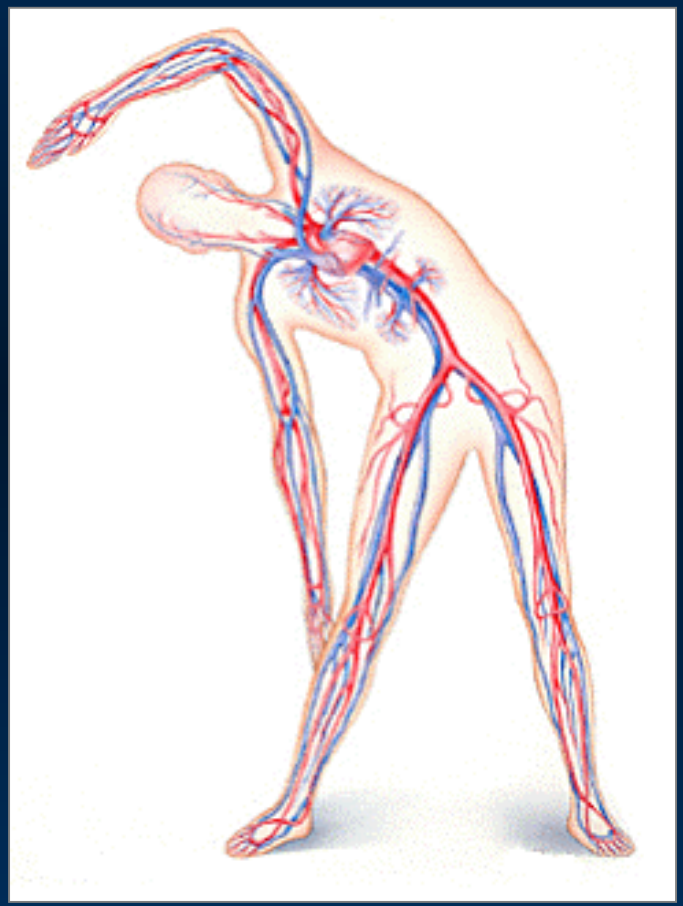
Mathematical Modelling of Vascular Disease



Professor Nick Hill

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Park City Mathematics Institute, 2005

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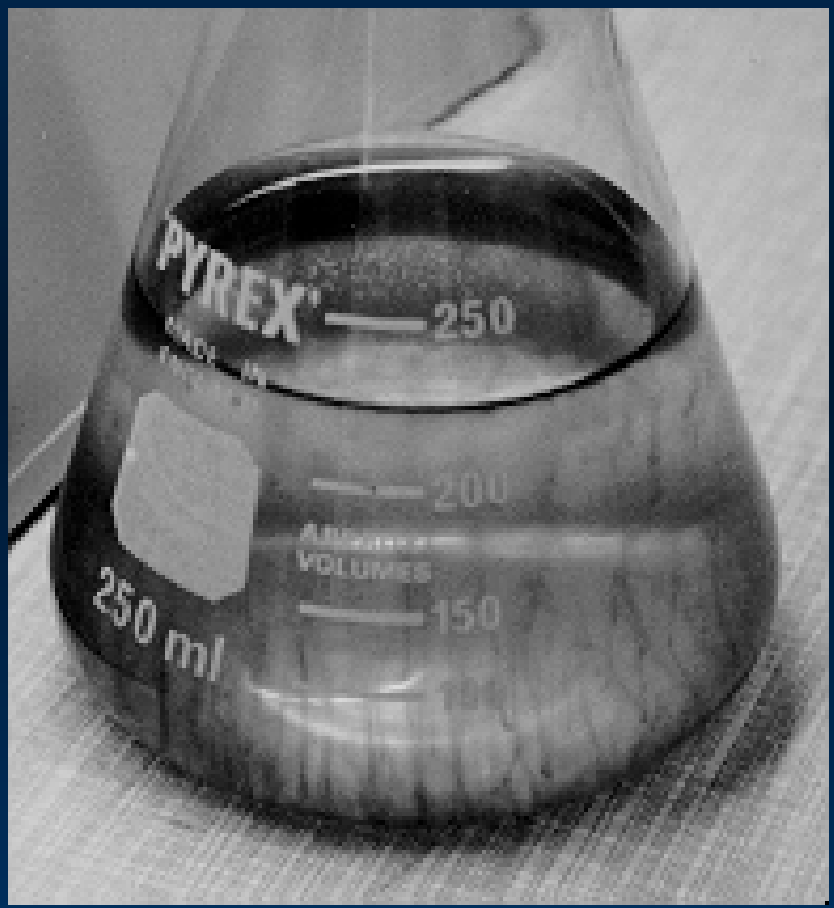
Mathematical Biology

- Mathematical modelling applied to problems in biology and medicine
- Interdisciplinary →
- Leads to new applied mathematics and new results in life sciences
- E.g. bioconvection ⟹ new random walk
  ⟹ angiogenesis

