Mathematical models for vulnerable plaques: MPI Workshop Delaware 2009

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1 Introduction

A plaque is an accumulation and swelling in the artery walls and typically consists of cells, cell debris, lipids, calcium deposits and fibrous connective tissue. A person is likely to have many plaques inside his/her body even if they are healthy. However plaques may become "vulnerable", "high-risk" or "thrombosis-prone" if the person engages in a high-fat diet and does not exercise regularly. Such plaques are characterized by a large lipid core, a thin fibrous cap and the presence of macrophages [1]. Vulnerable plaques have an increased likelihood of rupturing and causing cardiac infarction (a heart attack). In fact, about 70% of fatal heart attacks are caused by plaque rupture [3]. Hence their study is of great medical importance. It is the goal of our working group to develop models to understand the growth and rupture of vulnerable plaques.

The growth of a plaque is a very complicated process, coupling together cell biochemistry [7], solid mechanics [10] and fluid-structure interactions [8, 9]. A few of the biochemical factors that are thought to be important are shown in Fig. 1.

Within the workshop, we developed two separate models. The first is a mechanistic model of plaque growth. The second deals with some of the biochemical aspects.

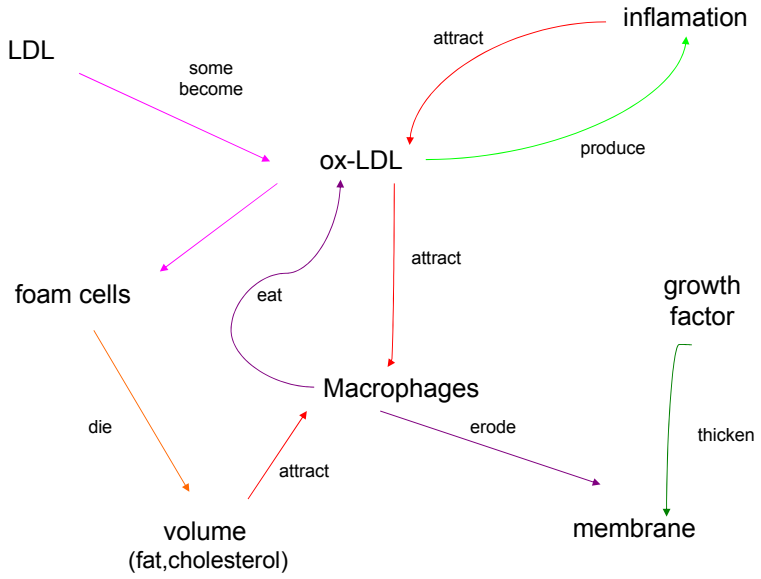

Figure 1: Schematic of a few processes that are important in the growth and rupture of plaques.

2 Mechanical model

2.1 Governing Equations

We developed a 2D model based on mechanical expansion of the plaque, treating the cap as an elastic balloon, the base as a rigid beam and performing a force balance at the shoulders. The main assumption is that the plaque cap (the interface between the core and the blood) is always a circular section: see Fig. 2. We also ignored the effect of microcalcifications in the cap that are thought to locally increase the stress [2]

The evolution of the cap is divided into two stages. In the first stage, we fix the footprint radius $s = 1$ and evolve the plaque volume V and angle α according to the two equations

$$\dot{V} = \mu(L(\alpha, s) - 2s), \quad (1)$$

$$V = V(\alpha, s). \quad (2)$$

where μ is a known constant. In equation (1) we assume that the rate of increase of the volume is proportional to $L - 2s$, a qualitative measure of the internal pressure in the core. Note that for a given V, α is determined by solving (2). The functions $V(\alpha, s)$ and $L(\alpha, s)$

