

Chapter 21

Mathematical Analysis and Numerical Simulations for a Model of Atherosclerosis

Telma Silva, Jorge Tiago and Adélia Sequeira

Abstract Atherosclerosis is a chronic inflammatory disease that occurs mainly in large and medium-sized elastic and muscular arteries. This pathology is essentially caused by the high concentration of low-density-lipoprotein (LDL) in the blood. It can lead to coronary heart disease and stroke, which are the cause of around 17.3 million deaths per year in the world. Mathematical modeling and numerical simulations are important tools for a better understanding of atherosclerosis and subsequent development of more effective treatment and prevention strategies. The atherosclerosis inflammatory process can be described by a model consisting of a system of three reaction-diffusion equations (representing the concentrations of oxidized LDL, macrophages and cytokines inside the arterial wall) with non-linear Neumann boundary conditions. In this work we prove the existence, uniqueness and boundedness of global solutions, using the monotone iterative method. Numerical simulations are performed in a rectangle representing the intima, to illustrate the mathematical results and the atherosclerosis inflammatory process.

Keywords Atherosclerosis · Reaction-diffusion equations · Nonlinear boundary conditions · Upper and lower solutions · Monotone sequences · Existence-comparison theorem

21.1 Introduction

Atherosclerosis is a systemic disease affecting the entire arterial tree, but lesions involving the coronary, cerebral, and lower extremity circulations have the most clin-

T. Silva · J. Tiago · A. Sequeira (✉)
Department of Mathematics and CEMAT, IST, ULisboa, 1049-001 Lisbon, Portugal
e-mail: adelia.sequeira@math.tecnico.ulisboa.pt

T. Silva
e-mail: telma.da.silva@tecnico.ulisboa.pt

J. Tiago
e-mail: jftiago@math.tecnico.ulisboa.pt

© Springer Japan 2016
Y. Shibata and Y. Suzuki (eds.), *Mathematical Fluid Dynamics, Present and Future*, Springer Proceedings in Mathematics & Statistics 183,
DOI 10.1007/978-4-431-56457-7_21

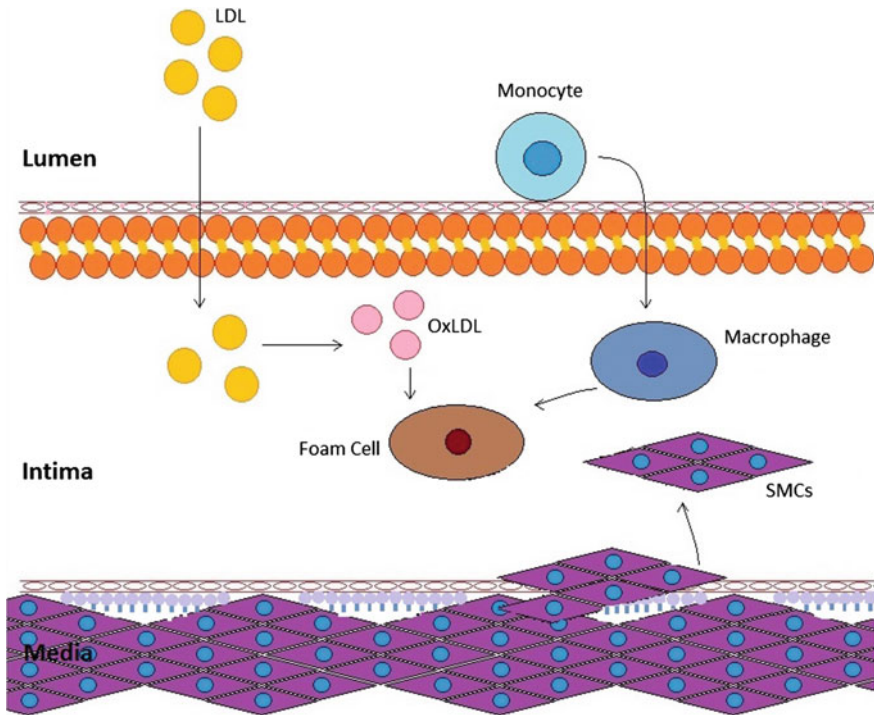


Fig. 21.1 Atherosclerosis schematics. The LDL penetrates the intima where it is oxidized. The oxLDL in the intima leads to monocytes recruitment. The monocytes penetrate the intima and differentiate into macrophages which phagocyte the ox-LDL leading to the formation of the foam cell and consequently to the chronic inflammatory reaction inside the intima. After a while, smooth muscle cells (SMCs) will migrate from media to intima creating a fibrous cap over the lipid deposit

ical significance for medical doctors. The pathogenesis of atherosclerosis involves a complex series of events, similar to a chronic inflammatory process, with the formation of atherosclerotic plaque as consequence [1, 2].

The genesis of atherosclerosis is still not known, but many researchers believe that the atherosclerosis starting point is the endothelial dysfunction, caused by high plasma concentration of cholesterol, in particular, the low-density-lipoprotein, (LDL), hyperglycemia, hypertension, infectious agents and/or smoking [1, 3]. High LDL concentration changes the permeability of the endothelial layer leading to subsequent deposition of lipids in the intima (the inner layer of the blood vessel) [4].

Intra intimal LDL undergoes oxidation (oxLDL) by oxidant mechanisms. Oxidized LDL is considered as a dangerous agent, hence an inflammatory reaction is launched: monocytes adhere to the endothelium, then they penetrate into the intima, where they differentiate into active macrophages (Fig. 21.1).

Active macrophages recognize and absorb oxLDL in the intima by the phagocytosis process. The ingestion of large amounts of oxLDL transforms the fatty macrophages into foam cells (lipid-laden cells) which in turn have to be removed by the immune system. Hence, they set up a chronic inflammatory reaction (auto-

amplification phenomenon) by secreting pro-inflammatory cytokines that promote the recruitment of new monocytes and the production of new pro-inflammatory cytokines.

The inflammation process involves the proliferation (growth or production of cells by multiplication of their parts) and the migration of smooth muscle cells (SMCs) to create a fibrous cap over the lipid deposit. This fibrous cap changes the geometry of the vessel and consequently modifies the blood flow.

Although atherosclerosis is asymptomatic in the beginning, with time can lead to cardiovascular diseases, such as coronary artery diseases, cerebrovascular diseases or peripheral arterial diseases, which are responsible for around 17.3 million deaths per year in the world [5]. Therefore, a deep understanding of this pathogenesis and subsequent development of more effective treatment and prevention strategies are essential. Mathematical modeling and numerical simulations are two powerful tools which have a key role in this framework.

Mathematical modeling of the atherosclerosis processes leads to complex systems of flow, transport, chemical reactions, interactions of fluid and elastic structures, movement of cells, coagulation and growth processes and additional complex dynamics of the vessel walls.

Partial differential equations have been used to model this complex process. As an example found in the literature, we can cite [6], where the authors present a model consisting of reaction-diffusion equations, describing how the concentration of macrophages and cytokines in the intima (a vessel layer) leads to an inflammatory disease. A model leading to the atherosclerotic plaque formation and the early atherosclerotic lesions was suggested in [7] and [8], respectively. Systems of convection-reaction-diffusion equations were used to describe the transport and the concentration of oxidized low densities lipoproteins (LDL), macrophages, foam cells and the pro-inflammatory signal emission in the intima. Recently, a more complex and realistic model was presented in [9]. The authors used reaction-diffusion equations to describe the distribution of substance in the intima, such as LDL, high densities lipoproteins (HDL), oxidized LDL, and free radicals, among others, and convection-reaction-diffusion equations for each species of cells, such as macrophages, T cells or foam cells.

