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A stochastic lipid structured model for macrophage dynamics in atherosclerotic plaques

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Abstract

We propose to model certain aspects of the dynamics of a macrophage that moves randomly in a one dimensional space in arterial wall tissue and grows by accumulating localized lipid particles, thus reducing its motility. This phenomenon has been observed in the context of atherosclerotic plaque formation. For this purpose, we use a system of stochastic differential equations satisfied by the position and diffusion coefficient of a Brownian particle whose diffusion coefficient is modified at each visit to the origin and with a dumping coefficient. The novelty of the model, with respect to [1, 15], is to include offloading of lipids through the dumping term. We find explicit necessary and sufficient conditions for macrophage trapping in the locally enriched region.

1 Introduction

Atherosclerosis is a major cause of death in industrialized societies since it is the primary cause of heart attack (acute myocardial infarction) and stroke (cerebrovascular accident). It is now accepted that atherosclerosis is a chronic inflammatory disease which starts within the intima, the innermost layer of an artery. It is driven by the accumulation of macrophage cells within the intima and promoted by modified low density lipoprotein (LDL) particles [17]. Inflammation occurs at sites within the arterial wall where modified low-density lipoproteins (LDL) accumulate after penetrating the wall from the bloodstream [26]. The immune response attracts circulating monocytes to these sites [25]. After crossing the endothelium (the layer of cells lining the lumen of the blood vessel), monocytes enter the blood vessel wall and usually differentiate into macrophages that remove LDL by phagocytosis [18]. When the macrophages accumulate internalised lipid, they produce inflammatory signals that promote the recruitment of additional monocytes [24, 16]. In this way,

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the persistent influx of LDL and the influx of monocytes into the arterial wall produce large numbers of lipid-laden macrophages. This positive feedback loop creates an unresolved inflammatory response [19] that thickens and enlarges the arterial wall, to produce an atherosclerotic plaque.

Plaques can continue to grow throughout life and accumulate lipid-rich necrotic debris (designated as the necrotic core) through necrotic cell death of live and apoptotic macrophages [17]. Plaques may rupture due to the deterioration of the arterial wall, resulting in the release of thrombotic (blood clot-forming) material. If these blood clots block arteries, they can cause heart attacks or strokes.

The intensity of inflammation, in general, depends on the number of LDL particles and macrophages located within the arterial wall. The number of monocyte-derived macrophages inside the plaque is determined by the balance between rapid monocyte recruitment [25, 18], macrophage proliferation [12], programmed cell death (apoptosis) [17], or macrophage emigration from the arterial wall [14]. Macrophages accumulate lipids by phagocytosis of LDL and apoptotic cells.

The recent demonstration of the dynamic nature of inflammatory macrophage populations (see [18]) has led to the development of a new line of mathematical modeling of atherosclerotic plaque immunology (eg [9]). Many mathematical models divide the macrophage population into "macrophages" and "foam cells". This is true in ODE models [6], spatially resolved PDE models [4, 11, 10, 2, 3] and other computational models [20]. However, it is now clear that there is a continuous distribution of lipid loads in macrophage populations, ranging from monocytes with low lipid loads to macrophages that can be labeled as foam cells in atherosclerosis. The variation in lipid load within a macrophage population suggests that it may be instructive to develop structured models in which macrophages are characterized by their intracellular lipid load, similar to adipocytes [23], in the spirit of [16, 9].

In this paper, we model a single macrophage that is moving randomly through tissue where lipid is distributed in a non-uniform way. When the macrophage is at the same position as the lipid, it ingests lipid. Ingested lipid reduces the macrophage's motility and this is modelled as a reduction in the diffusion coefficient that governs the macrophage's rate of motion. We assume that lipid is concentrated at a point which we denote $x = 0$ and whenever a macrophage passes $x = 0$ it ingests lipid.

More precisely, to model the undergoing random movement of a single macrophage in an arterial wall, we identify the arterial wall with the real line and the lipid-enriched region with the point 0 (see Fig. 1). Our model gives the position X_t of a macrophage cell and its diffusion coefficient A_t , at time t , as solution of the following system of stochastic differential equations

$$(1) \quad \begin{cases} dX_t &= \sqrt{2A_t}dW_t, \\ dA_t &= -A_t^\alpha dL_t^0(X) + \lambda A_t dt, \end{cases}$$

with initial condition (X_0, A_0) , $X_0 \in \mathbb{R}$, $A_0 > 0$, where λ and α are two nonnegative parameters, $(W_t, t \geq 0)$ is a given one dimensional Brownian motion, and $(L_t^0(X), t \geq 0)$ is the local time process at 0 of the unknown process $X = (X_t, t \geq 0)$.

The aim of our analysis is to find the conditions which lead to a macrophage becoming unable to move due to lipid ingestion. The system (1) will provide answers depending on the parameters $X_0, A_0, \alpha, \lambda$. They are presented in Proposition 2.3 and analyzed in section 6.

We start the biological justification of (1) by explaining the presence of local time. The notion of local time has been already used to model $((X_t, A_t), t \geq 0)$ in [1, 15]. Indeed their model corresponds to the case $\lambda = 0$. For a rigorous introduction to the notion of local time one can see e.g. [22]. Intuitively, $L_t^0(X)$ represents the time spent by X at point 0 during the time interval $[0, t]$, and actually $(L_t^0(X), t \geq 0)$ is an increasing process which increases only at times when X equals 0. Hence according to (1) each crossing of the origin by the macrophage cell tends to decrease its diffusion coefficient $(A_t, t \geq 0)$, or equivalently to decelerate the cell. Such a decrease in local mobility is due to the internalization and accumulation of lipid particles by macrophages. It can be related to several phenomena: increase in volume or change in cell fate depending on the amount of LDL ingested.

