A mathematical model of atherogenesis as an inflammatory response

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We construct a mathematical model of the early formation of an atherosclerotic lesion based on a simplification of Russell Rossâ paradigm of atherosclerosis as a chronic inflammatory response. It is now understood that when chemically modified low-density lipoproteins (LDL cholesterol) enter into the wall of the human artery, they can trigger an immune response mediated by biochemical signals sent and received by immune and other cells indigenous to the vasculature. The presence of modified LDL can also corrupt the normal immune function triggering further immune response and ultimately chronic inflammation. In the construction of our mathematical model, we focus on the inflammatory component of the pathogenesis of cardiovascular disease (CVD). Because this study centers on the interplay between chemical and cellular species in the human artery and bloodstream, we employ a model of chemotaxis and present our model as a coupled system of non-linear reaction diffusion equations describing the state of the various species involved in the disease process. We perform numerical simulations demonstrating that our model captures certain observed features of CVD such as the localization of immune cells, the build-up of lipids and debris and the isolation of a lesion by smooth muscle cells.

Turing and Krasnoselsky

This model will be a simplification and idealization, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge. (Turing, 1952)

If you want deliver talk , then present one result (Theorem) (Krasnoselsky) , 1980

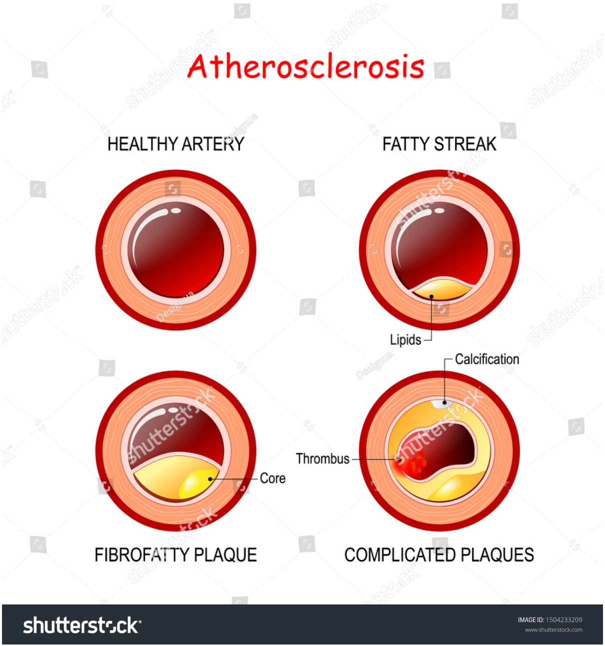

Figure 1: Russel's Schematic Stages

Highlights

- We generalize Einstein's probabilistic method for the Brownian motion to study dynamics of the cell movement under chemotactic force
- By relating the expected displacement per unit time with the gradient of chemo-attractant
- Nonlinear PDE system for the density function is obtained
- Disease development stated as instability of the linearized system .
- Decay estimates for the solutions for all time, and particularly, their exponential convergence as time tends to infinity.
- For this purpose Linear Stability procedure was implemented

Traditional Concept

1. Continuity equation(Material Balance, in divergence form), which link major players of the system

$$\frac{\partial n_1}{\partial t} - \nabla \cdot (\mu_1 \nabla n_1) + \nabla \cdot \left(\chi n_1 \frac{\nabla c}{c} \right) = 0 \qquad (0.1)$$

$$\frac{\partial n_3}{\partial t} - \nabla \cdot (\mu_3 \nabla n_3) + F(n_3, c^*) n_1 = 0 \qquad (0.2)$$

$$\frac{\partial c}{\partial t} - \nabla \cdot (\mu_2 \nabla c) + \alpha n_1 c - f(n_3) n_3 = 0 \qquad (0.3)$$

$$n_1(x,0) = n_{1,0}(x), n_3(x,0) = n_{3,0}(x), c(x,0) = c_{1,0}(x). \qquad (0.4)$$

2. Constitutive equations $F, f, \alpha n_1 c$, which link cellular functions and chemical, which essential came from kinetic system compartmental dynamic equations

This lead to the system (linear or quasi-linear, degenerate) of parabolic equation with respect to the functions which represent players of the interest in divergent form.