Bioconvection plumes in a suspension of C. *nivalis* algae



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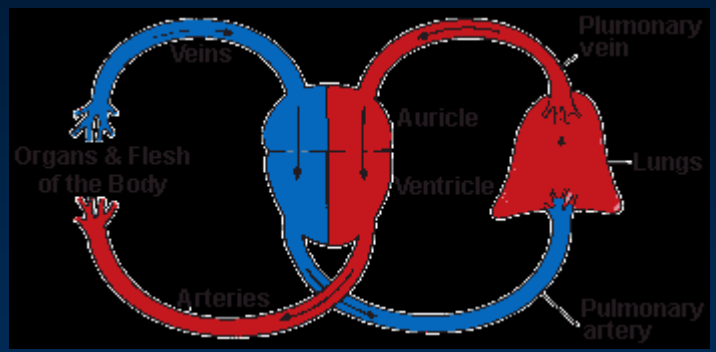
History of Vascular Modelling

William Harvey – discovery of the circulation
1628

William Harvey (1578-1657)



Since all things, both argument and ocular demonstration, show that the blood passes through the lungs and heart by the force of the ventricles, and is sent for distribution to all parts of the body, where it makes its way into the veins and porosites of the flesh, and then flows by the veins from the circumference on every side to the centre, from the lesser to the greater veins, and is by them finally discharged into the vena cava and right auricle of the heart, and this in such a quantity or in such a flux and reflux thither by the arteries, hither by the veins, as cannot possibly be supplied by the ingesta, and is much greater than can be required for mere purposes of nutrition; it is absolutely necessary to conclude that the blood in the animal body is impelled in a circle, and is in a state of ceaseless motion. (1628)

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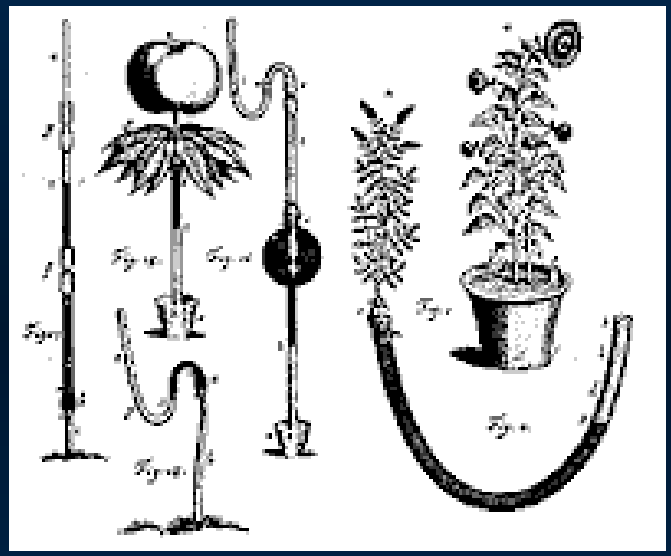
History of Vascular Modelling

Stephen Hales
1677 – 1761



Vegetable staticks 1733

- blood pressure measurements
- flow resistance occurs mainly in the microcirculation
- effects of elasticity of the arteries

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History of Vascular Modelling

Development of fluid dynamics

- Euler
- Daniel Bernoulli (Professor of Anatomy)
- Poiseuille (Physician)

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History of Vascular Modelling

Thomas Young
1773 –1829

Developed the theory of wave propagation in elastic tubes

Thomas Young (1773-1829)

` … the enquiry, in what manner, and in what degree, the circulation of the blood depends on the muscular and elastic powers of the heart and of the arteries, supposing the nature of those powers be known, must become simply a question belonging to the most refined departments of the theory of hydraulics.' 1809

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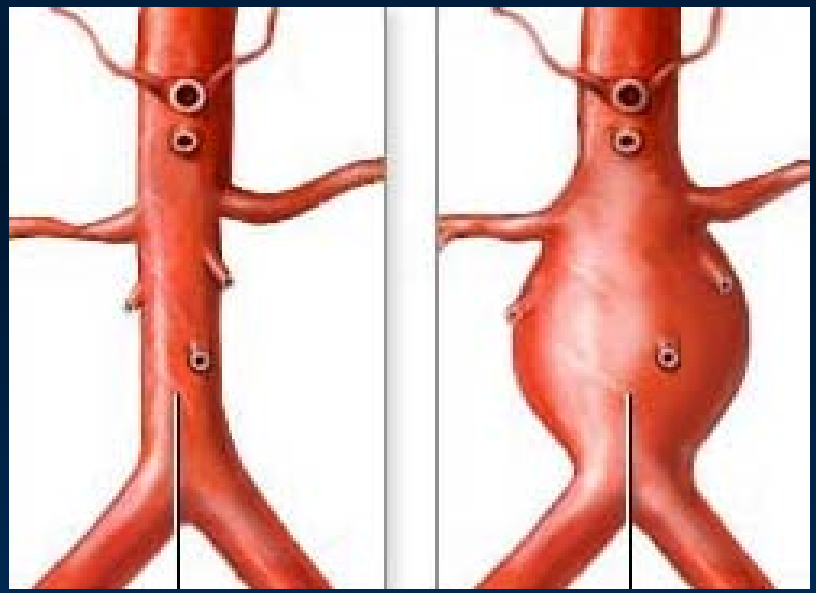
History of Vascular Modelling

Flow profile and the link with atherosclerosis

- Wormersley 1955 – velocity profile and viscosity
- Caro, Fitz-Gerald & Schroter 1971 – correlation between low wall shear stress and fatty streaks
- Fry 1973 – transport of lipoproteins through the arterial wall