The parameter α describes the intensity of the internalization: the higher the α , the lower the internalization. Indeed, an healthy macrophage (without lipids) moves slowly through tissue (A_0 is not large i.e. $A_0 < 1$) and A_t decreases with each passage through the lipid-dense zone. In such a case, the positive parameter α describes the change in mobility when passing through the lipid-dense region. The smaller the α parameter, the greater the change. If $\alpha = 0$, then the internalization is the same, and constant, at each macrophage passage through the origin. Therefore, this parameter is related to both the amount of lipid located at point 0 of the arterial wall and to the capacity of each macrophage to internalize lipid. The case $\alpha = 0$ corresponds to a very large amount of lipids located at point 0 and a very high capacity of macrophages to internalize lipids. In summary, the α parameter is related to the inflammatory state of the lesion.

In contrast, the term $\lambda A_t dt$ describes the loss of lipids by the macrophage and its tendency to recover its natural state. Therefore, the parameter λ describes the natural immune defenses or medical treatment.

Finally, the initial condition (X_0, A_0) is related to the condition of the arterial wall. Indeed X_0 represents the distance between the macrophage penetrating the wall and a lipid-enriched region. A small value of X_0 can be interpreted as a situation where lipid-enriched regions are frequent. Similarly, a small value of A_0 means a very inflamed macrophage with a low ability to move.

Note that $(A_t, t \geq 0)$ is continuous and starts from $A_0 > 0$. The first time t when $A_t = 0$, is the time of the cell arrest. It allows us to quantify the necrotic core.

The couple $((X_t, A_t), t \geq 0)$ describes the dynamics of a monocyte - derived macrophages population structured by its lipid accumulation, see Fig. 2. It accounts for the impact of lipids ingested by macrophages on their size, dynamics and structure. At the core of our model is this state variable, which plays a similar role to age in age-structured population models and to size in size-structured models [27, 5].

Although simple, the biophysical question that the model (1) raises is whether spatially localized mobility perturbations have consequences on diffusion at all scales,

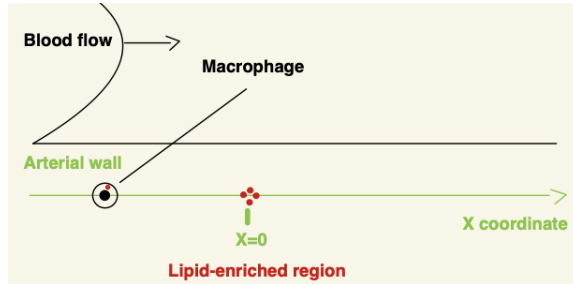


Figure 1: A diagram showing coordinates at the scale of a single cell where $x=0$ denotes a point in the neighbourhood of the macrophage where lipids are abundant and can be ingested by the macrophage.

such as the emergence of a dynamical transition to an absorbing static state. In the context of atherosclerosis, this dynamical transition can be viewed as a minimal mechanism that causes macrophages to aggregate in lipid-enriched regions and thereby to the formation of atherosclerotic plaques (necrotic core). The model (1) incorporates cellular processes which are known to play a significant role in the dynamics of macrophages, apoptotic cells and necrotic material within plaques.

The remainder of this paper is organised as follows. In section 2 we describe the main results: the explicit unique solution of (1) and its arrest time. To establish them, we first give in section 3 an equivalent system to (1). In section 4 we prove the main results. In section 5 we show that the solution of (1) in the case $\lambda = 0$ (corresponding to the model introduced in [1, 15]) can be obtained as the limit of the cases $\lambda > 0$ as λ tends to 0. In section 6 we discuss our results and draw conclusions. In particular, we underline the possibility when $\alpha < 1/2$ (cases of high inflammatory intensity) for the initial condition (X_0, A_0) to determine the fate of a macrophage governed by (1). This sensitivity to the initial condition, that is the initial inflammatory state, should strengthen the interest of the model (1).

2 Main results

Our objective is to study the competition between cell mobility and intracellular lipid accumulation to see whether, after several visits to the lipid-enriched region, the macrophage cell will eventually be trapped (corresponding to necrosis) and thus contribute to atherosclerotic plaque formation or whether the offload will be strong enough and prevent plaque formation.

As introduced in section 1, the cell arrest is the first time A hits 0. Denote it by $T_0(A)$. More precisely: $T_0(A) = \inf \{t \geq 0 : A_t = 0\}$, with the usual convention $\inf \emptyset = +\infty$. Note that $T_0(A) = +\infty$ is compatible with $\lim_{t \rightarrow +\infty} A_t = 0$, but does not imply it. The event $\{T_0(A) < \infty\}$ corresponds to the situation where the particle gets trapped at the origin in finite time.

In the present framework it makes no sense to go beyond the time $T_0(A)$, hence

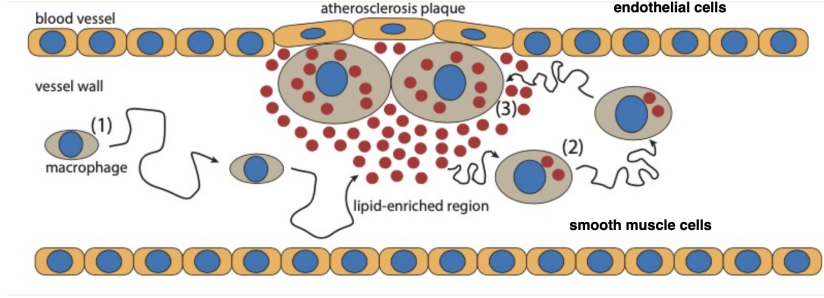


Figure 2: Sketch of the different stages of atherosclerosis plaque formation: (1) diffusion of a "free" macrophage cell; (2) upon entering a localized lipid-enriched region, the macrophage accumulates lipids, and thereby becomes less mobile; and (3) after many visits to the lipid-enriched region, the macrophage eventually gets trapped, resulting in the formation of an atherosclerotic plaque.

a solution of (1) is actually a process $((X_t, A_t), 0 \leq t < T_0(A))$ satisfying (1) up to time $T_0(A)$. A solution of (1) is said to be *strong* if $(T_0(A), ((X_t, A_t), 0 \leq t < T_0(A)))$ is such that $T_0(A)$ is a stopping time of the Brownian motion $(W_t, t \geq 0)$ and $((X_t, A_t), 0 \leq t < T_0(A))$ is a continuous process adapted to $(W_t, t \geq 0)$ satisfying (1) until time $T_0(A)$.

