A Mathematical Model of Atherogenesis

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Atherogenesis

Atherosclerosis is characterized by the formation of fatty lesions in the walls of muscular arteries.

Macrophages, phagocytic immune cells, attempt to take up oxidized low density lipoproteins (oxLDL).

This process interrupts normal immune function—as macrophages accumulate lipids through failed phagocytosis becoming foam cells—and may trigger a dysfunctional, chronic inflammatory response.
Muscular arteries are like multilayered tubes. At the interface with the blood flow, there is a monolayer of endothelial cells. These are the arbiters of transport of cells and chemicals between blood flow and the artery wall. Large vessels may also have their own vessel network called the *vaso vasorum* as a secondary source of cellular and chemical material. Atherosclerosis occurs in the subendothelial intima.
Initiation of plaque formation

(a) Endothelial cells facilitate transfer of immune cells and LDL. (b) Foam cell formation results in a fatty streak.

Figure adapted by Salim Maa Bared (2005) from Ross (1999).
The model consist of a pair of coupled process:

Species Tracked: $I$: Immune cells, $D$: Debris (lesion content), and $C$: Chemo-attractant (positive chemotaxis inducing agents)

### Immune Response

- Monocytes enter into the tissue in response to chemical stimuli where they differentiate into macrophages.

- The immune cells defend against pathogens, aid in apoptosis, and regulate healing processes. In chronic inflammatory processes, dysfunctional immune cell response may lead to tissue damage—or as in atherosclerosis, foam cell and lesion development.

- The presence of oxidatively modified LDL cholesterol is implicated in triggering a failure of scavenger receptor down regulation and subsequent increase in inflammatory properties of macrophages.
The model consist of a pair of coupled process:

Species Tracked: $\mathcal{L}$: Native LDL, $\mathcal{L}_{\text{ox}}$: Modified LDL, and $\mathcal{R}$: Reactive Oxygen Species

**Lipid Chemistry**

- LDL particles enter the intima through the endothelium where their size and structure inhibit reverse transport.
- The particles are then vulnerable to oxidative modification by reactive oxygen species (abundant in the tissue as a byproduct of metabolic processes).
- A two-way chemical process may occur if anti-oxidant species are also present.
- If oxidation of the lipid core occurs, the resulting oxidized LDL stimulates an immune response with the potential for inciting chronic inflammation.
Factors to be modeled

The mathematical model is constructed by mass balance and consideration of the primary disease features of:

- motility of cells and diffusion
- cellular and chemical interactions (e.g. secretion, signal reading)
- cell-cell interactions (e.g. foam cell formation, immune function)
- chemical reactions (e.g. oxidation of lipids)
The domain of interest is a deformed cylinder representing the intima $\Omega$ bounded by the endothelium $\Gamma_I$ at the lumen and the internal elastic lamina $\Gamma_O$ at the tunica media.
The chemotactic response of immune cells is modeled in the interior of the domain ($\Omega$) via a Keller-Segal-Patlak flux, and at the endothelial interface ($\Gamma_I$) via a coupled third type boundary condition.

Immune Cell Flux (interior $\Omega$): \[ J_I = -\mu_I \nabla I + \chi(I, C) \nabla C \]

Boundary Transport (at endothelium $\Gamma_I$): \[ J_I \cdot n = -\alpha(C) \]

Here, $\alpha$ is a nonnegative monotone function of the chemoattractant $C$, and $\chi$ is a nonnegative *chemotactic sensitivity function* that may depend on both immune cells and chemoattractant concentration.
Governing Equations in the Sub-endothelial Intima

\[
\frac{\partial I}{\partial t} = \mu_I \nabla^2 I - \nabla \cdot (\chi(I, C) \nabla C) - aID - d_1 I - cIL_{ox} + M\phi
\]  

(1)

\[
\frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2 D - \hat{a}ID + \hat{c}IL_{ox}
\]  

(2)

\[
\frac{\partial C}{\partial t} = \mu_C \nabla^2 C - eCI - d_3 C + pD
\]  

(3)

\[
\frac{\partial L}{\partial t} = \mu_L \nabla^2 L - a_{46} k_R L R + k_A A_{ox} r L_{ox} - d_4 L + pL
\]  