Remark 1

The authors, understood flaws of the proposed model. Evidently, we need more data and experiments to examine the thought experiment. Maybe it too ambitious, one can compare this with so-called root pressure theory, where methods of interpretation exist for many decades, but we still need more experiments in order to understand why high tree can transport water to the top towards leafs The Einstein's thought experiment provide possible answer on this question. Namely, assume during time interval T_0 *channels due to capillary pressure transport water from the roots to the hight of the tree on the level* H_0*. Then it will "widen up" due to diffusion across the channels inside three in all directions and create mini-reservoir* U_0 *of the hight of tree of about* H_0*. Then process of transport will continue to the next level* H_1 *and so on. Of course one will need more experimental conformation of this hypothetical process, we just humbly put forth the ideas for the scientific community to examine.*

We will start with Einstein saying

Logic will get you from A to Z; imagination will get youeverywhere

Let $\rho(x,t)$ be the density at the point $x \in \mathbb{R}^n$ and time $t \in \mathbb{R}$. Let $\tau > 0$ be an input parameter at the time of observation. Let $\zeta \in \mathbb{R}^n$ be the random displacement of the particles. Assume that the probability of the particles moving from location x at time t to location $x+\zeta$, for $\zeta = (\zeta_1, \zeta_2, \ldots, \zeta_n)$, at time $t+\tau$ can be characterized by the probability distribution function $\phi(x,t,\zeta) \geq 0$ with expected value , and standard deviation

$$E_1(n_1, c), \sigma_1, \sigma_2, \sigma_3 \tag{0.5}$$

The Einstein type material balance equation take a form

$$\rho(x, t+\tau) = \int_{\mathbb{R}^n} \rho(x+\zeta, t)\phi(x,t,\zeta)d\zeta + \rho\nabla_x\left(E_1(x,t,\rho,c)\right) \tag{0.6}$$

With τ to be parameter such that one has an approximate formula

$$\frac{\partial\rho(x,t)}{\partial t} \approx \frac{1}{\tau}(\rho(x,t+\tau) - \rho(x,t)). \tag{0.7}$$

We will calculate $\rho(x, t+\tau)$ on the right-hand side of (0.7) by the material balance (0.6).

Derivation PDE

Assume the function $\zeta \mapsto \phi(x, t, \zeta)$ is supported in a small ball centered at the origin. By the Taylor's

$$\rho(x+\zeta, t) \approx \rho(x, t) + \zeta \cdot \nabla \rho(x, t) + \frac{1}{2} \sum_{i,j=1}^{n} \zeta_i \zeta_j \frac{\partial^2 \rho(x, t)}{\partial x_i \partial x_j}.$$

Then using (0.6), we can approximate

$$\rho(x, t+\tau) \approx \rho(x, t) + E(x, t) \cdot \nabla \rho(x, t) + \frac{1}{2} \sum_{i,j=1}^{n} \bar{a}_{ij}(x, t) \frac{\partial^2 \rho(x, t)}{\partial x_i \partial x_j}, \quad (0.8)$$

$$E(x, t) = \int_{\mathbb{R}^n} \phi(x, t, \zeta) \zeta d\zeta, \quad (0.9)$$

$$\bar{a}_{ij}(x, t) = \int_{\mathbb{R}^n} \zeta_i \zeta_j \phi(x, t, \zeta) \zeta \text{ for } i, j = 1, \cdots, n \quad (0.10)$$

