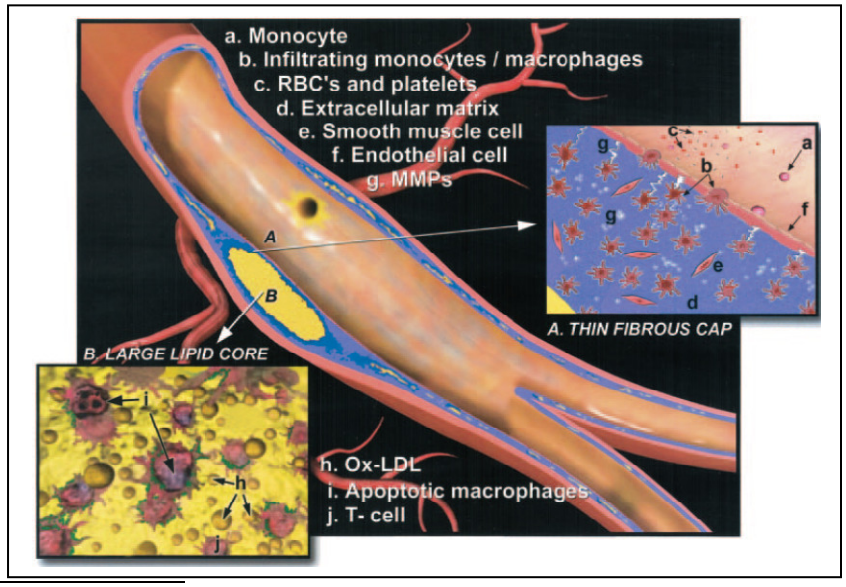
Atherosclerotic plaque development: strategies for modeling the growth and degradation of the fibrous cap

By

Jon Bell

Introduction

- Cardiovascular disease affects 80 million Americans (2006 data)[1]
  2200 Americans die of cardiovascular disease every day (2008)[2]
  Coronary heart disease was responsible for 1 out of 6 deaths in US
- 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 plaques") are responsible for most deaths
- In one study[3], 73% of all deaths examined from MI (myocardial infarction = heart attack) were caused by plaque rupture



[1] American Heart Association
[2] Roger, et al, 2012
[3] Davies, 1992

Talk Outline

- Review basic physiological events leading to a mature plaque and to cap formation

- Mention other modeling work and our alternative approach

- Model 1: Non-spatial model for basic chemical interactions with a cap biomass mechanism; preliminary simulations

- Model 2: 1-D spatial model giving framework of chemotactic events incorporating chemical events from model 1

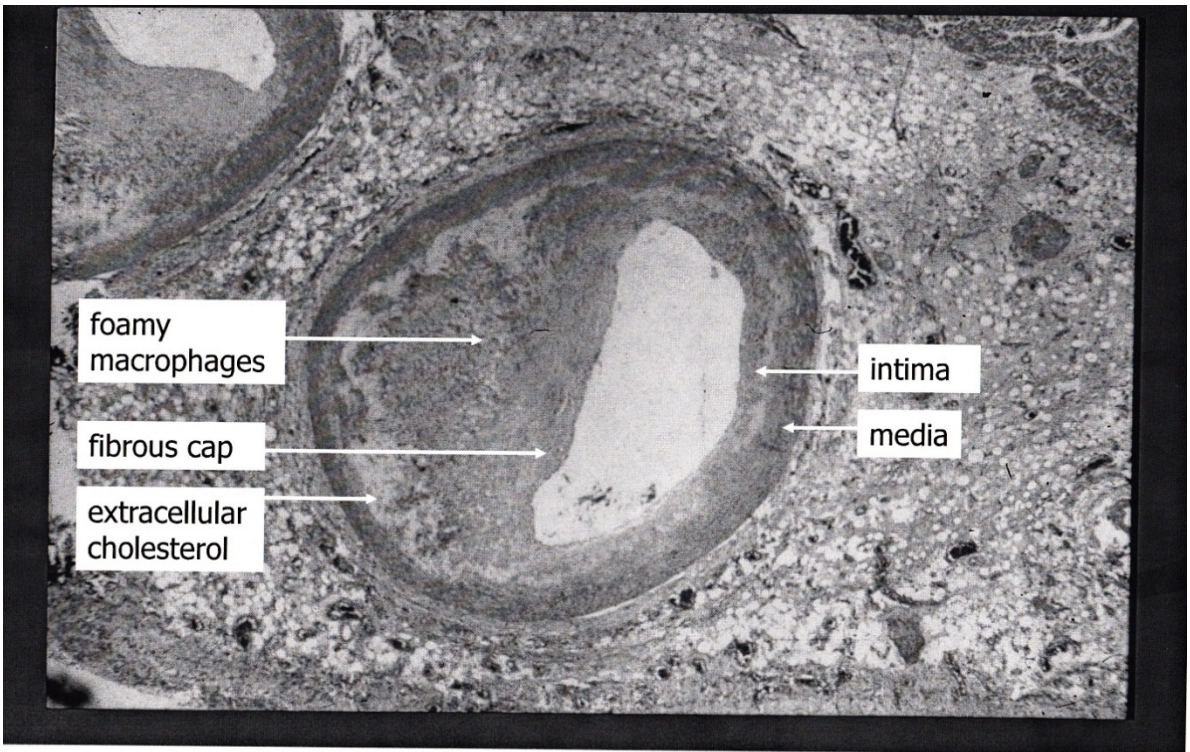
- Model 3: free boundary problem model for a cap dynamic growth and degradation mechanism (1-D spatial model)

