Challenges in Understanding Atherosclerotic Plaque Rupture: a Mathematical Modeling Strategy

Jon Bell, UMBC

Introduction

- Cardiovascular disease affects 80 million Americans (2006 data)[1] 2200 Americans die of cardiovascular disease every day (2008)[2] 6% of adult population (US, 2010) had coronary heart disease[3]

- A common form of cardiovascular disease is atherosclerosis

- Atherosclerosis is an inflammatory disease of large and medium arteries due to fatty lesions containing cholesterol and cell debris in the arterial wall

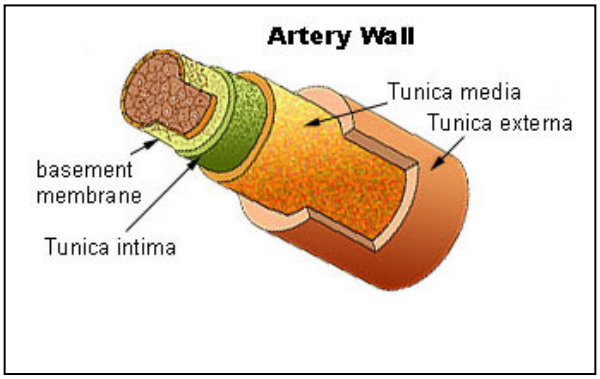
- Doctors now believe that rupture of certain plaques ("vulnerable" or unstable plaques) are responsible for most deaths

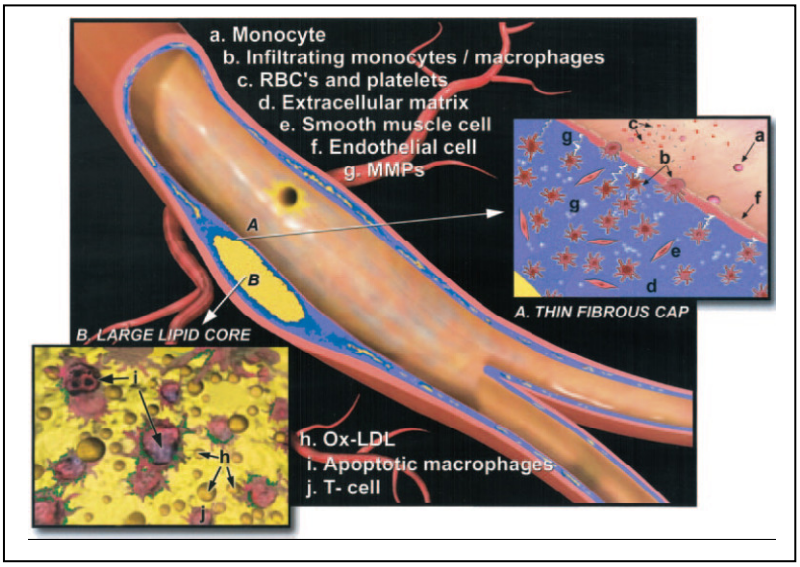
- If the artery is associated with the heart, rupture causes myocardial infarction; if associated with the brain, a stroke can result; other vulnerable areas include kidney and liver destruction, etc.

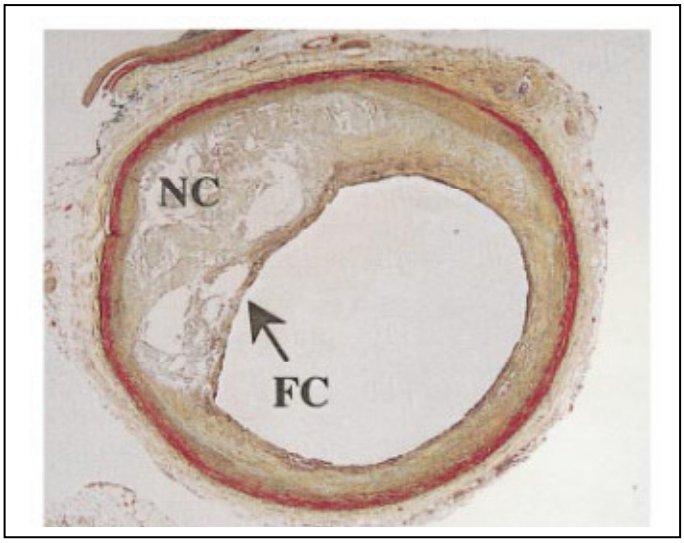
[1] American Heart Association
[2] Roger, et al, 2012
[3] CDC report

Arterial Plaques

- A plaque is a lesion that develops in the arterial wall layer, intima
- It is made up of immune cells, cell debris, lipids (cholesterol, fatty acids, …), fibrous connective tissue, etc
- Arterial plaque formation and growth involves complex chemical, hemodynamic, and biomechanical processes
- There are two types of plaques: stable plaques and unstable plaques (vulnerable plaques (VP), thin-cap fibroatheromas)





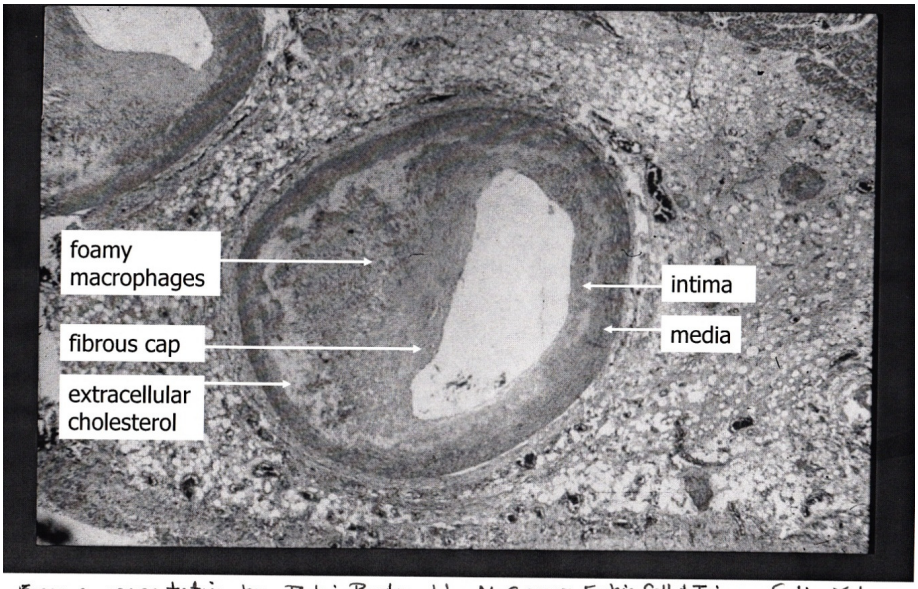


Talk Outline

- Some biology background
- A general modeling approach (hierarchical modeling)
- Preliminary report on 3 models and some mathematical analysis
- Further comments and potential projects