Chemotactic system (Simplest one) all coefficients are constants

$$\frac{\partial n_1}{\partial t} - \nabla \cdot (\mu_1 \nabla n_1) + \nabla \cdot \left(\chi n_1 \frac{\nabla c}{c} \right) = 0 \quad (0.11)$$

$$\frac{\partial n_3}{\partial t} - \nabla \cdot (\mu_3 \nabla n_3) + F(n_3, c^*) n_1 = 0 \quad (0.12)$$

$$\frac{\partial c}{\partial t} - \nabla \cdot (\mu_2 \nabla c) + \alpha n_1 c - f(n_3) n_3 = 0 \quad (0.13)$$

$$n_1(x,0) = n_{1,0}(x), n_3(x,0) = n_{3,0}(x), c(x,0) = c_{1,0}(x). \quad (0.14)$$

BC

$$\frac{\partial n_1}{\partial \nu} = -\beta_1 H(c - c^*), \frac{\partial n_3}{\partial \nu} = \frac{\partial c}{\partial \nu} = 0 \text{ on } \Gamma_1 \quad (0.15)$$

$$\frac{\partial n_1}{\partial \nu} = \frac{\partial n_3}{\partial \nu} = \frac{\partial c}{\partial \nu} = 0 \text{ on on } \Gamma_2 \quad (0.16)$$

$$\partial U = \Gamma_1 \cup \Gamma_2 \quad (0.17)$$

Here $H = \begin{cases} 0 & c \leq c^* \\ 1 & c > c^* \end{cases}$ -Heaviside function

Using standard technic for linearized equation around equilibrium point $n_{1,e}, n_{3,e}, c_e$ for functions $u = n_1 - n_{1,e}, v = n_2 - n_{2,e}, v = c - c_e$ we will get the following linear IBVP for the system of parabolic PDE

$$\frac{\partial u}{\partial t} - \mu_1 \Delta u + \chi \Delta w = 0 \tag{0.18}$$

$$\frac{\partial v}{\partial t} - \mu_1 \Delta v + \Psi v = 0 \tag{0.19}$$

$$\frac{\partial c}{\partial t} - \nu_1 \Delta + \alpha w + \beta u - G v = 0 \tag{0.20}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = \frac{\partial w}{\partial \nu} = 0 \text{ on } \partial U \tag{0.21}$$

$$u(x,0) = u_0 \phi_\lambda \ ; \ v(x,0) = v_0 \phi_\lambda ; w(x,0) = w_0 \phi_\lambda . \tag{0.22}$$

Here

$$\chi = \chi \frac{n_{1,e}}{c_{1,e}}, \Psi = -F(n_{3,e}, c_*), \alpha = \alpha n_{1,e} \tag{0.23}$$

$$\beta = \alpha n_{1,e}, \text{and } G = f(n_{3,e)}) + f'(n_{3,e)}) n_{3,e} \tag{0.24}$$

Main Biological Theorem, Based on Simplified System of three Equation

By using assumption that non trivial solution of the above system has a form

$$u = u_0\phi_\lambda e^{\sigma t}, v = v_0\phi_\lambda e^{\sigma t}, w = w_0\phi_\lambda e^{\sigma t}$$

Goal is to find conditions on parameters of the system such that exits u_0, v_0, w_0 such that one can provide biologically meaningful answer: When linearized system is definitely stable<unstable, and we do not know. Letting $\Psi = F(n_{3,e})n_{1,e}$ One of the conclusion is as follows letting If

$$\Psi > 0 \text{ increase in debris results in diminished immune response} \tag{0.25}$$

$$\Psi < 0 \text{ increase in debris increases in healthy immune response} \tag{0.26}$$

$$\Psi = 0 \quad \text{immune cells do not respond to changes in the debris} \tag{0.27}$$