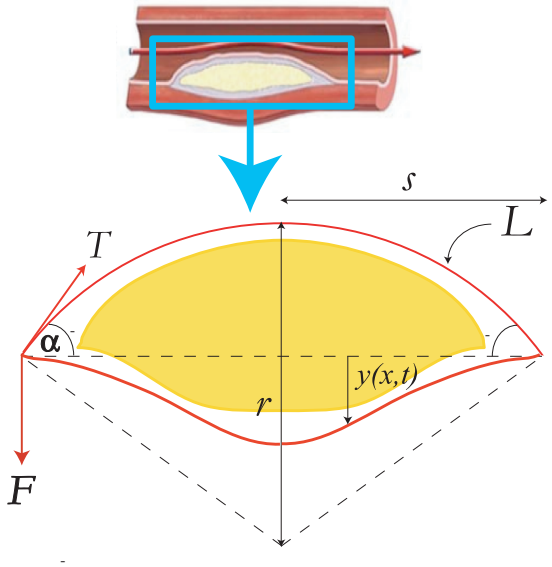

Figure 2: A 2D mechanical model of an inwardly growing plaque whose geometry is characterized by the contact angle α, arclength L, footprint radius s and basal deformation $y(x,t)$. Within the plaque shell (shown in red) is the lipid core (shown in yellow).

are determined from geometry:

$$V = \frac{s^2}{\sin\alpha}\left(\frac{\alpha}{\sin\alpha} - \cos\alpha\right), \tag{3}$$

$$L = \frac{2\alpha s}{\sin\alpha}. \tag{4}$$

F is then determined from the tension in the cap and a force balance at the shoulders: (see Fig. 2 for an explanation of the notation):

$$T = \lambda(L - 2s), \tag{5}$$

$$F = T\sin\alpha. \tag{6}$$

Here, λ is assumed to be a known constant. During the first stage, the volume V and the cap arc length L will grow. Therefore the angle α will grow since $V(\alpha, s)$ is an increasing function of α and $T\sin\alpha$ will also grow. When $T\sin\alpha$ reaches a predetermined value F_{crit}, the second stage of the plaque evolution begins. In this case, the footprint radius s is allowed to increase and it evolves according to the extra constraint

$$\lambda(L(\alpha, s) - 2s)\sin\alpha = F_{\text{crit}}. \tag{7}$$

Once the evolution of the upper surface of the plaque is determined (so V and T are known

