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A DYNAMIC MODEL OF ATHEROGENESIS AS AN INFLAMMATORY RESPONSE

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Abstract. Atherosclerosis is a disease of the vasculature that is characterized by chronic inflammation and the accumulation of lipids and apoptic cells in the walls of large arteries. This disease results in plaque growth in an infected artery typically leading to occlusion of the artery. Atherosclerosis is the leading cause of human mortality in the United States, much of Europe, and parts of Asia. Here we discuss a dynamic model of the biochemical aspects of atherosclerosis. In particular, we consider the interaction between immune response cells in the presence of chemically modified low density lipoprotein which are known to interfere with normal immune function. The general model consists of a system of nonlinear evolution equations governing the interaction of chemical and cellular species leading to the disease initiation and progression.
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1 Introduction

Atherosclerosis is a disease of the vasculature that is characterized by an accumulation of lipid laden immune cells and apoptic cells in the arterial wall. Recently, the authors proposed a mathematical model of the early stages of the disease [7]. The model is based on a view of the process consistent with the paradigm of Russell Ross that atherosclerosis is an inflammatory disease [13]. Throughout the West and in parts of Asia, coronary artery disease (which is caused primarily by atherosclerosis) is the leading cause of human mortality. An enhanced understanding of the disease, its progression, risk factors, precursors, and indicators, is essential to the development of more effective treatment and prevention strategies. Mathematical modeling is an important instrument in this endeavor. The following section contains a description of the disease forming the basis for the mathematical model presented in Section 3 and studied in Section 4.

2 The disease process

The larger arteries where atherosclerotic lesions typically form can be considered as thick walled tubes with the walls consisting of three layers. The othermost layer, called the adventitia, provides structural integrity through a strong collagen network. The middle layer, the media, provides flexibility and adaptability through layers of smooth muscle cells enmeshed in an elastin and collagen network. The thin, innermost layer, called the intima, is where atherosclerotic lesions form. A monolayer of endothelial cells forms the interface between the intima and the lumen through which blood flows. Atherogenesis typically begins with endothelial dysfunction allowing the transport of low density lipoproteins (LDL) and immune cells into the intima. Three primary processes of the disease follow the influx of LDL and immune cells into the intima: chemical modification (oxidation) of LDL cholesterol, corruption of the normal immune response (binding of oxidized LDL to macrophages), and subsequent lesion growth.

Lipoproteins are micellar particles produced by the liver and intestines which contain regulatory proteins that direct the blood trafficking of cholesterol and other lipids to various cells in the body. LDL particles transport cholesterol that is needed for various cellular functions such as cell membrane formation and hormone synthesis. About 60% to 70% of the total body cholesterol is contained in the LDL particles. High density lipoproteins (HDL) particles account for most of the remaining cholesterol. The function of the HDL particles appears to involve the return of excess lipids from tissues to the liver for subsequent processing (a process referred to as reverse transport). Many studies have unequivocally shown that elevated blood levels of LDL cholesterol confer a higher risk of developing cardiovascular disease (CVD). Although LDL particles are not found in atherosclerotic plaques, oxidatively modified LDL particles are.

In the plasma, where the concentration of free radicals is low and antioxidant particles are present, LDL usually remains in its native, unoxidized form. As an LDL particle is transported by pressure gradient into the intima [6, 9], it may expend all of its innate defenses against oxidation. Cobbold, Sherratt and Maxwell [1] study a mathematical model of these oxidative processes that was utilized (in greatly simplified form) by the authors [7] in their model of atherosclerosis in order to capture the effects of LDL modification in the disease process. This

process of LDL modification seems to be required for the formation of atherosclerotic plaque. In 1977, Goldstein *et al.* [4] discovered that certain immune cells, in particular macrophages, have a high affinity for oxidatively-modified LDL but not native LDL. This results in trapping cholesterol within the arterial wall. Macrophages engorged with lipids are referred to as foam cells. Unable to perform their normal duty of degrading debris, these lipid-laden cells accumulate and signal other immune cells to the site in a cascading progression to plaque growth.

