Reaction-Diffusion Model of Atherosclerosis Development

Nader El Khatib, Stéphane Génieys, Bogdan Kazmierczak, Vitaly Volpert

Reaction-Diffusion Model of Atherosclerosis Development

N. El Khatib[a], **S. Genieys**[a], **B. Kazmierczak**[b], **V. Volpert**[a]

[a] Institute of Mathematics, Université Lyon 1, UMR 5208 CNRS
69622 Villeurbanne, France
[b] Institute of Fundamental Technological Research of PAS
Świetokrzyska 21, 00-049 Warsaw, Poland

Abstract. Atherosclerosis begins as an inflammation in blood vessels walls (intima). Anti-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 show that atherosclerosis develops as a reaction-diffusion wave. The theoretical results are confirmed by the results of numerical simulations.

Key words: atherosclerosis, reaction-diffusion waves, nonlinear boundary conditions, existence, numerical simulations
AMS subject classification: 35K57, 92C50

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 can be sketched as follows [2, 3]: 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. As a result, 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-ladden 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., TNF-α, 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).

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 [5, 6].

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 [4]. The model represents a reaction-diffusion system in one space dimension:

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

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

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 equation (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.

We show 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 this model 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 positiveness 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 the general case these results are not applicable. In Section 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 (Section 4).

1.2. Mathematical model

We consider the system of equations

$$\frac{\partial M}{\partial t} = d_M \Delta M - \beta M, \tag{1.3}$$

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

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

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

with the boundary conditions

$$y = 0 : \ \frac{\partial M}{\partial y} = 0,\ \frac{\partial A}{\partial y} = 0, \ \ y = h : \ \frac{\partial M}{\partial y} = g(A),\ \frac{\partial A}{\partial y} = 0 \tag{1.5}$$

and the initial conditions

$$M(x, y, 0) = M_0(x, y), \ \ A(x, y, 0) = A_0(x, y). \tag{1.6}$$

Here M is the concentration of white blood cells inside the intima, A is the concentration of cytokines, d_M, d_A, β, γ, and b are positive constants, the constant b 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:

$$f(A) > 0 \text{ for } A > 0, \;\; f(0) = 0, \;\; f(A) \to f_+ \text{ as } A \to \infty,$$
$$g(A) > 0 \text{ for } A > A_0, \;\; g(A_0) = 0, \;\; g(A) \to g_+ \text{ as } A \to \infty,$$

and $g'(A) > 0$. We put $A_0 = \frac{b}{\gamma}$. 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. The values $A = A_0, M = 0$ is a stationary solution of problem (1.3)-(1.5). The matching condition for the initial and boundary conditions is satisfied, that is the functions $M_0(x,y)$ and $A_0(x,y)$ satisfy (1.5). These conditions provide the existence of a unique solution of problem (1.3)-(1.6) in the space $C^{2+\alpha,1+\alpha/2}(\bar{\Omega})$, $0 < \alpha < 1$ of Hölder continuous functions with respect to x and t (Section 2.1).

2. Positiveness and comparison of solutions

2.1. Existence of solutions

We begin with the result on global existence of solution of problem (1.3)-(1.6). 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.

Theorem 2.1. Suppose that $f(A) \in C^{1+\alpha}(\mathbb{R})$, $g(A) \in C^{2+\alpha}(\mathbb{R})$ for some α, $0 < \alpha < 1$, the initial condition $(M_0(x,y), A_0(x,y))$ of problem (1.3)-(1.6) belongs to $(C^{2+\alpha}(\bar{\Omega}))^2$ and satisfies boundary conditions (1.5). Then this problem has a unique global solution $(M(x,y,t), A(x,y,t))$ with the $C^{2+\alpha,1+\alpha/2}(\bar{\Omega} \times [0,T])$-norm bounded independently of T.

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 solution in the unbounded domain.

2.2. Positiveness for linear problems

Consider the linear parabolic problem

$$\frac{\partial u}{\partial t} = d_1 \frac{\partial^2 u}{\partial y^2} - \beta u, \tag{2.1}$$

$$\frac{\partial v}{\partial t} = d_2 \frac{\partial^2 v}{\partial y^2} + a(y,t)u + b(y,t)v - \gamma v, \tag{2.2}$$

$$y = 0: \ \frac{\partial u}{\partial y} = 0, \ \frac{\partial v}{\partial y} = 0, \ \ y = h: \ \frac{\partial u}{\partial y} = c(y,t)v, \ \frac{\partial v}{\partial y} = 0, \tag{2.3}$$

in the interval $0 \leq y \leq h$ with the initial conditions $u(0, y, v(0, y)$. The coefficients $a(y, t), b(y, t)$ belong to $C^{\alpha,\alpha/2}(\bar{\Omega}_T)$, and $c(y, t)$ to $C^{1+\alpha,(1+\alpha)/2}(\bar{S}_T)$, $a(y, t)$ and $c(y, t)$ are non-negative. We assume the matching conditions between the boundary and the initial conditions. This means that $u(y, 0)$, $v(y, 0)$ satisfies the boundary conditions (2.3). Then there exists a unique solution of this problem, and it is continuous for $t \geq 0$, $0 \leq x \leq h$.

Proposition 2.2. Let the initial condition of problem (2.1)-(2.3) be non-negative functions,

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

Then the solution $u(y, t), v(y, t)$ of problem (2.1)-(2.3) is nonnegative for all y and t. If moreover $u(y, 0) \not\equiv 0$, $v(y, 0) \not\equiv 0$, then the solution is strictly positive.