(4)

\[
\frac{\partial L_{ox}}{\partial t} = \mu_{L_{ox}} \nabla^2 L_{ox} + c_{46} k_{R_0} L R - A_{ox} r L_{ox} - fIL_{ox}
\]  

(5)

\[
\frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46} k_R L R - hA_{ox} R + pR
\]  

(6)
Governing Equations in the Sub-endothelial Intima

\[
\frac{\partial I}{\partial t} = \mu_I \nabla^2 I - \nabla \cdot (\chi(I, C) \nabla C) - aID - d_1I - cIL_{ox} + M\phi \tag{1}
\]

\[
\frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2D - \hat{a}ID + \hat{c}IL_{ox} \tag{2}
\]

\[
\frac{\partial C}{\partial t} = \mu_C \nabla^2 C - eCI - d_3C + pD \tag{3}
\]

\[
\frac{\partial L}{\partial t} = \mu_L \nabla^2 L - a_{46}k_RL_R + k_AA_{ox}rL_{ox} - d_4L + p_L \tag{4}
\]

\[
\frac{\partial L_{ox}}{\partial t} = \mu_{L_{ox}} \nabla^2 L_{ox} + c_{46}k_{R_0}L_R - A_{ox}rL_{ox} - fIL_{ox} \tag{5}
\]

\[
\frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46}k_RL_R - hA_{ox}R + p_R \tag{6}
\]
Governing Equations in the Sub-endothelial Intima

\[
\frac{\partial I}{\partial t} = \mu_I \nabla^2 I - \nabla \cdot (\chi(I, C) \nabla C) - aID - d_1 I - cIL_{ox} + M\phi \tag{1}
\]

\[
\frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2 D - \hat{a}ID + \hat{c}IL_{ox} \tag{2}
\]

\[
\frac{\partial C}{\partial t} = \mu_C \nabla^2 C - eCI - d_3 C + pD \tag{3}
\]

\[
\frac{\partial L}{\partial t} = \mu_L \nabla^2 L - a_{46} k_R L R + k_A A_{ox} rL_{ox} - d_4 L + pL \tag{4}
\]

\[
\frac{\partial L_{ox}}{\partial t} = \mu_{L_{ox}} \nabla^2 L_{ox} + c_{46} k_{R_0} LR - A_{ox} rL_{ox} - fIL_{ox} \tag{5}
\]

\[
\frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46} k_R LR - hA_{ox} R + pR \tag{6}
\]
Governing Equations in the Sub-endothelial Intima

\[ \frac{\partial I}{\partial t} = \mu_1 \nabla^2 I - \nabla \cdot (\chi(I,C) \nabla C) - aID - d_1I - cI\mathcal{L}_{ox} + M\phi \quad (1) \]

\[ \frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2D - \hat{a}ID + \hat{c}I\mathcal{L}_{ox} \quad (2) \]

\[ \frac{\partial C}{\partial t} = \mu_C \nabla^2 C - eCI - d_3C + pD \quad (3) \]

\[ \frac{\partial \mathcal{L}}{\partial t} = \mu_L \nabla^2 \mathcal{L} - a_{46}k_R \mathcal{L}R + k_A A_{ox} r \mathcal{L}_{ox} - d_4\mathcal{L} + p\mathcal{L} \quad (4) \]

\[ \frac{\partial \mathcal{L}_{ox}}{\partial t} = \mu_{L_{ox}} \nabla^2 \mathcal{L}_{ox} + c_{46}k_{R_0} \mathcal{L}R - A_{ox} r \mathcal{L}_{ox} - fI\mathcal{L}_{ox} \quad (5) \]

\[ \frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46}k_R \mathcal{L}R - hA_{ox} R + pR \quad (6) \]
Governing Equations in the Sub-endothelial Intima