Define $(Y_t, t \geq 0)$ as the Ornstein-Uhlenbeck process solution of

$$(2) \quad Y_t = \frac{X_0}{\sqrt{2A_0}} + W_t - \frac{\lambda}{2} \int_0^t Y_s ds.$$

Denote by $(L_t^0(Y), t \geq 0)$ the local time process at 0 of Y .

The following theorem gives the explicit solution of (1) for any $\alpha \geq 0$, $\lambda \geq 0$, $A_0 > 0$ and any real X_0 .

Theorem 2.1. *For any couple (α, λ) of nonnegative real numbers, the system (1) with initial condition (X_0, A_0) , $A_0 > 0$, has a unique strong solution given by*

$$(3) \quad ((X_t, A_t), 0 \leq t < T_0(A)) = \left((\sqrt{2A_t} Y_t, A_t), 0 \leq t < T_0(A) \right).$$

If $\alpha = 1/2$, then a.s. $T_0(A) = +\infty$ and

$$(A_t, t \geq 0) = \left(A_0 \exp\{\lambda t - \sqrt{2}L_t^0(Y)\}, t \geq 0 \right).$$

If $\alpha \neq 1/2$, then

$$\begin{aligned} & (A_t, 0 \leq t < T_0(A)) \\ &= \left(A_0 e^{\lambda t} \left(1 + \sqrt{2} \left(\alpha - \frac{1}{2} \right) A_0^{\alpha - \frac{1}{2}} \int_0^t e^{\lambda(\alpha - \frac{1}{2})s} dL_s^0(Y) \right)^{\frac{1}{\frac{1}{2} - \alpha}}, 0 \leq t < T_0(A) \right). \end{aligned}$$

For $\alpha \neq 1/2$, the nature of $T_0(A)$ depends on the value of the parameters α , λ , X_0 and A_0 . To reduce the general case $(\alpha, \lambda, X_0, A_0)$ to the case $(\alpha, \lambda, 0, A_0)$, we will establish Proposition 2.2 below. To enunciate it, we make use of $T_0(X)$ the first time X hits 0 and define $T_0(A_{T_0(X)+\cdot})$ on $\{T_0(X) < \infty\}$ by: $T_0(A_{T_0(X)+\cdot}) = \inf \{t \geq 0 : A_{T_0(X)+t} = 0\}$. Note that $T_0(X) \leq T_0(A)$ a.s.

Proposition 2.2. *For $((X_t, A_t), 0 \leq t < T_0(A))$ solution of (1) with initial condition (X_0, A_0) , one has: $T_0(X) < \infty$ a.s. and the process $((X_{T_0(X)+t}, A_{T_0(X)+t}), 0 \leq t < T_0(A_{T_0(X)+\cdot}))$ satisfies (1) with respect to another Brownian motion \tilde{W} , and initial condition $(0, \tilde{A}_0)$ where*

$$\tilde{A}_0 = A_0 + \lambda \frac{X_0^2}{2N^2},$$

and N is a real standard Gaussian variable independent of \tilde{W} .

To describe the nature of $T_0(A)$ when $\alpha \neq 1/2$, it is hence sufficient to consider the cases with initial condition $(0, A_0)$, $A_0 > 0$. Note that when $X_0 = 0$, the Ornstein-Uhlenbeck process $(Y_t)_{t \geq 0}$ is independent of A_0 .

For $\alpha < 1/2$ and $\lambda > 0$, set

$$(4) \quad V_{\alpha, \lambda} = \int_0^\infty \exp \left\{ -\lambda s \left(\frac{1}{2} - \alpha \right) \right\} dL_s^0(Y).$$

Note that $V_{\alpha, \lambda}$ is a random time decreasing with $\lambda(\frac{1}{2} - \alpha)$.

Proposition 2.3. *Let $((X_t, A_t), 0 \leq t < T_0(A))$ be the solution of (1) with initial condition $(0, A_0)$ ($A_0 > 0$).*

- *If $\alpha < 1/2$ and $\lambda > 0$,
then $\mathbb{E}[V_{\alpha, \lambda}] < \infty$ and the following dichotomy holds:*
 - *on $\{V_{\alpha, \lambda} > \frac{A_0^{\frac{1}{2}-\alpha}}{\sqrt{2}(\frac{1}{2}-\alpha)}\}$, one has $T_0(A) < \infty$ and $\lim_{t \rightarrow T_0(A)}(X_t, A_t) = (0, 0)$,*
 - *on $\{V_{\alpha, \lambda} \leq \frac{A_0^{\frac{1}{2}-\alpha}}{\sqrt{2}(\frac{1}{2}-\alpha)}\}$, one has $T_0(A) = \infty$, $\lim_{t \rightarrow \infty} A_t = +\infty$, and X is recurrent.*
- *If $\alpha < 1/2$ and $\lambda = 0$ then a.s. $T_0(A) < \infty$ and $\lim_{t \rightarrow T_0(A)}(X_t, A_t) = (0, 0)$.*
- *If $\alpha \geq 1/2$ and $\lambda \geq 0$, then a.s. $T_0(A) = \infty$, and 0 is a recurrent point for X . Moreover one has:*
 - *if $\alpha = 1/2$, then a.s. $\limsup_{t \rightarrow \infty} e^{-\lambda t} A_t \leq A_0$ and $\limsup_{t \rightarrow \infty} \frac{te^{-\lambda t}|X_t|}{\log t} \leq 2\sqrt{A_0}$,*
 - *if $1/2 < \alpha < 1$, then a.s. $\liminf_{t \rightarrow \infty} A_t = 0$,*
 - *if $\alpha = 1$, then a.s. $\liminf_{t \rightarrow \infty} A_t = 0$, $\limsup_{t \rightarrow \infty} A_t = +\infty$, and X is recurrent.*
 - *if $\alpha > 1$, then a.s. $\limsup_{t \rightarrow \infty} A_t = +\infty$ and X is recurrent.*

We will interpret in section 6 the results presented by Proposition 2. Nevertheless we already make the following comments.