Many works have been devoted to the understanding of the atherosclerosis process through numerical simulations [7–12]. Nevertheless, concerning the mathematical analysis there are still many open problems. In 2009, Khatib et. al. presented results of existence of traveling waves for a system with two reaction-diffusion equations in a strip with nonlinear boundary conditions [13] and in 2012, for the same model, they proved the existence and uniqueness of global solutions in Hölder spaces, [6]. Results of existence, uniqueness and boundedness of global solutions, based on the monotone sequences method, as well as the analysis of stability and the long time behavior of the solutions for a system of three reaction-diffusion equations in 1D with homogeneous Neumann boundary conditions was presented in [14].

The main contribution of the present paper consists in extending the results given in [14] for the two-dimensional case. Based on the monotone sequences method, we prove the existence, uniqueness and boundedness of global solutions for a sys-

tem of three reaction-diffusion equations in 2D with non-linear Neumann boundary conditions. In fact, this result can directly be applied to the 3D case, without any additional restriction. The monotone iterative method consists in using an upper or a lower solution as the initial iteration in a suitable iterative process, to obtain a monotone sequence that converges to a solution of the problem [15].

To illustrate the mathematical results, we perform numerical simulations for the concentration of oxLDL, macrophages and cytokines in a 2D geometry representing the intima.

This paper is organized as follows. In Sect. 21.2, we present the description of a 2D atherosclerosis model imposing some mathematical assumptions. In Sect. 21.3 we describe the core results of this work. We start by introducing some notations and rewriting the mathematical model as a parabolic problem with nonlinear boundary conditions. These will be used to describe the monotone iterative method, that appears thereafter. We then prove the existence, uniqueness and boundedness of global solutions and we make some comments about the simplified model with linear boundary conditions. Finally, in Sect. 21.4, numerical results are presented to illustrate the mathematical model.

21.2 Atherosclerosis Mathematical Modeling

Let the inner layer of the blood vessel (the intima) be defined as a two-dimensional domain, $\Omega = (0, L) \times (0, h)$, where L and h are respectively, the length and the height of the intima. Let the boundary of Ω be denoted by, $\partial\Omega = \Gamma_{in} \cup \Gamma_{end} \cup \Gamma_{med} \cup \Gamma_{out}$, where Γ_{end} represents the interface between the intima and the lumen (the endothelium layer), Γ_{med} is the interface between the intima and the media, Γ_{in} and Γ_{out} are respectively the proximal and distal sections (see Fig. 21.2).

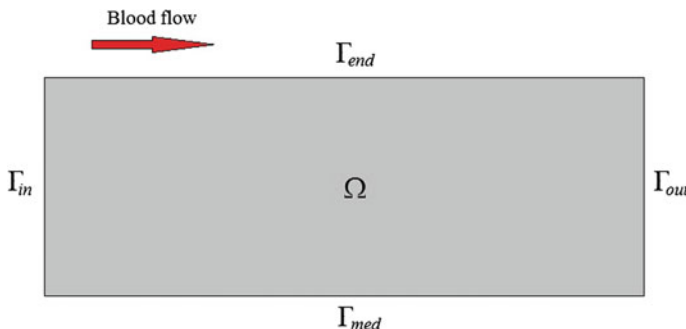


Fig. 21.2 A rectangular representation of the intima layer

The atherosclerosis inflammatory process can be described by the following system of three reaction-diffusion equations,

$$\partial_t O_x - d_{ox} \Delta O_x = -\beta O_x \cdot M \quad (21.1a)$$

$$\partial_t M - d_M \Delta M = -\beta O_x \cdot M \quad (21.1b)$$

$$\partial_t S - d_S \Delta S = \beta O_x \cdot M - \lambda S + \gamma (O_x - O_x^{th}) \quad (21.1c)$$

in Ω , for all $t \in \mathbb{R}^+$, with the boundary conditions

$$\nabla O_x \cdot \mathbf{n} = \tau(x) C_{LDL} \quad \text{on } \Gamma_{end} \quad \text{and} \quad \nabla O_x \cdot \mathbf{n} = 0 \quad \text{on } \partial\Omega \setminus \Gamma_{end} \quad (21.1d)$$

$$\nabla M \cdot \mathbf{n} = g(S) \quad \text{on } \Gamma_{end} \quad \text{and} \quad \nabla M \cdot \mathbf{n} = 0 \quad \text{on } \partial\Omega \setminus \Gamma_{end} \quad (21.1e)$$

$$\nabla S \cdot \mathbf{n} = 0 \quad \text{on } \partial\Omega \quad (21.1f)$$

for all $t \in \mathbb{R}^+$, where \mathbf{n} is the outward unit normal vector to $\partial\Omega$, and with the initial conditions

$$O_x(x, 0) = O_{x0}(x), M(x, 0) = M_0(x), S(x, 0) = S_0(x) \quad \text{in } \Omega. \quad (21.1g)$$

The functions O_x , M and S are, respectively, the concentrations of oxidized LDL, macrophages and inflammatory signal (a generic chemoattractant which gathers the cytokines), which are continuously differentiable in t and twice continuously differentiable in x .

The second term on the left-hand side of each reaction-diffusion equation of system (21.1), represents the diffusion term, and d_{ox} , d_M and d_S are the diffusion coefficients, which are positive constants. The first term on the right-hand side represents the ingestion of oxLDL by the macrophages. The parameter β is a positive constant of proportionality.

The second term in the Eq. (21.1c) denotes the natural death of the cells and λ is the degradation rate. The starting point of the signal emission is assumed to be a too high oxidized LDL concentration in the intima. This is described by the third term $\gamma (O_x - O_x^{th})$, where O_x^{th} corresponds to a given oxLDL quantity and γ is the activation rate. In order to have an inflammatory response O_x should be greater than O_x^{th} .

In the boundary conditions on Γ_{end} , we assume that LDL and monocytes enter the tunica intima through the endothelial layer. The function τ in the boundary condition (21.1d) is the permeability of the vessel wall, which depends on the wall shear stress (WSS), the mechanical force imposed on the endothelium by the flowing blood. As we know, low WSS favors the penetration of both LDL and monocytes [2]. The permeability function τ is defined to be a smooth and nonnegative function of WSS .¹ The parameter C_{LDL} is a given LDL-cholesterol concentration, which is positive. We

¹The wall shear stress function, WSS , is computed using the solution of the blood flow model (for instance a generalized Navier-Stokes model).

assume that the incoming monocytes immediately differentiate into macrophages and the recruitment of new monocytes depends on a general pro-inflammatory signal which gathers both chemokines and cytokines. The boundary condition (21.1e) considers that this signal acts through the function g , which is defined to impose a limit in the macrophages recruitment. There are many ways to define the function g , see for instance [6, 8, 15]. Here, for simplicity, we have, $g(S) = S / (1 + S)$ and

$$g(S) > 0 \text{ for } S > 0, \quad g(0) = 0, \quad \text{and } g(S) \rightarrow 1 \text{ as } S \rightarrow \infty.$$

The functions $Ox_0(x)$, $M_0(x)$ and $S_0(x)$ defined in (21.1g) are smooth and nonnegative functions satisfying the boundary conditions (21.1d)–(21.1f) at $t = 0$.