- Model 4 ideas: refinement of geometry giving rise to hemodynamic affects; model variable shear stress; other aspects of the problem to consider at some point

- Final Comments

Arterial Plaques

- A plaque is a lesion that develops in the arterial wall layer called the intima
- It is made up of immune cells, cell debris, lipids (cholesterol, fatty acids, …), fibrous connective tissue, etc
- Lesions form early in life but often disappear during childhood
- Arterial plaque formation and growth involves complex chemical, hemodynamic, and biomechanical processes
- Arterial plaques have lipid cores separated from the blood flow by a fibrous cap
- There are basically two types of plaques: stable plaques and unstable plaques (vulnerable plaques (VP), high-risk plaques, thin-cap fibroatheromas (TCFAs))



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

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

Other characteristics:

- 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.)

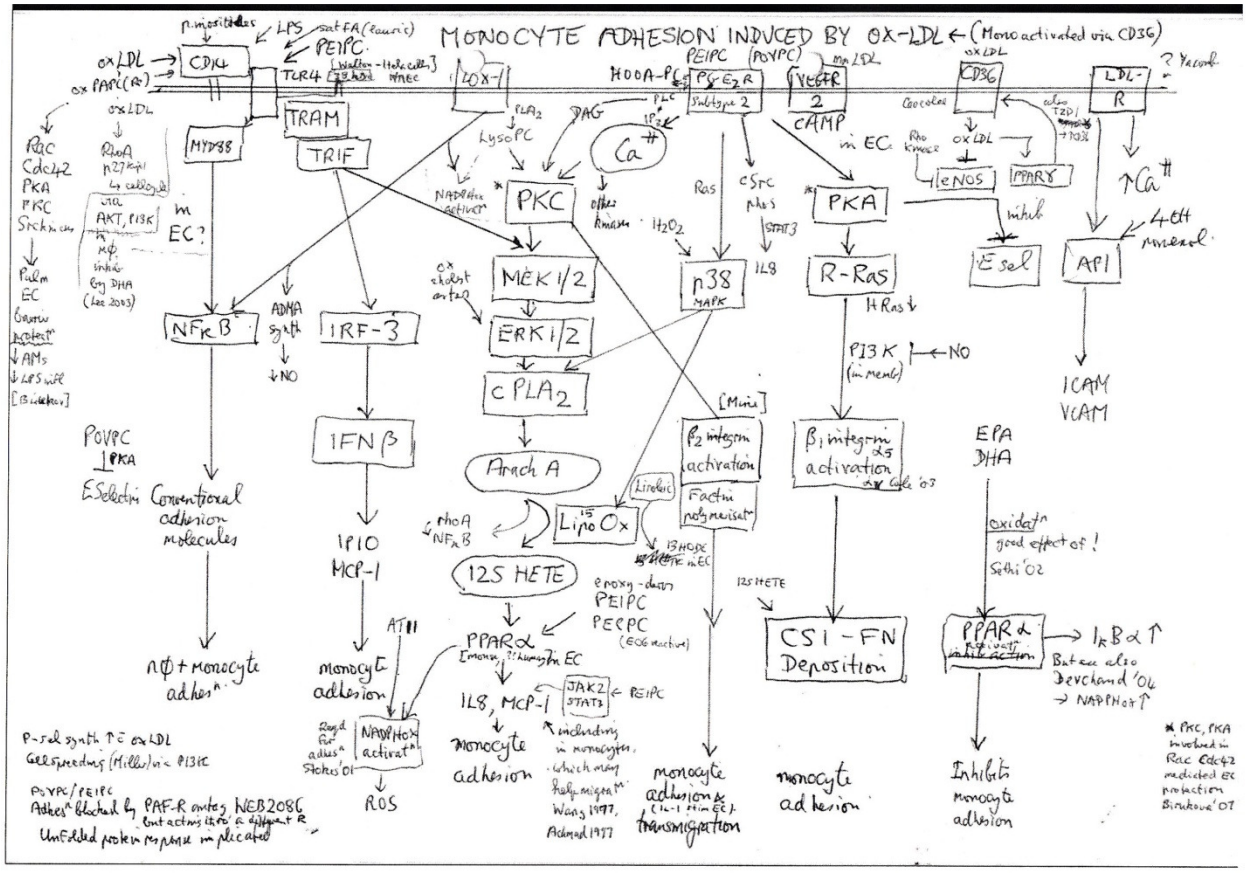
Other Players

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

Reduced Model of Plaque Development

- Some insult (injury) to EL causing inflammatory response (exact cause for lesion initiation still matter of debate), perhaps triggered by LDL excess
- Once in intima, LDL is rapidly oxidized by free radicals. Free radicals are oxidative agents released by ongoing chemical reactions within cells
- ECs display adhesion molecules on lumen side latching onto monocytes and other immune cells. Secreted chemoattractants lure monocytes into intima that quickly mature into macrophages. Macrophages have scavenger receptors that recognize ox-LDLs, allowing macrophages to ingest them