For $\alpha \geq 1/2$: one has $\mathbb{P}[T_0(A) < \infty] = 0$, whatever the value of the other parameters.

For $\alpha < 1/2$: $\mathbb{P}[T_0(A) < \infty] = \mathbb{P}[V_{\alpha,\lambda} > \frac{A_0^{\frac{1}{2}-\alpha}}{\sqrt{2}(\frac{1}{2}-\alpha)}]$. Since for $X_0 = 0$, $(Y_t)_{t \geq 0}$ is independent of A_0 , so is $V_{\alpha,\lambda}$. One sees hence immediately that $\mathbb{P}[T_0(A) < \infty]$ is a decreasing function of A_0 . Moreover, since $V_{\alpha,\lambda}$ is a decreasing function of λ , $\mathbb{P}[T_0(A) < \infty]$ is also a decreasing function of λ .

As it has been mentioned in the introduction of the α parameter, to make sense with the modelisation with the macrophage dynamic, A_0 must be taken small. With elementary computations, one obtains when $A_0 \leq e^2$ that $\mathbb{P}[T_0(A) < \infty]$ is a decreasing function of α .

In Proposition 2.3, the results concerning $\lambda = 0$ have all been already established in [15]. Since when $\lambda = 0$, the Ornstein-Uhlenbeck process Y is the Brownian motion W , their asymptotics when $\alpha \geq 1/2$ are more precise.

3 An equivalent system to (1)

We give a system equivalent to (1), which will be simpler to handle.

Let (X, A) be a solution of (1) on $[0, T_0(A))$ with $A_0 > 0$. On $[0, T_0(A))$ define Y by

$$(5) \quad Y_t = \frac{X_t}{\sqrt{2A_t}}.$$

We obtain that (Y, A) is a solution of the following system

$$(6) \quad \begin{cases} Y_t &= Y_0 + W_t - \frac{\lambda}{2} \int_0^t Y_s ds, \\ dA_t &= -\sqrt{2}A_t^{\alpha+\frac{1}{2}} dL_t^0(Y) + \lambda A_t dt, \end{cases}$$

with $Y_0 = \frac{X_0}{\sqrt{2A_0}}$.

Indeed, using Ito's formula together with the fact that the measure $dL_s^0(X)$ is supported by the set $\{s : X_s = 0\}$, one has

$$\begin{aligned} Y_t &= Y_0 + \int_0^t \frac{dX_s}{\sqrt{2A_s}} - \int_0^t \frac{X_s}{2\sqrt{2}} A_s^{-3/2} dA_s \\ &= Y_0 + W_t + \int_0^t \frac{X_s}{(2A_s)^{3/2}} A_s^\alpha dL_s^0(X) - \lambda \int_0^t \frac{X_s A_s}{(2A_s)^{3/2}} ds \\ &= Y_0 + W_t - \frac{\lambda}{2} \int_0^t \frac{X_s}{\sqrt{2A_s}} ds \\ &= Y_0 + W_t - \frac{\lambda}{2} \int_0^t Y_s ds. \end{aligned}$$

Besides, there is a connection between the local times at 0 of X and Y :

$$dL_t^0(X) = \sqrt{2A_t}dL_t^0(Y).$$

This is a consequence of Tanaka's formula (see e.g. [22]) according to which

$$\begin{aligned} L_t^0(X) &= |X_t| - |X_0| - \int_0^t \operatorname{sgn}(X_s)dX_s = \sqrt{2A_t}|Y_t| - \sqrt{2A_0}|Y_0| - \int_0^t \operatorname{sgn}(Y_s)dX_s \\ &= \sqrt{2A_t}|Y_t| - \sqrt{2A_0}|Y_0| - \int_0^t \operatorname{sgn}(Y_s)\sqrt{2A_s}dY_s - \int_0^t |Y_s|\frac{dA_s}{\sqrt{2A_s}}. \end{aligned}$$

Since

$$\sqrt{2A_t}|Y_t| = \sqrt{2A_0}|Y_0| + \int_0^t \sqrt{2A_s}d(|Y_s|) + \int_0^t |Y_s|\frac{dA_s}{\sqrt{2A_s}},$$

it yields

$$L_t^0(X) = \int_0^t \sqrt{2A_s}dL_s^0(Y),$$

which leads to (6).

Conversely any couple (Y, A) solution of (6) on $[0, T_0(A))$, corresponds to a solution (X, A) of (1) on $[0, T_0(A))$, by setting $X_t = \sqrt{2A_t}Y_t$.

We now work with (Y, A) solution of (6) on $[0, T_0(A))$. The first equation in (6) defines an Ornstein-Uhlenbeck process $(Y_t, t \geq 0)$ which can be explicitly computed

$$(7) \quad Y_t = e^{-\frac{\lambda t}{2}}Y_0 + e^{-\frac{\lambda t}{2}} \int_0^t e^{\frac{\lambda s}{2}} dW_s,$$

where Y_0 is the given initial value of Y .

Alternatively, one can use the following expression of Y which is due to Doob [7]

$$(8) \quad (Y_t, t \geq 0) = \left(e^{-\frac{\lambda t}{2}} (Z_{u(t)} + Y_0), t \geq 0 \right),$$

where Z is a real Brownian motion starting from 0 and

$$(9) \quad u(t) = \frac{e^{\lambda t} - 1}{\lambda}.$$

Actually, Z is defined by

$$(10) \quad (Z_t, t \geq 0) = \left(\int_0^{\frac{1}{\lambda} \log(1+\lambda t)} e^{\frac{\lambda s}{2}} dW_s, t \geq 0 \right).$$

We have to study the behavior of $(A_t)_{t \geq 0}$ solution of the second equation of (6)

$$(11) \quad A_t = A_0 - \sqrt{2} \int_0^t A_s^{\alpha + \frac{1}{2}} dL_s^0(Y) + \lambda \int_0^t A_s ds,$$

with $A_0 > 0$ and $t \in [0, T_0(A))$.