Abdominal Aortic Aneurysms

an example of structural changes in disease



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Department of Mathematics

University of Glasgow

Dr Matthias Heil

Department of Mathematics

University of Manchester

Mr Simon Dodds

Department of Vascular Surgery

Good Hope Hospital NHS Trust

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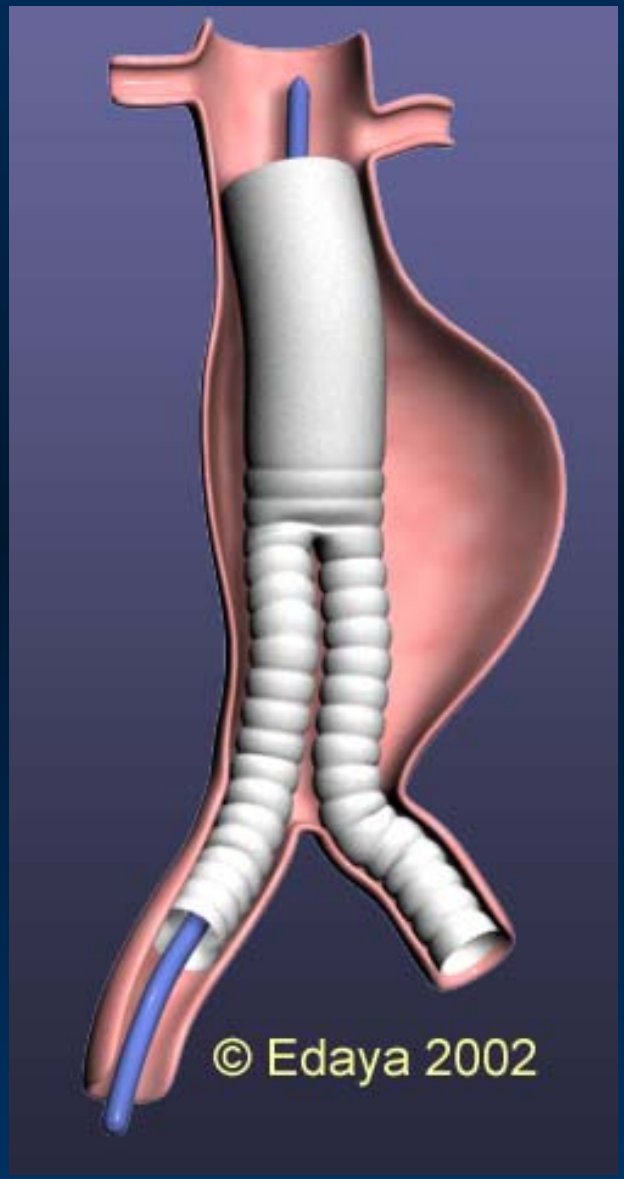
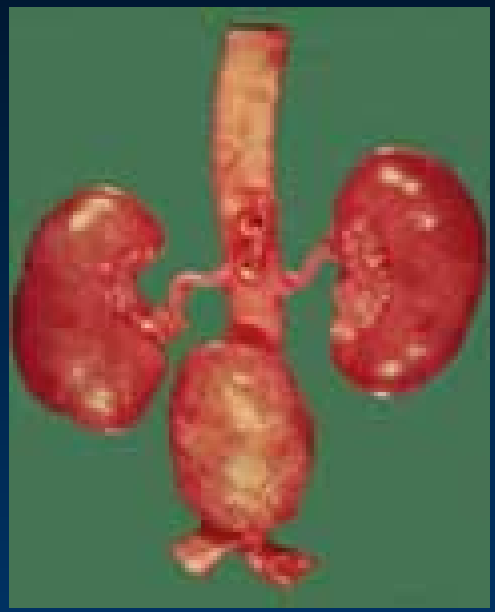
What is an abdominal aortic aneurysm?



A gradual dilation of the aorta that occurs over a period of 10 years usually between the renal arteries and the iliac bifurcation.