- The result is that macrophages turn into lipid-rich foam cells
- The action of endothelial cells, ox-LDLs, and macrophages release cytokines that cause smooth muscle cell (SMC) proliferation and migration into plaque (from *media*). They also move up a chemical gradient toward the EL, and with producing ECM material (collagen), a cap forms behind the EL
- Accumulation of foam cells and extracellular lipid cause the plaque to grow and cause arterial remodeling. Inward remodeling (thickening) impinges on the blood flow, causing shear stress on the EL and plaque
- Increased shear stress and production of matrix metalloproteinaces (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

Comments on Data and Mathematical Modeling

- Knowledge of when a plaque will become vulnerable is still lacking. VPs can be detected after rupture. Can a VP be identified before rupture?
- When will rupture lead to an acute coronary event?
- 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 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

My Emphasis and Strategic Approach

Dynamics of the cap and its interaction with plaque chemistry and fluid stress. What competing actions cause disruption?

Strategy

- 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

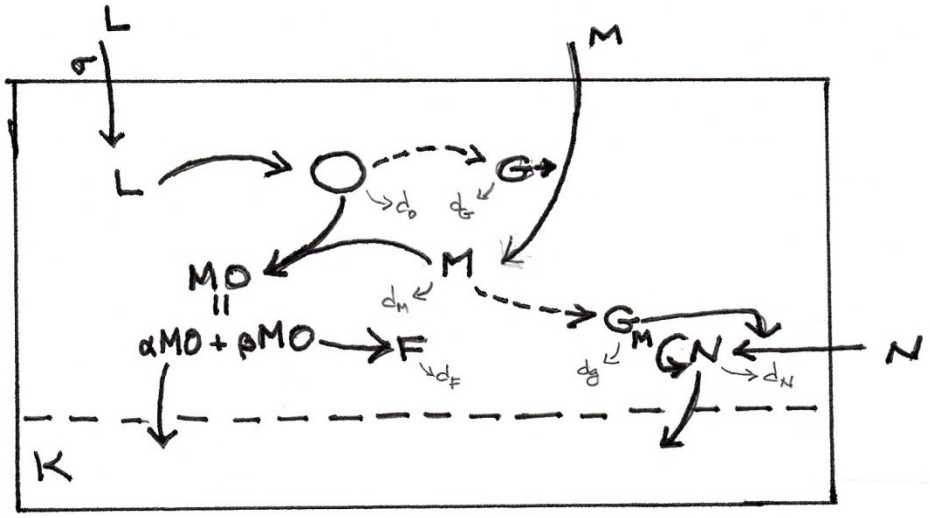
- Refine the spatial model to incorporate the free boundary characteristics of the growing cap (and plaque), so there is proper understanding between plaque growth and cap growth, and degradation