In [8], using (8) allows to obtain the following expression for the local time process at 0 of Y

$$(12) \quad (L_t^0(Y), t \geq 0) = \left(\int_0^{\frac{e^{\lambda t} - 1}{\lambda}} \frac{1}{\sqrt{1 + \lambda s}} dL_s^{-Y_0}(Z), t \geq 0 \right).$$

4 Proofs

4.1 Proof of Proposition 2.2

We use of Y and Z introduced in (7), (8) and (10). The parameters α and λ are fixed. For $X_0 \neq 0$, define

$$T_0(X) = \inf \{t \geq 0 : X_t = 0\}.$$

Since A is increasing on $[0, T_0(X))$, recalling the definition (5) of Y , one has $T_0(X) = T_0(Y)$. Using (7) it follows that a.s. $T_0(X) < \infty$.

The time $T_0(Y)$ is a stopping time for the natural filtration of W . Hence the process $(\tilde{W}_t, t \geq 0)$ defined by $\tilde{W} = (W_{T_0(X)+t} - W_{T_0(X)}, t \geq 0)$ is a Brownian motion starting from 0, independent of $(W_t, t \in [0, T_0(X)])$. The process $(Y_{T_0(X)+t}, t \geq 0)$ is the unique solution of

$$y_t = \tilde{W}_t - \frac{\lambda}{2} \int_0^t y_s ds.$$

By (11), we see that $A_t = A_0 \exp(\lambda t)$ for $t \in [0, T_0(X)]$ and in particular it holds that $A_{T_0(X)} = A_0 \exp(\lambda T_0(Y))$. Hence, $A_{T_0(X)}$ is independent of \tilde{W} . Moreover, $(A_{T_0(X)+t}, t \geq 0)$ is solution of

$$a_t = A_{T_0(X)} - \int_0^t \sqrt{2} a_s^{\alpha + \frac{1}{2}} dL_s^0(Y_{T_0(Y)+\cdot}) + \lambda \int_0^t a_s ds.$$

Consequently, $((Y_{T_0(X)+t}, A_{T_0(X)+t}), t \geq 0)$ is solution of (6) with respect to \tilde{W} with initial condition $(0, A_{T_0(X)})$. This implies that $((X_{T_0(X)+t}, A_{T_0(X)+t}), t \geq 0)$ is solution of (1) with respect to \tilde{W} with initial condition $(0, A_{T_0(X)})$.

Set $\tilde{A}_0 = A_{T_0(X)}$. Thanks to (8), we have

$$T_0(Y) = \frac{1}{\lambda} \log \left(1 + \lambda T_{\frac{-X_0}{\sqrt{2A_0}}}(Z) \right),$$

where for all $a \in \mathbb{R}$, $T_a(Z)$ is defined by

$$T_a(Z) = \inf \{t \geq 0 : Z_t = a\}.$$

Thanks to the reflexion principle, one sees that $T_a(Z) \stackrel{(\text{law})}{=} (\frac{a}{Z_1})^2$, which leads to

$$\tilde{A}_0 = A_0 + \lambda \frac{X_0^2}{2N^2},$$

where N is a real standard Gaussian variable independent of \tilde{W} .

4.2 Proof of Theorem 2.1 and Proposition 2.3

To solve (1) we use the equivalent system (6). We start with the case $\alpha = 1/2$ and then study the case $\alpha \neq 1/2$.

4.2.1 Case $\alpha = 1/2$

In this case (11) reads

$$A_t = A_0 + \int_0^t A_s(\lambda ds - \sqrt{2}dL_s^0(Y)), \quad t \in [0, T_0(A)],$$

which admits as unique solution on $[0, T_0(A))$

$$(13) \quad A_t = A_0 \exp\left(\lambda t - \sqrt{2}L_t^0(Y)\right).$$

Consequently, A can not reach 0 at finite time, hence $\mathbb{P}[T_0(A) = \infty] = 1$.

Assume now that $X_0 = 0$. Since: $X_t = \sqrt{2}A_t Y_t$, using (13) together with (8) one easily obtains:

$$|X_t| = \sqrt{2A_0} |Z_{u(t)}| \exp\left(-\frac{1}{\sqrt{2}}L_t^0(Y)\right),$$

with u defined by (9). Thanks to (12), one obtains

$$|X_t| \leq \sqrt{2A_0} |Z_{u(t)}| \exp\left(-\frac{1}{\sqrt{2}}\frac{L_{u(t)}^{-Y_0}(Z)}{\sqrt{1 + \lambda u(t)}}\right),$$

where $L_{u(t)}^{-Y_0}(Z)$ stands for the local time at level $-Y_0$ and time $u(t)$ of the process Z .

From Kesten's asymptotic results on the supremum of the local times of Z , see [13], it follows that a.s.

$$\liminf_{t \rightarrow \infty} L_t^{-Y_0}(Z) \frac{\sqrt{\log \log t}}{\sqrt{t}} < \infty,$$

hence a.s.

$$(14) \quad \liminf_{t \rightarrow \infty} \frac{L_t^{-Y_0}(Z)}{\sqrt{t}} = 0.$$

Using (14) together with the law of iterated logarithm for Z , we get that a.s.

$$\limsup_{t \rightarrow \infty} \frac{te^{-\lambda t}|X_t|}{\log t} \leq 2\sqrt{A_0}.$$

Besides, one has

$$A_t \leq A_0(1 + \lambda u(t)) \exp\left(-\sqrt{2}\frac{L_{u(t)}^{-Y_0}(Z)}{\sqrt{1 + \lambda u(t)}}\right),$$

which with (14) gives: $\limsup_{t \rightarrow \infty} e^{-\lambda t} A_t \leq A_0$ a.s.

