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4 Atherosclerotic plaque rupture

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4.1 Introduction

The arterial system is more than an intricate plumbing system for the transport of blood; it is a highly complex organ that interacts with its environment. The major function of the vessel wall, and more specifically the endothelial lining, is to maintain an adequate blood supply to the end organ that it is supplying. This is achieved by regulatory mechanisms that control vascular tone, inflammation and anticoagulation.

The vessel wall requires an adequate supply of nutrients to maintain healthy function, and whilst some of these can be derived from the vessel lumen itself, the walls of larger arteries (exceeding 1mm in diameter) receive an additional supply from the *vasa vasorum* (vv), which is a vascular network serving the arterial wall. The vessels of the vv originate either from the parent artery or from a neighbour, pass into the outer layer of the vessel wall, and break up into a capillary network reaching the inner parts of the vessel wall.

As with any organ, the vessel wall is prone to disease. Vascular disease causes significant morbidity and mortality in the Western world, and ranges from benign fatty streaks in early life to complicated atheromatous plaques. Substantial plaque deposit can lead to ischaemic symptoms through the gradual restriction of blood flow as the plaque enlarges to occupy progressively larger proportions of the arterial lumen. Furthermore, the health risk is not simply correlated with the degree of stenosis (blockage) but also with the vulnerability of the plaque, *i.e.* the tendency for the plaque to rupture and for thromboses and emboli to be carried downstream and block smaller vessels, leading to potentially life threatening events.

The risk of plaque rupture depends upon the composition of the plaque and the mechanical stresses that act on it. A vulnerable plaque contains a large necrotic core and is covered by a thin fibrous cap. Disruption can occur when the plaque is exposed to triggering events of sufficient magnitude and duration that the structural integrity of the plaque is compromised, *e.g.* shear forces exerted by the blood flowing at high velocity through a severe stenosis. In addition, the atherosclerotic region of the arterial wall may be particularly rich in the capillaries of the vv. These capillary walls are thin and prone to haemorrhage, leading to deposition of blood products and a subsequent build-up of pressure within the plaque. Furthermore, the increased blood flow within the arterial wall implies a large inward (lumen-directed) pressure gradient in the stenosed region of

the artery, since the luminal blood flow creates a region of low pressure centred in the narrowest point of the stenosis (Bernoulli principle) while the vv arises in a high-pressure region. It is hypothesised that these increases in plaque pressure result in a new mechanism for plaque rupture, in which the rupture should be interpreted as a "blow-in" into the lumen, rather than as a "blow-out" from the lumen [1].

The study group was asked to consider the following problems:

- As the plaque slowly enlarges it will encroach more into the vessel lumen causing stenosis. At what degree of stenosis will there be a significant pressure gradient across the stenosis?
- Atheromatous plaques cause vessel narrowing. The stenosis will eventually cause a significant pressure gradient. The vasa vasorum obtains its supply from upstream and may be exposed to a higher pressure than the plaque which is exposed to the lumen adjacent to the distal part of the plaque. What effect will this have on the potential site of vasa vasorum rupture, haemorrhage and potential plaque rupture/activation?
- The vessel wall is dependent on two nutrient supplies - one from the lumen and one from the vasa vasorum. What nutrient/oxygen gradients exist across the vessel wall and what is the effect of disease (thickening) on this?

In an attempt to address these issues, we develop and solve appropriate mathematical models as described below.