Various immune cells are responsible for the degradation of apoptic cells and for combating threatening agents such as certain bacteria or viruses throughout the human body. When immune response is required, it is typically mediated by the excretion of various chemical signals. One of the many functions of endothelial cells is the signaling of immune response cells during time of injury. Changes in the permeability of the endothelial layer and subsequent deposition of lipids in the intima cause an up-regulation of chemoattractants. Macrophages are phagocytic immune cells that seek out and engulf apoptic or foreign bodies. It is now understood that macrophages become corrupted in the presence of oxidized LDL and are a major player in the inflammatory process of atherosclerosis [14]. Attracted by oxidized LDL, the macrophages in the artery wall attempt to internalize the lipoprotein particles. This results in an accumulation of cholesterol esters and subsequent transformation of a macrophage into a foam cell unable to perform its immune function. Dead or apoptic cells and other debris (including foam cells) are therefore allowed to build up. Subsequently, chemical signals are secreted by the foam and endothelial cells to summon immune response resulting in an inflammatory cycle.

Most advanced atherosclerotic lesions consist of a lipid core surrounded by a fibrous cap of SMCs and connective tissue. In the media, SMCs are in a contractile, nonmobile phase. However, these cells may be stimulated chemically to become mobile and migrate into the intima to surround a forming lesion [12]. This process is mediated by chemoattractants which entice SMCs into the region as well as chemo-inhibitors that keep the SMCs outside of the lesion core [1] [10]. As the lesion forms, the arterial wall may undergo remodeling (expansion). Continued growth, however, results in ablumenal encroachment. The disease plaque may cause moderate (40%–50%) to severe ($> 90\%$) arterial occlusion. However, the danger of clinically significant ischemia imposed by such a lesion has more to do with the stability of the plaque (which is primarily determined by the composition of the cap and the lipid core) than the degree of occlusion [2, 3]. This is due to the potential for sudden rupture in a plaque with a nonuniform or thin cap. Inclusion of a mechanism for cap formation was an important feature of the modeling framework in [7] as well as in the present contribution.

[1] Private conversations with Dr. P. L. Weissberg, University of Cambridge, and Dr. M. Bennet, University of Cambridge, at the Texas-United Kingdom Collaborative Research Initiative: Cardiology Workshop in Houston Texas April 2004.

3 The mathematical model

The first step in modeling the inflammatory biochemical processes involved in atherosclerosis is the identification of several (generalized) cellular and chemical species inherent in the disease and a mathematical description of their interactions and evolution. The cellular species fall into three categories:

- Immune Cells: Cells involved in the immune response. These are primarily monocyte derived macrophages but may also include T-lymphocytes.
- Smooth Muscle Cells: This generalized species can also include any cells responsible for production of extra cellular matrix.
- Debris: This is a broad category that may include cells that are dead or apoptic, necrotic tissue, and foam cells.

Similarly, the chemical species are one of three main types:

- Chemoattractant: This is intended to denote any chemical that induces positive chemotaxis (of immune cells or smooth muscle cells). Here, no distinction is made among various types of chemoattractants such as macrophage colony stimulating factor, monocyte chemotactic protein, interleukin-1, and others.
- Native Lipoproteins: LDL cholesterol (in a nonoxidized state) is the primary species of interest. However, it can also be expanded to include HDL, the role of which is included in the model of LDL oxidation provided by Cobbold Sherratt and Maxwell [1].
- Oxidized LDL.

For each species, an evolution equation is derived through the classical approach of imposing a mass balance in an arbitrary control volume and subsequent reduction to a pointwise statement. The primary means of transport for the debris species as well as for all three chemical species is assumed to be simple diffusion. However, for the immune cells and smooth muscle cells, the highly interactive nature of their transport in the inflammatory process is accounted for primarily through chemotaxis. In particular, the classical mathematical model of chemotaxis given by Keller and Segel in 1971 [8] is employed to describe this process.

Let n_1, n_2, and n_3 denote the concentration of immune cells, smooth muscle cells, and debris, respectively, and c_1, c_2, and c_3 the concentration of chemoattractant, native lipoproteins, and oxidized LDL, respectively. Define the flux, $\mathbf{J}_{n_i}$ of species n_i that exhibits chemotactic movement in response to chemical species c_j, diffusive transport, and transport sensitivity to gradients of the other cellular species and debris by

$$\mathbf{J}_{n_i} = -\mu_i \nabla n_i + \sum_{j \neq i} \xi_{ij}(n_j, n_i) \nabla n_j + \sum_{j=1} \chi_{ij}(c_j, n_i) \nabla c_j. \tag{1}$$