21.3 Existence, Uniqueness and Boundedness of Solutions

System (21.1) is coupled through the boundary conditions, as well as through the differential equations themselves and, in this sense, the analysis becomes more complex than the one performed in [14] for homogeneous Neumann boundary conditions. Nevertheless, the monotone iterative method used to establish the existence-comparison theorem in [14] can be extended to system (21.1), which is a two-dimensional model with nonlinear boundary conditions. But in this case, we should require the quasimonotone property of the boundary function $\mathbf{G} = (G_1, G_2, G_3)$ together with the quasimonotone property of the reaction function $\Phi = (\Phi_1, \Phi_2, \Phi_3)$. For the 3D case, we can use the same argument as in 2D, without any additional requirement.

The results in this section are based in the general theory of parabolic problems presented in [15].

21.3.1 Notations

Let Ω be an open set in \mathbb{R}^d . We denote by $\partial\Omega$ the boundary of Ω and by $\overline{\Omega}$ its closure. For each $T > 0$, let $\Omega_T = \Omega \times (0, T]$ be a domain in \mathbb{R}^{d+1} , $\partial\Omega_T = \partial\Omega \times (0, T]$ and $\overline{\Omega}_T$ the closure of Ω_T .

We denote by $C^{2,1}(\Omega_T)$ the space of all functions that are twice continuously differentiable in x and once continuously differentiable in t , for all (x, t) in Ω_T .

The product function space $(C^k(Q))^3$, where Q can be Ω_T or $\overline{\Omega}_T$ is denoted by $\mathcal{C}^k(Q)$. For any vector function $\mathbf{U} = (U_1, U_2, U_3)$ in $\mathcal{C}^k(Q)$ the components U_1, U_2, U_3 are each one in $C^k(Q)$, which is the set of all continuous functions whose partial derivatives up to the k^{th} order are continuous in Q . When $Q = \Omega_T$ we denote by $\mathcal{C}^{2,1}(\Omega_T)$ the product space whose components are in $C^{2,1}(\Omega_T)$.

21.3.2 Parabolic Problem with Nonlinear Boundary Conditions

Let $\Omega_T = \Omega \times (0, T]$ and $\partial\Omega_T = \partial\Omega \times (0, T]$, for an arbitrary finite $T > 0$.

We define the concentrations

$$(C_1, C_2, C_3) = (Ox, M, S), \tag{21.2}$$

the diffusion coefficients

$$(d_1, d_2, d_3) = (d_{ox}, d_M, d_S), \tag{21.3}$$

the reaction functions

$$\Phi_1 = \Phi_2 = -\beta C_1 \cdot C_2 \text{ and } \Phi_3 = \beta Ox \cdot M - \lambda S + \gamma (Ox - Ox^{th}) \tag{21.4}$$

and the boundary functions

$$G_1 = \tau(x)C_{LDL}\psi(x), \quad G_2 = g(C_3)\psi(x) \text{ and } G_3 = 0 \text{ on } \partial\Omega, \tag{21.5}$$

where $\psi(x)$ is a bump function.²

With these notations, system (21.1) with the boundary conditions (21.1d)–(21.1f) and the initial conditions (21.1g) can be rewritten, as follows

$$\begin{aligned} \partial_t C_i - d_i \Delta C_i &= \Phi_i && \text{in } \Omega_T \\ \partial_n C_i &= G_i && \text{on } \partial\Omega_T \\ C_i(x, 0) &= C_{i,0}(x) && \text{in } \Omega \end{aligned} \tag{21.6}$$

for $i = 1, 2, 3$, where the functions $(C_{1,0}, C_{2,0}, C_{3,0}) = (Ox_0, M_0, S_0)$ and $\partial_n C_i$ denotes the outward normal derivative of C_i on $\partial\Omega_T$.

Let

$$\mathbf{C} = (C_i, [\mathbf{C}]_{a_i}, [\mathbf{C}]_{b_i}) \tag{21.7}$$

be the split notation of the vector function \mathbf{C} , where, $[\mathbf{C}]_{a_i}$ and $[\mathbf{C}]_{b_i}$ denote, respectively, the a_i and b_i -components of the vector \mathbf{C} . We rewrite the function Φ_i as

$$\Phi_i(\mathbf{C}) = \Phi_i(C_i, [\mathbf{C}]_{a_i}, [\mathbf{C}]_{b_i}), \quad \text{for } i = 1, 2, 3, \tag{21.8}$$

²Let K be an arbitrary compact set and U an open subset of Γ_{end} , taken as a very small neighbourhood of K , containing K . There exists a bump function $\psi(x)$ which is equal to 1 on K and falls off rapidly to 0 outside of K , while still being smooth.

and the function G_i as

$$G_i(\mathbf{C}) = G_i(\cdot, C_i, [\mathbf{C}]_{\alpha_i}, [\mathbf{C}]_{\rho_i}), \text{ for } i = 1, 2, 3, \tag{21.9}$$

where a_i, b_i, α_i and ρ_i are nonnegative integers with $a_i + b_i = \alpha_i + \rho_i = 2$.

Considering the split notations (21.7), (21.8) and (21.9), the reaction-diffusion system (21.6) can be written as

$$\begin{aligned} \partial_t C_i - d_i \Delta C_i &= \Phi_i(C_i, [\mathbf{C}]_{a_i}, [\mathbf{C}]_{b_i}) && \text{in } \Omega_T \\ \partial_n C_i &= G_i(\cdot, C_i, [\mathbf{C}]_{\alpha_i}, [\mathbf{C}]_{\rho_i}) && \text{on } \partial\Omega_T \\ C_i(x, 0) &= C_{i,0}(x) && \text{in } \Omega \end{aligned} \tag{21.10}$$

for $i = 1, 2, 3$.

Since the initial conditions $C_{i,0}$ and the boundary functions G_i , for $i = 1, 2, 3$, are nonnegative, and for all $C_1, C_2, C_3 \geq 0$ we have

$$\begin{aligned} \Phi_1(0, C_2) &= 0, \\ \Phi_2(C_1, 0, C_3) &= 0, \\ \Phi_3(C_1, C_2, 0) &= \beta C_1 \cdot C_2 + \gamma(C_1 - C_{ox}^{th}) \geq 0, \end{aligned}$$

the nonnegativity of the solutions of (21.6) is preserved in time [15, 16].

21.3.3 Monotone Iterative Method

The monotone iterative method consists in using an upper or a lower solution as the initial iteration in a suitable iterative process, in order to obtain a monotone sequence which converges to a solution of the problem.

The definition of upper and lower solutions and the construction of monotone sequences depend on the quasimonotone property of the reaction function Φ and the boundary function G .

A function $\mathbf{F} = (f_1, f_2, \dots, f_n)$ is said to possess the quasimonotone property if for each i there exist nonnegative integers a_i, b_i with $a_i + b_i = n - 1$ such that $f_i(C_i, [\mathbf{C}]_{a_i}, [\mathbf{C}]_{b_i})$ is monotone nondecreasing in $[\mathbf{C}]_{a_i}$ and monotone nonincreasing in $[\mathbf{C}]_{b_i}$, (see [15]).

We need to see if $\Phi = (\Phi_1, \Phi_2, \Phi_3)$ and $G = (G_1, G_2, G_3)$ possess the quasimonotone property. Considering the reaction functions Φ_i , for $i = 1, 2, 3$, and for all $\mathbf{C} \geq 0$, we have

$$\begin{aligned} [\mathbf{C}]_{a_1} = 0 & \quad \text{and } [\mathbf{C}]_{b_1} = C_2 \\ [\mathbf{C}]_{a_2} = 0 & \quad \text{and } [\mathbf{C}]_{b_2} = C_1 \\ [\mathbf{C}]_{a_3} = (C_1, C_2) & \quad \text{and } [\mathbf{C}]_{b_3} = 0. \end{aligned}$$

Looking at the boundary functions G_i (with $i = 1, 2, 3$), since G_1 is linear and $G_3 = 0$, we just need to take into account G_2 . Therefore, for all $\mathbf{C} \geq 0$,

$$[\mathbf{C}]_{\alpha_2} = C_3 \text{ and } [\mathbf{C}]_{\rho_2} = 0.$$

Hence, we conclude that Φ and \mathbf{G} defined in (21.6), are quasimonotone in \mathbf{C} , for all $\mathbf{C} \geq 0$.