Proof. Consider first the Dirichlet problem

$$\frac{\partial u_1}{\partial t} = d_1 \frac{\partial^2 u_1}{\partial y^2} - \beta u_1, \tag{2.4}$$

$$\frac{\partial v_1}{\partial t} = d_2 \frac{\partial^2 v_1}{\partial y^2} + a(y,t)u_1 + b(y,t)v_1 - \gamma v_1, \tag{2.5}$$

$$y = 0, h: \ u = v = 0. \tag{2.6}$$

From the positiveness theorem for monotone systems [10], it follows that if the initial condition $(u_1^0(y), v_1^0(y))$ 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 for $t > 0$

$$y = 0: \ \frac{\partial u_1}{\partial y} > 0, \ \frac{\partial v_1}{\partial y} > 0, \ \ y = h: \ \frac{\partial u_1}{\partial y} < 0, \ \frac{\partial v_1}{\partial y} < 0. \tag{2.7}$$

We compare next the solution (u, v) of problem (2.1)-(2.3) with the solution (u_1, v_1) of problem (2.4)-(2.6). Denote by $(u_0(y), v_0(y))$ the initial condition of this problem. Let

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

for some small $\epsilon > 0$. We will prove that the solution of problem (2.1)-(2.3) is greater than the solution of problem (2.4)-(2.6). After that, we can pass to the limit as $\epsilon \to 0$. Therefore, we will obtain that the solution of problem (2.1)-(2.3) with non-negative initial conditions is positive if it is not identically zero.

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

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

Hence

$$\hat{u}_0(y) > u_1^0(y), \;\; \hat{v}_0(y) > v_1^0(y), \;\; 0 \le y \le h.$$

The solution of problem (2.1)-(2.3) with the initial condition $(\hat{u}_0(y), \hat{v}_0(y))$ exists and it is continuous for $t \ge 0$, $0 \le y \le h$. Therefore

$$u(y,t) > u_1(y,t), \;\; v(y,t) > v_1(y,t), \;\; 0 \le y \le h$$

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:

$$u(y_1,t_0) = u_1(y_1,t_0), \;\; v(y_1,t_0) = v_1(y_1,t_0) \tag{2.8}$$

for some y_0 and y_1. If these points are inside the interval $(0,h)$, that is

$$u(0,t_0) > 0, u(h,t_0) > 0, v(0,t_0) > 0, v(h,t_0) > 0,$$

then (2.8) cannot hold because of the comparison theorem. Consequently, one of the functions $u(y,t_0)$, $v(y,t_0)$ equals zero at the boundary of the interval. Suppose that $u(0,t_0) = 0$. Since $\partial u(0,t_0)/\partial y = 0$ and $u(y,t_0) \ge u_1(y,t_0)$, then $\partial u_1(0,t_0)/\partial y = 0$. This contradicts (2.7).

If $u(h,t_0) = 0$, then $\partial u(h,t_0)/\partial y \le 0$ since $u(y,t_0) \ge 0$. On the other hand, from the boundary condition (2.3) it follows that $\partial u(h,t_0)/\partial y \ge 0$. Hence $\partial u(h,t_0)/\partial y = 0$. Since $u(y,t_0) \ge u_1(y,t_0) \ge 0$ and $u_1(h,t_0) = 0$, then $\partial u_1(h,t_0)/\partial y = 0$. This contradicts (2.7).

Other cases, $v(0,t_0) = 0$, $v(h,t_0) = 0$ can be considered similarly. The proposition is proved.

A similar proposition holds for the two-dimensional problem

$$\frac{\partial u}{\partial t} = d_1 \Delta u - \beta u, \tag{2.9}$$

$$\frac{\partial v}{\partial t} = d_2 \Delta v + a(y,t)u + b(y,t)v - \gamma v, \tag{2.10}$$

$$y = 0 : \;\; \frac{\partial u}{\partial y} = 0, \;\; \frac{\partial v}{\partial y} = 0, \;\; y = h : \;\; \frac{\partial u}{\partial y} = c(y,t)v, \;\; \frac{\partial v}{\partial y} = 0 \tag{2.11}$$

in the domain Ω.

Proposition 2.2'. Let the initial condition of problem (2.9)-(2.11) be non-negative functions, $u(x,y,0) \ge 0, v(x,y,0) \ge 0$. Then the solution $u(y,t), v(y,t)$ of problem (2.9)-(2.11) is non-negative for all 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.

2.3. Comparison of solutions

Let (M_1, A_1) and (M_2, A_2) be two solutions of problem (1.3)-(1.5) from $C^{2+\alpha,1+\alpha/2}(\bar{Q}_T)$. We assume that all conditions of Section 1.2 are satisfied. Moreover, we will impose some additional conditions in the propositions below. Put

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

Then

$$\frac{\partial u}{\partial t} = d_M \Delta u - \beta u, \tag{2.12}$$

$$\frac{\partial v}{\partial t} = d_A \Delta v + a(x,t)u + b(x,t)v - \gamma v, \tag{2.13}$$

$$y = 0: \; \frac{\partial u}{\partial y} = 0, \; \frac{\partial v}{\partial y} = 0, \;\; y = h: \; \frac{\partial u}{\partial y} = c(x,t)v, \; \frac{\partial v}{\partial y} = 0, \tag{2.14}$$

where

$$a(x,t) = f(A_1(x,t)), \;\; b(x,t) = \frac{f(A_1(x,t)) - f_2(A(x,t))}{A_1(x,t) - A_2(x,t)} \, M_2(x,t) \; ,$$

$$c(x,t) = \frac{g(A_1(x,t)) - g_2(A(x,t))}{A_1(x,t) - A_2(x,t)} \; .$$

From Proposition 2.2 we immediately obtain the result about comparison of solutions.