\[
\begin{align*}
\frac{\partial I}{\partial t} &= \mu_I \nabla^2 I - \nabla \cdot (\chi(I, C) \nabla C) - aID - d_1I - cIL_{ox} + M\phi \\
\frac{\partial D}{\partial t} &= \mu_D \nabla^2 D - d_2D - \hat{a}ID + \hat{c}IL_{ox} \\
\frac{\partial C}{\partial t} &= \mu_C \nabla^2 C - eCI - d_3C + pD \\
\frac{\partial L}{\partial t} &= \mu_L \nabla^2 L - a_{46}k_R \mathcal{L}R + k_A A_{ox} rL_{ox} - d_4L + p\mathcal{L} \\
\frac{\partial L_{ox}}{\partial t} &= \mu_{L_{ox}} \nabla^2 L_{ox} + c_{46}k_{R_0} \mathcal{L}R - A_{ox} rL_{ox} - fIL_{ox} \\
\frac{\partial R}{\partial t} &= \mu_R \nabla^2 R - b_{46}k_R \mathcal{L}R - hA_{ox} R + pR
\end{align*}
\]
Governing Equations in the Sub-endothelial Intima

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\frac{\partial I}{\partial t} = \mu_I \nabla^2 I - \nabla \cdot (\chi(I,C) \nabla C) - aID - d_1I - cIL_{ox} + M\phi \\
\frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2D - \hat{a}ID + \hat{c}IL_{ox} \\
\frac{\partial C}{\partial t} = \mu_C \nabla^2 C - eCI - d_3C + pD \\
\frac{\partial L}{\partial t} = \mu_L \nabla^2 L - a_{46}k_R LR + k_A A_{ox} rL_{ox} - d_4L + pL \\
\frac{\partial L_{ox}}{\partial t} = \mu_{L_{ox}} \nabla^2 L_{ox} + c_{46}k_{R_0} LR - A_{ox} rL_{ox} - fIL_{ox} \\
\frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46}k_R LR - hA_{ox} R + pR
\]
Governing Equations in the Sub-endothelial Intima

\[ \frac{\partial I}{\partial t} = \mu_I \nabla^2 I - \nabla \cdot (\chi(I,C) \nabla C) - aID - d_1 I - cIL_{ox} + M\phi \]  \hspace{1cm} (1)

\[ \frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2 D - \hat{a}ID + \hat{c}IL_{ox} \]  \hspace{1cm} (2)

\[ \frac{\partial C}{\partial t} = \mu_C \nabla^2 C - eCI - d_3 C + pD \]  \hspace{1cm} (3)

\[ \frac{\partial L}{\partial t} = \mu_L \nabla^2 L - a_{46} k_R L R + k_A A_{ox} rL_{ox} - d_4 L + p_L \]  \hspace{1cm} (4)

\[ \frac{\partial L_{ox}}{\partial t} = \mu_{L_{ox}} \nabla^2 L_{ox} + c_{46} k_{R_0} LR - A_{ox} rL_{ox} - fIL_{ox} \]  \hspace{1cm} (5)

\[ \frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46} k_R LR - hA_{ox} R + p_R \]  \hspace{1cm} (6)
Governing Equations in the Sub-endothelial Intima

\[
\frac{\partial I}{\partial t} = \mu_I \nabla^2 I - \nabla \cdot (\chi(I, C) \nabla C) - aID - d_1I - cIL_{ox} + M\phi
\]  

(1)

\[
\frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2D - \hat{a}ID + \hat{c}IL_{ox}
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\]  

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\frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46}k_R L R - hA_{ox} R + pR
\]  

(6)
Governing Equations in the Sub-endothelial Intima

\[ \frac{\partial I}{\partial t} = \mu_I \nabla^2 I - \nabla \cdot (\chi(I,C) \nabla C) - aID - d_1I - cIL_{ox} + M\phi \]  
\[ \frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2D - \hat{a}ID + \hat{c}IL_{ox} \]  
\[ \frac{\partial C}{\partial t} = \mu_C \nabla^2 C - eCI - d_3C + pD \]  
\[ \frac{\partial L}{\partial t} = \mu_L \nabla^2 L - a_{46}k_R L R + k_A A_{ox} rL_{ox} - d_4L + p_L \]  
\[ \frac{\partial L_{ox}}{\partial t} = \mu_{L_{ox}} \nabla^2 L_{ox} + c_{46} k_{R0} L R - A_{ox} rL_{ox} - fIL_{ox} \]  
\[ \frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46}k_R L R - hA_{ox} R + p_R \]
Governing Equations in the Sub-endothelial Intima