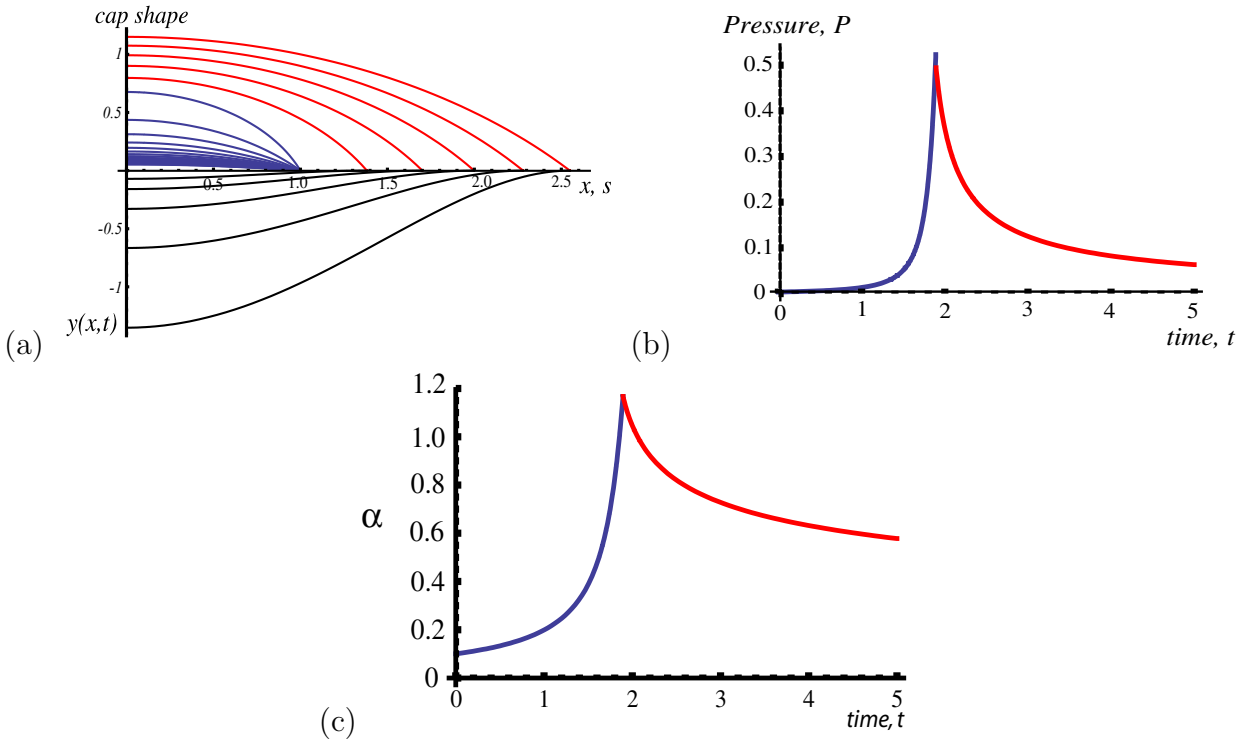

Figure 3: Results of integrating equations (1)-(12) (a) Plaque shapes for different times. The fibrous cap always takes the shape of a circular arc while the basal deformation $y(x,t)$ is determined by equation (9). (b) Pressure as a function of time. (c) The angle α as a function of time

for all time), the basal deformation y can be found via

$$\dot{E} = -\gamma V E, \tag{8}$$

$$P = \frac{T}{r}, \tag{9}$$

$$\frac{\partial^4 y}{\partial x^4} = -\frac{P}{E}, \tag{10}$$

where γ is a known constant, E is the Young's modulus and P is the pressure inside the plaque. Note that the pressure P in equation (9) does not account for the extra volume caused by the basal deformation and so equations (8)-(10) are only valid when these deformations are small compared to s. The equations are supplemented by boundary conditions at $x = \pm s$

$$y = 0, \tag{11}$$

$$\frac{\partial y}{\partial x} = 0. \tag{12}$$

The results of integrating equations (1)-(10) are shown in Fig. 3.

2.2 Conclusions

Our model predicts two qualitatively different evolutions for the plaque. The first stage consists of a localized growth (see blue curves in Fig. 3(a)) where the lateral extent of the plaque is constant. The basal deformation is relatively small in this case. In the second stage the plaque grows globally: the footprint radius and the arclength can both grow (see red curves in Fig. 3(a)) and the basal deformations are larger. With this second stage of growth, there is corresponding *decrease* in the interior pressure of the lipid core (see the red curve in Fig. 3(b)). In actual vulnerable plaques, such a reduction may lower the likelihood of rupture. This suggests that strategies of stabilizing plaques could focus on controlling the transition between the local and global growth stages. According to this mechanical model, it is desirable to start the second stage of growth as soon as possible as this prevents the interior pressure from building up. Therefore more work should be done to see (i) how the transition time between the two growth regimes changes as a function of the model parameters μ and λ and (ii) how μ and λ could be affected by factors such as diet, smoking and exercise. In our model, the plaque grew by "negative" remodeling: that is, it increased its size by gradually narrowing the vessel lumen and growing inwards. However, many vulnerable plaques grow by "positive" remodeling: they actually cause very little stenosis and grow outwards, causing the outer vessel wall to expand. As a result, they are harder to detect angiographically [4] and have larger cores than negatively remodeled plaques.

Also, more work should be done to explore how the plaque shoulders are "pinned" to the blood vessel lining and the nature of the forces involved.

3 Biochemical-stress model

3.1 Governing Equations

Matrix Metalloproteinases (MMPs) are thought to play an important role in plaque evolution because they degrade the fibrous cap [5] and therefore increase the likelihood of rupture. The model proposed in this section focuses on how stresses in the plaque cap can increase the concentration of MMPs and hence degrade the cap thickness.