The coefficients $\xi_{ij}(n_j, n_i)$ and $\chi_{ij}(c_j, n_i)$ are called the tactic sensitivity functions. These are typically assumed to be linear in the cellular species n_i, [8, 11] which leads to an advective term in the resulting equation. There results a system of partial differential equations for the species $n_j(x,t)$ of the form

$$\frac{\partial n_i}{\partial t} = -\nabla \cdot \mathbf{J}_{n_i} + r_{n_i}, \tag{2}$$

with r_{n_i} denoting a net production term for species n_i. Each of the chemical species c_i is subject to random diffusion and some net production, say q_{c_i}, so in general

$$\frac{\partial c_i}{\partial t} = \nabla \cdot (\nu_i \nabla c_i) + q_{c_i}. \tag{3}$$

In Ibragimov *et al.* [7], all taxis is assumed to be in response to the relative gradient of the relevant species. That is,

$$\chi_{ij}(c_j, n_i) = \frac{\chi^0_{ij} n_i}{c_j}, \quad \chi^0_{ij} = constant,$$

similarly

$$\xi_{ij}(n_j, n_i) = \frac{\xi^0_{ij} n_i}{n_j}, \quad \xi^0_{ij} = constant.$$

This accounts for a high sensitivity to changes in concentration at very low concentrations of a given species as well as a saturation effect at high concentrations (common assumptions in models of chemotaxis). The model is completed by specifying the net production terms.

Each of the immune and SMCs are assumed to have a net decay corresponding to normal cellular turn over, i.e.

$$r_{n_i} = -d_i n_i.$$

Here, it is assumed that smooth muscle cells do not actually proliferate within the intima—their concentration is increased strictly by migration. This is consistent with the fact that increases in macrophages occurs only through migration and differentiation of monocytes. The debris is given the production term

$$r_{n_3} = d_1 n_1 + d_2 n_2 - F(n_3, c_3) n_1.$$

The first two terms capture the assumption that dead cells are part of the debris species. The final term reflects the immune response. This says that debris is *removed* by immune cells at a rate F per unit immune cells. The rate F is assumed to be determined by two factors: the level of debris and the presence of oxidized LDL. This is intended to capture both the individual factors (e.g. genetic differences) affecting the immune response as well as the observed impedance to healthy immune function caused by oxLDL. Moreover, it is permitted (and expected) that for high levels of oxLDL, $F \leq 0$ is possible. In such a case, this final term would be strictly a source term corresponding to the build up of debris—that is, lesion growth.

The chemoattractant assumed to be produced at a rate of $f_1(n_3)$ per unit of debris. The chemical signals are molecules that are "heard" by cells through adherence to a receptor on the cell membrane, c_1 is reduced by each of the cellular species at constant rates of α_i per unit n_i per unit chemoattractant. Whence

$$q_{c_1} = -\alpha_1 n_1 c_1 - \alpha_2 n_2 c_1 + f_1(n_3) n_3.$$

Finally, imposing only the simplest (one step reaction with constant radical concentration) version of Cobbold Sherratt and Maxwell's model of LDL oxidation, the governing equations can be written as

$$\begin{aligned}
\frac{\partial n_1}{\partial t} &= \nabla \cdot \quad \mu_1 \nabla n_1 - \chi^0_{11} \frac{n_1}{c_1} \nabla c_1 - \chi^0_{13} \frac{n_1}{c_3} \nabla c_3 \\
&- d_1 n_1 && (4)\\
\frac{\partial n_2}{\partial t} &= \nabla \cdot \quad \mu_2 \nabla n_2 - \chi^0_{21} \frac{n_2}{c_1} \nabla c_1 + \xi^0_{21} \frac{n_2}{n_1} \nabla n_1 \\
&- d_2 n_2 && (5)\\
\frac{\partial n_3}{\partial t} &= \nabla \cdot (\mu_3 \nabla n_3) + d_1 n_1 + d_2 n_2 - F(n_3, c_3) n_1 && (6)\\
\frac{\partial c_1}{\partial t} &= \nabla \cdot (\nu_1 \nabla c_1) - \alpha_1 n_1 c_1 - \alpha_2 n_2 c_1 + f_1(n_3) n_3 && (7)\\
\frac{\partial c_2}{\partial t} &= \nabla \cdot (\nu_2 \nabla c_2) - k R c_2 && (8)\\
\frac{\partial c_3}{\partial t} &= \nabla \cdot (\nu_3 \nabla c_3) + k R c_2. && (9)
\end{aligned}$$

In Ibragimov *et al.* , the authors considered variations of this system on a thin annulus for fixed initial and boundary conditions as well as specific forms for the functions F and f_1. Through simulations, several known features of the disease process were observed including localization of immune cells, growth of debris assuming high fixed levels of oxLDL and smooth muscle cell migration.

