Reaction–diffusion model of atherosclerosis development

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Abstract Atherosclerosis begins as an inflammation in blood vessel walls (intima). The inflammatory response of the organism leads to the recruitment of monocytes. Trapped in the intima, they differentiate into macrophages and foam cells leading to the production of inflammatory cytokines and further recruitment of white blood cells. This self-accelerating process, strongly influenced by low-density lipoproteins (cholesterol), results in a dramatic increase of the width of blood vessel walls, formation of an atherosclerotic plaque and, possibly, of its rupture. We suggest a 2D mathematical model of the initiation and development of atherosclerosis which takes into account the concentration of blood cells inside the intima and of pro- and anti-inflammatory cytokines. The model represents a reaction–diffusion system in a strip with nonlinear boundary conditions which describe the recruitment of monocytes as a function of the concentration of inflammatory cytokines. We prove the existence of travelling waves described by this system and confirm our previous results which suggest that atherosclerosis develops as a reaction–diffusion wave. The theoretical results are confirmed by the results of numerical simulations.

Keywords Atherosclerosis · Reaction–diffusion equations · Nonlinear boundary conditions · Existence of travelling waves · Numerical simulations

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1 Introduction

1.1 Biological background

High plasma concentration of low density lipoprotein (LDL) cholesterol is one of the principal risk factors for atherosclerosis. Its mechanism (see Fig. 1) can be sketched as follows (Ross 1999; Østerud and Bjørklid 2003; Fan and Watanabe 2003): the process of atherosclerosis begins when LDLs penetrate into the intima of the arterial wall where they are oxidized. Oxidized LDL (ox-LDL) in the intima is considered by the immune system as a dangerous substance, hence an immune response is launched: chemoattractants (which mediate the adhesion of the monocytes to the endothelium and the penetration of the monocytes through the endothelium) are released and endothelial cells are activated so that monocytes circulating in the blood adhere to the endothelium and then they penetrate to the arterial intima. Once in the intima, these monocytes are converted into macrophages.

The macrophages phagocytose the ox-LDL but this eventually transforms them into foam cells (lipid-laden cells) which in turn have to be removed by the immune system. In the same time they set up a chronic inflammatory reaction (auto-amplification phenomenon): they secrete pro-inflammatory cytokines (e.g., $\text{TNF-}\alpha$, IL-1) which increase endothelial cells activation, promote the recruitment of new monocytes and support the production of new pro-inflammatory cytokines.

This auto-amplification phenomenon is compensated by an anti-inflammatory phenomenon mediated by the anti-inflammatory cytokines (e.g., IL-10) which inhibit the production of pro-inflammatory cytokines (biochemical anti-inflammation). Next, the inflammation process involves the proliferation and the migration of smooth muscle cells to create a fibrous cap over the lipid deposit which isolates this deposit center from the blood flow (mechanical anti-inflammation).

Fig. 1 Schematic representation of the model. The LDL penetrates the intima of the blood vessel where it is oxidized. The ox-LDL triggers the recruitment of the monocytes. The monocytes penetrate the intima and transform into macrophages which phagocytose the ox-LDL leading then to the formation of the foam cell and then to the inflammatory propagation inside the intima

This mechanical inhibition of the inflammation may become a part of the disease process. Indeed the fibrous cap changes the geometry of the vasculature and modifies the blood flow. The interaction between the flow and the cap may lead to a thrombus, or to the degradation and rupture of the plaque liberating dangerous solid parts in the flow (Li et al. 2006a,b).

In this study we do not address the fluid–structure interaction between the blood flow and the plaque, and only consider the set up of the chronic inflammatory reaction with its biochemical and mechanical inhibitions. In our previous work, we have developed a simplified model of the reactions arising in the arterial intima (El Khatib et al. 2007). The model represents a reaction–diffusion system in one space dimension:

$$\frac{\partial M}{\partial t} = d_M \frac{\partial^2 M}{\partial x^2} + G(A) - \beta M, \quad (1.1)$$

$$\frac{\partial A}{\partial t} = d_A \frac{\partial^2 A}{\partial x^2} + f(A)M - \gamma A + b_s, \quad (1.2)$$

where M is the concentration of monocytes, macrophages and foam cells in the intima, A is the concentration of cytokines. The function $G(A)$ describes the recruitment of monocytes from the blood flow, $f(A)M$ is the rate of production of the cytokines which depends on their concentration and on the concentration of the blood cells. The negative terms correspond to the natural death of the blood cells and of the chemical substances, while the last term in the right-hand side of Eq. (1.2) describes the ground level of the cytokines in the intima. This model allows us to give the following biological interpretation: at low LDL concentrations the auto-amplification phenomenon does not set up and no chronic inflammatory reaction occurs. At intermediate concentrations a perturbation of the non inflammatory state may lead to the chronic inflammation, but it has to overcome a threshold for that. Otherwise the system returns to the disease free state. At large LDL concentrations, even a small perturbation of the non inflammatory state leads to the chronic inflammatory reaction (El Khatib et al. 2007). We suggested in El Khatib et al. (2007) that inflammation propagates in the intima as a reaction–diffusion wave. In the case of intermediate LDL concentrations, where a threshold occurs, there are two stable equilibria. One of them is disease free, another one corresponds to the inflammatory state. The travelling waves connects these two states and corresponds to the transition from one to another. The second situation, where the concentration of LDL is high, corresponds to the monostable case where the disease free equilibrium is unstable.

Though the model (1.1)–(1.2) captures some essential features of atherosclerosis development, it does not take into account a finite width of the blood vessel wall. This approximation signifies that the vessel wall is very narrow and the concentrations across it are practically constant. In a more realistic situation, we should consider a multi-dimensional model and take into account the recruitment of monocytes from the blood flow. The flux of monocytes depends on the concentration of cytokines at the surface of endothelial cells which separate the blood flow and the intima. This should be described by nonlinear boundary conditions which change the mathematical nature of the problem. We will study it in this work. We present the mathematical model in the next section. Section 2 is devoted to positivity and comparison theorems which

appear to be valid for the problem under consideration. We take into account here the particular form of the system and of the boundary conditions. In Sect. 3, we use them to study the existence of travelling waves in the monostable case. The results concerning wave existence are confirmed by the numerical simulations (Sect. 4).

1.2 Mathematical model

We consider the system of equations

$$\frac{\partial M}{\partial t} = d_M \Delta M - \beta M, \quad (1.3)$$

$$\frac{\partial A}{\partial t} = d_A \Delta A + f(A)M - \gamma A + b_s, \quad (1.4)$$

in the two-dimensional strip $\Omega \subset \mathbb{R}^2$,

$$\Omega = \{(x, y), -\infty < x < \infty, 0 \leq y \leq h\} \quad (1.5)$$

with the boundary conditions

$$y = 0 : \frac{\partial M}{\partial y} = 0, \quad \frac{\partial A}{\partial y} = 0, \quad y = h : \frac{\partial M}{\partial y} = g(A), \quad \frac{\partial A}{\partial y} = 0 \quad (1.6)$$

and the initial conditions

$$M(x, y, 0) = M_0(x, y), \quad A(x, y, 0) = A_0(x, y). \quad (1.7)$$

Here M is the concentration of white blood cells (monocytes) inside the intima, A is the concentration of cytokines, d_M, d_A, β, γ , and b_s are positive constants, b_s describes a constant source of the activator in the intima. It can be oxidized LDL coming from the blood. Assuming that its diffusion into the vessel wall is sufficiently fast we can describe it by means of the additional term in the equation and not as a flux through the boundary as in the case of monocytes. The functions f and g are sufficiently smooth and satisfy the following conditions:

$$\begin{aligned} f(A) &> 0 \quad \text{for } A > 0, \quad f(0) = 0, \quad f(A) \rightarrow f_+ \quad \text{as } A \rightarrow \infty, \\ g(A) &> 0 \quad \text{for } A > \mathcal{A}, \quad g(\mathcal{A}) = 0, \quad g(A) \rightarrow g_+ \quad \text{as } A \rightarrow \infty, \end{aligned}$$

and $g'(A) > 0$. We put $\mathcal{A} = \frac{b_s}{\gamma}$. This is a constant level of cytokines in the intima such that the corresponding concentration of the monocytes is zero, and they are not recruited through the boundary. Then $(M, A) = (0, \mathcal{A})$ is a stationary solution of problem (1.3)–(1.6).