4.2 Model formulation

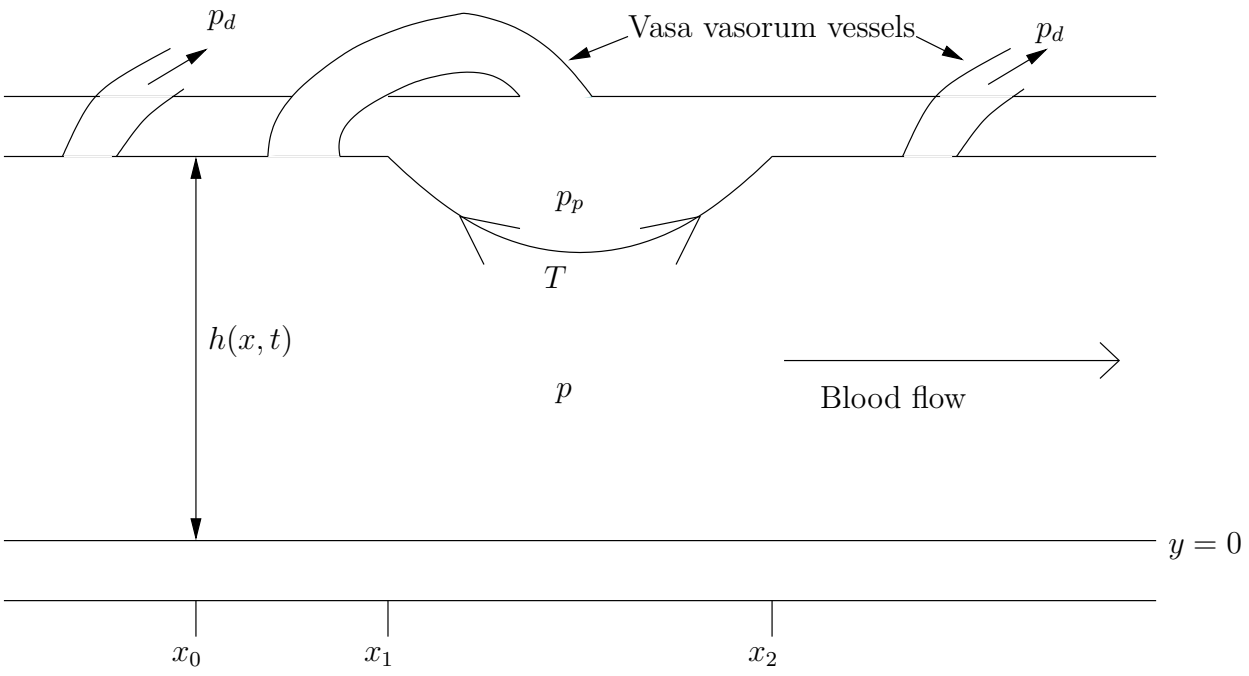


Figure 23: Diagram showing model parameters.

We consider a single (straight), two-dimensional artery containing a single plaque. Coordinates (x, y) are taken, with x the coordinte along the artery, and time is denoted by t. The width of the artery is denoted by $h(x, t)$, and we assume the plaque occupies a region of length $(x_2 - x_1)$ (see figure 23). Away from the plaque the artery wall is taken to be rigid, but in the region $x_1 \leq x \leq x_2$, we model the plaque as consisting of fluid at a pressure $p_p(t)$ and assume the plaque-lumen interface to behave as a membrane with tension T.

The blood vessels of the vasa vasorum branching from the artery are also considered to be rigid. We assume that in general they drain into the venous and lymphatic systems, which are at pressure p_d, and, without loss of generality, we take $p_d = 0$. However, those vasa vasorum vessels that branch from the artery in the region $x_0 < x < x_1$ drain into the plaque. As a further simplification we have assumed no vasa vasorum vessels arise in the region $x_1 \leq x \leq x_2$, which contains the plaque.

We model the blood as a homogeneous, incompressible, Newtonian fluid, with kinematic viscosity ν and density ρ. In the channel the velocity components are (u, v), and the pressure is p. In the artery, far upstream of the plaque, the volume flux is Q_0, and the channel width $h(x, t) = h_0$ when $x < x_1$ and $x > x_2$.

4.3 Governing equations

We assume that the channel width $h(x, t)$ is slowly varying in x so that the velocity profile is approximately flat and transverse velocities are negligible. We will consider an unsteady, one-dimensional model. The channel width h, fluid pressure p and cross-sectionally averaged longitudinal velocity u are taken to be functions of the longitudinal coordinate x and time t.

Mass conservation

Suppose q_{out} is the volume flux of blood into the vasa vasorum per unit length of artery. Then, since mass is conserved, we obtain:

$$h_t + (uh)_x = -q_{out}, \tag{4.1}$$

where the subscripts denote partial derivatives.

We assume that q_{out} is proportional to the pressure difference across the vasa vasorum. Then, if there are N vasa vasorum vessels per unit length of artery, and each vessel has conductivity k_v we obtain:

$$h_t + (uh)_x = \begin{cases} -Nk_v p & \text{if } x < x_0, \quad x > x_2, \\ -Nk_v(p - p_p) & \text{if } x_0 < x < x_1, \\ 0 & \text{if } x_1 \leq x \leq x_2. \end{cases} \tag{4.2}$$

Momentum conservation

The momentum equation is

$$u_t + \chi u u_x = -\frac{1}{\rho} p_x - \frac{12\nu u}{h^2}, \tag{4.3}$$

where the last term on the RHS accounts for the viscous friction, which has a large effect when the channel width, $h(x,t)$, becomes small. Following Jensen & Pedley [4] the constant $0 < \chi \leq 1$ allows us model in an *ad hoc* manner the boundary layer separation which might occur in the region downstream of the plaque. We define x_c to be the position at which separation occurs. In the region $x < x_c$ we take $\chi = 1$; downstream of the plaque, in $x > x_c$ we take $\chi = \chi_0$, where $0 < \chi_0 < 1$. The situation in which $\chi \equiv 1$ everywhere corresponds to the case of no flow separation.