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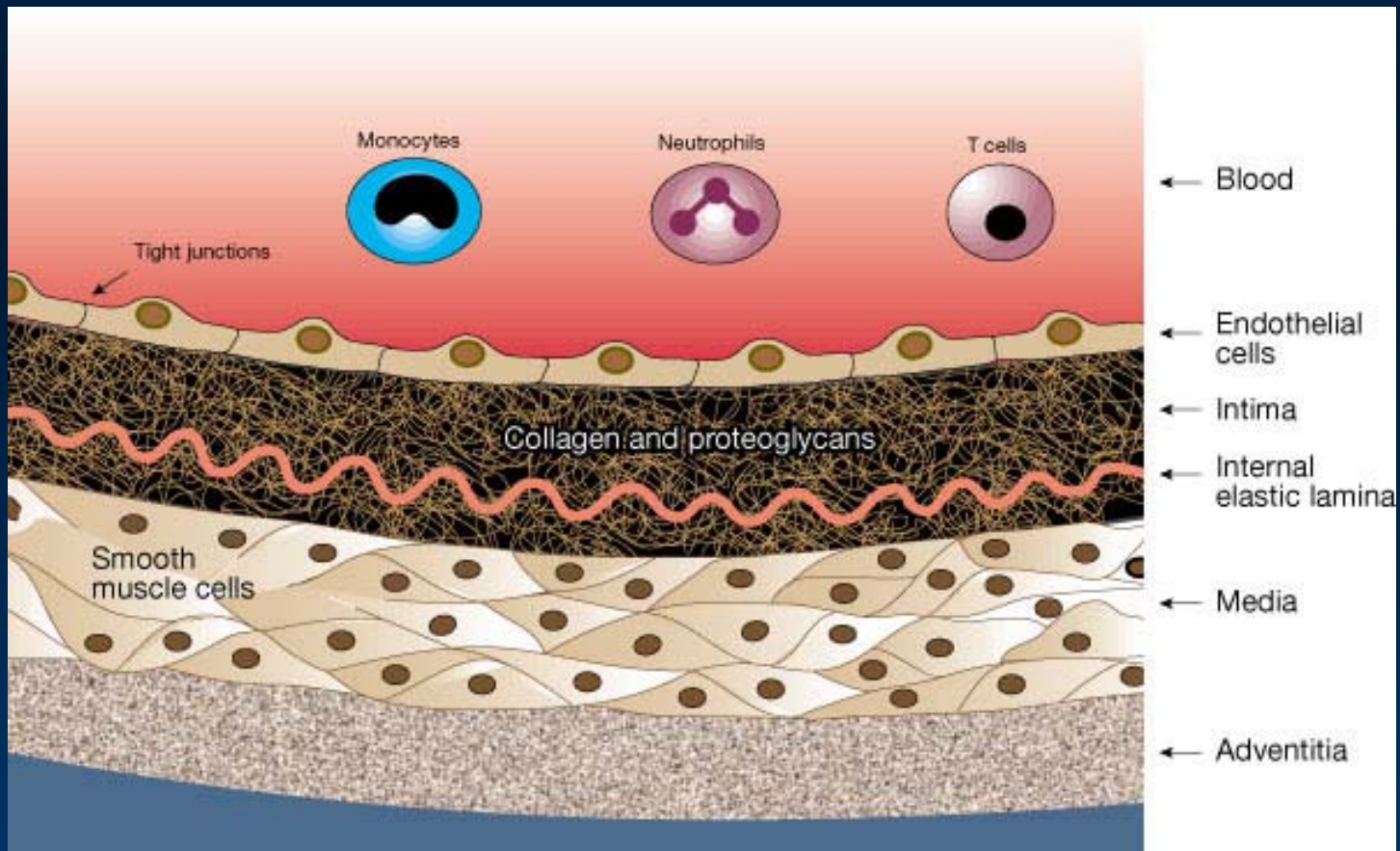
Abdominal Aortic Aneurysms

- Localised dilation of the abdominal aorta.
- Affects 3-5% of population.
- Aneurysm may rupture with high mortality rate (80%).
- Surgery high risk - 1/20 risk of failure (death).
- There is a critical diameter (>5cm) for which risk of rupture exceeds risk of operation. However, small aneurysms may rupture, whilst larger ones remain intact.
- Mathematical models may yield improved rupture criteria:
  - identifying critical regions of stress/strain
  - predicting future dilation

Structure and material properties of the arterial wall

Holzapfel, G.A., Gasser, T.C. & Ogden, R.W., 2000



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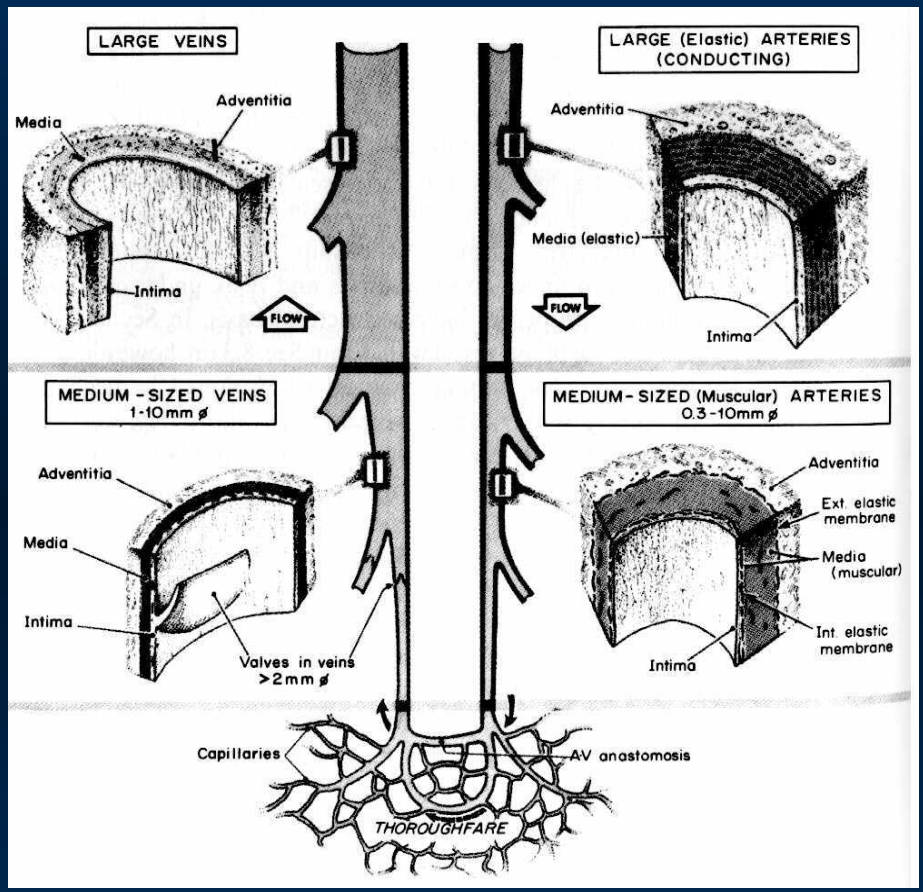
Constructing a Model

- Driving mechanism - Degradation of elastin. Aneurysms develop over a number of years, the diameter increases by a factor of 2-3, elastin degrades to 10-20% of its original value.
- Arterial remodelling - Arteries adapt to changes in their mechanical environment in order to restore or optimize some basic mechanical or functional characteristic.
- Structure - only tissues of importance are elastin and collagen.
- Gene for elastin is switched off after puberty
- Collagen fibres are in a continual state of deposition and degradation.
- Remodelling - Given that elastin degrades, how will collagen remodel?