Proposition 2.3. In addition to conditions of Section 1.2, suppose that $f'(A)$ and $g''(A)$ satisfy the Lipschitz condition. Let (M_1, A_1) and (M_2, A_2) be two solutions of problem (1.3)-(1.5). If

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

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

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

then the inequalities for the solutions are strict for $t > 0$.

Proof. It is sufficient to verify that the coefficients of problem (2.12)-(2.14) satisfy required regularity conditions. We have

$$\frac{f(A_1(x,t)) - f_2(A(x,t))}{A_1(x,t) - A_2(x,t)} = \int_0^1 f'\left(sA_1(x,t) + (1-s)A_2(x,t)\right) ds.$$

If the derivative $f'(A)$ satisfies the Lipschitz condition, then $b(x,t) \in C^{\alpha,\alpha/2}(\bar{Q}_T)$. Similarly, if the derivative $g''(A)$ satisfies the Lipschitz condition, then $c(x,t) \in C^{1+\alpha,(1+\alpha)/2}(\bar{S}_T)$. 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 of problem (1.3)-(1.5) is such that

$$d_M \Delta M - \beta M > 0, \;\; d_A \Delta A + f(A)M - \gamma A + b > 0.$$

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)-(1.5) with respect to t, we obtain

$$\frac{\partial u}{\partial t} = d_M \Delta u - \beta u, \tag{2.15}$$

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

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

Since $M, A \in C^{2+\alpha,1+\alpha/2}(\bar{Q}_T)$ and the derivatives $f'(A)$, $g''(A)$ satisfy the Lipschitz condition, then $f(A), f'(A)M \in C^{\alpha,\alpha/2}(\bar{Q}_T)$ and $g'(A) \in C^{1+\alpha,(1+\alpha)/2}(\bar{Q}_T)$. Moreover, the derivatives $\partial M/\partial t$ and $\partial A/\partial t$ belong to $C^{2+\alpha,\alpha/2}(\bar{Q}_T)$. Hence u, v satisfy the matching conditions and

$$u(x,y,0) = d_M \Delta M - \beta M > 0, \ \ v(x,y,0) = d_A \Delta A + f(A)M - \gamma A + b > 0.$$

Since $f(A) \geq 0, g'(A) > 0$, then u and v are positive for $t > 0$. 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:

$$\frac{\partial M}{\partial t} = d_M M^{''} - \beta M, \tag{3.1}$$

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

$$y = 0 : \ M^{'} = A^{'} = 0, \ \ y = h : \ M^{'} = g(A), \ A^{'} = 0, \tag{3.3}$$

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

$$M = 0, A = A_0.$$

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

$$d_M M^{''} - \beta M = \lambda M, \tag{3.4}$$

$$d_A A^{''} + f(A_0)M - \gamma A = \lambda A, \tag{3.5}$$

$$y = 0 : \ M^{'} = A^{'} = 0, \ \ y = h : \ M^{'} = g^{'}(A_0)A, \ A^{'} = 0. \tag{3.6}$$

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 $\sigma_2 = \sqrt{\gamma/d_A}$,

$$k = -\frac{f(A_0)}{d_A \sigma_1^2 - \gamma} = \frac{f(A_0)}{d_A(\sigma_2^2 - \sigma_1^2)} \ .$$

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 $y = h$,

$$c_1\sigma_1(e^{\sigma_1 h} - e^{-\sigma_1 h}) = g'(A_0)\left(c_3(e^{\sigma_2 h} + e^{-\sigma_2 h}) + kc_1(e^{\sigma_1 h} + e^{-\sigma_1 h})\right),$$

$$c_3\sigma_2(e^{\sigma_2 h} - e^{-\sigma_2 h}) + kc_1\sigma_1(e^{\sigma_1 h} - e^{-\sigma_1 h}) = 0.$$

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

$$\sigma_1 \sinh(\sigma_1 h) - kg^{'}(A_0)\cosh(\sigma_1 h) = -\frac{k\sigma_1 g^{'}(A_0)}{\sigma_2} \ \frac{\cosh(\sigma_2 h)}{\sinh(\sigma_2 h)} \ \sinh(\sigma_1 h)$$

or

$$\mu_1 \coth(\sigma_1 h) = 1 + \mu_2 \coth(\sigma_2 h), \tag{3.7}$$

where

$$\mu_i = \frac{kg'(A_0)}{\sigma_i} = \frac{f(A_0)g'(A_0)}{d_A\sigma_i(\sigma_2^2 - \sigma_1^2)} \ , \quad i = 1, 2.$$

Solutions of equation (3.7) give zero eigenvalues of problem (3.4)-(3.6). Denote the left-hand side of equation (3.7) by $s_1(h)$. Then it is a decreasing function for $h > 0$,

$$s_1(h) \sim \frac{f(A_0)g'(A_0)}{d_A\sigma_1^2(\sigma_2^2 - \sigma_1^2)} \ \frac{1}{h}, \quad h \to 0, \quad s_1(h) \to \frac{f(A_0)g'(A_0)}{d_A\sigma_1(\sigma_2^2 - \sigma_1^2)}, \ h \to \infty. \tag{3.8}$$