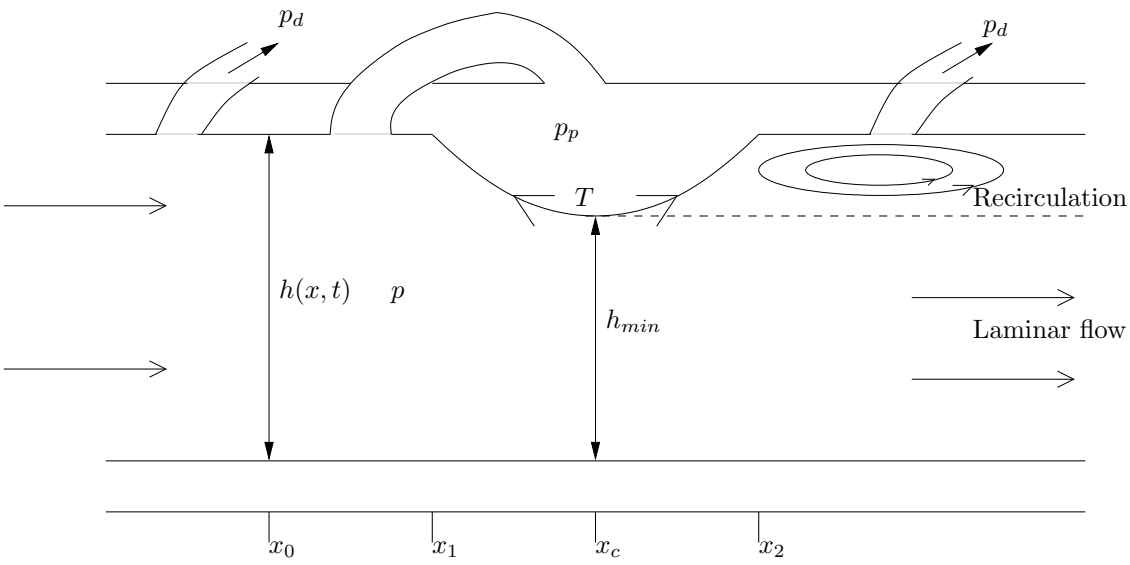


Figure 24: Separation.

Wall law

The tension relation for the membrane covering the plaque is given by the Young-Laplace equation, which relates the curvature of the membrane to the pressure jump across its surface as follows:

$$T h_{xx} = p_p - p, \;\; x_1 \leq x \leq x_2. \tag{4.4}$$

We also have, as previously stated:

$$h = h_0 \;, \;\; x < x_1, \;\; x > x_2. \tag{4.5}$$

Conservation of material entering the plaque

We assume blood can flow out of the plaque via a capillary network, which eventually joins the venous and lymphatic systems (which are at pressure $p_d = 0$). We assume there are n such capillaries draining the plaque, each with conductivity k_c. Then, conservation of mass gives:

$$\int_{x_0}^{x_1} Nk_v(p-p_p)dx - nk_cp_p = \frac{d}{dt}\int_{x_1}^{x_2}(h_0-h)dx. \tag{4.6}$$

4.3.1 Nondimensionalisation

We nondimensionalise the system as follows (where the tildes denote dimensionless quantities):

$$x = x_1 + (x_2-x_1)\widetilde{x},\ h = h_0\widetilde{h},\ u = \frac{Q_0}{h_0}\widetilde{u},\ t = \frac{(x_2-x_1)h_0}{Q_0}\widetilde{t},\ (p,p_p) = \rho\frac{Q_0^2}{h_0^2}(\widetilde{p},\widetilde{p_p}), \tag{4.7}$$

and introduce the following parameters (where $\Delta x = x_2 - x_1$):

$$l = \frac{(x_1-x_0)}{\Delta x}\ ,\ \gamma = \frac{12\nu\Delta x}{Q_0h_0}\ ,\ \delta = \frac{\rho Q_0 N k_v \Delta x}{h_0^2}\ ,\ \alpha = \frac{\rho Q_0^2(\Delta x)^2}{Th_0^3}\ ,\ \beta = \frac{nk_c}{Nk_v\Delta x}. \tag{4.8}$$

The dimensionless governing equations are now (dropping tildes):

$$h_t + (uh)_x = \begin{cases} -\delta p & x < -l, x > 1 \\ -\delta(p-p_p) & -l < x < 0, \\ 0 & 0 \le x \le 1, \end{cases} \tag{4.9}$$

$$u_t + \chi u u_x = -p_x - \frac{\gamma u}{h^2}, \tag{4.10}$$

$$h_{xx} = \alpha(p_p - p),\ 0 \le x \le 1, \tag{4.11}$$

$$h = 1,\ x < 0, x > 1, \tag{4.12}$$

$$\int_{-l}^{0} p dx - (l+\beta)p_p = \frac{1}{\delta}\frac{d}{dt}\int_0^1 (1-h)dx. \tag{4.13}$$