Based on the quasimonotone property of $\Phi = (\Phi_1, \Phi_2, \Phi_3)$ and $\mathbf{G} = (G_1, G_2, G_3)$ we have the following definition of upper and lower solutions.

Definition 21.1 Two smooth functions $\tilde{\mathbf{C}} = (\tilde{C}_1, \tilde{C}_2, \tilde{C}_3)$, $\hat{\mathbf{C}} = (\hat{C}_1, \hat{C}_2, \hat{C}_3)$ in $\mathcal{C}(\bar{\Omega}_T) \cap \mathcal{C}^{2,1}(\Omega_T)$ are called a pair of **coupled upper and lower solutions** of (21.6) if $\tilde{\mathbf{C}} \geq \hat{\mathbf{C}}$ and if they satisfy the inequalities

$$\partial_t \tilde{C}_i - d_i \Delta \tilde{C}_i \geq \Phi_i \left(\tilde{C}_i, [\tilde{\mathbf{C}}]_{a_i}, [\hat{\mathbf{C}}]_{b_i} \right) \quad \text{in } \Omega_T \quad (21.11a)$$

$$\partial_t \hat{C}_i - d_i \Delta \hat{C}_i \leq \Phi_i \left(\hat{C}_i, [\hat{\mathbf{C}}]_{a_i}, [\tilde{\mathbf{C}}]_{b_i} \right) \quad \text{in } \Omega_T \quad (21.11b)$$

$$\partial_n \tilde{C}_i \geq G_i \left(\cdot, \tilde{C}_i, [\tilde{\mathbf{C}}]_{\alpha_i}, [\hat{\mathbf{C}}]_{\rho_i} \right) \quad \text{on } \partial\Omega_T \quad (21.11c)$$

$$\partial_n \hat{C}_i \leq G_i \left(\cdot, \hat{C}_i, [\hat{\mathbf{C}}]_{\alpha_i}, [\tilde{\mathbf{C}}]_{\rho_i} \right) \quad \text{on } \partial\Omega_T \quad (21.11d)$$

$$\tilde{C}_i(x, 0) \geq C_{i,0}(x) \geq \hat{C}_i(x, 0) \quad \text{in } \Omega \quad (21.11e)$$

for $i = 1, 2, 3$.

The differential inequalities (21.11a) and (21.11b) can be written explicitly as

$$\partial_t \tilde{C}_1 - d_1 \Delta \tilde{C}_1 \geq -\beta \tilde{C}_1 \cdot \tilde{C}_2 \quad (21.12a)$$

$$\partial_t \tilde{C}_2 - d_2 \Delta \tilde{C}_2 \geq -\beta \hat{C}_1 \cdot \tilde{C}_2 \quad (21.12b)$$

$$\partial_t \tilde{C}_3 - d_3 \Delta \tilde{C}_3 \geq \beta \tilde{C}_1 \cdot \tilde{C}_2 - \lambda \tilde{C}_3 + \gamma (\tilde{C}_1 - O x^{th}) \quad (21.12c)$$

$$\partial_t \hat{C}_1 - d_1 \Delta \hat{C}_1 \leq -\beta \hat{C}_1 \cdot \tilde{C}_2 \quad (21.12d)$$

$$\partial_t \hat{C}_2 - d_2 \Delta \hat{C}_2 \leq -\beta \tilde{C}_1 \cdot \hat{C}_2 \quad (21.12e)$$

$$\partial_t \hat{C}_3 - d_3 \Delta \hat{C}_3 \leq \beta \hat{C}_1 \cdot \hat{C}_2 - \lambda \hat{C}_3 + \gamma (\hat{C}_1 - O x^{th}) \quad (21.12f)$$

in Ω_T and the boundary inequalities (21.11c) and (21.11d) as

$$\partial_n \tilde{C}_1 \geq \tau(x) C_{LDL} \psi(x) \quad (21.13a)$$

$$\partial_n \tilde{C}_2 \geq g(\tilde{C}_3) \psi(x) \quad (21.13b)$$

$$\partial_n \tilde{C}_3 \geq 0 \quad (21.13c)$$

$$\partial_n \widehat{C}_1 \leq \tau(x) C_{LDL} \psi(x) \tag{21.13d}$$

$$\partial_n \widehat{C}_2 \leq g(\widehat{C}_3) \psi(x) \tag{21.13e}$$

$$\partial_n \widehat{C}_3 \leq 0 \tag{21.13f}$$

on $\partial\Omega_T$.

For a given pair of coupled upper and lower solutions $\widetilde{C}, \widehat{C}$, the sector $(\widehat{C}, \widetilde{C})$ is defined by the functional interval

$$(\widehat{C}, \widetilde{C}) \equiv \{C \in \mathcal{C}(\overline{\Omega_T}) : \widehat{C} \leq C \leq \widetilde{C}\} \tag{21.14}$$

where the inequalities between vectors should be interpreted in the componentwise sense.

The reaction function Φ and the boundary function G are continuous in $\Omega_T \times (\widehat{C}, \widetilde{C})$ and in $\partial\Omega_T \times (\widehat{C}, \widetilde{C})$, respectively, and continuously differentiable in $(\mathbb{R}^+)^3$ with respect to C . Therefore, they satisfy the Lipschitz condition,

$$\begin{aligned} |\Phi_i(C) - \Phi_i(C')| &\leq R_i |C - C'|, \quad \text{for } C, C' \in (\widehat{C}, \widetilde{C}) \\ |G_i(\cdot, C) - G_i(\cdot, C')| &\leq R_i |C - C'|, \quad \text{for } C, C' \in (\widehat{C}, \widetilde{C}) \end{aligned} \tag{21.15}$$

where $\widehat{C}_i \leq C'_i \leq C_i \leq \widetilde{C}_i$ and the Lipschitz constant, R_i , are given by

$$R_i = \sup \left\{ \left| \frac{\partial \Phi_i}{\partial C_i} \right| : \widehat{C}_i \leq C_i \leq \widetilde{C}_i, \right\}, \text{ for } i = 1, 2, 3. \tag{21.16}$$

Consequently the one-sided Lipschitz conditions

$$\begin{aligned} \Phi_i(C_i, [C]_{a_i}, [C]_{b_i}) - \Phi_i(C'_i, [C]_{a_i}, [C]_{b_i}) &\geq -R_i (C_i - C'_i) \\ G_i(\cdot, C_i, [C]_{\alpha_i}, [C]_{\rho_i}) - G_i(\cdot, C'_i, [C]_{\alpha_i}, [C]_{\rho_i}) &\geq -R_i (C_i - C'_i) \end{aligned} \tag{21.17}$$

are also satisfied.