4.2.2 Case $\alpha \neq 1/2$

Let β be a non zero real number. By Ito's formula, one obtains on $[0, T_0(A))$

$$A_t^\beta = A_0^\beta - \sqrt{2}\beta \int_0^t A_s^{\beta+\alpha-\frac{1}{2}} dL_s^0(Y) + \lambda\beta \int_0^t A_s^\beta ds.$$

Choose $\beta = \frac{1}{2} - \alpha$ and set $B_t = A_t^\beta$. For t in $[0, T_0(A))$, we have

$$(15) \quad B_t = B_0 - \sqrt{2}\beta L_t^0(Y) + \lambda\beta \int_0^t B_s ds,$$

with $B_0 = A_0^\beta$.

By differentiation of $B_t e^{-\lambda\beta t}$, one sees that

$$d\left(B_t e^{-\lambda\beta t}\right) = -\sqrt{2}\beta e^{-\lambda\beta t} dL_t^0(Y),$$

which leads to

$$(16) \quad B_t = e^{\lambda\beta t} \left(B_0 - \sqrt{2}\beta \int_0^t e^{-\lambda\beta s} dL_s^0(Y) \right).$$

We now study $T_0(A)$ according to the value of α .

Case $\alpha < 1/2$: In this case $\beta > 0$ and (16) leads to

$$(17) \quad A_t = e^{\lambda t} \left(B_0 - \sqrt{2} \left(\frac{1}{2} - \alpha \right) \int_0^t e^{-\lambda(\frac{1}{2}-\alpha)s} dL_s^0(Y) \right)^{\frac{1}{(\frac{1}{2}-\alpha)}}, \quad t \in [0, T_0(A)).$$

Moreover we have

$$T_0(A) = T_0(B) = \inf \left\{ t \geq 0 : \int_0^t e^{-\lambda\beta s} dL_s^0(Y) \geq \frac{B_0}{\sqrt{2}\beta} \right\}.$$

Assume now that $X_0 = 0$. Under this assumption Y starts from 0 and is independent of A_0 . Note that

$$\mathbb{E} \left[\int_0^\infty e^{-\lambda\beta s} dL_s^0(Y) \right] = \mathbb{E} [L_{\mathbf{e}}^0(Y)],$$

where \mathbf{e} is an exponential variable with parameter $\lambda(\frac{1}{2} - \alpha)$, independent of Y .

Using the fact that Y_t has a Gaussian law with mean 0 and variance $\frac{1-e^{-\lambda t}}{\lambda}$, one has

$$\begin{aligned} \mathbb{E}[L_{\mathbf{e}}^0(Y)] &= \sqrt{\frac{\lambda}{2\pi}} \int_0^\infty e^{-\lambda\beta s} (1 - e^{-\lambda s})^{-1/2} ds \\ &= \frac{1}{\sqrt{2\pi\lambda}} \int_0^\infty e^{-\beta s} (1 - e^{-s})^{-1/2} ds < \infty. \end{aligned}$$

Consequently a.s.

$$V_{\lambda,\alpha} := \int_0^\infty \exp\left(-\lambda s\left(\frac{1}{2} - \alpha\right)\right) dL_s^0(Y) < \infty.$$

On $\{V_{\lambda,\alpha} > \frac{A_0^{\frac{1}{2}-\alpha}}{\sqrt{2}(\frac{1}{2}-\alpha)}\}$: $T_0(A) < \infty$ and $\lim_{t \rightarrow T_0(A)} X_t = 0$.

On $\{V_{\lambda,\alpha} \leq \frac{A_0^{\frac{1}{2}-\alpha}}{\sqrt{2}(\frac{1}{2}-\alpha)}\}$: $T_0(A) = +\infty$ and

$$\lim_{t \rightarrow \infty} B_t = \lim_{t \rightarrow \infty} e^{\lambda(\frac{1}{2}-\alpha)t} \left(A_0^{\frac{1}{2}-\alpha} - \sqrt{2}\left(\frac{1}{2} - \alpha\right)V_{\lambda,\alpha} \right) = +\infty,$$

which implies that $\lim_{t \rightarrow \infty} A_t = +\infty$ and

$$\liminf_{t \rightarrow \infty} X_t = -\infty, \quad \limsup_{t \rightarrow \infty} X_t = +\infty.$$

Case $\alpha > 1/2$: In this case $\beta < 0$. Set $\gamma = -\beta = \alpha - 1/2 > 0$. We have

$$B_t = e^{-\lambda\gamma t} \left(B_0 + \sqrt{2}\gamma \int_0^t e^{\lambda\gamma s} dL_s^0(Y) \right),$$

hence $B_t > 0$ for every $t \geq 0$.

The process A reaches 0 in finite time if B takes an infinite value in finite time. Using (15) we see that

$$B_t \leq B_0 + \sqrt{2}\gamma L_t^0(Y).$$

Obviously $(L_t^0(Y))_{t \geq 0}$ can not blow-up in finite time. Hence $\mathbb{P}[T_0(A) < \infty] = 0$ and

$$(18) \quad A_t = e^{\lambda t} \left(B_0 + \sqrt{2}\gamma \int_0^t e^{\lambda\gamma s} dL_s^0(Y) \right)^{-1/\gamma}, \quad t \geq 0.$$

We have: $B_t \underset{t \rightarrow \infty}{\sim} \sqrt{2}\gamma e^{-\lambda\gamma t} \int_0^t e^{\lambda\gamma s} dL_s^0(Y)$.

To compute $\int_0^t e^{\lambda\gamma s} dL_s^0(Y)$, we use (12), make the time change $v(s) = \frac{1}{\lambda} \log(1 + \lambda s)$, and then an integration by part to finally obtain:

$$(19) \quad \int_0^t e^{\lambda\gamma s} dL_s^0(Y) = \frac{L_{u(t)}^{-Y_0}(Z)}{(1 + \lambda u(t))^{1-\alpha}} - \lambda(\alpha - 1) \int_0^{u(t)} L_s^{-Y_0}(Z) (1 + \lambda s)^{\alpha-2} ds.$$

To finish proving Proposition 2.2, we assume now that $X_0 = 0$ and consider the three different cases: $\alpha = 1$, $\alpha > 1$ and $1/2 < \alpha < 1$.