Motivated by the above equations, we now consider the limit $\delta \to 0$, corresponding to the blood flow in the vasa vasorum being a negligible percentage of the arterial blood flow, and rescale time: $t = \delta^{-1}\widehat{t}$, corresponding to long times. In the regions $x < 0$ and $x > 1$ we obtain the trivial solutions $u = h = 1$. The interesting behaviour occurs in the plaque region $0 \le x \le 1$, where the governing equations are

$$hu = 1\ ,\ \chi u u_x = -p_x - \frac{\gamma u}{h^2}\ ,\ h_{xx} = \alpha(p_p - p)\ ,\ -\frac{d}{dt}\int_0^1 h dx = \int_{-l}^{0} p dx - (l+\beta)p_p. \tag{4.14}$$

4.4 Results

Equations (4.14)a–c may be combined into a single, third-order, nonlinear ODE:

$$h_{xxx} = \alpha h^{-3}(\gamma - \chi h_x)\ , \tag{4.15}$$

requiring three boundary conditions. We set

$$h(0) = h(1) = 1 \text{ and } h_{xx}(0) = \alpha p_p(t)\ , \tag{4.16}$$

where the last condition is equivalent to setting $p(0) = 0$. This problem is solved using AUTO [3]. The solution for h will be a function of $p_p(t)$. The stability of the solutions is determined as follows. We have

$$\frac{d}{dt}\int_0^1 (1-h)dx = \gamma l^2/2 - (l+\beta)p_p \tag{4.17}$$

and taking $\beta = 1$ and $l = 0.5$ gives $p_p = \gamma/12$ in equilibrium. The integral $\int_0^1 (1-h)dx$ depends on t only via $p_p(t)$ (see 4.16). Writing $\int_0^1 (1-h)dx = H(p_p(t))$, (4.17) may be written as

$$\frac{dH}{dp_p}\frac{dp_p}{dt} = \gamma l^2/2 - (l+\beta)p_p \ . \tag{4.18}$$

Thus, the stability of an equilibrium solution is determined by examining how $H(p_p)$ varies with p_p (all other parameters being fixed). If $H(p_p)$ is increasing (decreasing) in p_p the solution is stable (unstable).

Figure 25(a) shows how the equilibrium value of the plaque volume varies with α; here $\gamma = 0.1$ and $\chi = 1$ (corresponding to no flow separation). We see that two equilibrium solutions exist for α up to a critical value, beyond which no equilibrium solutions exist. We postulate, therefore, that plaque rupture occurs when α exceeds this critical value. The stability of these equilibrium solutions is also indicated (where thick lines indicate stable solutions). Note the existence of two stable solutions for small values of α. In figure 25(b), the equilibrium plaque profiles for several values of α are plotted.

Similar plots are shown in figure 26, illustrating the dependence of the solutions on γ (now $\alpha = 1$ and $\chi = 1$). As before, a critical value of γ exists beyond which no equilibrium solutions are found (corresponding to larger viscosities). For each γ the solution with the lower value of $\int_0^1 (1-h)dx$ is stable while the other solution is unstable.

In figure 27 the dependence of the solutions on p_p is shown (where $\gamma = 0.1,\ \chi = 1$). Equilibrium solutions correspond to $p_p = \gamma/12 = 1/120$. Since $\int_0^1 (1-h)dx$ increasing with p_p indicates stable solutions we see that both equilibrium solutions are stable when $\alpha = 0.1$, whereas when $\alpha = 1$, one stable and one unstable solution exists (figure 27).

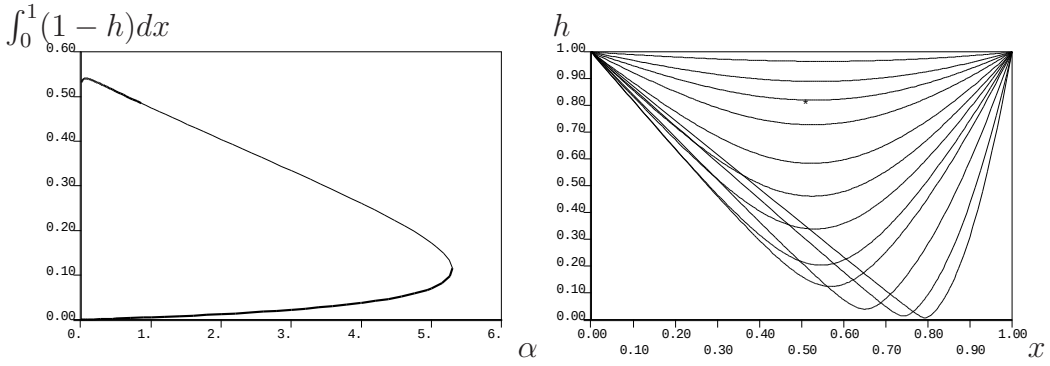
Finally, figure 28 illustrates that the degree of flow separation, χ_0, does not affect the qualitative behaviour of the results. As χ_0 increases the critical values of the parameters (either α_c or γ_c), at which (we postulate) rupture occurs, decrease.