- Generalize the model to a 2D cross-section model and 3D longitudinal model; use more realistic geometry, spatial variability leading to incorporating effects of fluid shear stress, and other hemodynamic affects

Model 1: Non-Spatial Cell-Dynamics Model

Assumptions:

- SMCs (*N*) are responsible for ECM as building material for cap. Their migration into intima "space" is due to multi-source chemotaxis.
- Macrophage population (*M*) is responsible for destructive mmps. Macrophages dominate all immune cells types involved. 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).This is considered a very fast reaction relative to the other time scales. Free radical dynamics treated as a parameter.
- Development of foam cells, *F*, is represented as a simple 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 macrophage-derived chemokine, G_M , that serve multiple duties.



Model 1 Continued*

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

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

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: *F* does not produce chemokines or feedback into other dynamics in this model, so is ignored below.

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

Model 1 Continued

Remark: Cap biomass model mechanism

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

Numerical Simulations:

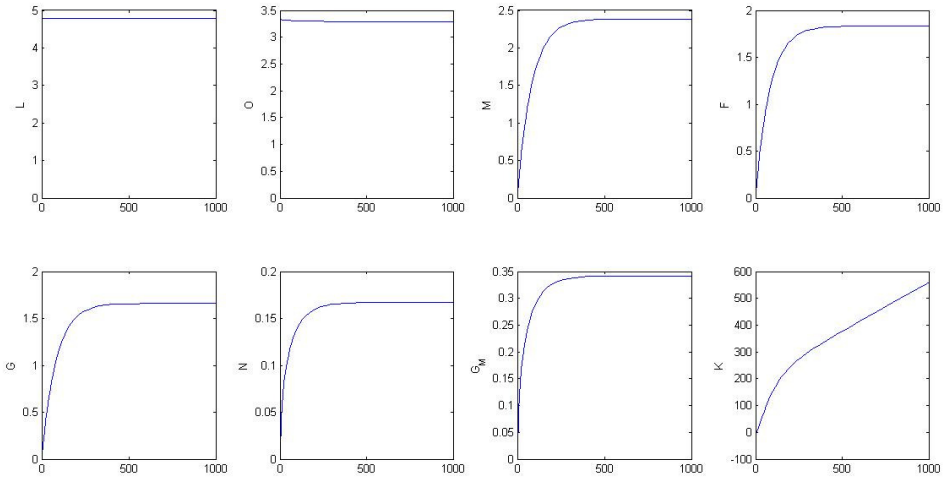


Fig. 1: b1=350

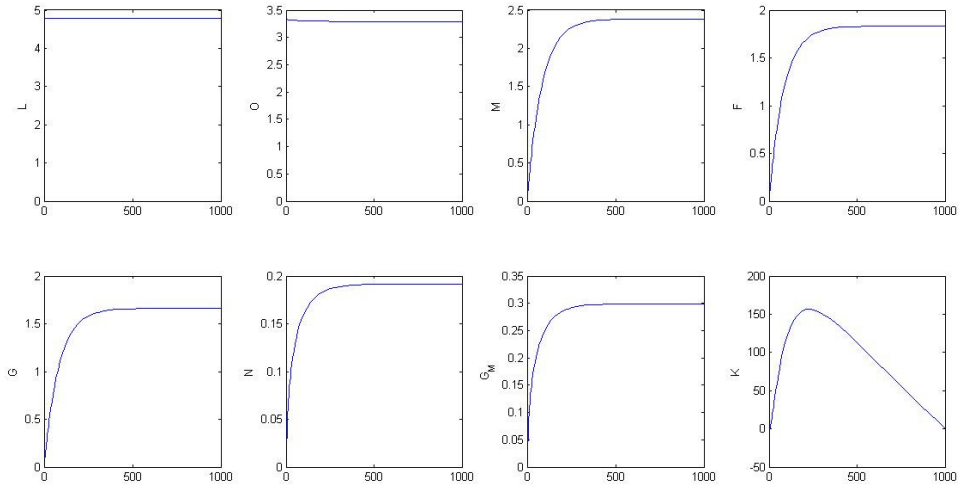


Fig. 2: b1=271.23

Model 2: 1D Spatial Model

In the intima layer:

G=generic chemoattractant

L=LDL protein concentration

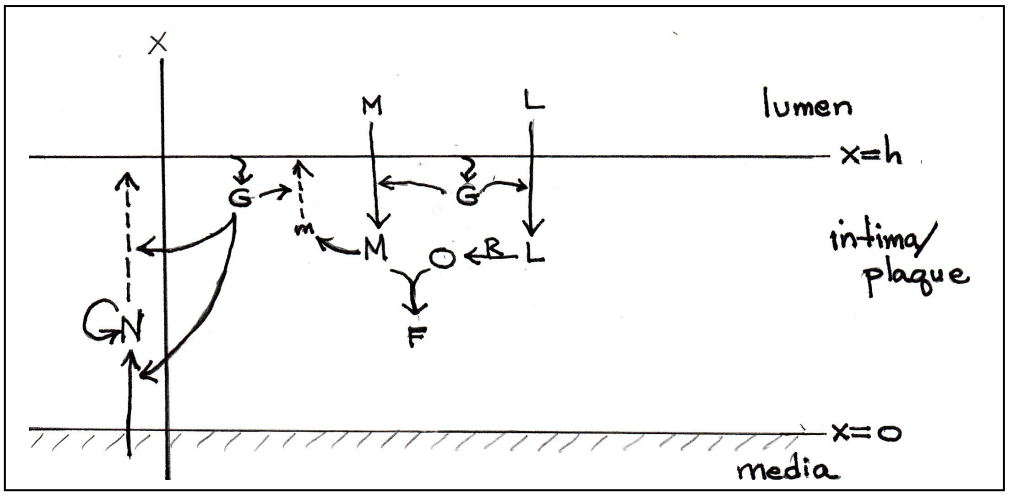
O=oxidized-LDL concentration

M=macrophage density

m=mmp concentration

F=foam cell density

N=SMC density



Question: With limited use of cytokines, chemokines (chemoattractant concentrations), can we get N, hence ECM, and m, in sufficient concentrations near the EL boundary ($x \cong h-$)?

$$G_t = D_G G_{xx} - \mu_G G$$
$$L_t = D_L L_{xx} - k_1 RL$$
$$O_t = D_O O_{xx} + k_1 RL - k_2 MO - \mu_O O$$
$$M_t = D_M M_{xx} - k_2 MO - \mu_M M$$
$$m_t + \chi(mG_x)_x = D_m m_{xx} + k_3 nM$$
$$F_t = k_2 MO - \mu_F F$$
$$N_t + \chi_1(NG_x)_x = D_N N_{xx} - \mu_N N + f(N)$$

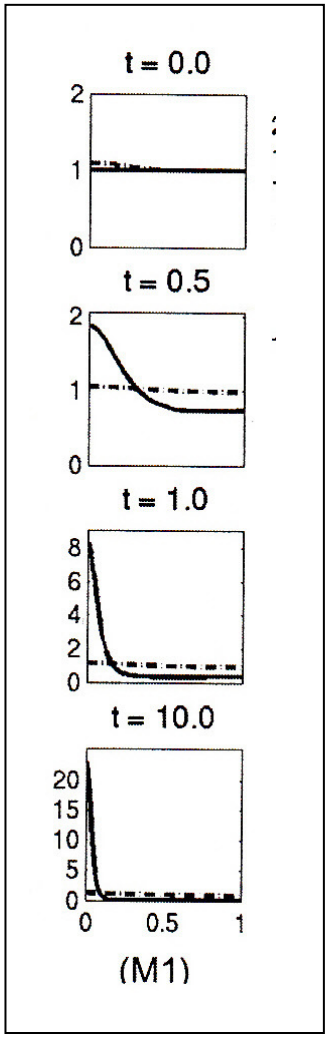
$t=0$:	$x=0$:	$x=h$:
$G=0$	$G_x=0$	$G_x=\sigma$
$L=0$	$L_x=0$	$L_x=\alpha_1(G)$
$O=0$	$O_x=0$	$O_x=0$
$M=0$	$M_x=0$	$M_x=\alpha_2(O)$
$m=0$	$m_x=0$	$m_x=0$
$F=0$	$F_x=0$	$F_x=0$
$N=N_0(x)$	$-D_N N_x=\alpha_3(G)$	$\varphi_N=0$

Chemotaxis

Origin: Keller-Segel JTB 1970, 1971

(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
- Immune cells migrating to sites of inflammation