If $\alpha = 1$, then

$$B_t \underset{t \rightarrow \infty}{\sim} \sqrt{2}\gamma \frac{L_{u(t)}^0(Z)}{(1 + \lambda u(t))^{1/2}}.$$

Using the law of iterated logarithm for local times of a real Brownian motion [21], we obtain a.s.

$$(20) \quad \limsup_{t \rightarrow \infty} \frac{L_t^0(Z)}{\sqrt{2t \log_2 t}} = 1,$$

hence $\liminf_{t \rightarrow \infty} A_t = 0$.

Using (14), it follows that $\liminf_{t \rightarrow \infty} B_t = 0$, thus $\limsup_{t \rightarrow \infty} A_t = +\infty$.

Using the same argument as in [15] one obtains that X is recurrent on \mathbb{R} with $\liminf_{t \rightarrow \infty} X_t = -\infty$ and $\limsup_{t \rightarrow \infty} X_t = +\infty$.

If $\alpha > 1$, then from (19), we deduce that there exists a positive constant C such that

$$(21) \quad B_t \leq C \frac{L_{u(t)}^0(Z)}{u(t)^{1/2}}$$

and hence (14) leads similarly to $\limsup_{t \rightarrow \infty} A_t = +\infty$. Moreover using (21), for t big enough it holds

$$|X_t| = \sqrt{2A_t} |Y_t| \geq C \frac{|Z_{u(t)}|}{\sqrt{u(t)}} \left(\frac{\sqrt{u(t)}}{L_{u(t)}^0(Z)} \right)^{\frac{1}{2\gamma}}.$$

Finally, using (20), a.s. for all t big enough we have

$$\frac{\sqrt{u(t)}}{L_{u(t)}^0(Z)} \geq C \frac{1}{\sqrt{\log_2 u(t)}}.$$

Recalling Strassen's Law of the Iterated Logarithm

$$\limsup_{t \rightarrow \infty} \frac{Z_t}{\sqrt{2t \log_2 t}} = 1 \text{ a.s.}$$

we obtain: $\limsup_{t \rightarrow \infty} |X_t| = +\infty$, which leads by symmetry and continuity to $\liminf_{t \rightarrow \infty} X_t = -\infty$ and $\limsup_{t \rightarrow \infty} X_t = +\infty$.

If $1/2 < \alpha < 1$, then (19) leads to

$$B_t \geq C \frac{L_{u(t)}^0(Z)}{u(t)^{1/2}},$$

and (20) gives: $\liminf_{t \rightarrow \infty} A_t = 0$ a.s.

□

5 The case $\lambda = 0$ as a limit case

For $\alpha \geq 0$, $\lambda \geq 0$, $X_0 \in \mathbb{R}$ and $A_0 > 0$ fixed, there exists a unique strong solution of (1). Various continuity properties of this solution with respect to this parameters,

can be studied. In particular for $\alpha \geq 0$ and $A_0 > 0$ fixed, denote by $(X(\lambda), A(\lambda))$ the solution of (1) with initial condition $(0, A_0)$. Motivated by the fact that the case $\lambda = 0$ with initial condition $(0, A_0)$, has been previously explored in [15], we show that the solution $(X(0), A(0))$ of

$$(22) \quad \begin{cases} dX_t &= \sqrt{2A_t}dW_t \\ dA_t &= -A_t^\alpha dL_t^0(X), \end{cases}$$

with initial conditions $X_0 = 0$ and $A_0 > 0$, can be obtained as a limit solution of (1) when $\lambda > 0$ and decreases to 0.

Proposition 5.1. *Let $\alpha > 0$ be fixed. Denote by $(X(\lambda), A(\lambda))$ the solution of (1) for $\lambda > 0$ with initial condition $(0, A_0)$. As λ decreases to 0, $(X(\lambda), A(\lambda))$ converges in probability uniformly on compact sets to the solution of (22).*

Nevertheless this continuity property at $\lambda = 0$ of the solution of (1) is compatible with the fact that for $\alpha < 1/2$, in view of the nature of the cell arrest, 0 is a critical value for λ (Proposition 2.3).

Proof. For $\lambda > 0$ denote by $Y(\lambda) = (Y_t(\lambda), t \geq 0)$ the solution of (2) starting from 0. One easily checks that a.s. $Y(\lambda)$ converges to W pointwise, uniformly on compacts, as λ tends to 0. Denote by $(L_t^0(W), t \geq 0)$ (resp. $(L_t^0(Y(\lambda)), t \geq 0)$) the local time process at 0 of W (resp. $Y(\lambda)$). Let τ be a stopping time for W with finite second moment. Using Tanaka's formula and Burkholder-Davis-Gundy inequalities (see e.g. [22]), one obtains

$$\mathbb{E} \left[\sup_{0 \leq s \leq \tau} |L_s^0(Y(\lambda)) - L_s^0(W)|^2 \right] \xrightarrow{\lambda \rightarrow 0} 0.$$

Consequently, one has:

$$(23) \quad ((L_t^0(Y(\lambda)), Y_t(\lambda)), 0 \leq t \leq \tau) \xrightarrow{\lambda \rightarrow 0} ((L_t^0(W), W_t), 0 \leq t \leq \tau)$$

in probability for the infinite norm of \mathbb{R}^2 -valued continuous functions on compact sets.

If $\alpha \geq 1/2$, then we choose for stopping time τ any deterministic time $t > 0$ and using Theorem 2.1 we obtain the convergence for the infinite norm in probability of $((X_s(\lambda), A_s(\lambda)), 0 \leq s \leq t)$ to $((X_s, A_s), 0 \leq s \leq t)$.