4.5 Nutrient diffusion problem

Here we develop a model for nutrient delivery in the arterial wall, in order to determine the nutrient gradients across the vessel wall.

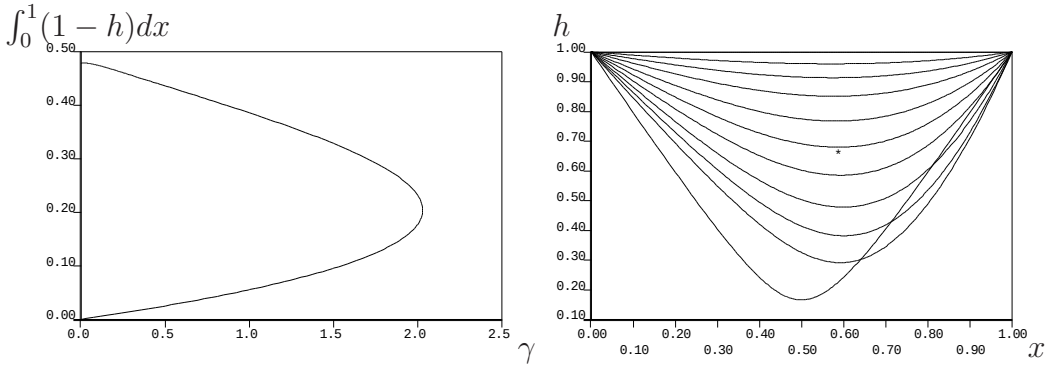
4.5.1 Steady State Equations & Boundary Conditions

We consider the steady state problem only and model the artery wall as divided into two parts: an inner region where the nutrients are supplied solely from the vessel lumen ($0 < z < \eta$) and an outer layer into which the vasa vasorum penetrates ($\eta < z < L$);



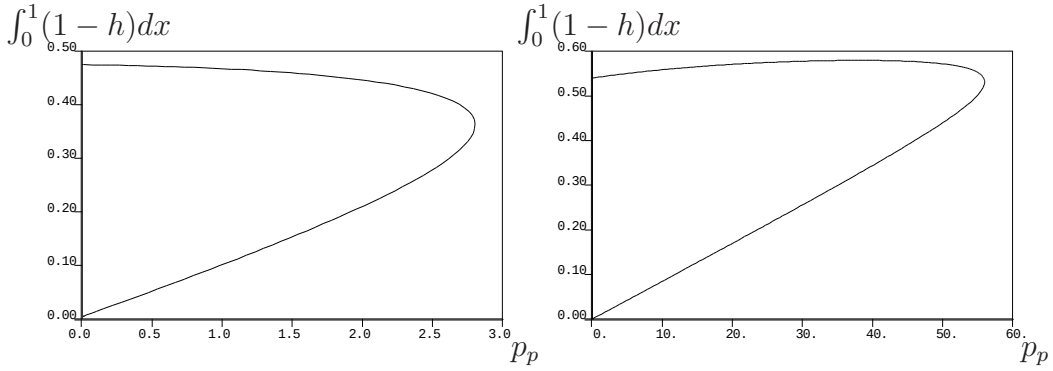
(a) (b)

Figure 25: (a) α-diagram of equilibrium solutions for fixed $\gamma = 0.1$, $\chi = 1$. The thick lines indicate the *stable* solutions. (b) Profiles at various points along the curve in the α-diagram, starting from $h \equiv 1$ for $\alpha = 0$; when α approaches 0 again the minimum of the profile tends to 0. The profile corresponding to the critical value of α is marked with an asterix.



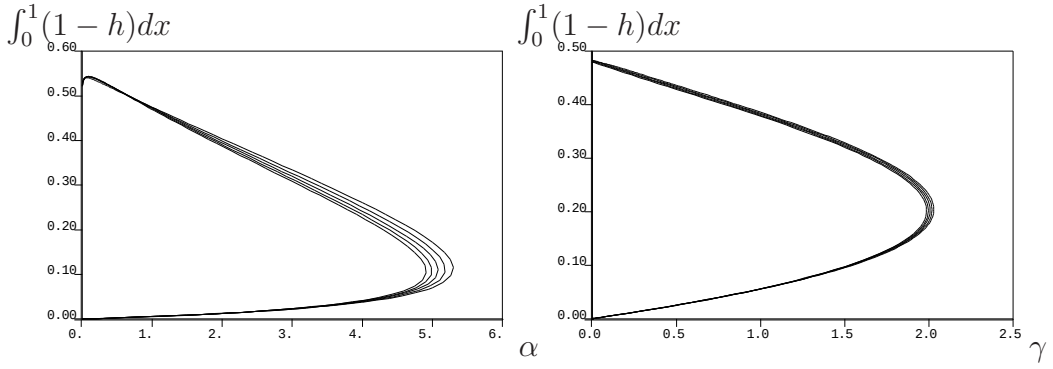
(a) (b)