The right-hand side $s_2(h)$:

$$s_2(h) \sim \frac{f(A_0)g'(A_0)}{d_A\sigma_2^2(\sigma_2^2 - \sigma_1^2)} \ \frac{1}{h}, \quad h \to 0, \quad s_1(h) \to 1 + \frac{f(A_0)g'(A_0)}{d_A\sigma_2(\sigma_2^2 - \sigma_1^2)}, \ h \to \infty. \tag{3.9}$$

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 $f(A_0)$ or $g'(A_0)$ 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 any h fixed and σ_1, σ_2 sufficiently large, λ_0 becomes negative (or with the negative real part). On the other hand, by virtue of (3.8), (3.9), 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 $f(A_0)$ or $g'(A_0)$ 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 growth 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 $h \to 0$.

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 $M = 0, A = A_0$ 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

$$M_s(y) > 0, \;\; A_s(y) > A_0, \; 0 < y < h \tag{3.10}$$

holds.

The existence and stability of a bifurcating solution follows from the standard arguments related to the topological degree. Inequality (3.10) follows from the positiveness 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

$$M(y) = \frac{g(A_1)}{2\sigma_1 \sinh(\sigma_1 h)} \left(e^{\sigma_1 y} + e^{-\sigma_1 y} \right),$$

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

$$A(y) = -\frac{f_0 g(A_h)}{2d_A(\sigma_1^2 - \sigma_2^2)} \times$$

$$\left(\frac{1}{\sigma_1 \sinh(\sigma_1 h)} \left(e^{\sigma_1 y} + e^{-\sigma_1 y} \right) - \frac{1}{\sigma_2 \sinh(\sigma_2 h)} \left(e^{\sigma_2 y} + e^{-\sigma_2 y} \right) \right) + \frac{b}{d_A \sigma_2^2} .$$

We obtain the following equation with respect to A_h:

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

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 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

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

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)-(1.5) assuming that the stationary solution $M = M_0, A = A_0$ is unstable and that there exists a stable stationary solution $M_s(y), A_s(y)$ in the section of the cylinder such that

$$M_0 < M_s(y), \quad A_0 < A_s(y), \quad 0 \le y \le h.$$

We will study here the existence of waves with the limits (M_0, A_0) at $x = -\infty$ and (M_s, A_s) at $x = +\infty$. We assume that there are no other stationary solutions such that

$$M_0 \le M(y) \le M_s(y), \quad A_0 \le A(y) \le A_s(y), \quad 0 \le y \le h. \tag{3.11}$$

Consider the problem

$$d_M \Delta M - c\frac{\partial M}{\partial x} - \beta M = 0, \tag{3.12}$$

$$d_A \Delta A - c\frac{\partial A}{\partial x} + f(A)M - \gamma A + b = 0, \tag{3.13}$$

$$y = 0: \ \frac{\partial M}{\partial y} = 0, \ \frac{\partial A}{\partial y} = 0, \quad y = h: \ \frac{\partial M}{\partial y} = g(A), \ \frac{\partial A}{\partial y} = 0. \tag{3.14}$$

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

$$x = -\infty: M = M_0, A = A_0, \quad x = +\infty: M = M_s, A = A_s. \tag{3.15}$$

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

$$\frac{\partial \mu}{\partial x} > 0, \ \frac{\partial \alpha}{\partial x} > 0, \quad (x, y) \in \Omega, \tag{3.16}$$

$$y = 0: \ \frac{\partial \mu}{\partial y} = 0, \ \frac{\partial \alpha}{\partial y} = 0, \quad y = h: \ \frac{\partial \mu}{\partial y} = g(\alpha), \ \frac{\partial \alpha}{\partial y} = 0. \tag{3.17}$$

Denote

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

Proposition 3.4. Let functions $\mu(x,y), \alpha(x,y)$ satisfy conditions (3.16), (3.17). If

$$c > \max(S_1(\mu,\alpha), S_2(\mu,\alpha)) \ , \tag{3.18}$$

then there exists a solution of problem (3.12)-(3.15).

Proof. From inequality (3.18) it follows that

$$d_M\Delta\mu - c\frac{\partial\mu}{\partial x} - \beta\mu < 0, \tag{3.19}$$

$$d_A\Delta\alpha - c\frac{\partial\alpha}{\partial x} + f(\alpha)\mu - \gamma\alpha + b < 0. \tag{3.20}$$