Characteristics of Vulnerable Plaques

- Large lipid core: more than 40% of the plaque volume
- Thin fibrous cap with little collagen fibers, cap thickness < 65 μm
- Ratio of plaque area occupied by lipid components (macrophages and extracellular lipids) versus fibromuscular components (smooth muscle cells and collagen) is large



From a presentation by Robin Poston, John McGregor, Sophia Collot-Teixera, Saliya Yilmaz
Cardiovascular Division, King's College, London

Other Characteristics of Vulnerable Plaques

- Large number of inflammatory cells, macrophages, foam cells, T-lymphocytes
- Endothelial denudation with platelet aggregation
- Outward (positive) remodeling
- Inward (negative) remodeling causing stenosis (partial blood flow blockage), and hence variable shear stress on endothelial layer and cap

Main Players in Our Story

- Monocytes and macrophages
- Foam cells
- Smooth muscle cells
- Endothelial cells and cell layer
- Low density lipoproteins (LDLs) and oxidized LDLs (ox-LDLs)
- Extracellular matrix (ECM) material
- Matrix metalloproteinases (mmps)
- Various cytokines (TGF-β, TNF-α, IL-1, PDGF, etc.)

Other Players

- T-cells, antigen-presenting cells, HDLs, adhesion molecules, calcified macrophages, …

Comments

Knowledge of when a plaque will become vulnerable is still lacking. Vulnerable lesions cannot be characterized by currently available imaging techniques prior to rupture

Present imaging modalities:

Ultrasound (IVUS),

Light (optical cohence tomography, angioscopy, near infrared spectroscopy)

Magnetic (MRI)

Electronic (electron beam resonance imaging), heat (thermography)

Mathematical models of plaque development take the form of ODEs and PDEs

- **For ODEs** (like Bulelzai and Dubbeldam, 2012; Ougrinovskaia, et al, 2010; Bulelzai, et al, 2011), authors study the interaction of macrophages and foam cells inside plaque; early genesis of lesion dynamics, LDL to oxidized LDL dynamics, etc.

- **For PDE models** (like Fok, 2011; Ibragimov, et al, 2005, 2010; El Khatib, et al, 2012), consider cell densities in arterial cross-sections, the goal being to mimic the main features of plaques such as necrotic or lipid core development.

- Some authors (like Calvez, et al 2010; Li, et all, 2000; Thompson, et al, 2012; Vengrenyuk, et al, 2006) couple hemodynamics to transport different cell populations and chemical species

Author	LDL	oxidized LDL	macro-phages	smooth muscle cells	foam cells/debris	Chemo-attractors	Other variables	Comments
Ibragimov, et al, 2007	x	x	x	x	x	x		PDE
Bulelzai, el al, 2011		x	x		x		monocytes	ODE
Calvez, et al, 2010	x	x			x	x	biomass	Fluid model, PDE
Calvez, et al, 2009		x	x		x	x	biomass	PDE
Cobbold, et al, 2002	x	x					Free radicals	ODE L->oxLDL
El Khatib, et al, 2012			x			x	M=macro+ mono+foam	PDE
Ibragimov, et al, 2010	x	x	x		x	x	Free radicals	PDE
Bell	x	x	x	x	x	x	mmp, R	ODE, PDE
McKay, et al, unpublished	x	x	x	x		x	HDL, mono, T-cells, prolif factor necrotic core, ECM	ODE
Ougrinovskaia, et al, 2010	x		x		x			ODE
Zohdi, et al, 2004	x	x	x				Shear stress	Computer model
Fok, 2011		x	x		x		oxygen	PDE

Reduced Model of Plaque Development

- Some insult (injury) to endothelial layer (EL) ⇒ inflammatory response, perhaps triggered by **LDL** excess

- Once in intima, **LDL**s ⇒ **ox-LDLs,** i.e. **LDLs** are rapidly oxidized by **free radicals**

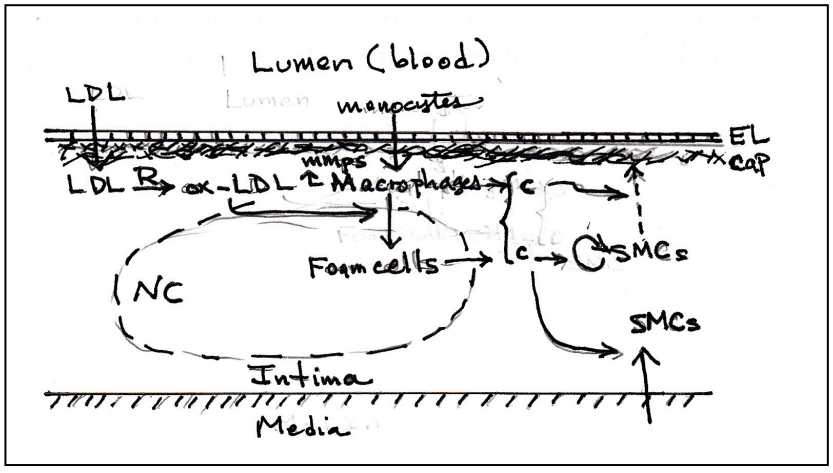
- **Endothelial cells** (ECs) display adhesion molecules that latch onto **monocytes** and other immune cells in lumen. Secreted chemo-attractants lure monocytes into intima that quickly mature into **macrophages**. Macrophages have scavenger receptors that ingest ox-LDLs