Below, we describe the construction of monotone sequences by an iterative process, choosing as initial iterations

$$\overline{C}^{(0)} = (\widetilde{C}_1, \widetilde{C}_2, \widetilde{C}_3) \quad \text{and} \quad \underline{C}^{(0)} = (\widehat{C}_1, \widehat{C}_2, \widehat{C}_3). \tag{21.18}$$

The upper and lower sequences

$$\{\overline{C}^{(k)}\} = \{\overline{C}_1^{(k)}, \overline{C}_2^{(k)}, \overline{C}_3^{(k)}\} \quad \text{and} \quad \{\underline{C}^{(k)}\} = \{\underline{C}_1^{(k)}, \underline{C}_2^{(k)}, \underline{C}_3^{(k)}\} \tag{21.19}$$

are obtained through the following iterative process

$$\partial_t \bar{C}_i^{(k)} - d_i \Delta \bar{C}_i^{(k)} + R_i \bar{C}_i^{(k)} = R_i \bar{C}_i^{(k-1)} + \Phi_i \left(\bar{C}_i^{(k-1)}, [\bar{\mathbf{C}}^{(k-1)}]_{a_i}, [\underline{\mathbf{C}}^{(k-1)}]_{b_i} \right) \text{ in } \Omega_T \tag{21.20a}$$

$$\partial_t \underline{C}_i^{(k)} - d_i \Delta \underline{C}_i^{(k)} + R_i \underline{C}_i^{(k)} = R_i \underline{C}_i^{(k-1)} + \Phi_i \left(\underline{C}_i^{(k-1)}, [\underline{\mathbf{C}}^{(k-1)}]_{a_i}, [\bar{\mathbf{C}}^{(k-1)}]_{b_i} \right) \text{ in } \Omega_T \tag{21.20b}$$

and

$$\partial_n \bar{C}_i^{(k)} + R_i \bar{C}_i^{(k)} = R_i \bar{C}_i^{(k-1)} + G_i \left(\cdot, \bar{C}_i^{(k-1)}, [\bar{\mathbf{C}}^{(k-1)}]_{\alpha_i}, [\underline{\mathbf{C}}^{(k-1)}]_{\rho_i} \right) \text{ on } \partial\Omega_T \tag{21.21a}$$

$$\partial_n \underline{C}_i^{(k)} + R_i \underline{C}_i^{(k)} = R_i \underline{C}_i^{(k-1)} + G_i \left(\cdot, \underline{C}_i^{(k-1)}, [\underline{\mathbf{C}}^{(k-1)}]_{\alpha_i}, [\bar{\mathbf{C}}^{(k-1)}]_{\rho_i} \right) \text{ on } \partial\Omega_T \tag{21.21b}$$

with initial conditions

$$\bar{C}_i^{(k)}(x, 0) = C_{i,0}(x) = \underline{C}_i^{(k)}(x, 0) \quad \text{in } \Omega \tag{21.22}$$

for $k = 1, 2, \dots$ and $i = 1, 2, 3$. Here, R_i (with $i = 1, 2, 3$) are the Lipschitz constants defined in (21.16) and in this case they are given by

$$\begin{aligned} R_1 &= \sup_{\tilde{C}_2 \leq C_2 \leq \tilde{C}_2} \{\beta C_2\}, \\ R_2 &= \sup_{\tilde{C}_1 \leq C_1 \leq \tilde{C}_1} \{\beta C_1\}, \\ R_3 &= \lambda. \end{aligned}$$

Since for each k , (21.20)–(21.22) are uncoupled scalar linear problems (which have a unique solution in Ω_T) and by the properties of Φ_i and G_i , the sequences $\{\bar{\mathbf{C}}^{(k)}\}$ and $\{\underline{\mathbf{C}}^{(k)}\}$ are well defined (for the proof see [15] pp. 58, 493). The following lemma gives the monotone property of these sequences.

Lemma 21.1 *The upper and the lower sequences $\{\bar{\mathbf{C}}^{(k)}\}$, $\{\underline{\mathbf{C}}^{(k)}\}$ given by the iterative process (21.20)–(21.22), with $\bar{\mathbf{C}}^{(0)} = \tilde{\mathbf{C}}$ and $\underline{\mathbf{C}}^{(0)} = \hat{\mathbf{C}}$, possess the monotone property*

$$\hat{\mathbf{C}} \leq \underline{\mathbf{C}}^{(k)} \leq \underline{\mathbf{C}}^{(k+1)} \leq \bar{\mathbf{C}}^{(k+1)} \leq \bar{\mathbf{C}}^{(k)} \leq \tilde{\mathbf{C}} \quad \text{in } \bar{\Omega}_T \tag{21.23}$$

for every k .

Proof Let $\mathbf{U}^{(0)} = \overline{\mathbf{C}}^{(0)} - \overline{\mathbf{C}}^{(1)} = \tilde{\mathbf{C}} - \overline{\mathbf{C}}^{(1)}$. By the property of upper solutions (21.11a) and (21.11c), and using the sequences (21.20), we have

$$\begin{aligned} \partial_t U_i^{(0)} - d_i \Delta U_i^{(0)} + R_i U_i^{(0)} &= \partial_t \tilde{C}_i - d_i \Delta \tilde{C}_i - \Phi_i \left(\tilde{C}_i, [\tilde{\mathbf{C}}]_{a_i}, [\widehat{\mathbf{C}}]_{b_i} \right) \geq 0 \text{ in } \Omega_T \\ \partial_n \tilde{U}_i^{(0)} + R_i U_i^{(0)} &= \partial_n \tilde{C}_i - G_i \left(\cdot, \tilde{C}_i, [\tilde{\mathbf{C}}]_{\alpha_i}, [\widehat{\mathbf{C}}]_{\rho_i} \right) \geq 0 \text{ on } \partial\Omega_T \end{aligned}$$

for $i = 1, 2, 3$.

From the initial conditions (21.11e), we obtain

$$U_i^{(0)}(x, 0) = \tilde{C}_i(x, 0) - C_{i,0}(x) \geq 0.$$

By the maximum principle [15, 16], $U_i^{(0)} \geq 0$ or equivalently

$$\overline{\mathbf{C}}^{(1)} \leq \overline{\mathbf{C}}^{(0)}.$$

Similarly, using the property of lower solutions (21.11b) and (21.11d), and by the sequences (21.21), we have

$$\underline{\mathbf{C}}^{(1)} \geq \underline{\mathbf{C}}^{(0)}.$$

Now, let $\mathbf{U}^{(1)} = \overline{\mathbf{C}}^{(1)} - \underline{\mathbf{C}}^{(1)}$, then, by the sequences (21.20)–(21.21), the one-sided Lipschitz condition (21.17) and the monotone property of Φ_i and G_i , we have

$$\begin{aligned} \partial_t U_i^{(1)} - d_i \Delta U_i^{(1)} + R_i U_i^{(1)} &= R_i \left(\overline{C}_i^{(0)} - \underline{C}_i^{(0)} \right) + \\ &+ \left[\Phi_i \left(\overline{C}_i^{(0)}, [\overline{\mathbf{C}}^{(0)}]_{a_i}, [\underline{\mathbf{C}}^{(0)}]_{b_i} \right) - \Phi_i \left(\underline{C}_i^{(0)}, [\underline{\mathbf{C}}^{(0)}]_{a_i}, [\overline{\mathbf{C}}^{(0)}]_{b_i} \right) \right] \geq 0 \text{ in } \Omega_T \end{aligned}$$

and

$$\begin{aligned} \partial_n U_i^{(1)} + R_i U_i^{(1)} &= R_i \left(\overline{C}_i^{(0)} - \underline{C}_i^{(0)} \right) + \\ &+ \left[G_i \left(\overline{C}_i^{(0)}, [\overline{\mathbf{C}}^{(0)}]_{\alpha_i}, [\underline{\mathbf{C}}^{(0)}]_{\rho_i} \right) - G_i \left(\underline{C}_i^{(0)}, [\underline{\mathbf{C}}^{(0)}]_{\alpha_i}, [\overline{\mathbf{C}}^{(0)}]_{\rho_i} \right) \right] \geq 0 \text{ on } \partial\Omega_T \end{aligned}$$

for $i = 1, 2, 3$.