Nonconstant levels of either LDL or oxLDL were not considered in [7]. Moreover, simulations exhibited blow up of the solution in finite time—a phenomenon that is clearly not consistent with clinical observations. Such blow up solutions are common in models involving chemotaxis (see for example the review of Horstmann [5] and the references therein). This is in part due to the fact that we have placed no limit on aggregation due to taxis (nor on the boundary influx of cells) and have imposed a domain of fixed volume. One remedy is to allow the boundary of the domain to move–as happens with luminal encroachment–resulting in a free boundary value problem. Another approach to preventing blow up is to impose a limiting device that accounts for a fixed carrying capacity. Both approaches are the subject of ongoing investigation.

4 A stability analysis

One view of the onset of a lesion is that it results from an instablility in a healthy uniform state. The notion of aggregation resulting from an unstable perturbation is classical in the study of chemotactic organisms (c.f. Keller and Segel 1971). Consider here is a linear stability analysis where the healthy intima contains a homogeneous distribution of immune cells n_1, SMCs n_2 and debris n_3. In this context, the chemical species are considered environmental parameters influencing lesion initiation. The

stability analysis is studied on a domain Ω representing the intima and its boundaries Γ_1, the endothelial layer, and Γ_2, the intima/media interface.

The stability analysis proceeds by assuming that at some time t_0 a critical amount of LDL has entered the intima and has become trapped. There is initially no oxLDL, but at some time $t_1 > t_0$ all but an arbitrarily small quatity of LDL has become modified to form oxLDL. Assume that at time t_1 there are stable distributions of cells and chemoattractant

$$n_1(x,y,t_1) = n_{1,0}(x,t), \quad n_2(x,y,t_1) = 0,$$

$$n_3(x,y,t_1) = n_{3,0}(x,t), \quad c_1(x,y,t_1) = c_{1,0}(x,t).$$

The second condition says that at this early onset stage there are no appreciable motile SMCs present. Ignoring normal cell turnover and taking constant diffusion and motility coefficients results in the system

$$\begin{aligned}
\frac{\partial c_2}{\partial t} &= \nabla\cdot(\nu_2\nabla c_2) - kRc_2 && (10)\\
\frac{\partial c_3}{\partial t} &= \nabla\cdot(\nu_3\nabla c_3) + kRc_2. && (11)\\
c_2(x,y,t_0) &= c_2^0(x,y), \quad c_3(x,y,t_0) = 0, && (12)\\
\frac{\partial c_2}{\partial \vec{n}} &= \frac{\partial c_3}{\partial \vec{n}} = 0 \quad (x,y)\in\Gamma_1\cup\Gamma_2 && (13)
\end{aligned}$$

and from the time $t = t_1 > t_0$, the system

$$\begin{aligned}
\frac{\partial n_1}{\partial t} &= \nabla\cdot\left(\mu_1\nabla n_1 - \chi_{11}^0\frac{n_1}{c_1}\nabla c_1\right) && (14)\\
\frac{\partial n_3}{\partial t} &= \nabla\cdot(\mu_3\nabla n_3) - F(n_3,c_*)n_1 && (15)\\
\frac{\partial c_1}{\partial t} &= \nabla\cdot(\nu_1\nabla c_1) - \alpha_1 n_1 c_1 + f_1(n_3)n_3 && (16)\\
n_1(x,y,t_1) &= n_{1,0}(x,y), && (17)\\
n_3(x,y,t_1) &= n_{3,0}(x,y), && (18)\\
c_1(x,y,t_1) &= c_{1,0}(x,y) && (19)\\
\frac{\partial n_1}{\partial \vec{n}} &= \frac{\partial n_3}{\partial \vec{n}} = \frac{\partial c_1}{\partial \vec{n}} = 0, \text{ on } \Gamma_1\cup\Gamma_2. && (20)
\end{aligned}$$

Consider a perturbation from the equilibrium state $(n_{1,e}, n_{3,e}, c_{1,e})$

$$n_1 = n_{1,e} + u, \quad n_3 = n_{3,e} + v, \quad \text{and} \quad c_1 = c_{1,e} + w.$$