- The result is that macrophages turn into lipid-rich **foam cells**

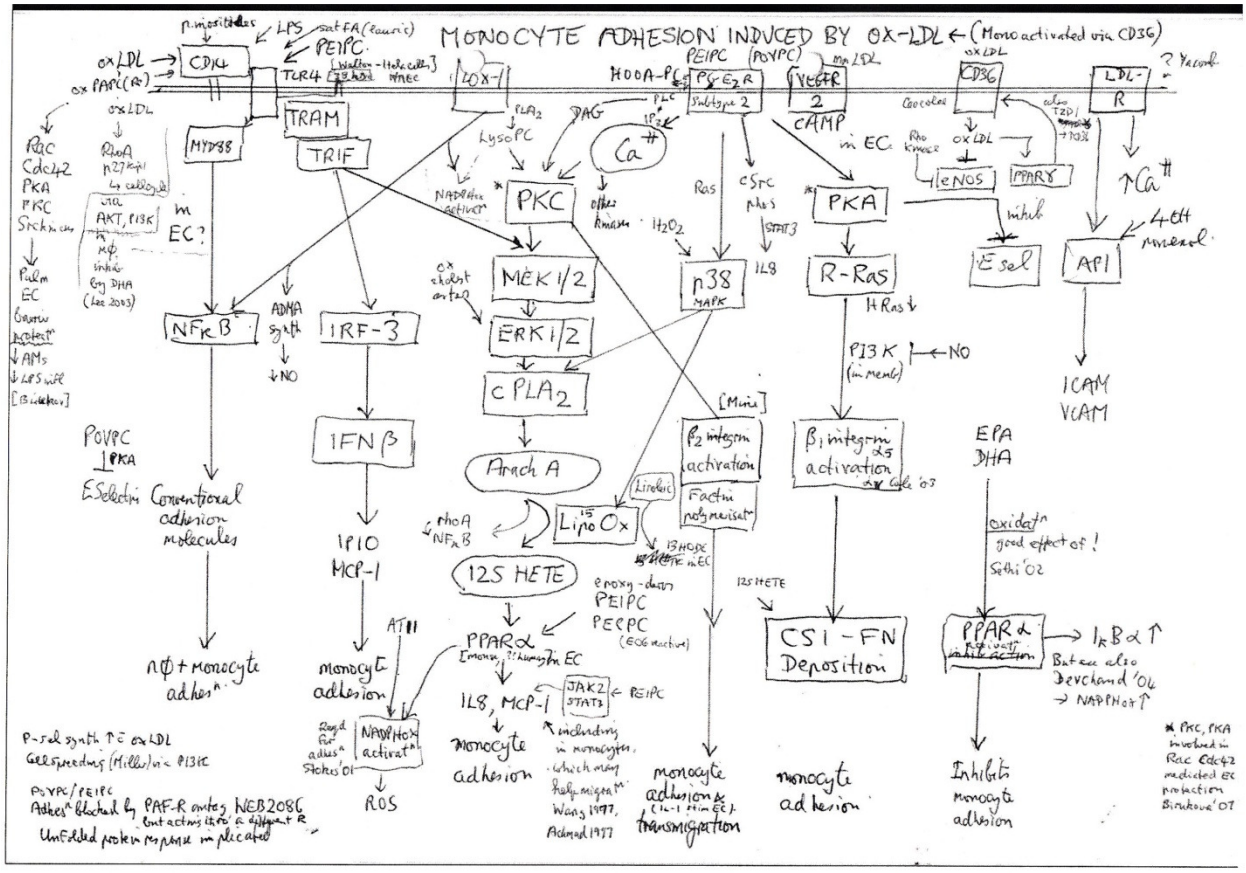
- The action of ECs and macrophages release **cytokines** that stimulate **smooth muscle cell** (SMC) intimal proliferation and migration into plaque (from *media*). They also move up a chemical gradient toward the EL, and with producing **extracellular matrix material** (ECM), a **cap** forms behind the EL

- Accumulation of **foam cells** and extracellular lipid cause the plaque to grow (arterial remodeling). Inward remodeling impinges on the blood flow (stenosis), changing the distribution of **shear stress** on the EL and plaque

- Decreased shear stress and production of **matrix metalloprotein-aces** (mmps), from macrophages, negatively affect the structure and strength of the cap, and determine the stability of the plaque.



And you think my story is complicated...



From a presentation by R. Poston, J. McGregor, S. Collot-Teixera, S. Yilmaz, King's College, London

My Emphasis and Strategic Approach

- First develop a "minimalist" **non-spatial** model to understand mechanisms of accumulation of SMCs, hence ECM/collagen build-up versus accumulation of macrophages/foam cells and build-up of mmps, chemoattractants, etc.

- Fold chemical mechanisms into a **spatial** model to understand chemoattractant mechanisms needed to form a cap

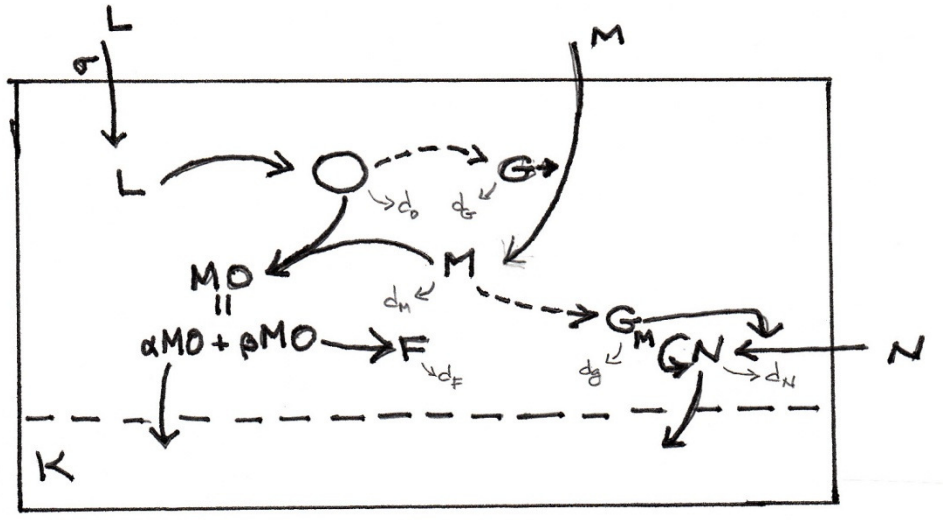
- Refine the spatial model to incorporate the development of the dynamic cap, so we can investigate cap growth and degradation