Thank you

Remark 2

1. *Thanks to* (9), *Since* $\tau > 0$ *the matrix* $A(x, t)$ *positive defined*
2. *If* $\zeta \mapsto \phi(x, t, \zeta)$ *is an even function, then, by* (9), $E(x, t) = 0$ *and we have*
$$\frac{\partial \rho}{\partial t} = \sum_{i,j=1}^{n} a_{ij} \frac{\partial^2 \rho}{\partial x_i \partial x_j}. \tag{0.28}$$
3. *Consider the case of mutually independent events with respect to the coordinates of the displacement* ζ*, that is,*
$$\phi(x, t, \zeta) = \phi_1(x, t, \zeta_1) \cdots \phi_n(x, t, \zeta_n), \tag{0.29}$$
$\phi_i(x, t, \zeta_i)$ *being a probability distribution function in the variable* $\zeta_i \in \mathbb{R}$*, Then*
$$\bar{a}_{ij} = \begin{cases} \bar{\sigma}_i \bar{\sigma}_j, & \text{for } i \neq j, \\ \bar{\sigma}_{i,i}^2, & \text{for } i = j, \end{cases} \tag{0.30}$$

where

Continue Remark 1

Remark 3

$$\bar{\sigma}_i(x,t) = \int_{\mathbb{R}^n} s\phi_i(x,t,s)ds, \bar{\sigma}_{i,i}(x,t) = \left(\int_{\mathbb{R}^n} s^2\phi_i(x,t,s)ds\right)^{1/2}. \tag{0.31}$$

Assume, in addition that each function $\phi_i(x,t,s)$, *for* $1 \le i \le n$, *is even in* $s \in \mathbb{R}$. *Then each* $\sigma_i = 0$, *and, hence,* $\bar{A}(x,t)$ *is the diagonal matrix* $\mathrm{diag}[\bar{\sigma}^2_{1,1}, \bar{\sigma}^2_{2,2}, \ldots, \bar{\sigma}^2_{n,n}]$.
Moreover, one finds that the function $\zeta \mapsto \phi(x,t,\zeta)$ *is even, then, by part 2, equation* (3) *becomes*

$$\frac{\partial \rho}{\partial t} = \sum_{i=1}^{n} \frac{\bar{\sigma}^2_{i,i}}{2\tau} \cdot \frac{\partial^2 \rho}{\partial x_i^2}. \tag{0.32}$$

Main Hypotheses On Expected Value for Macrophages Movement

$E(x,t)$ is the expected displacement from location x between the time t and $t+\tau$. Thus, $E(x,t)/\tau$ is the quotient

$$\frac{\text{average displacement}}{\text{time of travel}}$$

which can be seen as the average velocity. Therefore, with small τ, we can approximate this quotient $E(x,t)/\tau$ by the velocity $v(x,t)$ of the macrophages transport However, we will assume a much more general relation

Hypothesis 1

There is a dimensionless $n \times n$ matrix $M_0(x,t)$ such that

$$M(x,t) \cdot \frac{\nabla c}{c} = \frac{E(x,t)}{\tau}. \tag{0.33}$$

and

$$\xi^{\mathrm{T}} M_0(x,t)\xi \geq 0 \textit{ for all } \xi \in \mathbb{R}^n. \tag{0.34}$$

More on Main Hypothesis

The main hypothesis indicates that the velocity of the fluid $v(x,t)$ and the quotient $E(x,t)/\tau$ have some "alignment", that is,

$$v(x,t) \cdot \frac{E(x,t)}{\tau} \geq 0. \tag{0.35}$$

This is our fundamental assumption. It links the microscopic feature of the particles' movement in the media with the macroscopic property of the fluid flow – the velocity of the fluid to be exact in this case. This will lead us to main PDE

$$\frac{\partial \rho}{\partial t} = \langle A(x,t), D^2\rho \rangle + (M_0(x,t)v(x,t)) \cdot \nabla \rho. \tag{0.36}$$

In this equation, the term $\langle A(x,t), D^2\rho \rangle$ represents the diffusion in the non-divergence form, and the term $(M_0(x,t)v(x,t)) \cdot \nabla \rho$ represents the transport/convection.