Figure 26: (a) γ-diagram of equilibrium solutions for fixed $\alpha = 1$, $\chi = 1$. For each γ the solution with the lower $\int_0^1(1-h)dx$ is stable while the other one is unstable (this would be different if α were smaller). (b) Profiles at various points along the curve in the γ-diagram; starting from $h \approx 1$ for $\gamma = 0$, the minimum of the profile gradually decreases as we move along the curve, and as γ returns to 0 the profile becomes symmetric. The profile corresponding to the critical value of γ is marked with an asterix.



(a) (b)

Figure 27: p_p-diagram for fixed $\alpha = 1$ (a) and $\alpha = 0.1$ (b), ($\gamma = 0.1$, $\chi = 1$ in both cases). The equilibrium solutions correspond to $p_p = \frac{1}{120}$. Both equilibrium solutions are stable for $\alpha = 0.1$. For $\alpha = 1$, one equilibrium solution is stable (lower branch), while the other is unstable.



(a) (b)

Figure 28: (a) α-diagram ($\gamma = 0.1$) for various values of χ_0: $\chi_0 = 0, 0.25, 0.5, 0.75, 1$, where the curve moves to the left as χ_0 increases. (b) γ-diagram ($\alpha = 1$) for the same values of χ_0; the curve again moves to the left as χ_0 increases.

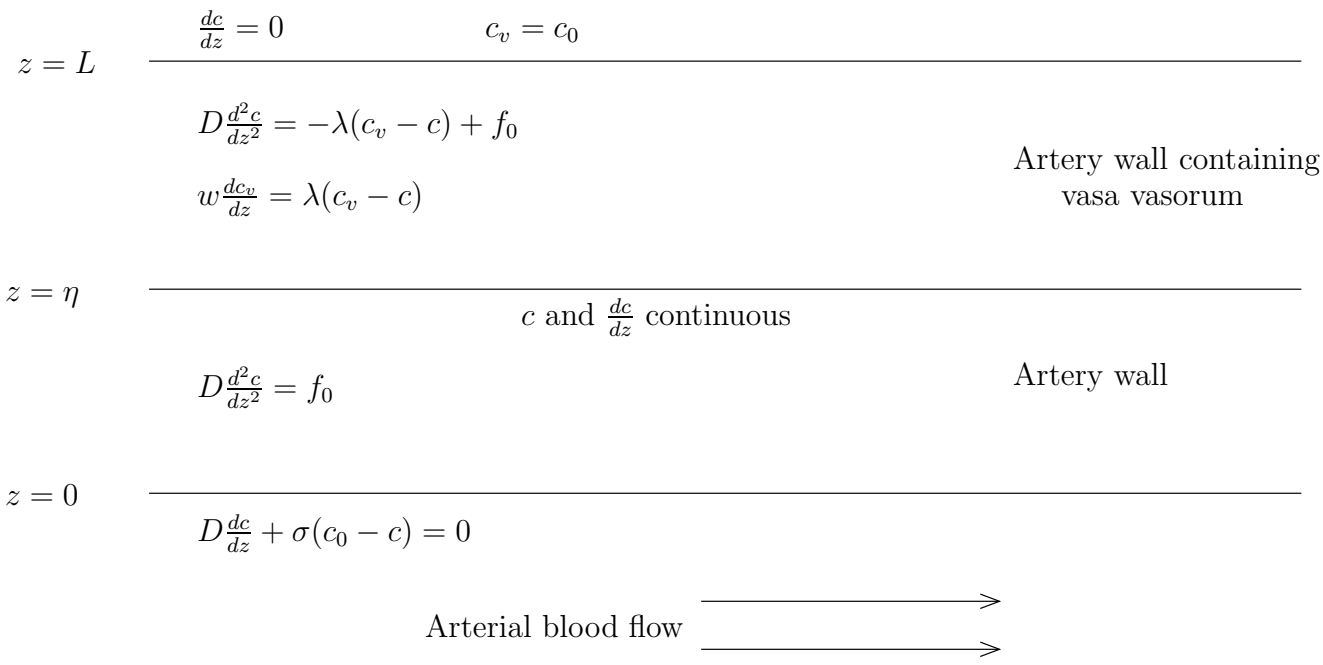


Figure 29: Nutrient diffusion through the artery wall.

see figure 29. Let the nutrient concentration in the artery wall be $c(z)$ and that in the vasa vasorum $c_v(z)$. We assume the nutrient concentration of 'fresh' blood in the artery to be c_0. We then propose the following reaction-diffusion equations with a term $f(c)$ representing nutrient uptake by the cells.