Classical model: u = cell density,

v = chemotactic concentration

$$\begin{cases} u_t = D\nabla^2 u - \chi u \nabla v \\ v_t = \nabla^2 v + u - v \end{cases}$$

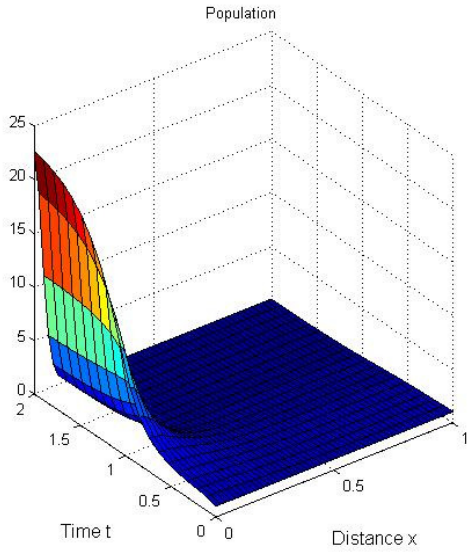
1D: solutions exist globally (Osaki, 2001)

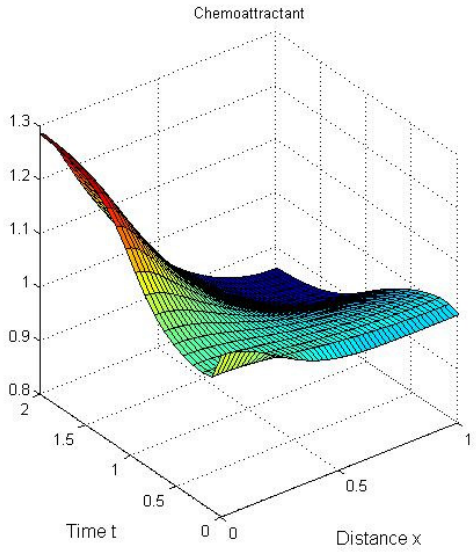
nD, $n > 1$: global existence depends on a threshold: $\Omega \subset \Re^n, L^{n/2}$

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

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

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





$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} - \chi\frac{\partial}{\partial x}(u\frac{\partial v}{\partial x})$$

$$\frac{\partial v}{\partial t} = \frac{\partial^2 v}{\partial x^2} + u - v$$

$u(x,0) \equiv 1, \quad v(x,0) = 1 + 0.1e^{-10x^2}$

No flux conditions at x=0,1, with $D = 0.1, \quad \chi = 5$

Model 3: Cap Dynamics

In the intima layer:

G=generic chemoattractant

L=LDL protein concentration

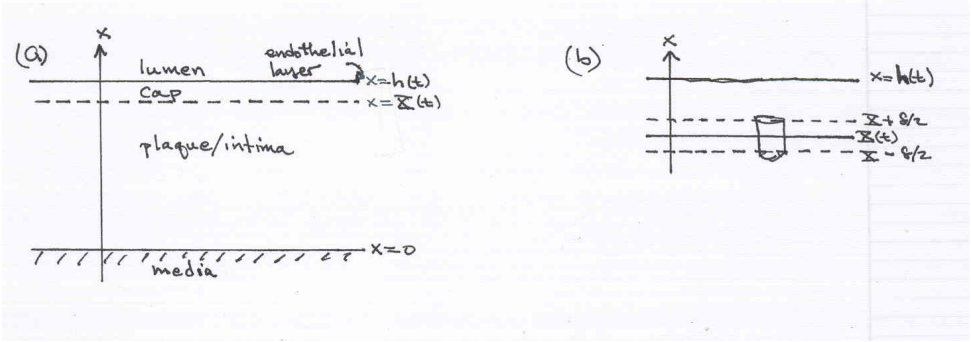
O=oxidized-LDL concentration

M=macrophage density

m=mmp concentration

F=foam cell density

N=SMC density



Changes to Model 2: New variable, N_c, cap concentration due to kinetics and flux of smooth muscle cells. Domain for G, L, O, M, m is $0 < x < h$, while for F, N it is $0 < x < X(t)$

In thin region about **cap boundary** $x = X(t)$: $\int_{X-\delta/2}^{X+\delta/2} N(x,t)dx \approx \delta N(X,t)$

So if $N_c(t) = \lim_{x \to X-} N(x,t)$, $\delta \dfrac{dN_c}{dt} = \dfrac{d}{dt}\int_{X-\delta/2}^{X+\delta/2} N(x,t)dx$