Mammalian Blood Vessels



Rhodin (1980) Handbook of Physiology

Scheme of a human artery with balloon dilation catheter

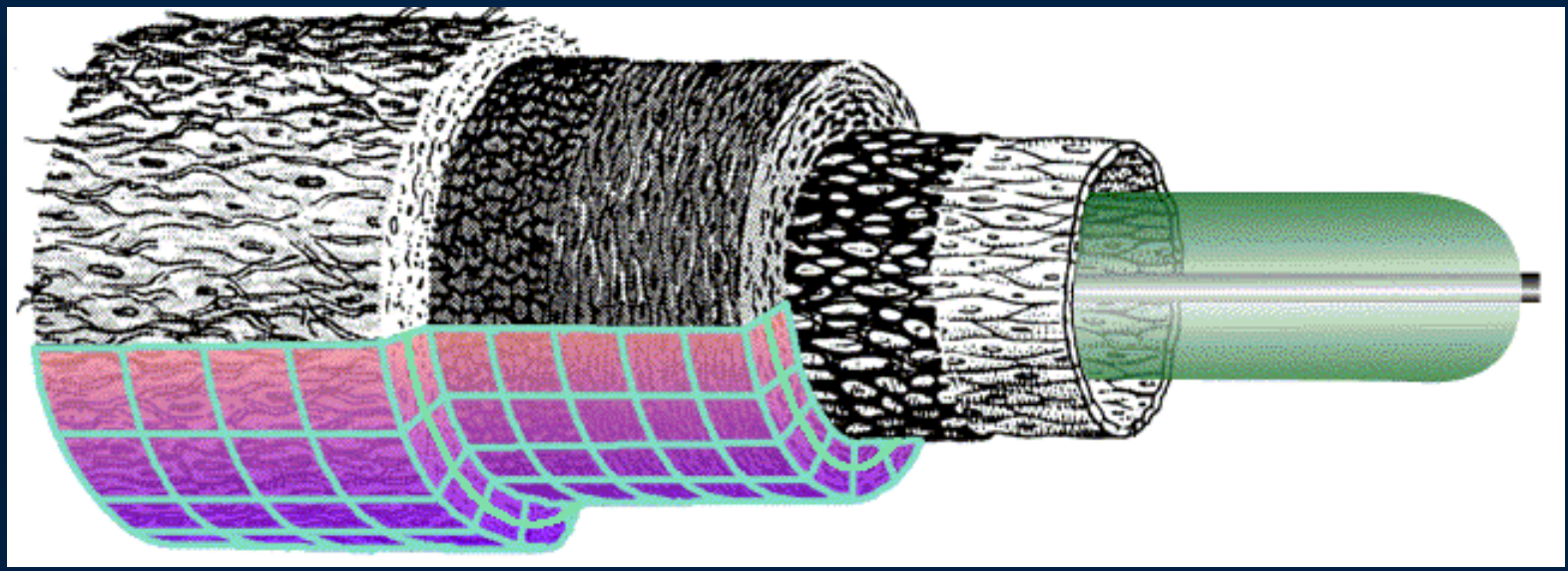


Image source: Leonhardt Helmut, Histologie, Zytologie und Mikroanatomie des Menschen, 1985