- Generalize model to a 2D cross-section model; incorporate effects of fluid shear stress, and resulting chemical cascade as it directly affects the integrity of the fibrous cap

Model 1: Non-Spatial Cell-Dynamics Model

Assumptions:

- SMCs (*N*) are responsible for ECM as building material for cap.
- Macrophage population (*M*) is responsible for destructive mmps. Monocytes evolve quickly to macrophages once inside intima
- Oxidation by free radicals (*R*) of LDL concentration (*L*) is simplified considerably: $L + R \rightarrow L_{ox}$ (O). Free radical dynamics treated as a parameter.
- Foam cell (*F*) formation is represented by reaction: $O + M \rightarrow F$.
- Chemoattractants can be released from a variety of sources, but we have one oxidized LDL-derived chemokine, *G*, and one macro-phage-derived chemokine, G_M , that serve multiple duties.



Model 1 Continued*

$$\begin{cases} \dot{L} = \sigma - a_1 RL \\ \dot{O} = a_1 RL - s_2 MO - lO \\ \dot{G} = k_1 O - \mu_G G \\ \dot{M} = s_1 G - s_2 MO - \mu_M M \\ \dot{F} = bMO - \mu_F F \\ \dot{G}_M = s_3 M - \mu_g G_M - \rho G_M N \\ \dot{N} = s_4 G_M + (p - \mu_N) N - m_N \dfrac{b_1 N}{b_2 + N} \end{cases}$$

$X = (X_i) = (L, O, G, M, F, G_M, N)$

L = LDL conc.

O = ox-LDL conc.

G = LDL-derived chemoatt.

M = macrophage density

F = foam cell density

G_M = M-derived chemoatt.

N = SMC density

Proposition: Let ***B*** be defined by $B = \{X \in \Re_+^7 : 0 \le X_i \le \overline{X}_i\}$, where

$$\overline{L} = \frac{\sigma}{a_1 R}, \overline{O} = \frac{\sigma}{\mu_O}, \overline{G} = \frac{\sigma k_1}{\mu_G \mu_O}, \overline{M} = \frac{\sigma k_1 s_1}{\mu_G \mu_M \mu_O}, \overline{G}_M = \frac{\sigma k_1 s_1 s_3}{\mu_g \mu_G \mu_M \mu_O}, \overline{N} = \frac{\sigma k_1 s_1 s_3 s_4}{\mu_g \mu_G \mu_M \mu_O (\mu_N + m_N - p)}$$

Then ***B*** is a positively invariant set in $\Re_+^7$ containing the single equilibrium state X^* and no periodic solutions. Also, if

$(\mu_g + \rho N^*)(\mu_N + m_N - p) > \rho s_4 G_M^*$ and $(s_2 M^* + \mu_O)(s_2 O^* + \mu_M) > s_2{}^2 O^*$,

Then X^* is asymptotically stable.

Remark: Cap biomass model mechanism

$$\dot{K} = m_N \frac{b_1 N}{b_2 + N} + dN - \alpha s_2 MO$$

*Work with student Wanwarat Anlamlert (Mohadol Univ., Bangkok)

Numerical Simulations:

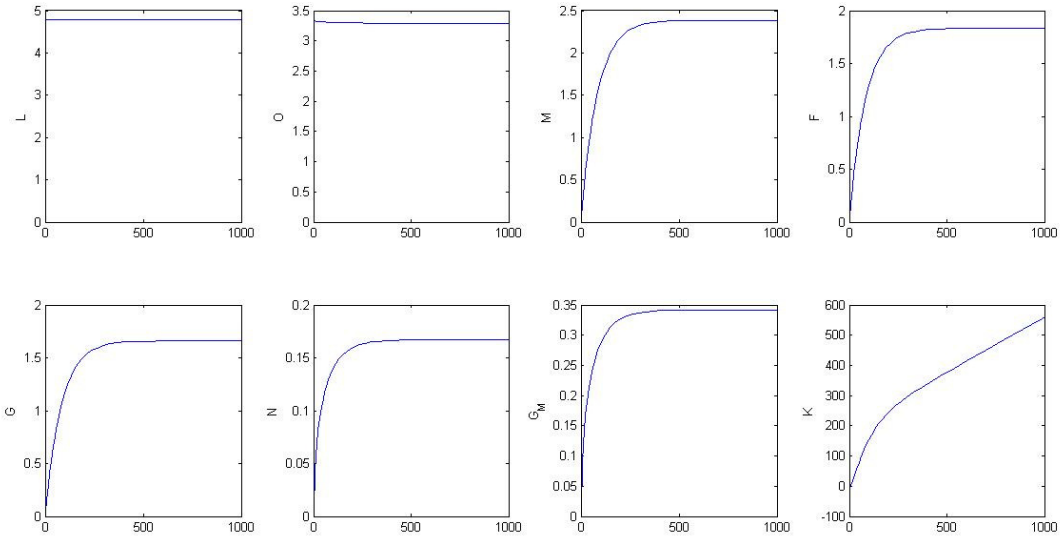


Fig. 1: b1=350

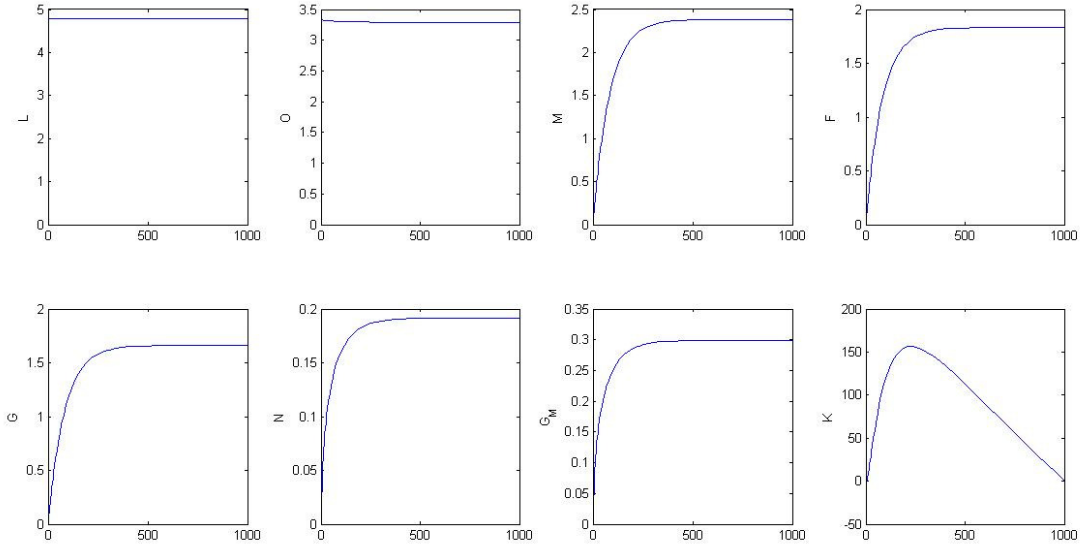


Fig. 2: b1=271.23

Model 2 Assumptions

- One space dimension, **intima** contained in interval $0 < x < 1$.

- Once inflammation begins, transfer of low-density lipoproteins (LDLs) and its oxidation is a fast process compared to plaque and fibrous cap growth, so dynamics is collapsed into oxidized-LDL migration.

- Smooth muscle cells (SMCs), both native to intima, and imported, are the source of extracellular matrix (ECM) building material for the cap. We assume ECM content is proportional to SMC density. In stable plaques, SMC density is much higher than macrophage density in the cap.

- Macrophages produce matrix metalloproteinases (mmps) that degrade the cap. We assume mmp concentration is proportional to macrophage density, which is high in fibrous caps of vulnerable plaques.

- Chemoattractant activity is important in plaque development. This includes production of macrophage chemoattractants, like chemotactic peptide-1 (MCP-1), from SMCs, and production of growth factors, like PDGF-B, from macrophages that play a role in SMC migration and proliferation.

- Oxidized LDLs have a major role in stimulating MCP-1 expression (and endothelial adhesion molecule activation)

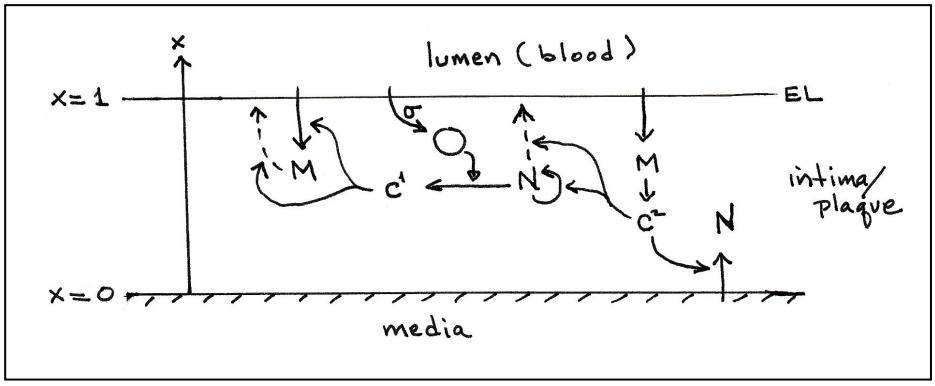
Model 2: 1D Spatial Model

a, b = chemoattractants

M = macrophage density

N = smooth muscle cell density

O = oxidized-LDL concentration



$$O_t = D_O O_{xx} - (\mu_O + \delta)O$$
$$M_t = D_M M_{xx} - \chi_1 (M a_x)_x - (\mu_M + \delta)M$$
$$N_t = D_N N_{xx} - \chi_2 (N b_x)_x + \rho(b)N$$
$$a_t = D_a a_{xx} + \gamma_1(O)N - \mu_a a$$
$$b_t = D_b b_{xx} + \gamma_2 M - \mu_b b$$

$x=0$:	$x=1$:	$t=0$:
$O_x = 0$	$O_x = -\sigma$	$O = 0$
$M_x = 0$	$M_x = f(a)$	$M = 0$
$N_x = g(b)$	$N_x = 0$	$N = N_0(x)$
$a_x = 0$	$a_x = 0$	$a = 0$
$b_x = 0$	$b_x = 0$	$b = 0$

Question: With limited use of cytokines, chemokines (i.e. chemoattractant concentrations), can we get N, hence ECM material, and M, hence mmp concentration, in sufficient concentration near the EL boundary ($x \approx 1-$)?

Chemotaxis Motivation

Origin: Keller-Segel JTB 1970, 1971

u = cell density a = chemotactic conc.

$$\begin{cases} u_t = \nabla \cdot (D\nabla u - \chi u \nabla a) \\ \gamma a_t = \nabla^2 a + u - a \end{cases}$$

(clustering of bacteria)

- Self-organizing in biology
- Sperm cells attracted to chemical releases from eggs
- Cell mobility in embryonic development
- Migrating cancer cells
- Worm C. elegans motility in response to external chemical signals

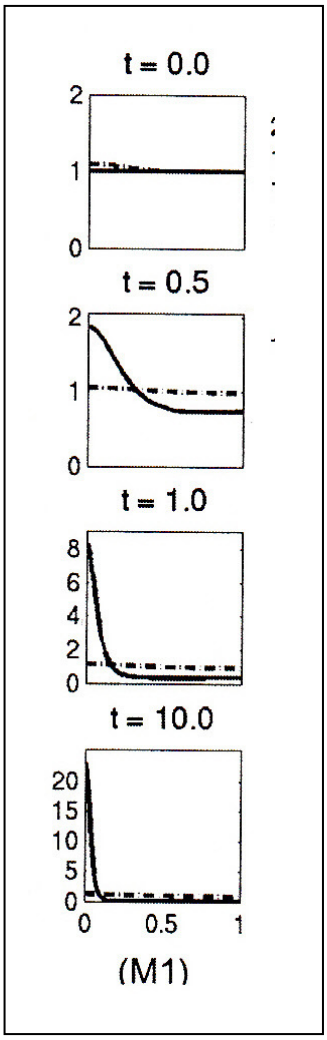


Figure: T. Hillen, K.J. Painter, JMB, 2009, $D = 0.1, \chi = 5$

- Immune cells migrating to sites of inflammation
- Pigmentation patterning in snakes, birds, fish
- Gravitational interaction of particles
- Electrostatic repulsion of charged particles
- etc.