\( \frac{\partial I}{\partial t} = \mu_I \nabla^2 I - \nabla \cdot (\chi(I, C) \nabla C) - aID - d_1I - cIL_{ox} + M\phi \) \hspace{1cm} (1)

\( \frac{\partial D}{\partial t} = \mu_D \nabla^2 D - d_2D - \hat{a}ID + \hat{c}IL_{ox} \) \hspace{1cm} (2)

\( \frac{\partial C}{\partial t} = \mu_C \nabla^2 C - eCI - d_3C + pD \) \hspace{1cm} (3)

\( \frac{\partial L}{\partial t} = \mu_L \nabla^2 L - a_{46}k_R L_R + k_A A_{ox} rL_{ox} - d_4L + pL \) \hspace{1cm} (4)

\( \frac{\partial L_{ox}}{\partial t} = \mu_{Lox} \nabla^2 L_{ox} + c_{46}k_{R0} L_R - A_{ox} rL_{ox} - fIL_{ox} \) \hspace{1cm} (5)

\( \frac{\partial R}{\partial t} = \mu_R \nabla^2 R - b_{46}k_R L_R - hA_{ox} R + pR \) \hspace{1cm} (6)
Letting

\[ \vec{U} = (I, D, C, L, L_{ox}, R)^T \]

equations (1)–(6) may be rephrased using the vector formalism

\[ \dot{\vec{U}} = \nabla \cdot \left( C \nabla \vec{U} \right) + f(\vec{U}) \]
Boundary Conditions

Strictly Homogeneous Boundary Conditions

The vaso vasorum serves as the sole source of any species.

\[
\frac{\partial \vec{U}}{\partial n} = 0, \quad \text{on} \quad \Gamma_I \cup \Gamma_O
\]

\[M_\phi > 0, \quad p_L > 0\]
Boundary Conditions

Third Type Boundary Conditions

LDL and chemoattractant transport across the endothelium in response to the chemical potential across the boundary. Immune cells exhibit chemotaxis at the endothelium in response to chemical stimuli at this interface.

\[
\mu_C \frac{\partial C}{\partial n} = -\alpha_C(C - C_*) , \quad \mu_L \frac{\partial L}{\partial n} = -\alpha_L(L - L_B) \\
\mu_I \frac{\partial I}{\partial n} = \hat{\alpha}_I(C) \quad \text{on} \quad \Gamma_I
\]

\(C_*\)–a baseline chemo-attractant level, \(L_B\)–serum LDL level

The remaining species satisfy a no flux condition at the endothelium, and all species satisfy a no flux condition at the internal elastic lamina.
A classical approach to mathematical models of biological phenomena—especially those characterized by pattern formation, morphogenesis, and aggregation is to consider significant state changes as resulting from a mathematical instability.

A general equilibrium state would be a solution of the equation

$$0 = \nabla \cdot \left( C \nabla \bar{u} \right) + f(\bar{u})$$

which need not be spatially uniform.
Spatially Uniform *Healthy* State

We’ll consider the restricted case of spatially uniform equilibria\(^1\)

\[ f(\vec{U}) = 0. \]

An equilibrium state is considered *healthy* state when inflammatory markers are sufficiently negligible. And a perturbation may be interpreted as a potential inflammatory trigger.

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\(^1\)Existence of such a state with \( I = D = C = 0 \) can be shown provided \( C_\ast = 0, \ M_\phi = M_\phi C, \) and \( L = L_B \) at equilibrium.
Stability Analysis

Let

\[ \vec{U}_e = (I_e, D_e, C_e, L_e, L_{ox}, R_e)^T \]

be a uniform equilibrium state. And define the perturbation

\[ u = (u, v, w, z, y, s)^T \]

by

\[ I = I_e + u, \quad D = D_e + v, \quad C = C_e + w, \]
\[ L = L_e + z, \quad L_{ox} = L_{oxe} + y, \quad \text{and} \quad R = R_e + s. \]
Stability Analysis