Constructing a Model

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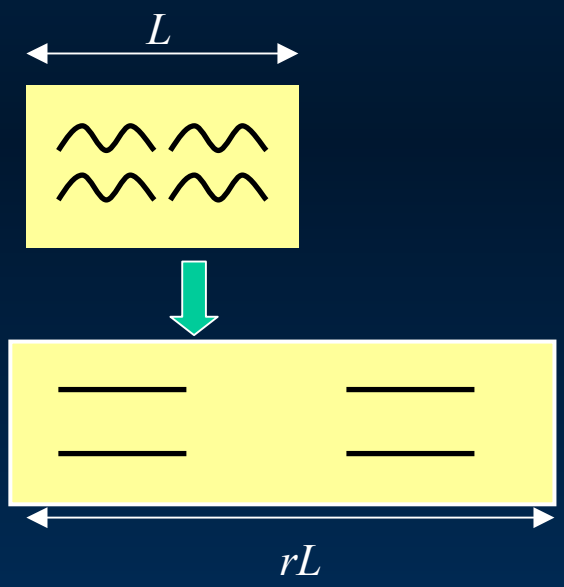
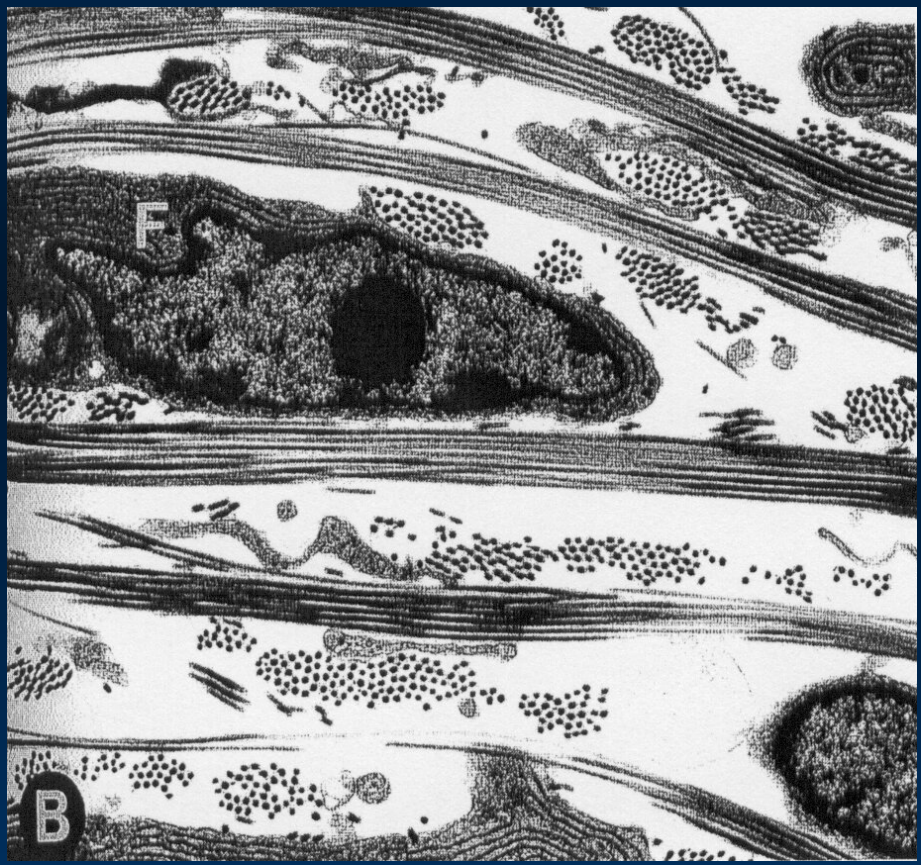
Collagen Recruitment: The *r* Factor

Crimped collagen is recruited when unstrained tissue is stretched by a factor ***r***.



- The strain in the elastin is zero in the unstrained system.
- In fact, collagen fibres will be distributed with a range of crimpedness.
- Thus ***r*** refers to fibres of minimum waviness and represents the minimum value the system must be stretched for the collagen to begin to bear load.
- Once recruitment begins it is assumed that the subsequent gross stress-strain relationship is known.

Fibroblasts and Collagen Fibres



Transmission electron micrograph of middermal region from dorsolateral trunk of a 15-day old chick. Collagin fibril bundles and the fibroblasts (F) are well-ordered.