In the region $0 < z < \eta$ we have

$$D\frac{d^2c}{dz^2} - f(c) = 0, \tag{4.19}$$

together with the boundary condition $D\ dc/dz{=}{-}\sigma(c - c_0)$ on $z = 0$. Here D is the nutrient diffusivity and σ is the artery wall permeability coefficient.

In the region $\eta < z < 1$ we have two coupled equations

$$D\frac{d^2c}{dz^2} + \lambda(c_v - c) - f(c) = 0\ ,\ w\frac{dc_v}{dz} = \lambda(c_v - c), \tag{4.20}$$

where w is the (averaged) velocity of blood in the vv and λ is the permeability of the vv capillaries. We also have the boundary conditions $dc/dz = 0$ (representing zero nutrient flux through the artery wall) and $c_v = c_0$ on $z = L$. Finally, we require that c and dc/dz be continuous at $z = \eta$.

For simplicity, we consider the case where $f(c) = f_0$ (constant) and nondimensionalise the model in the following way:

$$\widetilde{z} = \frac{z}{L}\ ,\ \widetilde{\eta} = \frac{\eta}{L}\ ,\ \widetilde{c} = \frac{c}{c_0}\ ,\ \widetilde{c_v} = \frac{c_v}{c_0}\ ,\ \widetilde{\lambda} = \frac{\lambda L^2}{D}\ ,\ \widetilde{f_0} = \frac{f_0 L^2}{Dc_0}\ ,\ \widetilde{w} = \frac{w}{L\lambda}\ ,\ \widetilde{\sigma} = \frac{\sigma L}{D}. \tag{4.21}$$

The model equations thus become (dropping the tildes):

$$\frac{d^2c}{dz^2} - f_0 = 0 \quad (0 < z < \eta) \tag{4.22}$$

$$\frac{d^2c}{dz^2} = -\lambda(c_v - c) + f_0 \ , \ w\frac{dc_v}{dz} = (c_v - c) \quad (\eta < z < 1) \ , \tag{4.23}$$

with boundary conditions $c = 1$, $dc/dz = -\sigma(1 - c)$ on $z = 0$ and $dc/dz = 0$ and $c_v = 1$ and $z = 1$. We also require that c and dc/dz be continuous at $z = \eta$.

The solution to this model for $0 < z < \eta$ is:

$$c = Az + B + \frac{f_0 z^2}{2} \tag{4.24}$$

and for $\eta < z < 1$:

$$c = C\exp(u_+ z) + D\exp(u_- z) + \frac{f_0(z-1)}{w} + c_0 - \frac{f_0}{\lambda} - \frac{f_0}{w^2}, \tag{4.25}$$

$$c_v = -\frac{1}{w}[Cu_+\exp(u_+ z) + Du_-\exp(u_- z) - f_0 z + \frac{f_0}{w} - w + f_0] \ , \tag{4.26}$$

where $u_\pm = (\lambda \pm \sqrt{\lambda^2 + 4\lambda w^2})/2w$. In obtaining the above solutions, we have imposed the boundary condition $c_v = 1$ on $z = 1$; the constants A-D are determined by imposing the two remaining boundary conditions, together with continuity of c and dc/dz at $z = \eta$, *i.e.*

$$\begin{aligned}
A + \sigma(1 - B) &= 0, \\
u_+ Ce^{u_+} + u_- De^{u_-} + \frac{f_0}{w} &= 0, \\
u_+ Ce^{u_+\eta} + u_- De^{u_-\eta} + \frac{f_0}{w} &= f_0\eta + A, \\
Ce^{u_+\eta} + De^{u_-\eta} + \frac{f_0\eta}{w} - \frac{f_0}{\lambda} - \frac{f_0}{w^2} - \frac{f_0}{w} + 1 &= \frac{f_0\eta^2}{2} + A\eta + B.
\end{aligned}$$

We now plot the concentration profiles, for given values of η and λ, with $f_0 = 0.1$, $\sigma = 1$ and $w = 1$ (see figures 30 and 31). In figure 31, a greater part of the artery wall is fed by the vv network. In both cases we see that as λ increases, corresponding to increased delivery of nutrient to the artery wall by the vasa vasorum, the nutrient concentration in the outer part of the wall is significantly raised. As can be seen from figures 30 and 31, varying η has very little effect on the form of the solution.