Linearizing about the steady state, the perturbation $\mathbf{u}$ is subject to the BVP

$$\dot{\mathbf{u}} = \nabla \cdot (\mathbf{C}_e \nabla \mathbf{u}) + \mathbf{M} \mathbf{u}$$  \hspace{1cm} (7)

subject to

$$\frac{\partial \mathbf{u}}{\partial n} = 0 \text{ on } \Gamma_i \cup \Gamma_o$$  \hspace{1cm} (8)

if no species is transported across the endothelium,
Stability Analysis

Linearizing about the steady state, the perturbation $u$ is subject to the BVP

$$\dot{u} = \nabla \cdot (C_e \nabla u) + \Lambda u$$

subject to

$$\frac{\partial u}{\partial n} - \left[ \text{diag} \left( 0, 0, -\frac{\alpha C}{\mu C}, -\frac{\alpha L}{\mu L}, 0, 0 \right) + \frac{\alpha I_0}{\mu I} e_1 e_3^T \right] u = 0 \quad \text{on } \Gamma_I,$$

and

$$\frac{\partial u}{\partial n} = 0 \quad \text{on } \Gamma_O \quad \text{(8)}$$

when immune cells, chemoattractant, and native LDL are subject to flux from the lumen.
Stability Analysis

\[ \mathbf{C}_e = \text{diag} \left( \mu_I, \mu_D, \mu_C, \mu_L, \mu_{L_{ox}}, \mu_R \right) - \chi_e \mathbf{e}_1 \mathbf{e}_3^T \]

The transition matrix

\[
\Lambda = \begin{bmatrix}
-(A + B) & -D & 0 & 0 & -E & 0 \\
-G & -H & 0 & 0 & J & 0 \\
-K & L & -M & 0 & 0 & 0 \\
0 & 0 & 0 & -P_1 & P_2 & -P_3 \\
Q_1 & 0 & 0 & Q_2 & -Q_3 & Q_5 \\
0 & 0 & 0 & -R_1 & 0 & -(R_2 + R_3)
\end{bmatrix}
\]

is the Jacobian of the reaction term \( \partial_{\vec{u}} \mathbf{f} \big|_{\vec{u}_e} \).
Stability Analysis

\[ \mathbf{C}_e = \text{diag} \left( \mu_I, \mu_D, \mu_C, \mu_L, \mu_{L_{\text{ox}}}, \mu_R \right) - \chi e_1 e_3^T \]

The transition matrix

\[ \Lambda = \begin{bmatrix} - (A + B) & -D & 0 & 0 & -E & 0 \\ -G & -H & 0 & 0 & J & 0 \\ -K & L & -M & 0 & 0 & 0 \\ 0 & 0 & 0 & -P_1 & P_2 & -P_3 \\ Q_1 & 0 & 0 & Q_2 & -Q_3 & Q_5 \\ 0 & 0 & 0 & -R_1 & 0 & -(R_2 + R_3) \end{bmatrix} \]

Parameters of particular interest: The motility of immune cells, and diffusivity of chemoattractant, and chemotaxis in the tissue.
Stability Analysis

\[ \mathbf{C}_e = \text{diag} \left( \mu_I, \mu_D, \mu_C, \mu_L, \mu_{L_{ox}}, \mu_R \right) - \chi_e \mathbf{e}_1 \mathbf{e}_3^T \]

The transition matrix

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Parameters of particular interest: Decay of chemoattractant, and any cellular turnover for immune cells or decay of debris that may occur.

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A Mathematical Model of Atherogenesis
Stability Analysis

\[ C_e = \text{diag}(\mu_I, \mu_D, \mu_C, \mu_L, \mu_{L_{ox}}, \mu_R) - \chi e_1 e_3^T \]

The transition matrix

\[ \Lambda = \begin{bmatrix}
-(A + B) & -D & 0 & 0 & -E & 0 \\
-G & -H & 0 & 0 & J & 0 \\
-K & L & -M & 0 & 0 & 0 \\
0 & 0 & 0 & -P_1 & P_2 & -P_3 \\
Q_1 & 0 & 0 & Q_2 & -Q_3 & Q_5 \\
0 & 0 & 0 & -R_1 & 0 & -(R_2 + R_3)
\end{bmatrix} \]

Parameters of particular interest: Anti-oxidant effect on oxLDL \((Q_3)\) and the ROS \((R_3)\), and LDL removal \((P_1)\)
Stability Analysis

\[ C_e = \text{diag}(\mu_I, \mu_D, \mu_C, \mu_L, \mu_{L_{ox}}, \mu_R) - \chi_e e_1 e_3^T \]