The governing equations take a general form

$$\dot{\sigma} = f(V) - r\sigma, \tag{13}$$

$$\dot{M} = g(\sigma, V) - \mu M, \tag{14}$$

$$\dot{V} = h(\sigma), \tag{15}$$

$$\dot{\xi} = \alpha\xi(\xi_0 - \xi) - \beta M. \tag{16}$$

where σ is the stress in the cap, M is the concentration of MMPs, V is the volume of the lipid core and ξ is the thickness of the cap.

Equation (13) stems from the cap mechanics. As the volume of the plaque grows, the cap is mechanically stressed. The $-r\sigma$ term represents a relaxation of the stress as the cells proliferate [11] and the cap remodels. Equation (14) describes the regulation of MMPs. MMPs are upregulated by stresses within the cap. Also, a larger lipid core arises from more

inflammatory cells which in turn secrete MMPs [5]. Hence we model g as depending on both σ and V. Equation (15) describes how stresses affect the production of signaling molecules such as PDGF [6] or cytokines which could attract (repel) inflammatory cells into (out of) the core with a resulting change in volume. Finally, (16) is an equation for the cap thickness. The $-\beta M$ term represents cap thinning through MMPs. The logistic growth term has a "preferred" cap thickness ξ_0 which is a stable fixed point when $M = 0$.

For definiteness, we assume specific forms for the functions f, g and h so that our system of equations becomes

$$\dot{\sigma} = f_0 V^{2/3} - r\sigma, \tag{17}$$

$$\dot{M} = k_1 V \left(\frac{\sigma}{\sigma_1 + \sigma} \right) - \mu M, \tag{18}$$

$$\dot{V} = k_2 \left(\frac{\sigma}{\sigma_0 + \sigma} \right), \tag{19}$$

$$\dot{\xi} = \alpha \xi (\xi_0 - \xi) - \beta M. \tag{20}$$

We use Hill forms for the dependence of $\dot{M}$ and $\dot{V}$ on the stress σ so that the rate of increase of MMPs and volume saturates for $\sigma \gg \sigma_0$ and $\sigma \gg \sigma_1$.

Unfortunately, most of the parameters in the model are unknown. There were some parameter values considered from a quick literature search on some tissues, but without corroboration with regard to plaque parameters, and lack of time, we simply set constants to 1 for initial computational purposes: see Table 1. $V(0)$ and ξ were estimated to be 10^{-3} mm^3 and $250\mu m$ respectively and the initial values for σ and M were taken to be the equilibrium values i.e. $\sigma(0) = f_0 V(0)^{2/3}/r$ and $M(0) = (k_1/\mu)V(0)\frac{\sigma(0)}{\sigma_1+\sigma(0)}$: see Table 2.

The results of integrating equations (17)-(20) are shown in Fig. 4. We see an increase in cap stress, an upregulation in MMPs, an increase in plaque volume and a thinning of the fibrous cap. A rupture time can be found by stopping the integration at a time t^* such that $\xi(t^*) = \xi_{\min}$ where $\xi_{\min}$ is a predetermined cap thickness below which the cap tears.

3.2 Conclusions

The proposed biochemical stress model incorporates some factors that are known to be important in the rupture of vulnerable plaques. In the model, increased cap stress and upregulation of MMPs leads to growth of the plaque and a subsequent thinning of the cap. Future studies and experimental work should focus on the measurement of the parameters in Fig. 1. Also, the system of equations (17)-(20) could be improved to account for the presence of oxidized lipoproteins, macrophage accumulation and other factors related to the inflammatory response. Further work also needs to be done to analyze how tissue stresses affect the production of signaling molecules such as cytokines and how these molecules affect macrophage behavior.