Denote

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

and consider the initial-boundary value problem for the system

$$\frac{\partial M}{\partial t} = d_M\Delta M - c\frac{\partial M}{\partial x} - \beta M, \tag{3.21}$$

$$\frac{\partial A}{\partial t} = d_A\Delta A - c\frac{\partial A}{\partial x} + f(A)M - \gamma A + b \tag{3.22}$$

in the domain Ω_N, with the boundary conditions

$$y = 0 : \ \frac{\partial M}{\partial\nu} = 0, \ \frac{\partial A}{\partial\nu} = 0, \ \ y = h : \ \frac{\partial M}{\partial\nu} = g(A), \ \frac{\partial A}{\partial\nu} = 0. \tag{3.23}$$

$$x = -N : \ M = M_N(y), A = A_N(y) \tag{3.24}$$

and the initial conditions

$$M(x,y,0) = M_N(y), A(x,y,0) = A_N(y). \tag{3.25}$$

We note that the boundary functions at the left boundary of the cylinder and the initials 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:

$$M_0 \le M_N(y) \le \mu(-N,y), \ A_0 \le A_N(y) \le \alpha(-N,y), \tag{3.26}$$

$$d_M M_N'' - \beta M_N \ge 0, \tag{3.27}$$

$$d_A A_N'' + f(A_N)M_N - \gamma A_N + b \ge 0, \tag{3.28}$$

$$M_N'(0) = A_N'(0) = 0; \quad M_N'(h) = g(A_N(h)), \ A_N'(h) = 0. \tag{3.29}$$

The existence of such functions follows from the instability of the solution M_0, A_0. 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

$$M_N(y) = M_0 + \tau_N \mu_0(y), \quad A_N(y) = A_0 + \tau_N \alpha_0(y)$$

satisfy conditions (3.26)-(3.28) for τ_N sufficiently small.

We should note, however, that instead of the condition $M_N'(h) = g(A_N(h))$ we have $M_N'(h) = g'(A_0)A_N(h)$. This is a minor technical detail which can be arranged by replacing the function $g(A)$ in (3.29) by $g'(A_0)A$ for $A_0 \leq A \leq A_0 + \epsilon$, and then considering a limiting procedure as $\epsilon \to 0$.

By virtue of conditions (3.26)-(3.29) and of Proposition 2.4 adapted for the problem under consideration, the solution of problem (3.21)-(3.25) increases in time for each $(x, y) \in \Omega_N$. On the other hand, from inequalities (3.19), (3.20) it follows that it is estimated from above:

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

Therefore, it converges to a stationary solution (u_N, v_N) of problem (3.21)-(3.25). From Lemma 3.5 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 $x \to +\infty$. Since the limiting functions satisfy the problem in the section of the cylinder, and there are no other solutions that satisfy inequality (3.11) except for (M_0, A_0) and (M_s, A_s), then

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

We consider the sequence of solutions (u_N, v_N) as $N \to -\infty$ and choose a convergence 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

$$u_N(0, h/2) = \frac{1}{2}(M_0 + M_s(h/2)).$$

Such values exists 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 $-N - k_N \to -\infty$ as $N \to \infty$.

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 (3.12)-(3.14). Moreover, they are non-decreasing with respect to x and $u_0(0, h/2) = \frac{1}{2}(M_0 + M_s(h/2))$. Hence the solution has limits (3.15) for $x = \pm\infty$. The proposition is proved.

Lemma 3.5. The solution of problem (3.21)-(3.25) 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. Differentiating problem (3.21)-(3.24) with respect to x, we obtain

$$\frac{\partial u}{\partial t} = d_M \Delta u - c\frac{\partial u}{\partial x} - \beta u, \tag{3.30}$$

$$\frac{\partial v}{\partial t} = d_A \Delta v - c\frac{\partial v}{\partial x} + f(A)u + f'(A)Mv - \gamma v \tag{3.31}$$

$$y = 0: \ \frac{\partial u}{\partial y} = 0, \ \frac{\partial v}{\partial y} = 0, \quad y = h: \ \frac{\partial u}{\partial y} = g'(A)v, \ \frac{\partial v}{\partial y} = 0. \tag{3.32}$$

For the solution of problem (3.10)-(3.13), the following estimate holds:

$$M_N(x,y,t) \geq M_b(y), \quad A_N(x,y,t) \geq A_b(y), \quad (x,y) \in \Omega_N, \ t > 0.$$

Therefore,

$$u(-N,y,t) \geq 0, \quad v(-N,y,t) \geq 0, \quad 0 \leq y \leq h, \ t > 0. \tag{3.33}$$

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

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

then the solution of this problem wouldbe identically zero. Since we have inequalities (3.33) 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 (3.12)-(3.15) 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 (3.16), (3.17). These solutions are strictly monotone with respect to x.

Proof. Existence of a solution (M_c, A_c) for $c > c_0$ follows from Proposition 3.4. Since these solutions are bounded in the $C^{2+\delta}(\bar{\Omega})$ norm for some $\delta \in (0,1)$ independently of c for c close to c_0, then we can pass to the limit as $c \to c_0$ 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)-(1.5) 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:

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

The functions $f(A)$ and $g(A)$ are taken in the form

$$f(A) = \frac{A}{1 + 43A/42}, \; g(A) = \epsilon \frac{2 + 8A}{1 + A}.$$

We carry out the simulations using the software Comsol©MultiPhysics.

In the approximation of thin domain, for such functions f and g we obtain the one-dimensional system (1.1), (1.2) in the monostable case [4]. Therefore we can expect the monostable behavior in the two-dimensional case. This means the absence of the threshold where even small perturbation of the disease free solution lead to the disease development. In this case, concentrations A and M grow and spread in the form of travelling waves.