Classical Chemotaxis (auto-attractant) Theory

One-dimension: solutions exist globally (Osaki, 2001)

Higher dimensions: global existence depends on a threshold:

$u_{|t=0} = u_0 < u_{th} \Rightarrow$ global solutions exist

$u_0 > u_{th} \Rightarrow$ finite time blowup (Horstman, 2003; Corrias, Perthame, Zaag, 2004; …)

Total mass > threshold (n = 2)

Local concentration is large (n > 2)

Other forms:

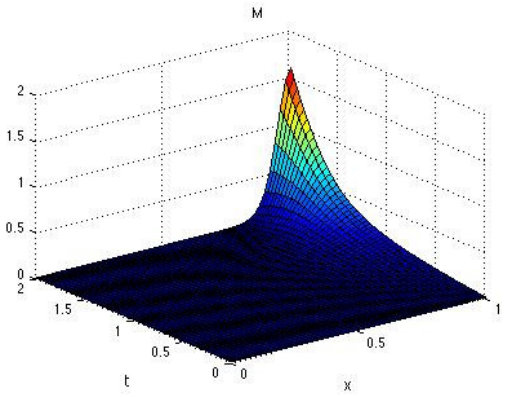
$$\begin{cases} u_t = \nabla \cdot (D\nabla u - \chi u B \nabla a) \\ \gamma a_t = \nabla^2 a + u - a \end{cases}$$

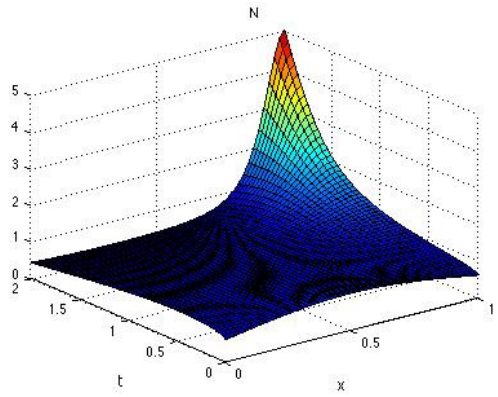
$$B = B(u,a) = 1 - \frac{u}{U}, \frac{1}{1+ku}, \frac{1+\beta}{a+\beta}, \frac{1}{(1+\beta a)^2}$$

Cross-Chemotaxis

$$
\begin{aligned}
M_t &= D_1 M_{xx} - \alpha_1 (M a_x)_x - \mu M \\
N_t &= D_2 N_{xx} - \alpha_2 (N b_x)_x + \rho N \\
a_t &= D_3 a_{xx} + g_1 N - h_1 a \\
b_t &= D_4 b_{xx} + g_2 M - h_2 b
\end{aligned}
$$

$t = 0:$	$M = 0,$	$N = N_0(x),$	$a = a_0(x), b = b_0(x)$
$x = 0:$	$M_x = 0,$	$-N_x = \varepsilon_1 b(0,t),$	$a_x = b_x = 0$
$x = 1:$	$M_x = \varepsilon_2 a(1,t),$	$N_x = 0,$	$a_x = b_x = 0$





Cross-Chemotaxis: Local Existence

Let $z=(M,N,a,b)^T=(z_1,z_2,z_3,z_4)^T$, with $z(x,0)=z_0(x)$.

Let $V=\{v\in H^2((0,1),\Re^4):v([0,1])=bounded\}$

Theorem: **Let** $z_0\in V$. **Then there exists a unique maximal solution**

$z(\cdot;z_0)\in C([0,T),V)\cap C^{2,1}((0,1)\times(0,T),\Re^4)$,

where $0<T=T(z_0)<\infty$.

The idea is to write the system as

$$z_t+A(z)z=Kz \qquad in \qquad (0,1)\times(0,T)$$
$$z(x,0)=z_0(x) \qquad x\in(0,1)$$
$$B(z)z_x=0 \qquad for \qquad x=0,1$$

where

$$A(z)z=-\partial_x(a(z)\partial_x z)\ ,\ a(z)=\begin{bmatrix} D_1 & 0 & -a_1z_1 & 0\\ 0 & D_2 & 0 & -a_2z_2\\ 0 & 0 & D_3 & 0\\ 0 & 0 & 0 & D_4\end{bmatrix}$$

$$K=\begin{bmatrix} -\mu & 0 & 0 & 0\\ 0 & \rho & 0 & 0\\ 0 & g_1 & -h_1 & 0\\ g_2 & 0 & 0 & -h_2\end{bmatrix},\ 0=B(\eta)z_x=\begin{cases}(\partial_x z_1,\partial_x z_2+\varepsilon_1\eta_4,\partial_x z_3,\partial_x z_4)^T & at \quad x=0\\ (\partial_x z_1-\varepsilon_2\eta_3,\partial_x z_2,\partial_x z_3,\partial_x z_4)^T & at \quad x=1\end{cases}$$

and apply a result of Amann's (Diff. and Int. Equations 3(1),1990,13-75).