C. Ploetz *et al*. (1991) J. Struct Biol 106, 73-81.

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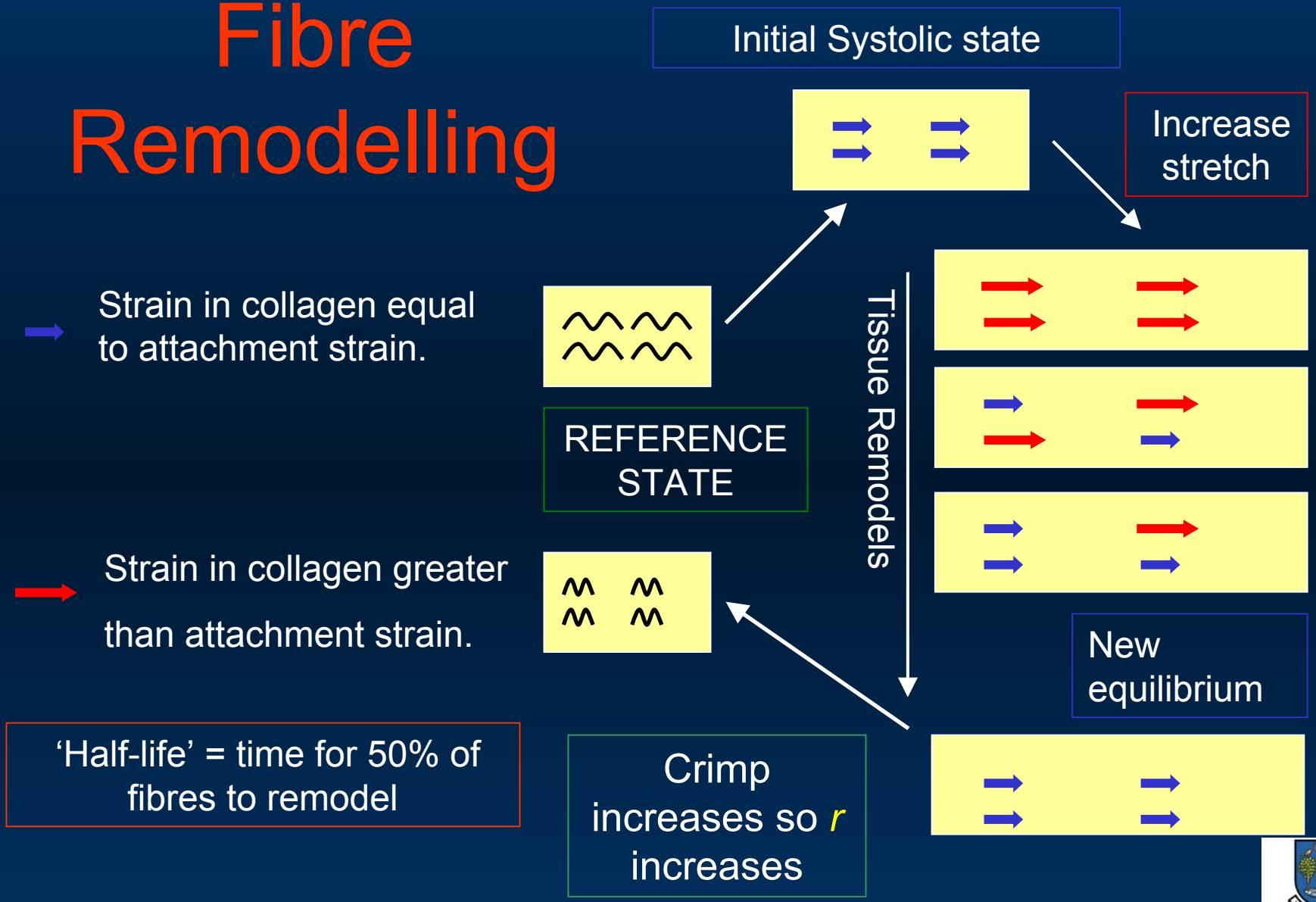
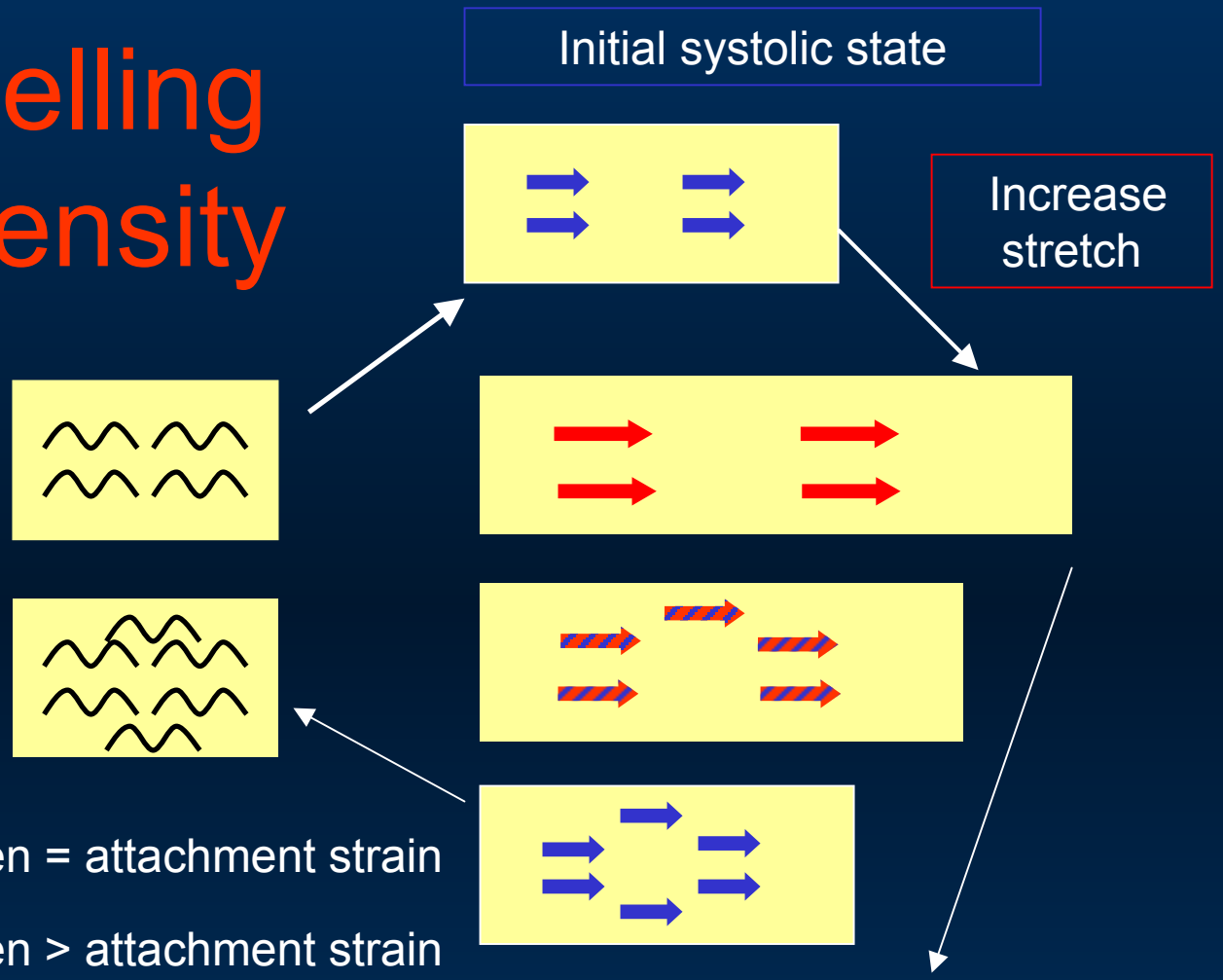
Remodelling

- Collagen fibres are in a state of continual deposition and degradation.
- There is a peak attachment strain ε_A for collagen fibres which occurs at systole.
- Want to find the deformations that occur for a constant systolic pressure as the elastin degrades and the collagen remodels to maintain its strain at ε_A.