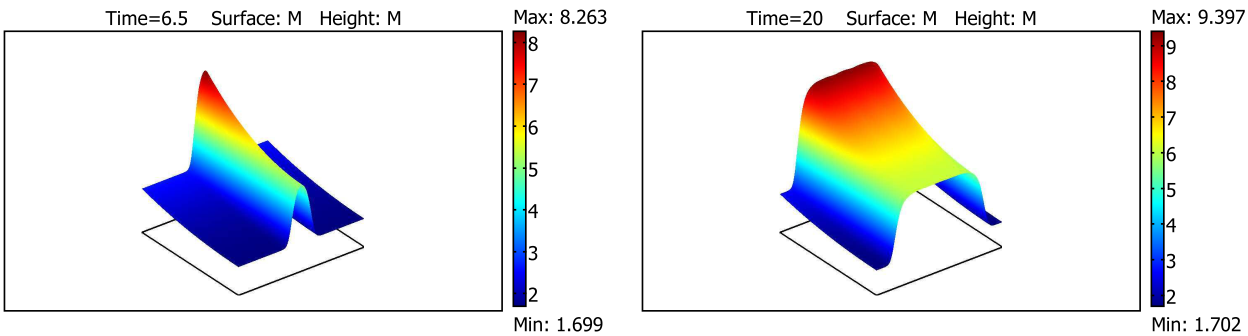

Figure 1: Left: beginning of the wave development. Right: the wave propagation.

Figure 1 (left) shows the set up of the wave front. At the fist stage of the development of inflammation, monocytes spread across the domain, that is in the y-direction (Figure 1, left) and then along the intima, that is in the x-direction (Figure 1, right). 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.

Figure 2 (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.

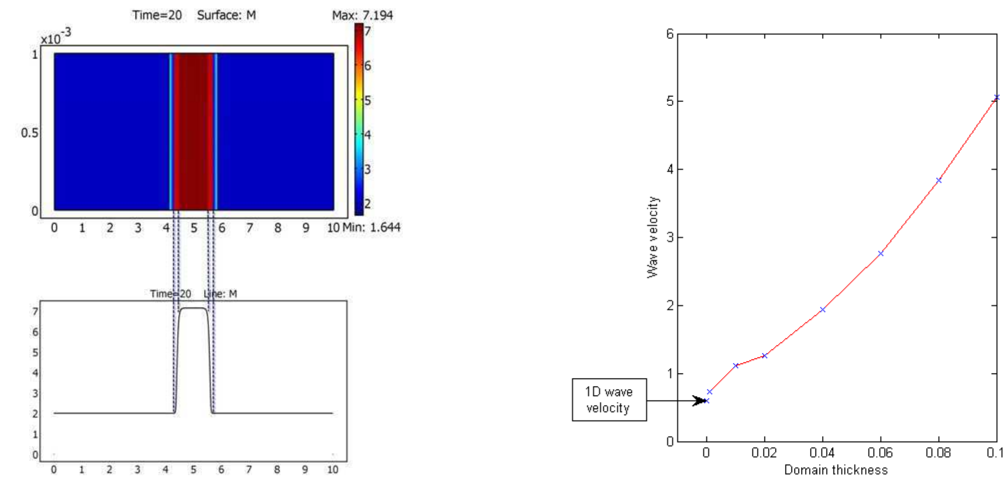

Figure 2: Left: comparison between the $2D$-model with a small thickness (upper part) and the $1D$-model (below). Right: dependence of the wave speed on the thickness of the strip.

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 [4]. 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 [4] 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 and explain the chronic inflammatory reaction as propagation of a travelling wave.

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 becomes crucial because it can result in the plaque rupture. There are numerous studies of these phenomena (see, e.g. [5, 6]). 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 lifetime. 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 the 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 and 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 shows a reduction of 28% reduction in LDL-C and 5% increase in high-density lipoprotein cholesterol [13]. The inhibition of the LDL by statins *"appears to be directly proportional to the degree to which they lower lipids"* [13]. Its action can be taken into account through the parameters of the mathematical model.

Another approach to modelling atherosclerosis is based on cellular automata [11]. 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 [11] confirm the conclusion of this work and of the previous work [4] that atherosclerosis development can be viewed as a wave propagation.

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)-(1.6) we will construct an appropriate supersolution. We consider the stationary equation (1.3) and look for its solution which depends only on the y variable. It satisfies the problem

$$dM'' - \beta M = 0, \quad M(h) = m > 0,\ M'(h) = a\,, a > 0, \tag{6.1}$$

where, for simplicity of notation, we replace d_M by d. Its solution has the following form:

$$M(a;y) = \frac{e^{\frac{\sqrt{\beta}}{\sqrt{d}}}\left(-\left(a\sqrt{d}\right) + \sqrt{\beta}\,m\right) + e^{-\left(\frac{\sqrt{\beta}}{\sqrt{d}}\right) + \frac{2\sqrt{\beta}\,y}{\sqrt{d}}}\left(a\sqrt{d} + \sqrt{\beta}\,m\right)}{2\sqrt{\beta}e^{\frac{\sqrt{\beta}\,y}{\sqrt{d}}}}\,.$$

We note that for

$$m = \coth\left(\frac{\sqrt{\beta}\,h}{\sqrt{d}}\right)a\sqrt{d}/\sqrt{\beta} \tag{6.2}$$

we obtain

$$M(a;y) = \frac{a\sqrt{d}\cosh(\frac{\sqrt{\beta}}{\sqrt{d}}\,y)}{\sqrt{\beta}\sinh(\frac{\sqrt{\beta}}{\sqrt{d}}\,h)} = m\frac{\cosh(\frac{\sqrt{\beta}}{\sqrt{d}}\,y)}{\cosh(\frac{\sqrt{\beta}}{\sqrt{d}}\,h)} \tag{6.3}$$

and both of the relations $M(y) \geq 0$ and $M'(0) = 0$ are satisfied.