We assume that the functions $f(A)$ and $g(A)$ are sufficiently smooth and that the matching condition for the initial and boundary data is satisfied, that is to say, the

functions $M_0(x, y)$ and $A_0(x, y)$ satisfy (1.6). These conditions provide the existence of a unique solution of problem (1.3)–(1.7) in the space $C^{2+\alpha, 1+\alpha/2}(\Omega)$, $0 < \alpha < 1$ of Hölder continuous functions with respect to x and t (Sect. 2.1).

2 Positivity and comparison of solutions

2.1 Existence of solutions

We begin with the result on global existence of solution of problem (1.3)–(1.7). We note that it is considered in an unbounded domain and has nonlinear boundary conditions. Therefore, we cannot directly apply the classical results for semi-linear parabolic problems (Volpert et al. 2000). Let Ω be given by (1.5) and

$$\Omega_T = \Omega \times [0, T]. \quad (2.1)$$

Theorem 2.1 *Suppose that $f(\cdot) \in C^{2+\alpha}(\mathbb{R})$, $g(\cdot) \in C^{2+\alpha}(\mathbb{R})$ for some α , $0 < \alpha < 1$, the initial condition $(M_0(x, y), A_0(x, y))$ belongs to $C^{2+\alpha}(\Omega) \times C^{2+\alpha}(\Omega)$ and satisfies boundary conditions (1.6). Then problem (1.3)–(1.7) has a unique global solution $(M(x, y, t), A(x, y, t))$ with $C^{2+\alpha, 1+\alpha/2}(\Omega_T)$ -norm bounded independently of $T > 0$.*

The proof of this theorem is given in the Appendix. We first prove the existence of solutions in bounded rectangles and then pass to the limit as the length of the rectangle increases. A priori estimates of solutions independent of the length of the rectangles allow us to conclude about the existence of solutions in the unbounded domain.

2.2 Positivity for linear problems

Consider the linear two-dimensional parabolic problem

$$\frac{\partial u}{\partial t} = d_1 \Delta u - \beta u, \quad (2.2)$$

$$\frac{\partial v}{\partial t} = d_2 \Delta v + a(x, y, t)u + b(x, y, t)v - \gamma v, \quad (2.3)$$

$$y = 0 : \frac{\partial u}{\partial y} = 0, \quad \frac{\partial v}{\partial y} = 0, \quad y = h : \frac{\partial u}{\partial y} = c(x, y, t)v, \quad \frac{\partial v}{\partial y} = 0, \quad (2.4)$$

in the strip Ω , with the initial conditions $u(x, y, 0)$, $v(x, y, 0)$. The coefficients $a(x, y, t)$, $b(x, y, t)$ belong to $C^{\alpha, \alpha/2}(\Omega_T)$, and $c(x, y, t)$ to $C^{1+\alpha, (1+\alpha)/2}(\Omega_T)$, $a(x, y, t)$ and $c(x, y, t)$ are assumed to be non-negative. We also assume the matching conditions between the boundary and the initial conditions. This means that $u(x, y, 0)$, $v(x, y, 0)$ satisfies the boundary conditions (2.4). Then there exists a unique solution of this problem, and it is continuous for $t \geq 0$, $(x, y) \in \Omega$.

Proposition 2.2 *Let the initial condition of problem (2.2)–(2.4) be non-negative functions,*

$$u(x, y, 0) \geq 0, \quad v(x, y, 0) \geq 0.$$

Then the solution $u(x, y, t)$, $v(x, y, t)$ of problem (2.2)–(2.4) is nonnegative for all x, y and t . If moreover $u(x, y, 0) \not\equiv 0$, $v(x, y, 0) \not\equiv 0$, then the solution is strictly positive.

Proof For technical reasons we will prove first that the thesis of the lemma holds in open rectangle-like regions R_l centered at the point $(u, v) = (0, 0)$ of arbitrarily large length $2l + 2\delta$ in x -direction with adequately smoothed boundaries characterized by the parameter $\delta < h/4$ (see Fig. 4). The similar rectangles are used in the Appendix to prove the existence of the solution in the strip by passing to the limit with the length parameter l . We assume that the functions u and v satisfy the Neumann boundary conditions of the form

$$\frac{\partial u}{\partial \nu} = r(x, y; l)c(x, y, t)v, \quad \frac{\partial v}{\partial \nu} = 0, \quad (2.5)$$

where ν denotes the unit normal vector outward to the boundary of R_l . Here r is an infinitely differentiable function given at the boundary of the open smoothed rectangle R_l , equal to the function $1 - s$ in Eq. (6.8) for $y \geq h - \delta$ and $r \equiv 0$ for $y < \delta$. In particular $r \equiv 1$ in $B_3 \setminus (B_{3*} \cup B_3^*)$ and $r \equiv 0$ at B_1 and at the lateral parts of the boundary $G_2 \cup B_2 \cup G_1 \cup G_4 \cup B_4 \cup G_3$ (see Fig. 4).

First, let us consider the problem

$$\frac{\partial u_1}{\partial t} = d_1 \Delta u_1 - \beta u_1, \quad (2.6)$$

$$\frac{\partial v_1}{\partial t} = d_2 \Delta v_1 + a(x, y, t)u_1 + b(x, y, t)v_1 - \gamma v_1, \quad (2.7)$$

with u and v satisfying the homogeneous Dirichlet boundary condition at the boundary of R_l

$$u = v = 0. \quad (2.8)$$

From the maximum principle (see e.g. Theorem 5, Chapter 3 of Protter and Weinberger 1967), it follows that if the initial condition $(u_1^0(x, y), v_1^0(x, y))$ is non-negative, then the solution is non-negative. If moreover the initial condition is not identically zero, then the solution is strictly positive. In this case, according to Hopf's Lemma (see e.g. Theorem 6 in Protter and Weinberger 1967), for $t > 0$,

$$\frac{\partial u_1}{\partial \nu} < 0, \quad \frac{\partial v_1}{\partial \nu} < 0, \quad \frac{\partial u_1}{\partial \nu} < 0, \quad \frac{\partial v_1}{\partial \nu} < 0. \quad (2.9)$$

We compare next the solution (u, v) of problem (2.2)–(2.4) with the solution (u_1, v_1) of problem (2.6)–(2.8). Denote by $(u_0(x, y), v_0(x, y))$ the initial condition of this problem. Let

$$u_0(x, y) = u_1^0(x, y) + \epsilon, \quad v_0(x, y) = v_1^0(x, y) + \epsilon$$

for some small $\epsilon > 0$. We will prove that the solution of problem (2.2)–(2.4) is greater than the solution of problem (2.6)–(2.8). After that, we can pass to the limit as $\epsilon \rightarrow 0$. Therefore, we will obtain that the solution of problem (2.2)–(2.4) with non-negative initial conditions is positive if it is not identically zero.

However, the initial condition $(u_0(x, y), v_0(x, y))$ introduced above may not satisfy the boundary conditions. In this case, we can introduce a modified initial condition $(\hat{u}_0(x, y), \hat{v}_0(x, y))$ such that it satisfies the boundary condition and

$$\sup |\hat{u}_0(x, y) - u_0(x, y)| \leq \frac{\epsilon}{2}, \quad \sup |\hat{v}_0(x, y) - v_0(x, y)| \leq \frac{\epsilon}{2}.$$

Hence

$$\hat{u}_0(x, y) > u_1^0(x, y), \quad \hat{v}_0(x, y) > v_1^0(x, y), \quad (x, y) \in \bar{R}_l.$$

The solution of problem (2.2)–(2.4) with the initial condition $(\hat{u}_0(x, y), \hat{v}_0(x, y))$ exists and it is continuous for $t \geq 0$, $(x, y) \in \bar{R}_l$. Therefore

$$u(x, y, t) > u_1(x, y, t), \quad v(x, y, t) > v_1(x, y, t), \quad (x, y) \in \bar{R}_l$$

at least for some small positive t . Suppose that this inequality holds for $0 < t < t_0$ and that it is not valid for $t = t_0$. Hence at least one of the following equalities hold:

$$u(x_0, y_0, t_0) = u_1(x_0, y_0, t_0), \quad v(x_1, y_1, t_0) = v_1(x_1, y_1, t_0) \quad (2.10)$$

for some (x_0, y_0) and (x_1, y_1) in $\bar{R}_l$. Now, according to the maximum principle these points should belong to the boundary of R_l . Consequently, one of the functions $u(x, y, t_0)$, $v(x, y, t_0)$ equals zero at some point $(x_0, y_0) \in \partial R_l$. If $u(x_0, y_0, t_0) = u_1(x, y, t_0) = 0$, then $\partial u_1(x_0, y_0, t_0)/\partial \nu \geq 0$ since, due to (2.5), $\partial u(x_0, y_0, t_0)/\partial \nu \geq 0$, and $u(x, y, t_0) > u_1(x, y, t_0)$ for all $(x, y) \in R_l$. This contradicts (2.9). The same arguments apply to v . Passing to the limits $\epsilon \rightarrow 0$ and $l \rightarrow \infty$ proves the proposition.