It follows from the initial conditions $U_i^{(1)}(x, 0) = 0$ that $U_i^{(1)} > 0$ for each $i = 1, 2, 3$. This shows that

$$\underline{\mathbf{C}}^{(0)} \leq \underline{\mathbf{C}}^{(1)} \leq \overline{\mathbf{C}}^{(1)} \leq \overline{\mathbf{C}}^{(0)} \text{ in } \overline{\Omega}_T. \tag{21.24}$$

For a fixed $k \in \mathbb{N}$, the function $U_i^{(k+1)} = \overline{C}_i^{(k)} - \underline{C}_i^{(k+1)}$ satisfies the relations

$$\begin{aligned} \partial_t U_i^{(k)} - d_i \Delta U_i^{(k)} + R_i U_i^{(k)} &= R_i \left(\overline{C}_i^{(k-1)} - \overline{C}_i^{(k)} \right) + \\ &+ \left[\Phi_i \left(\overline{C}_i^{(k-1)}, [\overline{C}^{(k-1)}]_{a_i}, [\underline{C}^{(k-1)}]_{b_i} \right) - \Phi_i \left(\overline{C}_i^{(k)}, [\overline{C}^{(k)}]_{a_i}, [\underline{C}^{(k)}]_{b_i} \right) \right] \geq 0 \text{ in } \Omega_T \end{aligned}$$

$$\begin{aligned} \partial_n U_i^{(k)} + R_i U_i^{(k)} &= R_i \left(\overline{C}_i^{(k-1)} - \overline{C}_i^{(k)} \right) + \\ &+ \left[G_i \left(\overline{C}_i^{(k-1)}, [\overline{C}^{(k-1)}]_{\alpha_i}, [\underline{C}^{(k-1)}]_{\rho_i} \right) - G_i \left(\overline{C}_i^{(k)}, [\overline{C}^{(k)}]_{\alpha_i}, [\underline{C}^{(k)}]_{\rho_i} \right) \right] \geq 0 \text{ on } \partial\Omega_T \end{aligned}$$

for $i = 1, 2, 3$. These relations and $U_i^{(k)}(x, 0) = 0$ ensure that $\overline{C}^{(k+1)} \leq \overline{C}^{(k)}$.

A similar argument yields $\underline{C}^{(k+1)} \geq \underline{C}^{(k)}$ and $\overline{C}^{(k+1)} \geq \underline{C}^{(k)}$.

By induction, we prove that the sequence $\{\overline{C}^{(k)}\}$ is monotone nonincreasing and $\{\underline{C}^{(k)}\}$ is monotone nondecreasing. And so, the monotone property

$$\widehat{C} \leq \underline{C}^{(k)} \leq \underline{C}^{(k+1)} \leq \overline{C}^{(k+1)} \leq \overline{C}^{(k)} \leq \widetilde{C} \text{ in } \overline{\Omega}_T$$

follows, for every $k = 0, 1, 2, \dots$

21.3.4 Existence of Upper and Lower Solutions

The main condition for the existence of a unique solution to problem (21.6) is the existence of a pair of coupled upper and lower solutions when the reaction function Φ_i and the boundary function G_i are quasimonotone.

Since

$$\begin{aligned} \Phi_1(0, [\mathbf{0}]_{a_i}, [\mathbf{C}]_{b_i}) &= 0 \\ \Phi_2(0, [\mathbf{0}]_{a_i}, [\mathbf{C}]_{b_i}) &= 0 \\ \Phi_3(0, [\mathbf{0}]_{a_i}, [\mathbf{C}]_{b_i}) &= 0 \end{aligned} \tag{21.25}$$

the function Φ_i satisfies the additional condition

$$\Phi_i(0, [\mathbf{0}]_{a_i}, [\mathbf{C}]_{b_i}) \geq 0 \text{ when } [\mathbf{C}]_{b_i} \geq 0, \tag{21.26}$$

for $i = 1, 2, 3$, where $[\mathbf{C}] \geq 0$ stands for $\mathbf{C} \geq 0$.

Remark 21.1 The last equality in (21.25) becomes true due to the relation $C_1 \geq O x^{th}$, considered as an assumption in order to have an inflammatory process. So, if $C_1 = 0$ then $O x^{th}$ also vanishes.

Since G_1 is linear and nonnegative, $G_3 = 0$ and $G_2(0, [\mathbf{0}]_{a_i}, [\mathbf{C}]_{b_i}) = 0$, each boundary function G_i satisfies the condition

$$G_i(\cdot, 0, [\mathbf{0}]_{a_i}, [\mathbf{C}]_{\rho_i}) \geq 0 \text{ when } [\mathbf{C}]_{\rho_i} \geq 0 \tag{21.27}$$

for $i = 1, 2, 3$.

From (21.26) and (21.27), we conclude that the trivial function $\mathbf{C} = 0$ is a lower solution.

Any positive function $\tilde{\mathbf{C}} = (\tilde{C}_1, \tilde{C}_2, \tilde{C}_3)$ satisfying

$$\begin{aligned} \partial_t \tilde{C}_i - d_i \Delta \tilde{C}_i &\geq \Phi_i(\tilde{C}_i, [\tilde{\mathbf{C}}]_{a_i}, [\mathbf{0}]_{b_i}) && \text{in } \Omega_T \\ \partial_{\mathbf{n}} \tilde{C}_i &\geq G_i(\cdot, \tilde{C}_i, [\tilde{\mathbf{C}}]_{a_i}, [\mathbf{0}]_{\rho_i}) && \text{on } \partial\Omega_T \\ \tilde{C}_i(x, 0) &\geq C_{i,0}(x) && \text{in } \Omega \end{aligned} \tag{21.28}$$

for $i = 1, 2, 3$, also satisfies the upper and lower inequalities (21.11). Therefore, the requirement of an upper solution is reduced to

$$\begin{aligned} \partial_t \tilde{C}_1 - d_1 \Delta \tilde{C}_1 &\geq 0 && \text{in } \Omega_T \\ \partial_t \tilde{C}_2 - d_2 \Delta \tilde{C}_2 &\geq 0 && \text{in } \Omega_T \\ \partial_t \tilde{C}_3 - d_3 \Delta \tilde{C}_3 &\geq \beta \tilde{C}_1 \cdot \tilde{C}_2 - \lambda \tilde{C}_3 + \gamma (\tilde{C}_1 - O x^{th}) && \text{in } \Omega_T \\ \partial_{\mathbf{n}} \tilde{C}_1 &\geq \tau(x) C_{LDL} \psi(x) && \text{on } \partial\Omega_T \\ \partial_{\mathbf{n}} \tilde{C}_2 &\geq g(\tilde{C}_3) \psi(x) && \text{on } \partial\Omega_T \\ \partial_{\mathbf{n}} \tilde{C}_3 &\geq 0 && \text{on } \partial\Omega_T \\ \tilde{C}_i(x, 0) &\geq C_{i,0} \end{aligned} \tag{21.29}$$

in Ω for $i = 1, 2, 3$.