Darcy-type constitutive equation with gravity

Assume the anisotropic Darcy's

$$v = -\bar{K}(x,t)\left(\nabla\rho + \vec{F}(\rho)\right) = \tag{0.37}$$

equation
where $\bar{K}(x,t)$ is an $n \times n$ matrix, and $\vec{g}$ is the gravitational acceleration for $n = 1, 2, 3$, and can be any constant vector for $n \geq 4$. Combining (17) with (18) yields

$$\frac{\partial\rho}{\partial t} = \langle A(x,t), D^2\rho\rangle - (K_0(x,t)\nabla\rho)\cdot\nabla\rho + \rho B_0(x,t)\cdot\nabla\rho, \tag{0.38}$$

where

$$K_0(x,t) = M_0(x,t)\bar{K}(x,t), \quad B_0(x,t) = M_0(x,t)\bar{K}(x,t)\vec{g}. \tag{0.39}$$

Next, we use equations of state to relate the pressure p and density ρ in (18).

From Darcy type equation to PDE for Density function

In the next , we will focus entirely on the mathematical aspect of of the property of density function($Lu \leq\geq 0$), here.

$$Lu = \frac{\partial u}{\partial t} - \langle A(x,t), D^2 u \rangle + uB(x,t) \cdot \nabla u + P'(u)(K(x,t)\nabla u) \cdot \nabla u \quad (0.40)$$

Theorem 1 (Maximum principle)

Assume

$$u \in C(\overline{U_T}) \cap C^{2,1}_{x,t}(U_T) \text{ and } u(U_T) \subset J. \tag{0.41}$$

Then If $Lu \leq 0$ on U_T, then

$$\max_{\overline{U_T}} u = \max_{\Gamma_T} u. \tag{0.42}$$

If $Lu \geq 0$ on U_T, then

$$min_{\overline{U_T}} u = \min_{\Gamma_T} u. \tag{0.43}$$

Theorem 2 (Strong Maximum principle)

Assume $A(x,t)$ and $B(x,t)$ and $K(x,t)$ satisfies standard assumptions condition Suppose u is bounded on U_T, and $Lu \leq 0$ (respectively, $Lu \geq 0$) on U_T. Let

$$M = \sup_{U_T} u(x,t) \text{ (respectively, } m = \inf_{U_T} u(x,t).)$$

Assume there is $(x_0, t_0) \in U_T$ such that

$$u(x_0, t_0) = M \quad (\text{respectively, } u(x_0, t_0) = m.) \tag{0.44}$$

Truncated Linearization

To remove the quadratic terms of the gradient, we introduce the following transformation of the Bernstein–Cole–Hopf type.
For a given function u, we define an operator $\mathcal{L}$ as follows

$$\mathcal{L}w = \frac{\partial w}{\partial t} - \langle A(x,t), D^2 w \rangle + u(x,t)B(x,t) \cdot \nabla w. \tag{0.46}$$

Note that $\mathcal{L}$ is a linear operator in w for each given function u.

Main Linearization Lemma

Lemma 3

Let

$$F_\lambda(s) = C \int_{s_0}^{s} e^{\lambda P(z)} dz + C' \text{ for } s \in J. \tag{0.47}$$

1. *Assume there is a constant* $c_1 \geq 0$ *such that*

   $$\xi^{\mathrm{T}} K(x,t)\xi \geq -c_1|\xi|^2 \text{ for all } (x,t) \in U_T \tag{0.48}$$

   If $Lu \leq 0$ *on* U_T*, then for any numbers* $\lambda \geq c_1/c_0$, $C > 0$*,the function* $w = F_\lambda(u)$ *satisfies* $\mathcal{L}w \leq 0$ *on* U_T*.*

2. *Assume there is a constant* $c_2 \geq 0$ *such that*

   $$\xi^{\mathrm{T}} K(x,t)\xi \leq c_2|\xi|^2 \tag{0.49}$$

   If $Lu \geq 0$ *on* U_T*, then for any numbers* $\lambda \leq -c_2/c_0$, $C > 0$*, the function* $w = F_\lambda(u)$ *satisfies* $\mathcal{L}w \geq 0$ *on* U_T*.*

Given $T > 0$, let U_T and Γ_T be "cylindrical".