2.3 Comparison of solutions

Let (M_1, A_1) and (M_2, A_2) be two solutions of problem (1.3)–(1.6) from $C^{2+\alpha, 1+\alpha/2}(Q_T)$. Set

$$u = M_1 - M_2, \quad v = A_1 - A_2.$$

Then

$$\frac{\partial u}{\partial t} = d_M \Delta u - \beta u, \quad (2.11)$$

$$\frac{\partial v}{\partial t} = d_A \Delta v + a(x, y, t)u + b(x, y, t)v - \gamma v, \quad (2.12)$$

$$y = 0 : \frac{\partial u}{\partial y} = 0, \quad \frac{\partial v}{\partial y} = 0, \quad y = h : \frac{\partial u}{\partial y} = c(x, y, t)v, \quad \frac{\partial v}{\partial y} = 0, \quad (2.13)$$

where

$$a(x, y, t) = f(A_1(x, y, t)), \quad b(x, y, t) = \frac{f(A_1(x, y, t)) - f(A_2(x, y, t))}{A_1(x, y, t) - A_2(x, y, t)} M_2(x, y, t),$$

$$c(x, y, t) = \frac{g(A_1(x, y, t)) - g(A_2(x, y, t))}{A_1(x, y, t) - A_2(x, y, t)}.$$

From Proposition 2.2 we obtain the result about comparison of solutions:

Proposition 2.3 *Let the conditions of Sect. 1.2 be fulfilled. Let (M_1, A_1) and (M_2, A_2) be two solutions of problem (1.3)–(1.6). If*

$$M_1(x, y, 0) \geq M_2(x, y, 0), \quad A_1(x, y, 0) \geq A_2(x, y, 0), \quad (x, y) \in \Omega,$$

then the same inequalities are valid for the solutions. If moreover

$$M_1(x, y, 0) \not\equiv M_2(x, y, 0), \quad A_1(x, y, 0) \not\equiv A_2(x, y, 0), \quad (x, y) \in \Omega,$$

then

$$M_1(x, y, t) > M_2(x, y, t), \quad A_1(x, y, t) > A_2(x, y, t),$$

for $(x, y) \in \Omega$ and $t > 0$.

Proof It is sufficient to verify that the coefficients of problem (2.11)–(2.13) satisfy the conditions required for Proposition 2.2.

We have

$$\frac{f(A_1(x, y, t)) - f(A_2(x, y, t))}{A_1(x, y, t) - A_2(x, y, t)} = \int_0^1 f'(sA_1(x, y, t) + (1-s)A_2(x, y, t)) ds.$$

Due to the assumptions of the proposition, we have $b(x, y, t) \in C^{\alpha, \alpha/2}(Q_T)$ and $c(x, y, t) \in C^{1+\alpha, (1+\alpha)/2}(\Omega_T)$.

Moreover, $a(x, y, t)$ is non-negative because f is non-negative and $c(x, y, t)$ is non-negative because g is increasing.

Finally, if M_i, A_i satisfy the matching conditions, then u and v also satisfy them. The proposition is proved.

Proposition 2.4 Suppose that the initial condition $(M(x, y, 0), A(x, y, 0))$ of problem (1.3)–(1.6) is such that

$$\begin{aligned} d_M \Delta M(x, y, 0) - \beta M(x, y, 0) &> 0, \\ d_A \Delta A(x, y, 0) + f(A(x, y, 0))M(x, y, 0) - \gamma A(x, y, 0) + b_s &> 0. \end{aligned} \quad (2.14)$$

Then the solution is strictly increasing with respect to t for each $x \in \Omega$.

Proof Denote

$$u = \frac{\partial M}{\partial t}, \quad v = \frac{\partial A}{\partial t}.$$

Differentiating problem (1.3)–(1.6) with respect to t , we obtain

$$\frac{\partial u}{\partial t} = d_M \Delta u - \beta u, \quad (2.15)$$

$$\frac{\partial v}{\partial t} = d_A \Delta v + f(A)u + f'(A)Mv - \gamma v, \quad (2.16)$$

$$y = 0 : \frac{\partial u}{\partial y} = 0, \quad \frac{\partial v}{\partial y} = 0, \quad y = h : \frac{\partial u}{\partial y} = g'(A)v, \quad \frac{\partial v}{\partial y} = 0. \quad (2.17)$$

Given the functions A and M , which are of $C^{2+\alpha, 1+\alpha/2}(Q_T)$ class, the function u is of $C^{\alpha, \alpha/2}(Q_T)$ class. As the functions g and f are of $C^{2+\alpha}$ class, then from Theorem IV.5.3 in Ladyzhenskaya et al. (1967) we infer that the function v satisfying Eq. (2.16) and homogeneous Neumann boundary conditions is of $C^{2+\alpha, 1+\alpha/2}(Q_T)$ class. Hence the function u is a classical solution of Eq. (2.15) together with the Neumann boundary conditions with the right-hand side of $C^{1+\alpha, (1+\alpha)/2}(Q_T)$ class (as g' is of $C^{1+\alpha}$ class). Thus, in fact, u is of $C^{2+\alpha, 1+\alpha/2}(Q_T)$ class. Hence both u, v are smooth, satisfy the matching conditions and $u(x, y, 0) > 0, v(x, y, 0) > 0$ according to inequalities (2.14). Thus $u(x, y, t) > 0, v(x, y, t) > 0$ for all $t \in [0, T]$ according to Proposition 2.2. The proposition is proved.

3 Existence of travelling waves

3.1 Stationary solutions in the interval

Consider the problem in the section of the strip:

$$\frac{\partial M}{\partial t} = d_M M'' - \beta M, \quad (3.1)$$

$$\frac{\partial A}{\partial t} = d_A A'' + f(A)M - \gamma A + b_s, \quad (3.2)$$

$$y = 0 : M' = A' = 0, \quad y = h : M' = g(A), \quad A' = 0, \quad (3.3)$$

where prime denotes the derivative with respect to y . It has a constant stationary solution

$$M = 0, \quad A = \mathcal{A}.$$

We linearize (3.1)–(3.3) about this solution and consider the corresponding eigenvalue problem:

$$d_M M'' - \beta M = \lambda M, \quad (3.4)$$

$$d_A A'' + f(\mathcal{A})M - \gamma A = \lambda A, \quad (3.5)$$

$$y = 0 : M' = A' = 0, \quad y = h : M' = g'(\mathcal{A})A, \quad A' = 0. \quad (3.6)$$

We consider the case $\lambda = 0$. From (3.4),

$$M(y) = c_1 e^{\sigma_1 y} + c_2 e^{-\sigma_1 y},$$

where $\sigma_1 = \sqrt{\beta/d_M}$. From (3.5),

$$A(y) = c_3 e^{\sigma_2 y} + c_4 e^{-\sigma_2 y} + k c_1 e^{\sigma_1 y} + k c_2 e^{-\sigma_1 y},$$

where $\sigma_2 = \sqrt{\gamma/d_A}$ and $k = -\frac{f(\mathcal{A})}{d_A \sigma_1^2 - \gamma} = \frac{f(\mathcal{A})}{d_A (\sigma_2^2 - \sigma_1^2)}$. From the boundary conditions at $y = 0$:

$$c_1 \sigma_1 - c_2 \sigma_1 = 0, \quad c_3 \sigma_2 - c_4 \sigma_2 + k(c_1 \sigma_1 - c_2 \sigma_1) = 0.$$

Therefore $c_1 = c_2$, $c_3 = c_4$. From the boundary condition at $y = h$,

$$\begin{aligned} c_1 \sigma_1 (e^{\sigma_1 h} - e^{-\sigma_1 h}) &= g'(\mathcal{A}) \left(c_3 (e^{\sigma_2 h} + e^{-\sigma_2 h}) + k c_1 (e^{\sigma_1 h} + e^{-\sigma_1 h}) \right), \\ c_3 \sigma_2 (e^{\sigma_2 h} - e^{-\sigma_2 h}) + k c_1 \sigma_1 (e^{\sigma_1 h} - e^{-\sigma_1 h}) &= 0. \end{aligned}$$