Let us take $a^* = g(\infty) + \rho$ with $\rho > 0$ arbitrarily small. Let $M^*(y) := M(a^*, y)$. Obviously, according to (6.3),

$$M(a^*, y)) > M(a, y) \quad \text{for } a \in [0, g(\infty)]. \tag{6.4}$$

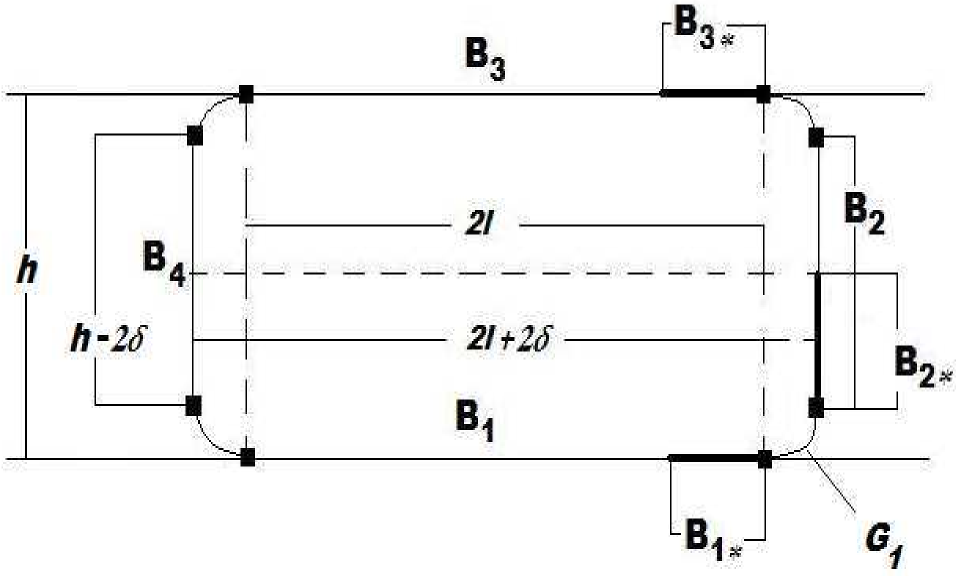

Figure 3: Bounded domain and boundary conditions (see the explanation in the text).

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 a 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" curves joining the boundary points of the straight boundaries (Figure 3).

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 $B_{1*} = B_1 \cap \{(x,y) : x \in [l-2\delta, l]\}$, $B_{3*} = B_3 \cap \{(x,y) : x \in [l-2\delta, l]\}$, $B_{2*} = B_2 \cap \{(x,y) : y \in [\delta, h/2]\}$.

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

$$\frac{\partial M}{\partial t} = d_M \Delta M - \beta M, \tag{6.5}$$

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

and construct the boundary conditions

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

in such a way that a) in the limit, as the length increases, we obtain the boundary condition (1.5), 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 can be defined in the following way. First of all, we can take them symmetric with respect to $x = 0$, $\Psi(x, y) = \Psi(-x, y)$. For $x \geq 0$ the function $\Psi(\cdot)$ is defined as follows:

$$z \in B_1 \setminus B_{1*} : \ \Psi(z) = 0, \quad z \in B_3 \setminus B_{3*} : \ \Psi(z) = g(A(z)),$$

$$z \in B_{3*} : \ \Psi(z) = (1 - s(x - (l - 2\delta)))g(A(z)),$$

$$z \in G_2 \cup B_2 \setminus B_{2*} : \ \Psi(z) \equiv 0, \quad z \in B_{2*} : \ \Psi(z) = -qs\left(2y\delta/(h/2 - \delta)\right),$$

$$z \in G_1 : \ \Psi(z) = -q, \quad z \in B_{1*} : \ \Psi(z) = -qs(x - (l - 2\delta)).$$

Here $s(\tau)$ is C^∞ function such that $s(\tau) \equiv 0$ for $\tau \leq 0$ and $s(\tau) \equiv 1$ for $\tau \geq 1$, $q > 0$ is a constant.

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

$$\begin{gathered} d_A \Delta A + f(A) M^*(y) - \gamma A + b = 0, \quad \text{in } \ R_l, \\ \frac{\partial A}{\partial \nu} = 0 \quad \text{on } \ \partial R_l. \end{gathered} \tag{6.8}$$

It is obvious that, given $M^*(\cdot)$, we can choose $q > 0$ sufficiently large, so 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 $\Omega \times (0, T)$. 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. □

6.2. Existence of solutions

6.2.1. Local existence of solutions

The local existence of solutions follows from the application of the contraction mapping principle. Let

$$\mathcal{L}_1 = \partial/\partial t - d_M \Delta, \ \ \mathcal{L}_2 = \partial/\partial t - d_A \Delta,$$

$$U = (U_1, U_2) = (M, A), \ \ \Phi(U) = (-\beta U_1, f(U_2)U_1 - \gamma U_2 + b).$$