Constant	Description	Unit	Value used
f_0	cap viscoelasticity	Pa/mm^2/year	1
r	Inverse relaxation time of tissue (remodeling rate)	1/year	1
k_1	Upregulation rate of MMPs	ng/mm^6/year	1
k_2	Macrophage inflammatory response rate	mm^3/year	1
μ	MMP degradation rate	1/year	1
σ_0	stress that saturates MMP growth	Pa	1
σ_1	stress that saturates macrophage response	Pa	1
α	Cell division rate per unit cap thickness	1/mm/year	1
β	Cap thinning rate (by MMPs)	1/year	1
ξ_0	"preferred" cap thickness	mm	0.2

Table 1: Table of parameters used to solve equations (17)-(20). Where values were found in the literature or estimated, they are given. Otherwise, the value of the constant is taken to be 1.

$\sigma(0)$	0.046 Pa
$M(0)$	10^{-3} ng/mm^3
$V(0)$	0.01 mm^3
$\xi(0)$	0.25 mm

Table 2: Initial values for the cap stress, MMP concentration, plaque volume and cap thickness used in Fig. 4.

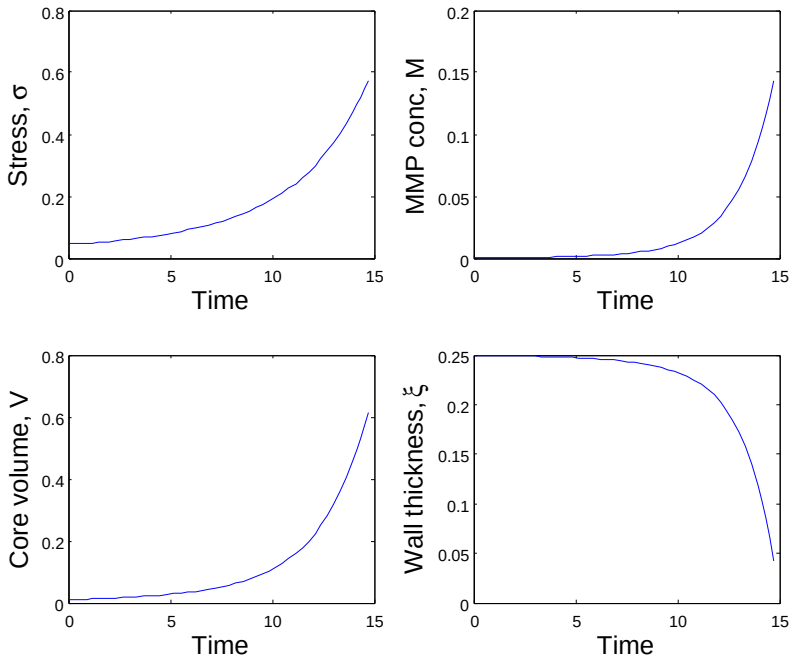

Figure 4: Evolution of cap stress (σ), MMP concentration (M), plaque volume (V) and cap thickness (ξ) measured in Pa, ng/mm^3, mm^3 and mm respectively. Time is measured in years.

4 Project summary

The rupture of vulnerable plaques is thought to responsible for a large fraction of fatal myocardiac infarctions. In this study group, we proposed two mathematical models to describe plaque growth and rupture. The first model is a mechanical one that approximately treats the plaque as an inflating elastic balloon. In this model, the pressure inside the core increases and then decreases suggesting that plaque stabilization and prevention of rupture is possible. The second model is a biochemical one that focuses on the role of MMPs in degrading the fibrous plaque cap. The cap stress, MMP concentration, plaque volume and cap thickness are coupled together in a system of phenomenological equations. The equations always predict an eventual rupture since the volume, stresses and MMP concentrations generally grow without bound. The main weakness of the model is that many of the important parameters that control the behavior of the plaque are unknown: see Table 1.

The two simple models suggested by this group could serve as a springboard for more realistic theoretical studies. But most importantly, we hope they will motivate more experimental work to quantify some of the important mechanical and biochemical properties of vulnerable plaques.

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