4.6 Conclusions

We have developed and solved simple mathematical models in order to address the questions asked. The flow model postulates that plaque rupture may occur when the governing dimensionless parameters exceed critical values. The concentration model illustrates the effectiveness of the vasa vasorum network in supplying the outer portion of the artery wall with nutrients.

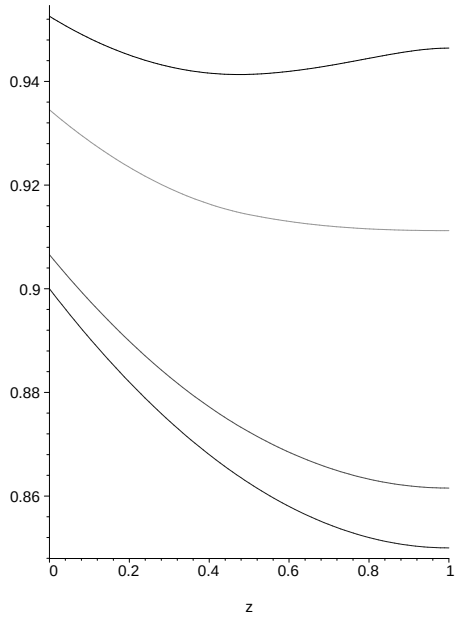


Figure 30: The concentration profiles for (top to bottom): $\lambda = 10$, $\lambda = 1$, $\lambda = 0.1$ and $\lambda = 0$. ($\eta = 0.5$ in all cases.)

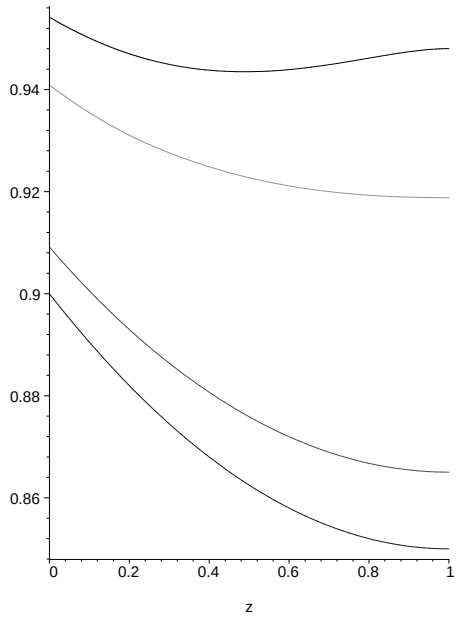


Figure 31: The concentration profiles for (top to bottom): $\lambda = 10$, $\lambda = 1$, $\lambda = 0.1$ and $\lambda = 0$. ($\eta = 0.25$ in all cases.)

One interesting result of the flow model is that the larger the dimensionless viscosity, γ, the more susceptible the plaque is to rupture (according to our hypothesis). This result suggests that it might be profitable to study the effectiveness of blood-thinning drugs (*e.g.* aspirin) for patients with vascular disease (aspirin is currently used to prevent Deep Vein Thrombosis and heart attacks).

However, many refinements need to be made to both models. The artery has been modelled as a two-dimensional channel and a simple extension is to consider the artery as an axisymmetric tube. We have not yet incorporated the elasticity of the artery or the pulsatility of the blood flow (our model averaged over many pulses). For example, Ku & McCord (1993) [2] hypothesise that the low luminal pressures centred in the narrowest point of the stenosis (Bernoulli principle) results in a compressive stress that may buckle the fibres in the arterial wall. Oscillations in the compressive loading of the arterial wall may induce a fracture fatigue in the surface of the atherosclerotic plaque, causing rupture of the plaque cap. We have also assumed that all the vasa vasorum vessels branch from the artery upstream of the plaque, while it is likely that some also originate downstream of the plaque. The plaque has also been modelled as a "blood blister", when in reality its structure is much more complex, as it has a fibrous cap and contains, for example, cholesterol and lipids. Finally, we have pinned the plaque at its ends (at $x = x_1$ and $x = x_2$) whereas in reality the plaque will grow.

In the case of the nutrient problem, limitations include the assumption that the cells of the artery wall take up nutrients at a constant rate (in reality, we would expect saturation, with the cells ceasing to take up nutrient when the nutrient concentration reaches some critical level). We also prescribed the position of the boundary between that part of the artery wall containing vasa vasorum, and that containing no vasa vasorum. However, physiologically, we would expect this boundary to move as the vasa vasorum proliferates in response to nutrient demand (although these preliminary results indicate that varying η has a very small effect). Finally, it would be instructive to consider the situation in which the number and permeability of the vv vessels depends on the nutrient concentration, so that the effects of vv proliferation in response to a local decrease in nutrient concentration can be captured.

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