21.3.5 Existence-comparison Theorem

By the monotone property (21.23), the pointwise and componentwise limits

$$\lim_{k \rightarrow \infty} \overline{\mathbf{C}}^{(k)}(x, t) = \overline{\mathbf{C}}(x, t), \quad \lim_{k \rightarrow \infty} \underline{\mathbf{C}}^{(k)}(x, t) = \underline{\mathbf{C}}(x, t)$$

exist and satisfy the relation

$$\widehat{\mathbf{C}} \leq \underline{\mathbf{C}} \leq \overline{\mathbf{C}} \leq \tilde{\mathbf{C}} \text{ in } \overline{\Omega}_T. \tag{21.30}$$

Due to the quasimonotone property of Φ_i and G_i , the one-sided Lipschitz condition (21.17), the Lipschitz condition (21.15) and the monotone property relation

(21.23) we can conclude, by applying the existence-comparison theorem for parabolic problems proved in [15] (pp. 494), that the limits of $\{\bar{\mathbf{C}}^{(k)}\}$ and $\{\underline{\mathbf{C}}^{(k)}\}$ coincide and yield to a unique solution of problem (21.6).

These conclusions can be summarized in the following result.

Theorem 21.1 *Let $\tilde{\mathbf{C}} = (\tilde{C}_1, \tilde{C}_2, \tilde{C}_3)$ and $\hat{\mathbf{C}} = (\hat{C}_1, \hat{C}_2, \hat{C}_3)$ be a pair of nonnegative coupled upper and lower solutions of (21.6) and let $\Phi = (\Phi_1, \Phi_2, \Phi_3)$ and $\mathbf{G} = (G_1, G_2, G_3)$ be quasimonotone functions satisfying the global Lipschitz condition (21.15). Then, the upper and lower sequences $\{\bar{\mathbf{C}}^{(k)}\}, \{\underline{\mathbf{C}}^{(k)}\}$ given by (21.20)–(21.22), converge monotonically to a unique solution $\mathbf{C} = (C_1, C_2, C_3)$ with*

$$(\hat{C}_1, \hat{C}_2, \hat{C}_3) \leq (C_1, C_2, C_3) \leq (\tilde{C}_1, \tilde{C}_2, \tilde{C}_3) \text{ in } \Omega_T. \tag{21.31}$$

The existence-comparison theorem can directly be applied to the 3D case, imposing similar conditions.

21.3.6 The Case of Linear Boundary Conditions

In the literature it has also been suggested to describe atherosclerosis using mathematical models with linear boundary conditions [7, 11]. In the case of homogeneous Neumann boundary conditions, such models can be seen as simplified versions of the parabolic problem with nonlinear boundary conditions (21.6), presented in Sect. 21.2.

The mathematical model of the atherosclerosis inflammatory process, under homogeneous Neumann boundary conditions, can be described as follows

$$\begin{aligned} \partial_t C_i - d_i \Delta C_i &= F_i && \text{in } \Omega_T \\ \partial_{\mathbf{n}} C_i &= 0 && \text{on } \partial \Omega_T \\ C_i(x, 0) &= C_{i,0}(x) && \text{in } \Omega \end{aligned} \tag{21.32}$$

for $i = 1, 2, 3$, where the reaction functions (F_1, F_2, F_3) are defined as

$$F_1(x, C_1, C_2) = -\beta C_1 \cdot C_2 + \tau(x) C_{LDL}, \tag{21.33a}$$

$$F_2(C_1, C_2, C_3) = -\beta C_1 \cdot C_2 + g(C_3), \tag{21.33b}$$

$$F_3(C_1, C_2, C_3) = \beta C_1 \cdot C_2 - \lambda C_3 + \gamma(C_1 - O x^{th}), \tag{21.33c}$$

If the term $\tau(x)C_{LDL}$ in the function F_1 is defined only on the boundary $\Gamma_T^{end} = \Gamma_{end} \times (0, T]$, we have

$$\begin{aligned} \partial_t C_1 - d_1 \Delta C_1 &= -\beta C_1 \cdot C_2 && \text{in } \Omega_T \\ \partial_{\mathbf{n}} C_1 &= \tau(x)C_{LDL} && \text{on } \Gamma_T^{end} \\ \partial_{\mathbf{n}} C_1 &= 0 && \text{on } \partial \Omega_T \setminus \Gamma_T^{end} \\ C_1(x, 0) &= C_{1,0}(x) && \text{in } \Omega \end{aligned} \tag{21.34}$$

Problem (21.34) with C_2 and C_3 defined as in (21.32) leads to a 2D model, with linear Neumann boundary conditions.

The existence, uniqueness and boundedness of global solutions of these problems can be proved by the monotone iterative method following the same reasoning as in the one dimensional case presented in [14], since the boundary conditions are independent of C_i and the function $\mathbf{F} = (F_1, F_2, F_3)$ is quasimonotone.

21.4 Numerical Simulations

Numerical simulations are an important tool to better understand the atherosclerosis mechanism and to improve the mathematical models. In this section we present numerical results concerning the concentrations of oxidized low density lipoproteins, macrophages and signal path between cells inside the intima. To represent the intima, we consider a rectangle $(0, L) \times (0, h)$, with length $L = 0.5$ cm and height $h = 0.167$ cm and the following physical and biological parameters, taken from [1]:

$$\begin{aligned}d_{ox} &= d_S = 10^2 \times d_M = 10^{-3} \text{ cm/s} \\ \lambda &= 10 \text{ s}^{-1} \\ \beta &= 1 \text{ cm}/(\text{g} \cdot \text{s}) \\ \gamma &= 1 \text{ s}^{-1}\end{aligned}$$

The model (21.1a)–(21.1g) presented in Sect. 21.2 assumes that atherosclerosis starts with the penetration of LDL into the intima, through the endothelial cells, where they are oxidized (oxLDL). Choosing a region of LDL penetration, Γ_{end}^p , we can define the permeability function τ as a smooth step function that is equal to one in Γ_{end}^p and zero otherwise. We consider that $C_{LDL} = 0.1 \text{ g/cm}^3$ is a given quantity of LDL that enters in the region where $\tau(x) = 1$. Figure 21.3 shows the evolution in time of oxLDL concentration in the intima.

As we expected, in the region Γ_{end}^p , the concentration of Ox is higher and will spread out in time across the domain.

The model also considers that if the concentration of oxLDL (Ox) exceeds a threshold Ox^{th} , an inflammatory reaction will set up promoting the recruitment of monocytes, which will transform in active macrophages (M) to phagocyte the dangerous product, oxLDL. In Fig. 21.4 we can observe how the macrophages concentration depends on the concentration of oxLDL. Moreover, we can also observe the effect of diffusion over time.

The recruitment of monocytes depends on a general pro-inflammatory signal (S) which acts through the function g . The time evolution of signal concentration in the intima is presented in Fig. 21.5.