The transition matrix

\[
\Lambda = \begin{bmatrix}
-(A + B) & -D & 0 & 0 & -E & 0 \\
-G & -H & 0 & 0 & J & 0 \\
-K & L & -M & 0 & 0 & 0 \\
0 & 0 & 0 & -P_1 & P_2 & -P_3 \\
Q_1 & 0 & 0 & Q_2 & -Q_3 & Q_5 \\
0 & 0 & 0 & -R_1 & 0 & -(R_2 + R_3)
\end{bmatrix}
\]

Parameters of particular interest: Rates of oxidation of lipids (Q_2 & R_1 and (Q_5) and production of chemoattractant (L).
Stability Analysis
Geometric and Boundary Transport Parameters

Additional Geometry \(^2\) Dependent Parameters (introduced via integral inequalities):

(Poincaré Inequality) \[ \int_{\Omega} u^2 \leq \frac{1}{|\Omega|} \left( \int_{\Omega} u \right)^2 + C_p \int_{\Omega} |\nabla u|^2. \]

(Sobolev Trace) \[ \int_{\partial \Omega} u^2 \, ds \leq C_1 \int_{\Omega} (u^2 + |\nabla u|^2) \, dx, \quad \text{and} \]

(General Friedrich) \[ C_2 \int_{\Omega} u^2 \, dx \leq \int_{\Omega} |\nabla u|^2 \, dx + C_3 \int_{\partial \Omega} u^2 \, ds. \]

Boundary Transport Parameters: \( \alpha_1^0 \), \( \alpha_C \) (chemotaxis), and \( \alpha_4 \) (lipid source)

\(^2\) artery length, cross sectional area, boundary surface area, mean diameter
Stability Analysis

A Lyapunov method is employed to establish sufficient conditions for linear asymptotic stability of the equilibrium state.

**Definition of Stability**

The equilibrium state is called asymptotically stable if every solution $u$ of the linearized initial boundary value problem (7), subject to boundary conditions (8), vanishes at infinity in the sense that there exists a positive functional

$$F(u) = \Psi(t) \quad \text{such that} \quad \lim_{t \to \infty} \Psi(t) = 0.$$  

In constructing $F$ we obtain conditions on the parameters that are open to biomedical interpretation.
Obtaining Sufficient Conditions for Stability of an Equilibrium Solution

Stability Result: Zero Transport Across the Endothelium

Stability criteria arise as specific inequalities:

1. $2\mu_I > \chi_e$ and $2\mu_C > \chi_e$ — immune cell motility and chemoattractant diffusion dominate chemotaxis

2. $2A + C_p\mu_I > Q_1 + C_p\chi_e/2$ — cell motility outpaces LDL oxidation and chemotaxis

3. $2M + C_p\mu_C > L + C_p\chi_e/2$ — chemical diffusion outpaces chemoattractant production

4. $2P_1 + 2C_p\mu_L > (P_2 + P_3 + Q_2 + R_1)$ — LDL diffuses or is removed at a rate outpacing free radical attack
Stability Result: With Chemotaxis at the Endothelium

We obtain analogous inequalities with boundary transport effects:

- \( \mu_I > C_1 \left( \alpha_I^0 + \frac{\chi e \alpha_C}{\mu_C} \right) + \frac{\chi e}{2} \) — cell motility and diffusion must overcome chemotaxis in the tissue (\( \chi_e \)) and at the boundary (\( \alpha_I^0, \alpha_C \))

- \( 2A > C_1 \left( \alpha_I^0 + \frac{\chi e \alpha_C}{\mu_C} \right) \) — cell turnover and chemical diffusion (\( \mu_C \)) must overcome chemotaxis in the tissue (\( \chi_e \)) and at the boundary (\( \alpha_I^0, \alpha_C \))

- \( 2M > L + \frac{C_2}{C_3} \alpha_C \left( \frac{\alpha_I^0}{\alpha_C} + \frac{\chi e}{\mu_C} - 2 \right) \) — chemical diffusion must overcome chemoattractant production and boundary flux
Stability Result: With Chemotaxis at the Endothelium