Assumption 1

Let $A : U_T \to \mathcal{M}^{n\times n}_{\text{sym}}$ *and* $b : U_T \to \mathbb{R}^n$ *be such that*

- label= A *to be elliptic, for some constant* $c_0 > 0$, *and*
- label= *there are constants* $M_1 > 0$ *and* $M_2 \geq 0$ *such that*

$$\mathrm{Tr}(A(x,t)) \leq M_1, \quad |b(x,t)| \leq M_2 \text{ for all } (x,t) \in U_T. \tag{0.50}$$

Define the linear operator $\widetilde{L}$ by

$$\widetilde{L}w = w_t - \langle A(x,t), D^2 w\rangle + b(x,t)\cdot\nabla w \text{ for } w \in C^{2,1}_{x,t}(U_T). \tag{0.51}$$

Lemma 4 (Lemma of Growth)

$$\beta = \frac{1}{4c_0}\max\left\{2(M_1 + M_2 R), \frac{R^2}{T}\right\}, \quad T_* = \frac{R^2}{4c_0\beta}, \quad \eta_* = 1 - (r_0/R)^{2\beta}. \tag{0.52}$$

If $\widetilde{L}w \leq 0$ *on* U_T *and* $w \leq 0$ *on* $\Gamma \times [0,T]$, *then one has*

$$\max\{0, \max_{x\in\bar{U}} w(x,T_*)\} \leq \eta_* \max\{0, \max_{x\in\bar{U}} w(x,0)\}. \tag{0.53}$$

Main Asymptotic Nonlinear Equation

We study the following initial boundary value problem

$$\begin{cases} \dfrac{\partial u}{\partial t} - \langle A, D^2 u\rangle + uB\cdot\nabla u + P'(u)(K\nabla u)\cdot\nabla u = 0, & \text{on } U\times(0,\infty),\\ u(x,t) = u_*, & \text{on } \Gamma\times(0,\infty),\\ u(x,0) = u_0(x), & \text{on } U, \end{cases}$$

Theorem 5

- *If $m_*, M_* \in J$, then there exist a number $C_0 > 0$ depending on c_0, c_1, c_2, M_0, M_1, m_*, M_*, and a number $\nu > 0$ depending on c_0, M_0, M_1, m_*, M_* such that*

$$\max_{x\in\bar U}|u(x,t) - u_*| \le C_0 e^{-\nu t}\max_{x\in\bar U}|u_0(x) - u_*| \quad \textit{for } t\ge 0. \tag{0.54}$$

-

$$\limsup_{t\to\infty}\max_{x\in\bar U} u(x,t) \le u_*. \tag{0.55}$$

If, in addition, $u_* = m_*$, then

$$\lim_{t\to\infty}\max_{x\in\bar U}|u(x,t) - u_*| = 0. \tag{0.56}$$

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$$\liminf_{t\to\infty}\min_{x\in\bar U} u(x,t) \ge u_*. \tag{0.57}$$

If, in addition, $u_* = M_*$, then one has (0.56).

Possible application of the rigorous mathematics

1. Probabilistic(Einstein) Method for density evaluation w.r.t. depth(Solution is different from linear one)
2. Paleontology problem-Age of the ammonite evaluation through the asymptotic behavior of the density

Geometrical Scheme

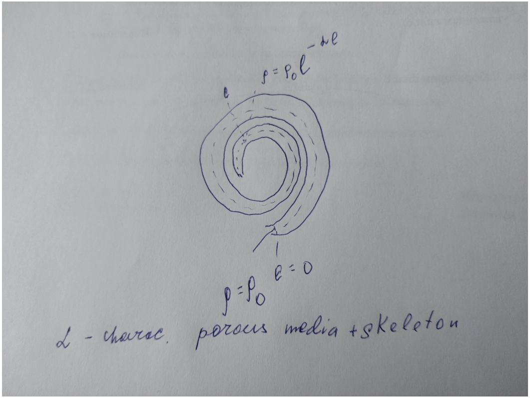

Figure 2: Geometrical Scheme

End for To Day

THANK YOU!!!