We express c_3 from the second equation and substitute into the first equation:

$$c_1 \sigma_1 \sinh(\sigma_1 h) - c_1 k g'(\mathcal{A}) \cosh(\sigma_1 h) = -c_1 \frac{k \sigma_1 g'(\mathcal{A})}{\sigma_2} \frac{\cosh(\sigma_2 h)}{\sinh(\sigma_2 h)} \sinh(\sigma_1 h) \quad (3.7)$$

that is to say, if $c_1 \neq 0$,

$$\mu_1 \coth(\sigma_1 h) = 1 + \mu_2 \coth(\sigma_2 h), \quad (3.8)$$

where

$$\mu_i = \frac{k g'(\mathcal{A})}{\sigma_i} = \frac{f(\mathcal{A}) g'(\mathcal{A})}{d_A \sigma_i (\sigma_2^2 - \sigma_1^2)}, \quad i = 1, 2.$$

If Eq. (3.8) is true, then there exists $M \neq 0$, $A \neq 0$ solution of problem (3.4)–(3.6) in the case $\lambda = 0$. In that case $\lambda = 0$ is an eigenvalue of problem (3.4)–(3.6).

Denote the left-hand side of Eq. (3.8) by $s_1(h)$. Then it is a decreasing function for $h > 0$ and

$$s_1(h) \sim \frac{f(A)g'(A)}{d_A\sigma_1^2(\sigma_2^2 - \sigma_1^2)} \frac{1}{h}, \quad h \rightarrow 0, \quad s_1(h) \rightarrow \frac{f(A)g'(A)}{d_A\sigma_1(\sigma_2^2 - \sigma_1^2)}, \quad h \rightarrow \infty. \quad (3.9)$$

For the right-hand side $s_2(h)$:

$$s_2(h) \sim \frac{f(A)g'(A)}{d_A\sigma_2^2(\sigma_2^2 - \sigma_1^2)} \frac{1}{h}, \quad h \rightarrow 0, \quad s_2(h) \rightarrow 1 + \frac{f(A)g'(A)}{d_A\sigma_2(\sigma_2^2 - \sigma_1^2)}, \quad h \rightarrow \infty. \quad (3.10)$$

Proposition 3.1 *Suppose that $\mu_i \neq 0$, $\sigma_i \neq 0$, $i = 1, 2$, $\sigma_1 \neq \sigma_2$. For all h sufficiently small, the principal eigenvalue of problem (3.4)–(3.6) is in the right-half plane. If $f(A)$ or $g'(A)$ are sufficiently small and h sufficiently large, then the principal eigenvalue is in the left-half plane.*

Proof Denote by λ_0 the principal eigenvalue of problem (3.4)–(3.6), that is the eigenvalue with the maximal real part. Clearly, if we increase β and γ by the same value, then λ_0 is decreased by the same value. Therefore, for σ_1, σ_2 sufficiently large, λ_0 has a negative real part. On the other hand, by virtue of (3.9), (3.10), in this case, $s_2(h) > s_1(h)$. Hence, if this inequality is satisfied, then λ_0 is in the left-half plane.

It can be easily verified that $s_1(h) > s_2(h)$ for h small enough and $\sigma_1 \neq \sigma_2$. Therefore, when we decrease h , the principal eigenvalue crosses the imaginary axes and passes in the right-half plane.

If $f(A)$ or $g'(A)$ are sufficiently small, then $s_2(h) > s_1(h)$ for h large enough. The proposition is proved.

Remark 3.2 From the Krein–Rutman theorem it follows that the principal eigenvalue is simple, real and the corresponding eigenfunction is positive. Contrary to the Dirichlet boundary conditions for which the principal eigenvalue grows with the length of the interval being negative for small h , in the problem under consideration it is positive for small h . It is related to the singular character of this problem as $h \rightarrow 0$.

Proposition 3.3 *If the principal eigenvalue of problem (3.4)–(3.6) crosses the origin from negative to positive values, then the stationary solution $M = 0$, $A = A$ of problem (3.1)–(3.3) becomes unstable and two other stable stationary solutions bifurcate from it. For one of these solutions, $M_s(y)$, $A_s(y)$, the inequality*

$$M_s(y) > 0, \quad A_s(y) > A, \quad 0 < y < h \quad (3.11)$$

holds.

The existence and stability of a bifurcating solution follows from the standard arguments related to the topological degree (Krasnoselskii and Zabreiko 1984).

Inequality (3.11) follows from the positivity of the eigenfunction corresponding to the zero eigenvalue.

At the end of this section, we will find explicitly stationary solutions of problem (3.1)–(3.3) in the particular case where $f(A) = f_0$ is a constant. From the first equation we have

$$M(y) = \frac{g(A_h)}{2\sigma_1 \sinh(\sigma_1 h)} (e^{\sigma_1 y} + e^{-\sigma_1 y}),$$

where $A_h = A(h)$. Substituting this expression into the second equation, we find

$$\begin{aligned} A(y) = & -\frac{f_0 g(A_h)}{2d_A(\sigma_1^2 - \sigma_2^2)} \\ & \times \left(\frac{1}{\sigma_1 \sinh(\sigma_1 h)} (e^{\sigma_1 y} + e^{-\sigma_1 y}) - \frac{1}{\sigma_2 \sinh(\sigma_2 h)} (e^{\sigma_2 y} + e^{-\sigma_2 y}) \right) + \frac{b}{d_A \sigma_2^2}. \end{aligned}$$

We obtain the following equation with respect to A_h :

$$A_h = -\frac{f_0 g(A_h)}{d_A(\sigma_1^2 - \sigma_2^2)} \left(\frac{\cosh(\sigma_1 h)}{\sigma_1 \sinh(\sigma_1 h)} - \frac{\cosh(\sigma_2 h)}{\sigma_2 \sinh(\sigma_2 h)} \right) + \frac{b}{d_A \sigma_2^2}.$$

The number of its solutions is determined by the function $g(A)$. For small σ_1 and σ_2 , using the approximation $\exp(\pm \sigma_i h) \approx 1 \pm \sigma_i h$, we obtain the approximate equation

$$A_h = \frac{f_0 g(A_h)}{d_A h \sigma_1^2 \sigma_2^2} + \frac{b}{d_A \sigma_2^2}.$$

We obtain the same equation if we integrate the equalities

$$d_M M'' - \beta M = 0, \quad d_A A'' + f_0 M - \gamma A + b_s = 0$$

from 0 to h , use the boundary conditions (3.3) and suppose that M and A do not depend on y .

3.2 Existence of waves in the monostable case

We consider in this section problem (1.3)–(1.6) assuming that the stationary solution $M = 0$, $A = \mathcal{A}$ is unstable and that there exists a stable stationary solution $(M_s(y), A_s(y))$ in the section of the cylinder such that

$$0 < M_s(y), \quad \mathcal{A} < A_s(y), \quad 0 \leq y \leq h.$$

This is the case for h sufficiently small, according to Propositions 3.1 and 3.3.

We will study here the existence of waves with the limits $(0, \mathcal{A})$ at $x = -\infty$ and (M_s, A_s) at $x = +\infty$. We assume that there are no other stationary solutions such that

$$0 \leq M(y) \leq M_s(y), \quad \mathcal{A} \leq A(y) \leq A_s(y), \quad 0 \leq y \leq h. \quad (3.12)$$

This means that we consider for (M_s, A_s) the smallest solution that is above $(0, \mathcal{A})$, which is isolated since problem (3.4)–(3.6) does not have a zero eigenvalue.