If $\alpha < 1/2$, then we choose

$$\tau = \inf \left\{ t \geq 0 : L_t^0(W) > \frac{A_0^{\frac{1}{2}-\alpha}}{\sqrt{2}(\frac{1}{2}-\alpha)} \right\}.$$

In this case the solution of (22) satisfies $T_0(A) = \tau$ (Theorem 2.1 for $\lambda = 0$). Similarly to the previous case, we obtain the convergence (23) but since on $\{T_0(A(\lambda)) < \tau\}$,

$A_t(\lambda)$ is not defined for $t \in (T_0(A(\lambda)), \tau)$ we can not immediately conclude. One has:

$$(T_0(A(\lambda)) \geq \tau) = \left(\int_0^\tau e^{-\lambda(\frac{1}{2}-\alpha)s} dL_s^0(Y(\lambda)) \leq \frac{A_0^{\frac{1}{2}-\alpha}}{\sqrt{2}(\frac{1}{2}-\alpha)} \right),$$

hence $(\mathbb{1}_{\{T_0(A(\lambda)) \geq \tau\}}(X_t(\lambda), A_t(\lambda)), 0 \leq t \leq \tau)$ converges uniformly in probability to the solution of (22).

Moreover for any $\lambda > 0$, using (12) we can write

$$(24) \quad \left(\int_0^t e^{-\lambda(\frac{1}{2}-\alpha)s} dL_s^0(Y(\lambda)), t \geq 0 \right) \\ \stackrel{(law)}{=} \left(\frac{L_{u(t)}^0(\overline{W})}{(1+\lambda u(t))^{1-\alpha}} + \lambda(1-\alpha) \int_0^{u(t)} \frac{L_s^0(\overline{W})}{(1+\lambda s)^{2-\alpha}} ds, t \geq 0 \right)$$

where \overline{W} is a real Brownian motion starting from 0.

Thanks to (24) one has

$$(25) \quad \int_0^\infty e^{-\lambda(\frac{1}{2}-\alpha)s} dL_s^0(Y(\lambda)) \stackrel{(law)}{=} \lambda(1-\alpha) \int_0^\infty \frac{L_s^0(\overline{W})}{(1+\lambda s)^{2-\alpha}} ds.$$

The scaling property of \overline{W} yields

$$\lambda(1-\alpha) \int_0^\infty \frac{L_s^0(\overline{W})}{(1+\lambda s)^{2-\alpha}} ds \stackrel{(law)}{=} \frac{(1-\alpha)}{\sqrt{\lambda}} \int_0^\infty \frac{L_s^0(\overline{W})}{(1+s)^{2-\alpha}} ds,$$

which provides with (25) the following limit

$$(26) \quad \lim_{\lambda \rightarrow 0} \int_0^\infty e^{-\lambda(\frac{1}{2}-\alpha)s} dL_s^0(Y(\lambda)) = +\infty \text{ in probability,}$$

i.e. for every $c > 0$,

$$\lim_{\lambda \rightarrow 0} \mathbb{P} \left[\int_0^\infty e^{-\lambda(\frac{1}{2}-\alpha)s} dL_s^0(Y(\lambda)) < c \right] = 0.$$

□

6 Conclusion

In this work, we propose and study a model for macrophage dynamics taking into account their lipid load. We incorporated essential parameters: intensity of inflammation α , immune defenses and medical treatments λ , and the initial inflammatory state (X_0, A_0) . Our mathematical study provides information on the dynamics of the macrophage and hence on the atherosclerotic plaque dynamics. In particular, depending on the value of the parameters, it can lead to the accumulation of macrophages in a particular region of the arterial wall. The key quantity to evaluate this risk is $\mathbb{P}[T_0(A) < \infty]$.

Here are the main conclusions that one can reach adopting this model.

1 - If $\alpha \geq 1/2$, which corresponds to a relatively low intensity of inflammation, no atherosclerotic plaque will form whatever λ , X_0 and A_0 are (equivalently: $\mathbb{P}[T_0(A) < \infty] = 0$). Unsurprisingly, in this case the introduction of the parameter λ in the system (22) previously studied in [15], does not change $\mathbb{P}[T_0(A) < \infty]$ which remains null.

2 - If $\alpha < 1/2$, which corresponds to a relatively high intensity of inflammation, then the introduction of the parameter λ affects the dynamics of the particle in several ways. Indeed for $\lambda = 0$, whatever the value of A_0 , one has $\mathbb{P}[T_0(A) < \infty] = 1$, which means cell arrest or apoptosis in finite time a.s. While for $\lambda > 0$, if A_0 is large enough (which means low intracellular load in lipids at time $t = 0$) with $X_0 = 0$, then $T_0(A) = \infty$ and $\lim_{t \rightarrow \infty} A_t = +\infty$. This infinite limit can be interpreted as the emigration of the macrophage and corresponds to no contribution from this cell to the formation of an atherosclerotic plaque at the origin. Moreover one can find an upper bound the risk $\mathbb{P}[T_0(A) < \infty]$ by using Markov inequality:

$$\mathbb{P}[T_0(A) < \infty] \leq \frac{\sqrt{2}(\frac{1}{2} - \alpha)\mathbb{E}[V_{\alpha,\lambda}]}{A_0^{\frac{1}{2}-\alpha}}.$$

Since $V_{\alpha,\lambda}$ is independent of A_0 , we clearly see that by increasing A_0 , one increases the probability of avoiding arrest or apoptosis.

But X_0 also plays a role in the case where $\alpha < 1/2$ and $\lambda > 0$. Using Proposition 2.2, we see that cell arrest (or apoptosis) occurs in finite time for the solution of (1) with initial condition (X_0, A_0) if and only if it is so for the solution of (1) with initial condition $(0, \tilde{A}_0)$. The variable \tilde{A}_0 increases stochastically with A_0 and $|X_0|$. Thus, given N , the state of the arterial wall can be improved by increasing A_0 or $|X_0|$. This corresponds to a lower intracellular load in lipids at time $t = 0$ or a greater dispersion of lipid sources at time $t = 0$, which means a lower initial inflammatory state.

Hence the introduction of λ not only offers the possibility to lower $\mathbb{P}[T_0(A) < \infty]$ in the cases when α , the inflammatory intensity, is high but this possibility takes into account the initial inflammatory state (X_0, A_0) .

Model (1) could be enriched by considering a population of macrophages instead of a single one. The role played by the accumulation of trapped macrophages on the still moving macrophages should be well understood to be taken into account by the enriched model.

Competing Interests The authors declare that no competing interests exist.

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