This leads in straight forward fashion to the linear system

$$\begin{aligned}
\frac{\partial u}{\partial t} &= \mu_1\nabla^2 u - \chi\nabla^2 w && (21)\\
\frac{\partial v}{\partial t} &= \mu_3\nabla^2 v + \Psi v && (22)\\
\frac{\partial w}{\partial t} &= \nu_1\nabla^2 w - \alpha w - \beta u + Gv && (23)
\end{aligned}$$

where the parameters are defined by

$$\chi = \chi_{11}^0\frac{n_{1,e}}{c_{1,e}}, \quad \Psi = -F_{,1}(n_{3,e},c_*)n_{1,e}, \quad \alpha = \alpha_1 n_{1,e},$$

$$\beta = \alpha_1 c_{1,e}, \quad \text{and} \quad G = f_1(n_{3,e}) + f_1'(n_{3,e})n_{3,e}.$$

Table 1: Bio-physiological Interpretation of Parameters

χ	Chemotactic sensitivity coefficient
Ψ	Net change in debris due to immune response
α, β	Constant rates of change in c_1 due to immune response
G	Rate of change of c_1 due to presence of debris

In the above, $F_{,1}$ denotes the first partial derivative of F with respect to n_3. The bio-physiological meanings of the newly introduced parameters appearing in (21)–(23) are summarized in the table 1.
Adopt the ansatz

$$u = u_0\phi_\lambda(x,y)e^{\sigma t}, \; v = v_0\phi_\lambda(x,y)e^{\sigma t}, \; w = w_0\phi_\lambda(x,y)e^{\sigma t} \tag{24}$$

in which (ϕ_λ, λ) is an eigenfunction/eigenvalue pair of the Neumann problem

$$\nabla^2\phi_\lambda = -\lambda\phi_\lambda, \quad \frac{\partial\phi_\lambda}{\partial\vec{n}} = 0 \quad \text{on} \quad \Gamma_1\cup\Gamma_2. \tag{25}$$

Substitution of (24) into equations (21)–(23) results in the algebraic equations

$$\begin{aligned}
(\sigma + \mu_1\lambda)u_0 - \chi\lambda w_0 &= 0\\
(\sigma + \mu_3\lambda - \Psi)v_0 &= 0\\
\beta u_0 - Gv_0 + (\sigma + \nu_1\lambda + \alpha)w_0 &= 0.
\end{aligned}$$

A nontrivial solution (u_0, v_0, w_0) exists if and only if the growth rate σ is one of the three values

$$\begin{aligned}
\sigma_1 &= \Psi - \mu_3\lambda && (26)\\
\sigma_2 &= \frac{1}{2}\left(-b + \sqrt{b^2 - 4c}\right) && (27)\\
\sigma_3 &= \frac{1}{2}\left(-b - \sqrt{b^2 - 4c}\right) && (28)
\end{aligned}$$

where

$$b = \mu_1\lambda + \nu_1\lambda + \alpha, \quad \text{and} \quad c = \mu_1\lambda(\nu_1\lambda + \alpha) + \beta\chi\lambda.$$

Only the first of these can have nonnegative real part. For a given level of hostility (i.e. level of oxLDL) Ψ is a measure of the marginal ability of the immune system to adjust to a change in the density of debris. It is positive whenever increases in debris further diminish the immune response. The physical meaning is intuitive and consistent with disease progression. $\Psi > 0$ corresponds to the case that disease effects are more significant that healthy immune or diffusive effects. Since $\mu_3 << 1$ and the smallest eigenvalue λ is near unity on a thin annular domain, this corresponds to an instability $\sigma_1 > 0$.

5 Conclusion

By considering the onset and progression of an atherosclerotic lesion as being governed by the interplay of reaction, diffusion and chemotaxis, a model of atherogenesis in the form of a system of nonlinear evolution equations is constructed. The model was shown through simulations in a previous study to be capable of exhibiting several

critical features of the disease process. These include the accumulation of lipids and immune cells to form a lesion core and the migration of smooth muscle cells to form a cap surrounding the core as seen in later stages of lesion growth. Here it is demonstrated that cellular aggregation results from a linear stability analysis of the model when a homogeneous system is subject to a perturbation to which it is unstable. Such an instability result is classical in the study of chemotaxis.

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