Consider the problem

$$d_M \Delta M - c \frac{\partial M}{\partial x} - \beta M = 0, \quad (3.13)$$

$$d_A \Delta A - c \frac{\partial A}{\partial x} + f(A)M - \gamma A + b_s = 0, \quad (3.14)$$

$$y = 0 : \frac{\partial M}{\partial y} = 0, \quad \frac{\partial A}{\partial y} = 0, \quad y = h : \frac{\partial M}{\partial y} = g(A), \quad \frac{\partial A}{\partial y} = 0. \quad (3.15)$$

Here c is the wave velocity. We will look for solutions (M, A) such that

$$x = -\infty : M = 0, A = \mathcal{A}, \quad x = +\infty : M = M_s, A = A_s. \quad (3.16)$$

Let $\mu(x, y)$ and $\alpha(x, y)$ be some functions continuous together with their second derivatives such that

$$\frac{\partial \mu}{\partial x} > 0, \quad \frac{\partial \alpha}{\partial x} > 0, \quad (x, y) \in \Omega, \quad (3.17)$$

$$y = 0 : \frac{\partial \mu}{\partial y} = 0, \quad \frac{\partial \alpha}{\partial y} = 0, \quad y = h : \frac{\partial \mu}{\partial y} = g(\alpha), \quad \frac{\partial \alpha}{\partial y} = 0. \quad (3.18)$$

and such that

$$(\mu(x, y), \alpha(x, y)) \rightarrow (0, \mathcal{A}) \quad \text{as } x \rightarrow -\infty \quad (3.19)$$

$$(\mu(x, y), \alpha(x, y)) \rightarrow (M_s(y), A_s(y)) \quad \text{as } x \rightarrow \infty \quad (3.20)$$

As a simple example we can take $\alpha(x, y)$ in the form

$$\alpha(x, y) = \mathcal{A} + \frac{A_s(y) - \mathcal{A}}{1 + \exp(-\eta x)}, \quad \eta > 0,$$

and $\mu(x, y)$, for every x , as the unique positive solution of the problem:

$$\begin{aligned} d_M \frac{\partial^2}{\partial y^2} \mu(x, y) - \beta \mu(x, y) &= 0, \\ \frac{\partial \mu(x, 0)}{\partial y} &= 0, \quad \frac{\partial \mu(x, h)}{\partial y} = g(\alpha(x, h)). \end{aligned}$$

Denote

$$S_1(\mu, \alpha) = \sup_{(x,y) \in \Omega} \frac{d_M \Delta \mu - \beta \mu}{\frac{\partial \mu}{\partial x}}, \quad S_2(\mu, \alpha) = \sup_{(x,y) \in \Omega} \frac{d_A \Delta \alpha + f(\alpha) \mu - \gamma \alpha + b_s}{\frac{\partial \alpha}{\partial x}}.$$

Proposition 3.4 *Let functions $\mu(x, y)$, $\alpha(x, y)$ satisfy conditions (3.17), (3.18). If*

$$c > \max(S_1(\mu, \alpha), S_2(\mu, \alpha)), \quad (3.21)$$

then there exists a solution of problem (3.13)–(3.16).

Proof From inequality (3.21) it follows that

$$d_M \Delta \mu - c \frac{\partial \mu}{\partial x} - \beta \mu < 0, \quad (3.22)$$

$$d_A \Delta \alpha - c \frac{\partial \alpha}{\partial x} + f(\alpha) \mu - \gamma \alpha + b_s < 0. \quad (3.23)$$

Denote

$$\Omega_N = \{(x, y) : x > -N, 0 \leq y \leq h\}$$

and consider the initial-boundary value problem for the system

$$\frac{\partial M}{\partial t} = d_M \Delta M - c \frac{\partial M}{\partial x} - \beta M, \quad (3.24)$$

$$\frac{\partial A}{\partial t} = d_A \Delta A - c \frac{\partial A}{\partial x} + f(A)M - \gamma A + b_s \quad (3.25)$$

in the domain Ω_N , with the boundary conditions

$$y = 0 : \frac{\partial M}{\partial \nu} = 0, \quad \frac{\partial A}{\partial \nu} = 0, \quad y = h : \frac{\partial M}{\partial \nu} = g(A), \quad \frac{\partial A}{\partial \nu} = 0, \quad (3.26)$$

$$x = -N : M = M_N(y), \quad A = A_N(y) \quad (3.27)$$

and the initial conditions

$$M(x, y, 0) = M_N(y), \quad A(x, y, 0) = A_N(y). \quad (3.28)$$

We note that the boundary functions at the left boundary of the cylinder and the initial conditions are the same functions which depend only on the y variable. Their choice depends on N . We suppose that they satisfy the following conditions:

$$0 \leq M_N(y) \leq \mu(-N, y), \quad \mathcal{A} \leq A_N(y) \leq \alpha(-N, y), \quad (3.29)$$

$$d_M M_N'' - \beta M_N \geq 0, \quad (3.30)$$

$$d_A A_N'' + f(A_N)M_N - \gamma A_N + b_s \geq 0, \quad (3.31)$$

$$M_N'(0) = A_N'(0) = 0; \quad M_N'(h) = g(A_N(h)), \quad A_N'(h) = 0. \quad (3.32)$$

The existence of such functions follows from the instability of the solution $(0, \mathcal{A})$. Indeed, let $(\mu_0(y), \alpha_0(y))$ be the eigenfunction corresponding to the principal (positive) eigenvalue of problem (3.4)–(3.6). Then the functions

$$M_N(y) = \tau_N \mu_0(y), \quad A_N(y) = \mathcal{A} + \tau_N \alpha_0(y)$$

satisfy system (3.29)–(3.31) for τ_N sufficiently small, if only the function $M_N(y) = \tau_N \mu_0(y)$ satisfies the condition $M'_N(h) = g(\mathcal{A} + \tau_N \alpha_0(h))$ instead of the condition $M'_N(h) = g'(\mathcal{A}) \tau_N \alpha_0(h)$ (as implied by (3.4)–(3.6)). As $g(\mathcal{A}) = 0$, these two conditions coincide, if g is linear in a neighborhood of $\mathcal{A}$. Hence, we can replace g by a function that is linear for $\mathcal{A} \leq A \leq \mathcal{A} + \epsilon$ and let $\epsilon \rightarrow 0$. This proves the existence of a solution to (3.29)–(3.32).

By virtue of conditions (3.29)–(3.32) and of Proposition 2.4 adapted for the problem under consideration, the solution of problem (3.24)–(3.28) increases in time for each $(x, y) \in \Omega_N$. On the other hand, from inequalities (3.22), (3.23) it follows that it is estimated from above:

$$M(x, y, t) \leq \mu(x, y), \quad A(x, y, t) \leq \alpha(x, y), \quad (x, y) \in \Omega_N, \quad t > 0.$$

Therefore, it converges to a stationary solution (u_N, v_N) of problem (3.24)–(3.28). From Lemma 3.5, which is formulated and proved below, it follows that the functions $u_N(x, y)$ and $v_N(x, y)$ are non-decreasing with respect to x . Therefore there exists their limits as $x \rightarrow +\infty$. Since the limiting functions satisfy the problem in the section of the cylinder, and since it has been assumed that there are no other solutions that satisfy inequality (3.12) except for $(0, \mathcal{A})$ and (M_s, A_s) , then

$$\lim_{x \rightarrow +\infty} u_N(x, y) = M_s(y), \quad \lim_{x \rightarrow +\infty} v_N(x, y) = A_s(y).$$

We consider the sequence of solutions (u_N, v_N) as $N \rightarrow \infty$ and choose a convergent subsequence in order to obtain a solution on the whole axis. For this we introduce the shifted functions

$$\tilde{u}_N(x, y) = u_N(x + k_N, y), \quad \tilde{v}_N(x, y) = v_N(x + k_N, y),$$

where k_N is chosen in such a way that

$$u_N(0, h/2) = \frac{1}{2} M_s(h/2).$$

Such values exist due the boundary conditions at $x = -N$ and the limiting values of the solutions at $+\infty$. These new functions are defined for $-N - k_N \leq x < +\infty$. Since $u_N(x, y) \leq \mu(x, y)$, $x \geq -N$, then $-N - k_N \rightarrow -\infty$ as $N \rightarrow \infty$.

Thus, we can choose a subsequence of the sequence (u_N, v_N) , for which we keep the same notations, which converges locally to some limiting functions (u_0, v_0) . They are defined in the whole cylinder Ω and satisfy problem (3.13)–(3.15). Moreover, they

are non-decreasing with respect to x and $u_0(0, h/2) = \frac{1}{2}M_s(h/2)$. Hence the solution has limits (3.16) for $x = \pm\infty$. The proposition is proved.