We balance this to net flux of ***N*** on left and attachment/detachment kinetics on the right:

$$\delta \frac{dN_c}{dt}(t) = -D_N N_x(X-,t) + \chi_1 N(X-,t) G_x(X,t) + k_{on} N_c(t) - k_{off}(m(X,t))$$, with

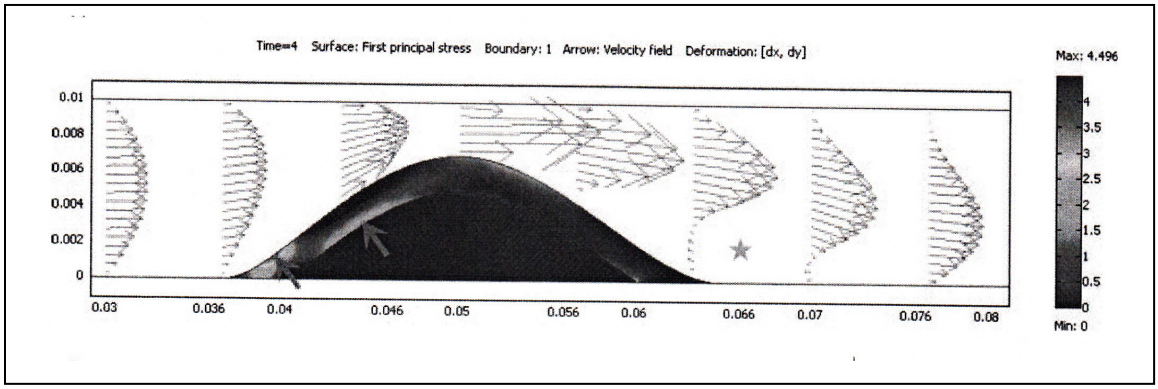
$N_c(0) = N_0(h)$. We identify ECM with SMCs, and these "particles" enter kinetic layer through taxis and chemical deposition, and are free to attach/detach, characterized by k_{on} and $k_{off} = k_{off}(m)$. The interface motion is governed by

$$\frac{dX}{dt} = \varepsilon v\left(k_{off}(m) - k_{on} N_c\right), \quad X(0) = h$$

If $dX/dt < 0$ for all $t > 0$, cap get thick enough ($h - X(t)$) so that the plaque becomes stable. If eventually X increases the cap can get thin enough to rupture ($< 60\ \mu m$). The question here is what conditions lead to, for some $\tau > 0$, $\dot{X}(\tau) = 0$, with $X(t) > 0$ for $t > \tau$?

Model 4: Accounting for Remodeling and Shear Stress on the Fibrous Cap

Cap vulnerability is thought to be a multi-factor process involving thinning of the fibrous cap by active macrophages and cytokines, and biomechanical shear stress exerted by the blood flow.



Transport across the EL is quite complex, involving many micro processes to facilitate adhesion molecules. High shear stress tend to impede microscale suspensions from adhering to the EL

Growth of the lipid core and subsequent negative remodeling (luminal restriction) can also contribute to cap failure through excess mechanical stress.

Flows are highly 3D and complex, requiring 3D blood flow computations to calculate wall shear stress σ_w.

Phase III plaques, the most vulnerable (large lipid cores, thin caps, and in region of the cap, density of macrophages much higher than density of SMCs)

A couple of simple ideas: Poiseuille flow, no-slip boundary conditions at arterial wall, velocity profile is parabolic: $v = v(r,t) = v_{\max}(t)\left(1-\left(\frac{r}{R}\right)^2\right)$, where R is lumen radius. With (Q,η) = (fluid volume, fluid viscosity), then

$$\sigma_w = -\eta \frac{\partial v}{\partial r}_{|r=R} = \frac{4Q\eta}{\pi R^3} \quad \Rightarrow \quad M_x|_{x=h} = \Gamma(O,\sigma_w)$$

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, IFN γ, TNF, TCR, …

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

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

Probably do not need to go to 3D spatial models to address cap rupture risk, but to include biomechanical effects, we need to consider 2D models

We need a research cardiologist specializing in atherosclerotic plaque studies to work with.

Acknowledgement: Question of forecasting cap rupture from Dr. Nowwar Mustafa, Cristiana Care, Norwalk, Delaware.

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When it comes to modeling physiology, I was reminded by Jim Murray of this 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.

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

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

Thank you for your attention