Cross-Chemotaxis: Positivity (with Neumann BCs, positive ICs)

$$\begin{cases} M_t = (D_1 M_x - \alpha_1 M a_x)_x - \mu M \\ N_t = (D_2 N_x - \alpha_2 N b_x)_x + \rho N \\ a_t = D_3 a_{xx} + g_1 N - h_1 a \\ b_t = D_4 b_{xx} + g_2 M - h_2 b \end{cases}$$

Let $H(u), G(u)$ be two decreasing C^3 functions defined on the reals such that $H(u), G(u) > 0$ for $u < 0$, $H(u) = G(u) = 0$ for $u \geq 0$, and they satisfy (i) $0 \leq H(u), G(u) \leq Cu^2$; (ii) $0 \leq H'(u)u, 0 \leq G'(u)u$; (iii) $0 \leq H''(u)u^2 \leq CH(u), 0 \leq G''(u)u^2 \leq CG(u)$. (There are straight forward ways of constructing such functions.) Define

$$\phi(t) = \int_0^1 H(M(x,t))dx, \quad \psi(t) = \int_0^1 G(N(x,t))dx$$

Then $\phi(0) = \int_0^1 H(M(x,0))dx = 0 = \psi(0)$ and

$$\phi'(t) = \int_0^1 H'(M)M_t dx = -\int_0^1 H''(M)M_x(D_1 M_x - \alpha_1 M a_x)dx - \mu\int_0^1 H'(M)Mdx$$

$$= -D_1\int_0^1 H''(M)(M_x)^2 dx + \alpha_1\int_0^1 H''(M)MM_x a_x dx - \mu\int_0^1 H'(M)Mdx$$

Now

$$\int_0^1 H''(M)MM_x a_x dx \leq \| a \|_{H^2} \int_0^1 H''(M)MM_x dx \leq \| a \|_{H^2} \int H''(M)\left(\frac{\gamma}{2}M^2 + \frac{1}{2\gamma}M_x^2\right)dx$$

Substituting, and using properties of $H(M)$

$$\phi'(t) \le \left(-D_1 + \frac{\alpha_1}{2\gamma} \| a \|_{H^2} \right) \int_0^1 H''(M)(M_x)^2 dx + \frac{\alpha_1 \gamma \| a \|_{H^2}}{2} C \int_0^1 H(M) dx - \mu \int_0^1 H'(M) M dx$$

$$\le \frac{\alpha_1 \gamma \| a \|_{H^2}}{2} C \int_0^1 H(M) dx$$

That is, for some $C > 0$, $\phi'(t) \le C\phi(t)$, for $0 < t < T$. Since $\phi(0) = 0$, $\phi(t) \equiv 0$, so $H(M(x,t)) = 0$ for $x \in (0,1), t \in [0,T)$, hence $M(x,t) \ge 0$.

Similarly, $\psi'(t) \le \left(\frac{\alpha_2 \gamma \| b \|_{H^2}}{2} C_1 + \rho C_2 \right) \int_0^1 G(N) dx = C\psi(t)$: by same argument $N(x,t) \ge 0$.

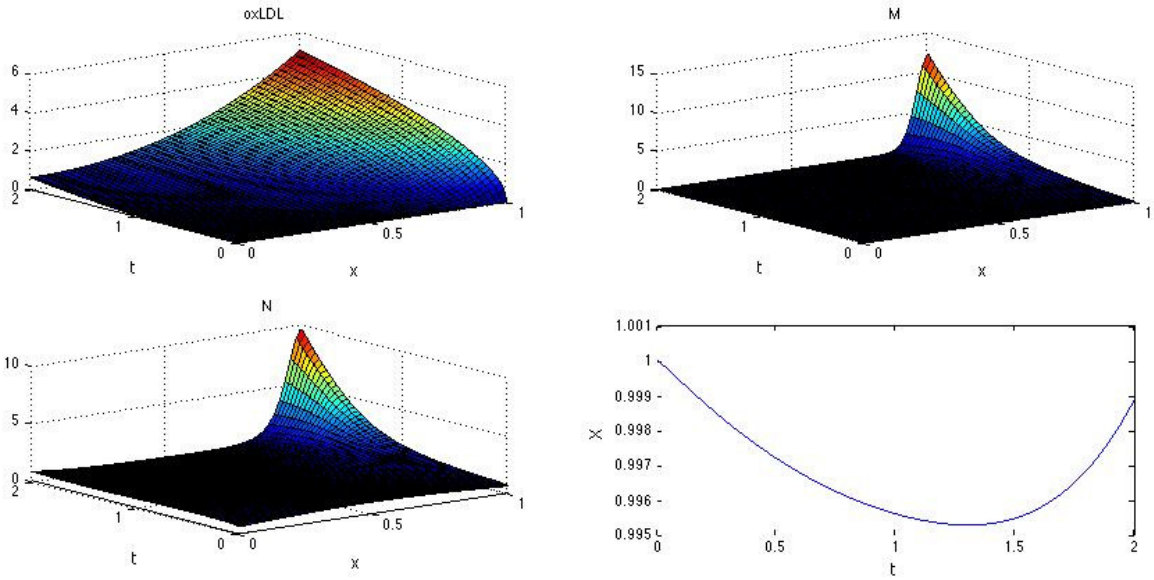
Since the a, b equations are forced by nonnegative terms, a maximum principle argument gives $a(x,t), b(x,t) \ge 0$.

Model 2

$$O_t = D_O O_{xx} - (\mu_O + \delta)O$$
$$M_t = D_M M_{xx} - \chi_1 (M a_x)_x - (\mu_M + \delta)M$$
$$N_t = D_N N_{xx} - \chi_2 (N b_x)_x + \rho(b)N$$
$$a_t = D_a a_{xx} + \gamma_1(O)N - \mu_a a$$
$$b_t = D_b b_{xx} + \gamma_2 M - \mu_b b$$

$x=0:$	$x=1:$	$t=0:$
$O_x = 0$	$O_x = -\sigma$	$O = 0$
$M_x = 0$	$M_x = e_1 O(1,t)$	$M = 0$
$N_x = -e_2 b(0,t)$	$N_x = 0$	$N = N_0(x)$
$a_x = 0$	$a_x = 0$	$a = 0$
$b_x = 0$	$b_x = 0$	$b = 0$

Remark: local existence follows in a similar way as the (M,N,a,b) system via Amann's theory.



Model 3: Fibrous Cap Equation

Assumptions:

- We assume no inward remodeling, so endothelial layer (EL) remains fixed at $x = 1$. The cap will be defined by $X(t) < x < 1$.

- The cap dynamics is considered a "competition" between SMCs (depositing ECM material), and macrophages (releasing mmps). Thus,

$$\frac{dX}{dt} = -\upsilon\left\{k_{on} N(X(t),t) - k_{off} M(X(t),t)\right\}, \quad X(0) = 1$$

where $\upsilon > 0$ is a small (units) positive constant.