Lemma 3.5 *The solution of problem (3.24)–(3.28) is monotonically increasing with respect to x for each y , $0 < y < h$ and $t > 0$.*

Proof To prove the lemma, we will write the problem for the new unknown functions

$$u(x, y, t) = \frac{\partial M_N(x, y, t)}{\partial x}, \quad v(x, y, t) = \frac{\partial A_N(x, y, t)}{\partial x}$$

and will show that its solution is positive. Let us note that, according to (3.28), $M(x, y, 0)$ and $A(x, y, 0)$ depend only on y , so $u(x, y, 0) = v(x, y, 0) = 0$. Differentiating problem (3.24)–(3.27) with respect to x , we obtain

$$\frac{\partial u}{\partial t} = d_M \Delta u - c \frac{\partial u}{\partial x} - \beta u, \quad (3.33)$$

$$\frac{\partial v}{\partial t} = d_A \Delta v - c \frac{\partial v}{\partial x} + f(A)u + f'(A)Mv - \gamma v \quad (3.34)$$

$$y = 0 : \frac{\partial u}{\partial y} = 0, \quad \frac{\partial v}{\partial y} = 0, \quad y = h : \frac{\partial u}{\partial y} = g'(A)v, \quad \frac{\partial v}{\partial y} = 0. \quad (3.35)$$

For the solution of problem (3.13)–(3.16), the following estimate holds:

$$M_N(x, y, t) \geq M(-N, y, t), \quad A_N(x, y, t) \geq A(-N, y, t), \quad (x, y) \in \Omega_N, \quad t > 0.$$

Therefore,

$$u(-N, y, t) \geq 0, \quad v(-N, y, t) \geq 0, \quad 0 \leq y \leq h, \quad t > 0. \quad (3.36)$$

If the boundary condition at $x = -N$ was

$$u(-N, y, t) = 0, \quad v(-N, y, t) = 0, \quad 0 \leq y \leq h, \quad t \geq 0,$$

then the solution of this problem would be identically zero. Since we have inequalities (3.36) at the boundary, then the solution is non-negative. The lemma is proved.

The main result of this section is given by the following theorem.

Theorem 3.6 *Problem (3.13)–(3.16) has a solution if and only if c satisfies the inequality*

$$c \geq c_0 = \inf_{\mu, \alpha} \max(S_1(\mu, \alpha), S_2(\mu, \alpha)),$$

where the infimum is taken with respect to all functions satisfying conditions (3.17), (3.18). These solutions are strictly monotone with respect to x .

Proof Existence of solutions (M_c, A_c) for $c > c_0$ follows from Proposition 3.4. These solutions are uniformly bounded in the $C^{2+\delta}(\Omega)$ norm for some $\delta \in (0, 1)$ independently of c , for c close to c_0 . This follows from their uniform boundedness and the apriori estimates derived in Sect. 6.2. Thus, we can pass to the limit as $c \rightarrow c_0$ and obtain a solution (M_{c_0}, A_{c_0}) for $c = c_0$. If there exists a solution (M_*, A_*) for some $c_* < c_0$, then

$$\max(S_1(M_*, A_*), S_2(M_*, A_*)) = c_* < c_0 = \inf_{\mu, \alpha} \max(S_1(\mu, \alpha), S_2(\mu, \alpha)).$$

This contradiction proves the theorem.

4 Numerical simulations

In this section we present numerical simulations of problem (1.3)–(1.6) in the bounded domain $\Omega_s = (x, y)$, $0 \leq x \leq 1$, $0 \leq y \leq 1$ with the additional boundary conditions at the sides of the rectangle:

$$x = 0, 1 : A = M = 0.$$

These conditions do not influence the behaviour of solutions far from the above boundaries. The form of the functions $f(A)$ and $g(A)$ is chosen so that in the approximation of thin domain $h \rightarrow 0$ we obtain the 1D model of El Khatib et al. (2007):

$$f(A) = \frac{\alpha_2 A}{1 + A/\tau_2}, \quad g(A) = h \frac{\alpha_1 + \beta_1 A}{1 + A/\tau_1}. \quad (4.1)$$

The parameters in Eqs. (1.3)–(1.6), (4.1) were estimated from Chow et al. (2005), except for α_1 , d_A and d_M . They are given in Table 1. Note that in Chow et al. (2005) the time unit is hours.

The parameter α_1 was not determined from Chow et al. (2005) since the initiation of inflammation is different than in our setting. Note that $\alpha_1 = g(0)$ describes the recruitment of immune cells in the absence of pro-inflammatory cytokines, i.e. at the beginning of the process. We expect α_1 to be an increasing function of the concentration of ox-LDL in the intima, and hence of the porosity of the endothelial surface layer of the vessel wall. We refer to Leiderman et al. (2008) and references therein for a study of this porosity, by considering flows of Newtonian fluids through this porous medium. But once the porosity and ox-LDL concentration in the intima are known, the determination of α_1 would involve the study of active bio-chemical phenomena like the rolling of immune cells on the vessel wall and their extravasation through the wall. This quantification seems to be out of reach at the moment.

But in the present study, the range of possible values of α_1 is limited by the qualitative behavior of the model: it is necessary that $\alpha_1 > \frac{\beta_1 \gamma}{\alpha_2} \simeq 0.095$ for the 1D limiting model to exhibit the monostable behavior (see El Khatib et al. 2007), and it is necessary that $\alpha_1 < \beta_1 \tau_1 = 1$ for g to be an increasing function of A . In the present simulations, the value $\alpha_1 = 0.6$ was chosen.

Table 1 Model parameters

Parameter	Value	Comment
α_2	2.97	Determined from Chow et al. (2005) by considering that A in the present paper was TNF in Chow et al. (2005) , but still retaining the stimulation of TNF secretion by IL6. In that case α_2 of the present paper corresponds to k_{TNFN} in Chow et al. (2005)
τ_2	0.059	Determined from Chow et al. (2005) in the same way as α_2 . It corresponds to x_{TNF6} in Chow et al. (2005)
γ	1.4	Determined from Chow et al. (2005) in the same way as α_2 . It corresponds to k_{TNF} in Chow et al. (2005)
β_1	2.5	Determined from Chow et al. (2005) by considering that M in the present paper corresponds to the activated macrophages in Chow et al. (2005) and by retaining only the influence of TNF on their recruitment. In that case $\beta_1 \tau_1$ corresponds to the rate constant of $\frac{\text{TNF}^2}{x_{\text{MTNF}}^2 + \text{TNF}^2}$ which is 1
τ_1	0.4	Determined from Chow et al. (2005) in the same way as β_1 . It corresponds to x_{MTNF} in Chow et al. (2005)
β	0.2	Determined from Chow et al. (2005) in the same way as β_1 . It corresponds to k_{MA} in Chow et al. (2005)

Fig. 2 Development of atherosclerosis in the intima. Initial condition (*left*) and two consecutive moments of time (*middle and right*) of the level lines of the concentration of immune cells

The diffusion coefficients d_M and d_A were not taken from [Chow et al. \(2005\)](#) since the spatial effects are not considered in that paper. The analysis in the present paper shows the existence of travelling waves if some diffusion is present, however small, which is typical from the monostable behavior. In the present simulation, we used for the cytokine diffusivity the value $d_A = 10^{-4} \text{ cm}^2/\text{h}$. Indeed this value is the order of magnitude of TNF diffusivity in the extracellular space of the brain used in [Edelstein-Keshet and Spiros \(2002\)](#), and is also the order of magnitude of LDL diffusivity in the arterial walls taken in [Vincent et al. \(2009\)](#). As for the immune cell diffusivity d_M , we used a value smaller than d_A , namely $d_M = 10^{-5} \text{ cm}^2/\text{h}$.

Figure 2 shows the propagation of the travelling wave. The wave is essentially two-dimensional. When the domain width is sufficiently large, the wave propagation occurs near the surface where there is an excess of monocytes. Their concentration there becomes high leading to an essentially higher speed of propagation. Their concentration inside the intima remains low.

Fig. 3 Left comparison between the 2D-model with a small thickness (*upper part*) and the 1D-model (*below*). Right dependence of the wave speed on the thickness of the strip

Fig. 4 Bounded domain and boundary conditions (see the explanation in the *text*)

Figure 3 (left) presents propagation of the travelling wave in both 1D and 2D models. The comparison shows a good agreement between these two cases when the strip thickness is small. The right figure demonstrates how the speed of propagation in the 2D case depends on the strip thickness. The speed of the 2D wave converges to the speed of the 1D wave as the width of the domain goes to zero. We recall that the 2D and 1D models are different. The former takes into account the monocyte recruitment through nonlinear boundary conditions, the latter includes a nonlinear production term in the equation. In some cases, the limiting passage from 2D to 1D as the width goes to zero can be justified (El Khatib et al. 2007). This is not proved for travelling waves. The results presented here show this convergence numerically.