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

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

with the above boundary conditions and initial conditions

$$U(x,y,0) = U_0(x,y) = (M_0(x,y), A_0(x,y)).$$

Let us assume that $0 \le U_0(x,y) \le (M^*(y), A^*(y))$. The local in time existence of such solution is guaranteed by Theorem IV.5.3 in [8]. In the set $\Omega_T = \Omega \times (0,T)$ let us consider the mapping

$$U = P(\widetilde{U}). \tag{6.9}$$

Let $\mathcal{M}_T = C^{1+\alpha,(1+\alpha)/2}(\Omega_T)$ and $B = \{U \in \mathcal{M} : \|U - U_0\|_{\mathcal{M}} \le 1\}$. From the Schauder estimates (see Theorem IV.5.3 in [8]) it follows that for T sufficiently small, $T \le T_*$ with some T_*, the mapping (6.9) acts from B into B and it is a contraction (see, e.g. [7]). Hence it has a unique fixed point U in B. The function U is in fact of the class $C^{2+\alpha,1+\alpha/2}(\Omega_T)$ and it is a solution of system (1.3)-(1.6). Obviously

$$0 \le U(x,y) \le (M^*(y), A^*(y)). \tag{6.10}$$

Knowing only L^∞ norm of the solution, we can obtain an a priori estimate of the solution in the $C^{1+\alpha,(1+\alpha)/2}(R_l)$ norm. First, from Theorem 6.49 of section VI in [9] we conclude that the following estimate for A holds

$$\|A\|_{C^{1+\beta,(1+\beta)/2}_{x,t}(R_l\times(0,T))} \le W\left[\|F\|_{L^\infty(R_l\times(0,T))} + \|A_0\|_{C^{1+\beta}_x(R_l)}\right] \tag{6.11}$$

for some constant W, where

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

According to (6.10), $f \in L^\infty(R_l \times (0,T))$. 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 [8], we can also estimate the $C^{2+\alpha,1+\alpha/2}(R_l \times (0,T))$ norm of the function M:

$$\|M\|_{C^{2+\alpha,1+\alpha/2}(R_l\times(0,T))} \le c_3(T). \tag{6.12}$$

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

$$\|A\|_{C^{2+\alpha,1+\alpha/2}(R_l\times(0,T))} \le c_4(T). \tag{6.13}$$

6.2.2. Global existence of solutions

According to a priori estimates (6.12) and (6.13), the vector function $U(x,y,T_*)$ has its $C^{2+\alpha}(R_l)$-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 $\Omega_{T_*+T_0}$ with some $T_0 > 0$. Continuing in this way, we obtain a global in time solution in $R_l \times (0,T)$ 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)-(1.6). The proof of uniqueness of solution is standard and it is left to the reader.

Acknowledgments

The authors are grateful to John McGregor for discussions about the inflammatory aspect of atherosclerosis and clarifying some important details about the risk factors.

References

[1] Jianglin Fan and Teruo Watanabe. *Inflammatory Reactions in the Pathogenesis of Atherosclerosis*. Journal of Atherosclerosis and Thrombosis, Vol. 10, 63-71, 2003.

[2] Russell Ross, *Atherosclerosis - An inflammatory disease*. Massachussets Medical Society 340: 115-120, 1999.

[3] Bjarne ∅STERUD and Eirik BJ∅RKLID. *Role of Monocytes in Atherogenesis*. Physiol Rev 83: 1070-1086, 2003.

[4] N. El Khatib, S. Genieys, V. Volpert. Atherosclerosis initiation modeled as an inflammatory process. Math. Model. Nat. Phenom., 2 (2007), No. 2, 126-141.

[5] Zhi-Yong Li, PhD; Simon P.S. Howarth, MRCS, Eng; Tjun Tang, MRCS Jonathan H. Gillard. *How Critical Is Fibrous Cap Thickness to Carotid Plaque Stability? A Flow Plaque Interaction Model*. Stroke 37: 1195-1196, 2006.

[6] Zhi-Yong Li, Simon Howarth, Rikin A. Trivedi, Jean M. U-King-Im, Martin J. Graves, Andrew Brown, Liqun Wang, Jonathan H. Gillard. *Stress analysis of carotid plaque rupture based on in vivo high resolution MRI*. Journal of Biomechanics 39(14): 2611-2612, 2006.

[7] B. Kazmierczak, Existence of global solutions to a model of chondrogenesis, Mathematical Methods in the Applied Sciences, Volume 32, Issue 3 , pp. 264 - 283.

[8] O.A. Ladyzhenskaya, V.A. Solonnikov, N.N. Uraltseva. Linear and quasi-linear equations of parabolic type. Moskva, Nauka, 1967.

[9] G.M. Lieberman, *Second Order Parabolic Differential Equations*, World Scientific, Singapore, 1996.

[10] A.I. Volpert, V.A. Volpert, V.A. Volpert. *Traveling Wave Solutions of Parabolic Systems*. American Mathematical Society, Providence Rhode Island, 2000.

[11] R.N. Poston and DRM Poston. *A Typical Atherosclerotic Plaque Morphology Produced in Silico by an Atherogenesis Model Based on Self-Perpetuating Propagating Macrophage Recruitment*. Math. Model. Nat. Phenom., 2 (2007), No. 2, 142-149.

[12] A. Lawrence Gould, Jacques E. Rossouw, Nancy C. Santanello, Joseph F. Heyse and Curt D. Furberg. *Cholesterol Reduction Yields Clinical Benefit : Impact of Statin Trials*. Circulation, 97, 946-952, 1998.

[13] John C. LaRosa, MD; Jiang He, MD, PhD; Suma Vupputuri, MPH. *Effect of Statins on Risk of Coronary Disease A Meta-analysis of Randomized Controlled Trials*. Journal of the American Medical Association, 282, 2340-2346, 1999.