Stability criteria relating to the transport of LDL across the endothelium can be divided into forward transport and reverse transport:

\[ P_1 > C_1 |\alpha_L| + \text{Oxidation Rates}(1 + |\Omega|), \]

when LDL enters from the blood stream into the tissue.

\[ P_1 > 0, \]

when transport is from the tissue to the blood stream.
Stability Result: With Chemotaxis at the Endothelium

Stability criteria relating to the transport of LDL across the endothelium can be divided into forward transport and reverse transport:

\[ P_1 > C_1 |\alpha_L| + \text{Oxidation Rates}(1 + |\Omega|), \]

when LDL enters from the blood stream into the tissue.

\[ P_1 > 0, \]

when transport is from the tissue to the blood stream.
Existence of an Unstable Equilibrium
(in the case of homogeneous boundary conditions)

A General Question
To what extent are the sufficiency criteria *tight*. That is, to what extent must one be violated to ensure that a perturbation will blow up?
Instability of an Equilibrium Solution

Existence of an Unstable Equilibrium
(in the case of homogeneous boundary conditions)

A Specific Question

In particular, if \((L_e, L_{oxe}, R_e)\) is a stable equilibrium of the lipid chemistry equations taken in isolation, under what conditions will \((0, 0, 0, L_e, L_{oxe}, R_e)^a\) be an unstable equilibrium for the full, coupled system?

\(^a\text{Recall that existence of such a state can be shown provided } C_\ast = 0, M\phi = M\phi_0 C, \text{ and } L_e = L_B.\)
Existence of an Unstable Equilibrium

The Critical Role of Anti-oxidants

Suppose \((0, 0, 0, \mathcal{L}_e, \mathcal{L}_{oxe}, \mathcal{R}_e)\) is an equilibrium solution of (7) subject to the homogeneous Neumann condition on the boundary.

Consider the perturbation

\[ u = e^{\sigma t} \phi_\lambda(x) \xi \]

where \(\phi_\lambda\) is an eigenfunction of the negative Laplacian on \(\Omega\) with homogeneous Neumann BC.

The system reduces to the algebraic system

\[ \sigma \xi = (\Lambda - \lambda \mathbf{C}_e) \xi. \]
Existence of an Unstable Equilibrium
The Critical Role of Anti-oxidants

The following asymptotic results are useful:

\[ L_{\text{oxe}} \propto A_{\text{ox}}^{-1}, \quad \text{and} \quad R_e \propto p_R, \quad \text{as} \quad A_{\text{ox}} \to 0^+ \]

and

\[ L_{\text{oxe}} \propto A_{\text{ox}}^{-2}, \quad \text{and} \quad R_e \propto A_{\text{ox}}^{-1}, \quad \text{as} \quad A_{\text{ox}} \to \infty. \]
Instability of an Equilibrium Solution

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The latter ensures that \((\mathcal{L}_e, \mathcal{L}_{\text{oxe}}, \mathcal{R}_e)\) can always be made a stable equilibrium of the lipid chemistry process alone by taking \(A_{\text{ox}}\) sufficiently large.
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\[ \mathcal{L}_{oxe} \propto A_{ox}^{-2}, \quad \text{and} \quad R_e \propto A_{ox}^{-1}, \quad \text{as} \quad A_{ox} \to \infty. \]

The former ensures that an eigenvalue \( \sigma \) with positive real part will exist whenever

\[ (\lambda \mu_D + d_2)(\lambda \mu_C + d_3) < (\lambda \chi_e - M\phi_0) \left( \frac{(c + f)p}{c} \right). \]

As the anti-oxidant level vanishes, the equilibrium can always be driven to be unstable by sufficiently large chemotactic sensitivity \( \chi_e \).
We’ve considered linear asymptotic stability of a spatially uniform equilibrium state of a model of atherogenesis with a perturbation interpreted as an inflammation trigger.

Both positive stability, in the sense of sufficient conditions for stability, and negative stability, in the sense of necessary and sufficient conditions for existence of a growing perturbation, have been obtained.

The positive stability criteria in particular appear as testable inequalities involving parameters that may be measurable.

Geometric effects are accounted for in a limited way. However mechanical properties of the tissue—including structural changes induced by disease progression—do not enter into the simple model considered herein.
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