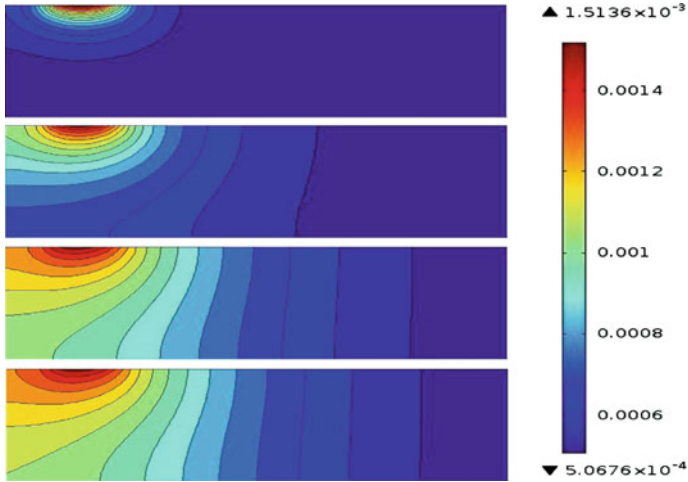


Fig. 21.3 The concentration of oxLDL in the intima for time values $T = 1, 10, 50$ and 100 s (respectively, first, second, third and last image starting from the top). Defining a region of LDL penetration, Γ_{end}^p , the concentration of Ox will spread out in time through all the domain

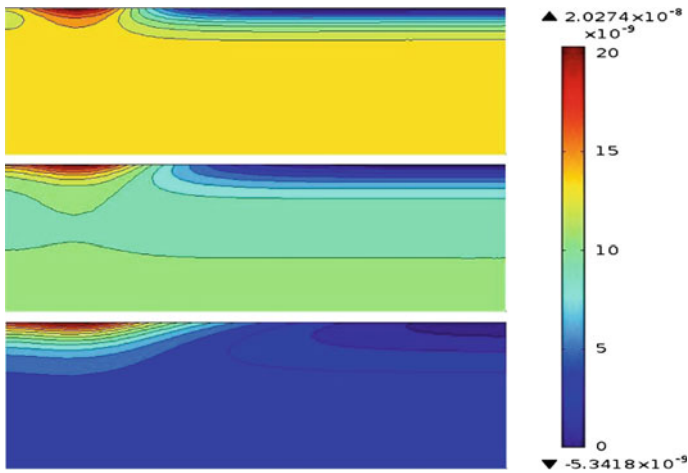


Fig. 21.4 The concentration of macrophages in the intima for time values $T = 30, 50$ and 100 s (respectively, first, second, and last image starting from the top). A high concentration of Ox in the Γ_{end}^p leads to an high value of M in the same region

Comparing the results of Figs. 21.3 and 21.5 we can notice a strong relation between the oxLDL and the signal near the endothelium, as well as the diffusion effect over time in all the domain.

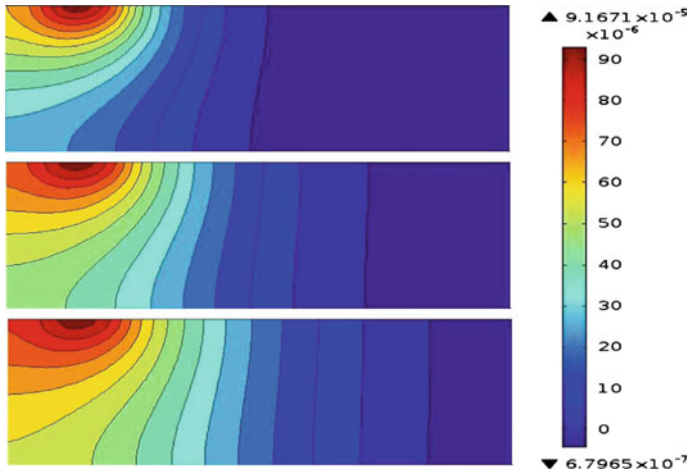


Fig. 21.5 The concentration of cytokines in the intima for time value $T = 30, 50$ and 100 s (respectively, first, second and last image starting from the *top*). An elevated value of Ox in the Γ_{end}^P contributes to high concentration of S in the same region

21.5 Conclusions

In this work, we presented the existence, uniqueness and boundedness of solutions for an atherosclerosis mathematical model, which describes how the variations in the concentration of oxLDL, macrophages and cytokines in the intima can lead to an inflammatory disease.

The model consists of a system of three reaction-diffusion equations with non-linear Neumann boundary conditions, defined in a two-dimensional domain, representing the intima.

Since the reaction and the boundary functions are quasimonotone, we could define a pair of upper and lower solutions and use an iterative process to construct monotone sequences. The smoothness of the reaction and boundary functions and monotonicity arguments have been used to prove the existence, uniqueness and boundedness of global solutions in 2D. However, the existence-comparison theorem can directly be applied to the 3D case, without any additional condition.

Numerical simulations have been performed to better understand the atherosclerosis mechanism described by the model.

Acknowledgements FCT (Fundação para a Ciência e a Tecnologia, Portugal) through the grant SFRH/BPD/66638/2009, the project EXCL/MAT-NAN/0114/2012 and the Research Center CEMAT-IST are gratefully acknowledged.

References

1. Mitchell, M.E., Sidawy, A.N.: The pathophysiology of atherosclerosis. *Semin. Vasc. Surg.* **3**(11), 134–141 (1998)
2. Ross, R.: Atherosclerosis—an inflammatory disease. *Mass. Med. Soc.* **340**(2), 115–126 (1999)
3. Mitrovaska, S., Jovanova, S., Matthiesen, I., Libermans, C.: *Atherosclerosis: Understanding Pathogenesis and Challenge for Treatment*. Nova Science Publishers Inc., New York (2009)
4. Guretzki, H.J., Gerbitza, K.D., Olgemöller, B., Schleicher, E.: Atherogenic levels of low density lipoprotein alter the permeability and composition of the endothelial barrier. *Elsevier* **107**(1), 15–24 (1994)
5. Mendis, S., Puska, P., Norrving, B.: *Global Atlas on Cardiovascular Disease Prevention and Control*. World Health Organization, Geneva (2011)
6. El Khatib, N., Génieys, S., Kazmierczak, B., Volpert, V.: Reaction-diffusion model of atherosclerosis development. *J. Math. Biol.* **65**, 349–374 (2012)
7. Calvez, V., Ebde, A., Meunier, N., Raoult, A.: Mathematical and numerical modeling of the atherosclerotic plaque formation. *ESAIM Proc.* **28**, 1–12 (2009)
8. Calvez, V., Houot, J., Meunier, N., Raoult, A., Rusnakova, G.: Mathematical and numerical modeling of early atherosclerotic lesions. *ESAIM Proc.* **30**, 1–14 (2010)
9. Hao, W., Friedman, A.: The LDL-HDL profile determines the risk of atherosclerosis- a mathematical model. *PLoS ONE* **9**(3), 1–15 (2014)
10. Liu, B., Tang, D.: Computer simulations of atherosclerosis plaque growth in coronary arteries. *Mol. Cell. Biomech.* **7**(4), 193–202 (2010)
11. Filipovic, N., Nikolic, D., Saveljic, I., Milosevic, Z., Exarchos, T., Pelosi, G., Parodi, O.: Computer simulation of three-dimensional plaque formation and progression in the coronary artery. *Comput. Fluids* **88**, 826–833 (2013)
12. Silva, T., Sequeira, A., Santos, R., Tiago, J.: Mathematical modeling of atherosclerotic plaque formation coupled with a non-Newtonian model of blood flow. In: *Hindawi Publishing Corporation Conference Papers in Mathematics* (2013)
13. El Khatib, N., Génieys, S., Kazmierczak, B., Volpert, V.: Mathematical modeling of atherosclerosis as an inflammatory disease. *Philos. Trans. R. Soc. A* **367**, 4877–4886 (2009)
14. Silva, T., Sequeira, A., Santos, R., Tiago, J.: Existence, uniqueness, stability and asymptotic behavior of solutions for a model of atherosclerosis, *DCDS-S, AIMS*, **9**(1), 343–362 (2016)
15. Pao, C.V.: *Nonlinear Parabolic and Elliptic Equations*. Plenum Press, New York (1992)
16. Fife, P.C.: *Mathematical Aspects of Reacting and Diffusing Systems*. Springer-Verlag, Berlin Heidelberg (1979)