5 Discussion

Atherosclerosis and other inflammatory diseases develop as a self-accelerating process which can be described with reaction–diffusion equations. In [El Khatib et al. \(2007\)](#) we have developed a one-dimensional model for the early stage of atherosclerosis. The model is applicable for the case of a small thickness of the intima (blood vessel wall), which corresponds to the biological reality. We prove the existence of travelling wave solution of the reaction–diffusion system. This is a first step towards explaining the chronic inflammatory reaction as propagation of a travelling wave. A second step would be to study the stability of these travelling waves.

During atherosclerosis development, the intima thickness grows and we need to take it into account. In this work we study the two-dimensional case where the second dimension corresponds to the direction across intima. Essential difference with the previous model is not only space dimension but also nonlinear boundary conditions which describe recruitment of monocytes through the epithelial layer of the intima. This is a new class of reaction–diffusion systems for which it appears to be possible to study the existence of travelling waves.

Numerical simulations confirm the analytical results. They show wave propagation and allow us to analyze its speed as a function of the parameters of the model.

Further development of atherosclerosis results in remodelling of the vessel. This means that the lumen (the channel where the blood flow takes place) can retract and the vessel wall takes the specific bell shape. This can essentially modify the characteristics of the flow, and mechanical interaction of the flow with the vessel walls become crucial because it can result in the plaque rupture. There are numerous studies of these phenomena (see, e.g. [Li et al. 2006a,b](#)). The blood flow influences the development of the plaque: the shear stress activates the receptors of the endothelial cells and accelerates the recruitment of monocytes.

Another important question is related to risk factors like hypercholesterolemia, diabetes or hypertension. They determine some parameters of the mathematical model. A more complete description would consist in supposing that this influence increases slowly during the life. The parameters of the model would evolve then slowly, and the system would pass from the disease-free case to the bistable state to reach finally the monostable state. In each state, the ignition itself would be due to an accidental disturbance, such as an injury that can initiate infection.

The action of these risk factors, which can be taken into account in the mathematical model, is as follows:

1. The influence of hypertension: it changes the properties of the blood flow and creates a higher pressure on the vessel wall which can activate the receptors and accelerate the recruitment of monocytes. It can also provoke the plaque rupture,
2. The influence of diabetes II: the monocytes and the platelets can be already activated because of the hyperglycemia. The active state of monocytes increases their recruitment and the active state of platelets can cause spontaneous coagulation (thrombosis),
3. The influence of hypercholesterolemia: the cholesterol level in blood can slowly increase during the lifetime. The parameter α_1 of the model, which shows the

level of bad cholesterol in blood vessel walls becomes time dependent. It increases slowly, and so the system passes from the disease-free state to the bistable state then to the monostable state. The other risk factors can modify the speed of these transitions.

Influence of the risk factors can be studied in relation to medical treatment, in particular with statins, which are inhibitors of the low density lipoprotein cholesterol. Recent studies show a 28% reduction in LDL-C and a 5% increase in high-density lipoprotein cholesterol (LaRosa et al. 1999). The inhibition of the LDL by statins “*appears to be directly proportional to the degree to which they lower lipids*” (LaRosa et al. 1999). Its action can be taken into account through the parameters of the mathematical model.

Another approach to modelling atherosclerosis is based on cellular automata (Poston and Poston 2007). The authors investigate “*the hypothesis that plaque is the result of self-perpetuating propagating process driven by macrophages*”. The macrophage recruitment rate is considered as a steeply rising function of the number of macrophages locally present in the intima. Smooth muscle cells dynamics also depend on the macrophage number. Macrophages can die with certain probability resulting in lipid accumulation. During the process, fatty streaks of macrophages set up at random sites, which may progress or regress. Some of them develop into progressive focal lesions, that is advanced pieces of plaque which are macrophage-rich and have a central fibrous cap-like region of smooth muscle cells. The main result of Poston and Poston (2007) support the conclusion of this work and of the previous work (El Khatib et al. 2007) that atherosclerosis development can be viewed as a wave propagation.

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6 Appendix: Existence of solutions of the evolution problem

We will prove here Theorem 2.1. The idea of the proof is quite standard. We first consider smoothed bounded rectangles and prove the existence of solutions in the bounded domains. We use here a priori estimates of solutions. Since they are independent on the length of the rectangle, we can construct a sequence of uniformly bounded solutions in the increasing domains and choose a convergent subsequence. The limiting function will be a solution of the problem in the unbounded strip.

6.1 A priori estimates

In order to obtain a priori estimates of solutions of problem (1.3)–(1.7) we will construct an appropriate supersolution. We consider the stationary Eq. (1.3) and look for its supersolution which depends only on the y variable. Let us consider the problem

$$d \frac{\partial^2 M}{\partial y^2} - \beta M = 0, \quad \frac{\partial M}{\partial y}(0) = a_0, \quad \frac{\partial M}{\partial y}(h) = a, \quad a_0 \leq 0, \quad a > 0, \quad (6.1)$$

where, for simplicity of notation, we have replaced d_M by d . Let us take $a^* = g(\infty) + \rho$ with $\rho > 0$ arbitrarily small. Then, the solution to (6.1) is a supersolution to Eq. (1.3) with the boundary condition given by (1.6). Its solution has the following form:

$$M(a, a_0; y) = \frac{\sqrt{d}}{\sqrt{\beta}} \left[\sinh \left(\frac{\sqrt{\beta} h}{\sqrt{d}} \right) \right]^{-1} \left(a \cosh \left(\frac{\sqrt{\beta}}{\sqrt{d}} y \right) - a_0 \cosh \left(\frac{\sqrt{\beta}}{\sqrt{d}} (h - y) \right) \right) \quad (6.2)$$

It is easy to note that for $a_0 < 0$, there exists a unique $y_0 = y_0(a, a_0) \in (0, h)$ such that $\partial M / \partial y(a, a_0, y) > 0$ for $y \in (y_0, h]$ and $\partial M / \partial y(a, a_0, y) < 0$ for $y \in [0, y_0)$. Moreover, $y_0(a, a_0) \rightarrow 0$ as $a_0 \rightarrow 0$. Let $M^*(y) := M(a^*, a_0, y)$. Obviously, according to (6.2),

$$M^*(y) > M(a, a_0, y) > M(a, 0, y) \quad \text{for } a \in [0, g(\infty)], \quad a_0 < 0. \quad (6.3)$$

We now construct a sequence of bounded domains. Let $\delta < h/4$, where h is the height of the domain Ω , and $l > 0$ be sufficiently large. Denote by R_l an open rectangle-like set with the boundary of C^3 class symmetric with respect to the point $(0, 0)$ and consisting of the sets $B_{1,3} = \{(x, y) : x \in [-l, l], y = 0, h\}$, $B_{2,4} = \{(x, y) : y \in [\delta, h - \delta], x = l + \delta, -(l + \delta)\}$, and the “monotone” smooth curves joining the boundary points of the straight boundaries (Fig. 4). Let G_1, G_2, G_3, G_4 denote the parts of the boundary joining B_1 with B_2 , B_2 with B_3 , B_3 with B_4 and B_4 with B_1 respectively. We note that the outer normal vector ν to G_1 and G_4 has negative y -component. Finally, let $B_{1*} = B_1 \cap \{(x, y) : x \in [l - 2\delta, l]\}$, $B_{3*} = B_3 \cap \{(x, y) : x \in [l - 2\delta, l]\}$, $B_1^* = B_1 \cap \{(x, y) : x \in [-l + 2\delta, -l]\}$, $B_3^* = B_3 \cap \{(x, y) : x \in [-l + 2\delta, -l]\}$.

Let us introduce an additional condition for δ . Namely, let

$$\delta < y_0(a^*, a_0). \quad (6.4)$$

Thus, for $y \in (0, \delta)$, $\partial M^* / \partial y(y) < 0$.

We consider system (1.3), (1.4) in the domains R_l

$$\frac{\partial M}{\partial t} = d_M \Delta M - \beta M, \quad (6.5)$$

$$\frac{\partial A}{\partial t} = d_A \Delta A + f(A)M - \gamma A + b_s \quad (6.6)$$

and construct the boundary conditions

$$\frac{\partial M}{\partial \nu} = \Psi(z, A(z)), \quad \frac{\partial A}{\partial \nu} = 0, \quad z = (x, y) \in \partial R_l, \quad (6.7)$$

in such a way that (a) in the limit, as the length increases, we obtain the boundary condition (1.6), (b) the function $(M^*(y), A^*(y))$ is a supersolution for the auxiliary problems in the bounded domains ($A^*(y)$ is defined below).