- $k_{on}, k_{off} \geq 0$ are rate parameters, constant for Model 3.

So, Model 3 is the $X(t)$ equation

$$\frac{dX}{dt} = -\upsilon\left\{k_{on}N(X(t),t) - k_{off}M(X(t),t)\right\}, \quad X(0)=1$$

plus Model 2:

$$O_t = D_O O_{xx} - (\mu_O + \delta)O$$

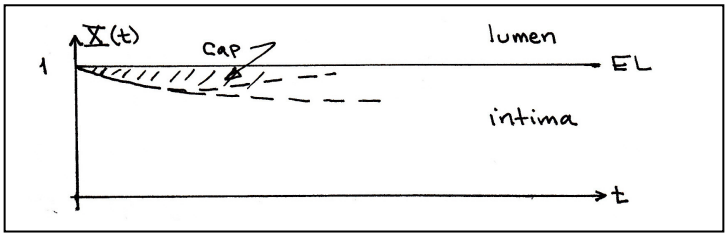
$$M_t = D_M M_{xx} - \chi_1 (M a_x)_x - (\mu_M + \delta)M$$

$$N_t = D_N N_{xx} - \chi_2 (N b_x)_x + \rho(b)N$$

$$a_t = D_a a_{xx} + \gamma_1(O)N - \mu_a a$$

$$b_t = D_b b_{xx} + \gamma_2 M - \mu_b b$$

Question: What conditions lead to the eventual rise of $X(t)$ (weakening of the cap: the vulnerable plaque case), versus continued decrease of $X(t)$ (cap thickening: the stable plaque case)?



Model 4: Extensions

Vascular remodeling $\Rightarrow$ distributed shear stress (ESS) on EL

Normal flow $\Rightarrow$ $\Leftarrow$ Disturbed flow

$\Downarrow$

Mechanotransduction

$\Downarrow$

Local biochemical signaling

$\Downarrow$

Altered EL function $\Rightarrow$ plaque

In undisturbed flow

ESS varies within a physiological range

ECs suppress pro-atherogenic genes $\Rightarrow$ stability

In disturbed flow

Low ESS $\Rightarrow$ pro-atherogenic genes up-regulated

$\Downarrow$

Promotes atherosclerotic process

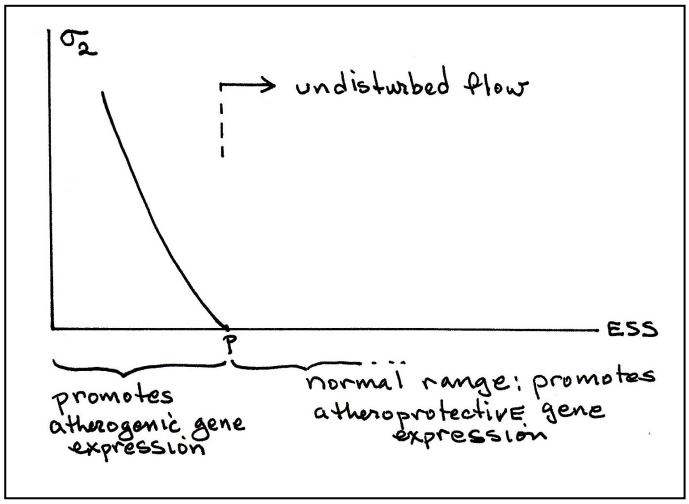
Model 4: Extensions continued

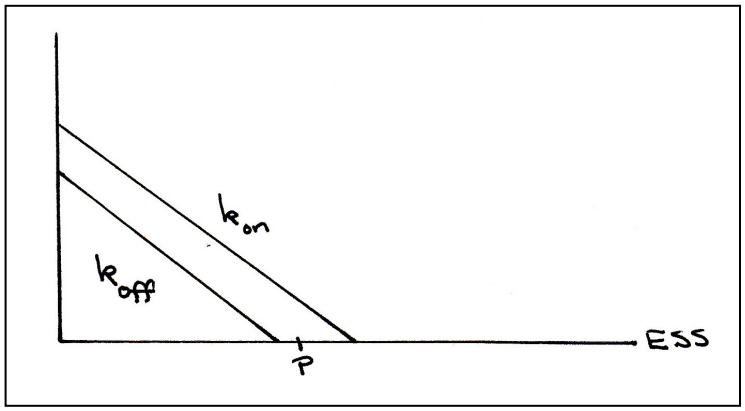
In the present modeling framework, ESS (as an adjustable parameter) is incorporated through

✓ Oxidative-LDL flux $\sigma =$ component initiating inflammation process + ESS-dependent component

$$= \sigma_1(t) + \sigma_2(ESS)$$

✓ Attachment and detachment rate parameters k_{on}, k_{off} depend on ESS.





Further Comments

Include more plaque dynamics, including

1) oxygen's role, apoptosis, and development of the necrotic core, and its role on cap stress

2) T-cell promotion of atherogenesis; T_H1 cell regulation, and hence action of APC, IL-10, 15, 18, IFNγ, TNF, TCR, …

3) inhibitory mechanisms of anti-inflammatory cytokines (IL10, TGFβ, …)

4) calcification of crystals in the cap, and its effects on cap integrity

More sophisticated modeling of the material properties of the plaque components (hyperelastic Maxwellian materials, etc.), and reasonable flow dynamics

Need not to go to 3D spatial models to address cap rupture risk, but to include more mechanotransduction and intracellular signaling pathways, we need to consider 2D models

Acknowledgement: Question of forecasting cap rupture from Dr. Nowwar Mustafa, Cristiana Care, Norwalk, Delaware. Informative discussion with Dr. Pak-Wing Fok, U. Delaware.

When it comes to modeling physiology, I was reminded of the quote:

…que se el fuera de su consejo al tiempo de la general criacion del mundo, i de lo que en el se encierra, i se halla ra con el, se huvieran producido i formado algunas cosas mejor que fueran hechas, i otras ni se hicieran, u se enmendaran i corrigieran.

If the Lord Almighty had consulted me before embarking on creation I should have recommended something simpler.

- Alphonso X (Alphonso the Wise), 1221-1284
- King of Castile and Leon (attributed)

Thank you for your attention