M_0 is the density of macrophages in the blood, v is the radial velocity satisfying

$$M_0 v_r = \lambda \frac{(M_0 - F)L}{\delta + H} - \mu_1(M_0 - F) - \mu_2 F, \quad v(t, 1) = 0, \ t > 0, \tag{11}$$

with the boundary conditions on $r = R(t)$

$$\frac{\partial L}{\partial n} + \alpha(L - L_0) = 0, \ \frac{\partial H}{\partial n} + \alpha(H - H_0) = 0, \ \frac{\partial F}{\partial n} + \beta F = 0, \tag{12}$$

L_0, H_0 are concentrations of L, H in the blood, on the blood vessel wall $r = 1$

$$\frac{\partial L}{\partial n} = \frac{\partial H}{\partial n} = \frac{\partial F}{\partial n} = 0. \tag{13}$$

The system (1)–(6) is complemented by prescribing initial conditions

$$L\,|_{t=0} = \frac{1}{2}L_0, \ H\,|_{t=0} = \frac{1}{2}H_0, \ F\,|_{t=0} = \frac{1}{2}M_0, \ R(0) = r_0. \tag{14}$$