The boundary conditions are defined in the following way. We take

$$\Psi(z, A(z)) \equiv 0 \quad \text{for } z \in B_1,$$

whereas for $z \in G_2 \cup B_2 \cup G_1 \cup G_4 \cup B_4 \cup G_3 \cup B_3$ the function $\Psi(\cdot)$ is defined as

$$\Psi(z, A(z)) = \left(1 - s \left[\frac{|x - (l - 2\delta)|}{2\delta} \right] \right) g(A(z)). \quad (6.8)$$

Here $s(\tau)$ is C^∞ function such that $s(\tau) \equiv 0$ for $\tau \leq 0$ and $s(\tau) \equiv 1$ for $\tau \geq 1$. It is seen in particular that

$$\begin{aligned} \Psi(z, A(z)) &= g(A(z)), \quad \text{for } z \in B_3 \setminus B_{3*} \setminus B_3^* \\ \Psi(z, A(z)) &\equiv 0, \quad \text{for } z \in G_2 \cup B_2 \cup G_1 \cup G_4 \cup B_4 \cup G_3 \end{aligned}$$

whereas $\Psi(z, A(z))$ changes smoothly from $g(A(z))$ to 0 on $B_{3*} \cup B_3^*$.

Now, let A^* denote the solution of the boundary value problem:

$$\begin{aligned} d_A \Delta A + f(A)M^*(y) - \gamma A + b_s &= 0, \quad \text{in } R_l, \\ \frac{\partial A}{\partial \nu} &= 0 \quad \text{on } \partial R_l. \end{aligned} \quad (6.9)$$

It is obvious that, $\partial M^*(y)/\partial \nu \geq \Psi(z)$ for $z \in \partial R_l$. Hence the following lemma holds.

Lemma 1 *Suppose that a classical solution to system (6.5)–(6.7) of class $C^{2+\alpha, 1+\alpha/2}$ exists on $R_l \times (0, T)$. Let $M(x, y, 0) \in [0, M^*(y))$, $A(x, y, 0) \in [0, A^*(y))$. Then, for $t \in [0, T)$, $0 \leq M(x, y, t) < M^*(y)$, $0 \leq A(x, y, t) < A^*(y)$.*

Taking into account the non-negativity of solution (proven above) the proof can be carried out via the maximum principle. $\square$

6.2 Existence of solutions

6.2.1 Local in time existence of solutions

First, we will consider the auxiliary initial boundary value problem (6.5)–(6.7) in the set R_l described above. We assume that the initial conditions $(M_0(x, y), A_0(x, y)) \in C^{2+\alpha, 1+\alpha/2}(R_l)$ satisfy the boundary conditions (6.7). The local existence of solutions follows from the application of the contraction mapping principle.

Let

$$\begin{aligned} \mathcal{L}_1 &= \partial/\partial t - d_M \Delta, \quad \mathcal{L}_2 = \partial/\partial t - d_A \Delta, \\ U &= (U_1, U_2) = (M, A), \quad \Phi(U) = (-\beta U_1, f(U_2)U_1 - \gamma U_2 + b_s). \end{aligned}$$

Given $\tilde{U} = (\tilde{U}_1, \tilde{U}_2)$, let $U = P(\tilde{U})$ denote the solution of the system

$$(\mathcal{L}_1 U_1, \mathcal{L}_2 U_2) = \Phi(\tilde{U}) \quad (6.10)$$

with the boundary conditions

$$\frac{\partial U_1}{\partial \nu} = \Psi(z, \tilde{U}_2(z)), \quad \frac{\partial U_2}{\partial \nu} = 0, \quad z = (x, y) \in \partial R_l, \quad (6.11)$$

and initial conditions

$$U(x, y, 0) = U_0(x, y) = (U_{10}(x, y), U_{20}(x, y)) = (M_0(x, y), A_0(x, y)).$$

Let us assume that $0 < U_0(x, y) \leq (M^*(y), A^*(y))$. The local in time existence of a solution to system (6.10) is guaranteed by Theorem IV.5.3 in [Ladyzhenskaya et al. \(1967\)](#). In the set $\mathcal{R}_{lT} = \tilde{R}_l \times [0, T]$ let us consider the mapping

$$U \rightarrow P(U). \quad (6.12)$$

Let $\mathcal{M}_T = C^{1+\alpha, (1+\alpha)/2}(\mathcal{R}_{lT})$ and $B = \{U \in \mathcal{M}_T : \|U - U_0\|_{\mathcal{M}_T} \leq 1\}$. From the Schauder estimates (see Theorem IV.5.3 in [Ladyzhenskaya et al. 1967](#)) it follows that $\|A(\cdot, t) - A_0(\cdot)\|_{C^2(R_l)} \rightarrow 0$, $\|M(\cdot, t) - M_0(\cdot)\|_{C^2(R_l)} \rightarrow 0$ as $t \rightarrow 0$ and $\|A - A_0\|_{\mathcal{M}_T} = O(T^\nu)$, $\|M - M_0\|_{\mathcal{M}_T} = O(T^\nu)$ for some $\nu > 0$. Moreover, for $\tilde{U}_1, \tilde{U}_2 \in B$ we have $\|P(\tilde{U}_1) - P(\tilde{U}_2)\|_{\mathcal{M}_T} < c\|\tilde{U}_1 - \tilde{U}_2\|_{\mathcal{M}_T}$ with $c < 1$, if T is sufficiently small. Thus for $T \leq T_*$ with some $T_* > 0$, the mapping (6.12) acts from B into B and is a contraction (see, e.g. [Kazmierczak 2009](#)). Hence it has a unique fixed point U in B . The function U is in fact of the class $C^{2+\alpha, 1+\alpha/2}(\mathcal{R}_{lT})$ and it is a solution of system (6.5)–(6.7). Obviously

$$0 \leq U(x, y) \leq (M^*(y), A^*(y)). \quad (6.13)$$

Knowing L^∞ norm of the solution, we can obtain an a priori estimate of the solution in the $C^{1+\alpha, (1+\alpha)/2}(\mathcal{R}_{lT})$ norm. First, from Theorem 6.49 of section VI in [Lieberman \(1996\)](#) we conclude that the following estimate for A holds

$$\|A\|_{C_{x,t}^{1+\beta, (1+\beta)/2}(\mathcal{R}_{lT})} \leq W \left[\|F\|_{L^\infty(\mathcal{R}_{lT})} + \|A_0\|_{C_x^{1+\beta}(R_l)} \right] \quad (6.14)$$

for some constant W , and some $\beta \in (0, \alpha)$, where

$$F = f(A)M - \gamma A + b_s$$

and, according to (6.13), $f \in L^\infty(\mathcal{R}_{lT})$. This estimate has a local character. Thus W can depend on T , but does not depend on l . Having this estimate and using Theorem

IV.5.3 in Ladyzhenskaya et al. (1967), we can also estimate the $C^{2+\alpha, 1+\alpha/2}(\mathcal{R}_{lT})$ norm of the function M :

$$\|M\|_{C^{2+\alpha, 1+\alpha/2}(\mathcal{R}_{lT})} \leq c_3(T). \quad (6.15)$$

Finally, we can estimate the $C^{2+\alpha, 1+\alpha/2}(\mathcal{R}_l \times (0, T))$ norm of A :

$$\|A\|_{C^{2+\alpha, 1+\alpha/2}(\mathcal{R}_{lT})} \leq c_4(T). \quad (6.16)$$

6.2.2 Global existence of solutions

Let us note that time T_* depends on $C^{2+\alpha}(\mathcal{R}_l)$ norm of U_0 and the coefficients of the system (6.5)–(6.7). According to the priori estimates (6.15) and (6.16), the vector function $U(x, y, T_*)$ has its $C^{2+\alpha}(\mathcal{R}_l)$ -norm bounded by a finite constant. Using $U(x, y, T_*)$ as a new initial condition and repeating the procedure we obtain the solution of the considered system in $\mathcal{R}_{l(T_*+T_0)}$ with some $T_0 > 0$. Continuing in this way, we obtain a global in time solution in $\bar{\mathcal{R}}_l \times [0, T]$ for any $T > 0$.

As we mentioned above, a priori estimates necessary for the global existence of solutions do not depend on l . Hence, passing to the limit, we obtain a global in time solution to the problem (1.3)–(1.7) in the strip Ω . The proof of uniqueness of the solution is standard and it is left to the reader.

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