Fibre Remodelling



Remodelling Fibre Density



Density Increases – tissue retracts, or limits rate of dilation

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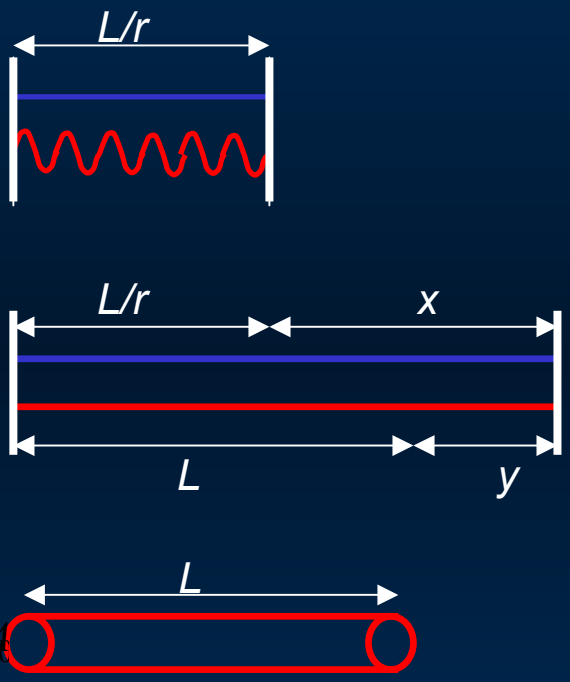
Collagen Fibre Strains

Unstrained Material



Collagen Fibre at onset of recruitment

$$\varepsilon_E = ([(x + L/r)/(L/r)]^2 - 1)/2$$

$$\varepsilon_C = ([(y + L)/L]^2 - 1)/2$$

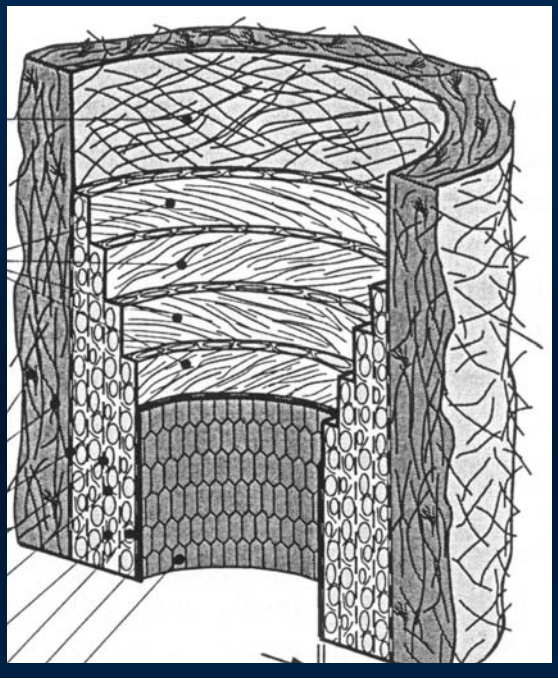
$$\Rightarrow \varepsilon_C = \frac{1}{r^2}(\varepsilon_E + (1 - r^2)/2)$$

Remodelling variables defined over membrane

$$r(x^1, x^2, t), \quad n(x^1, x^2, t)$$

N.B. Green's strains and nonlinear elasticity

3D Strain Energy Density Function



Holzapfel, G.A. *et al*. 2000 A new constitutive framework for the arterial wall.

$\varepsilon_{C_{Jp}}(x^1, x^2, t)$	strain in collagen fibres
$c_E(x^1, x^2, t)$	density of elastin
$n_{Jp}(x^1, x^2, t)$	density of fibres
$r_{Jp}(x^1, x^2, t)$	recruitment variables
$p = +/-$	pitch of collagen **+/-** β_{Jp}
k_x, k_E, k_J, a_J	physiological constants
$J=M, A$	Media (M), Adventitia (A)

$$w_{fibre} = f(\varepsilon_C(x^1, x^2))$$

$$W_C = n(x^1, x^2) w_{fibre}$$

$$W_M = (k_x + c_E(x^1, x^2, t)k_E)(\varepsilon_{11} + \varepsilon_{22} + \varepsilon_{33}) + \sum_{p=\pm} \left\{ n_{M_p} k_M (\exp(k_f \varepsilon^2_{C_{M_p}}) - 1) \right\}$$

$$W_A = k_x(\varepsilon_{11} + \varepsilon_{22} + \varepsilon_{33}) + \sum_{p=\pm} \left\{ n_{A_p} k_A (\exp(k_f \varepsilon^2_{C_{A_p}}) - 1) \right\}$$

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Resolving the Strains in the Collagen Fibres

$$\varepsilon^{C}_{E_{J_p}} = \varepsilon_{11}\sin^2\beta_{J_p} + \varepsilon_{22}\cos^2\beta_{J_p} + 2\varepsilon_{12}\sin\beta_{J_p}\cos\beta_{J_p}$$

$$\varepsilon_{C_{J_p}} = \frac{(\varepsilon^{C}_{E_{J_p}} + (1 - r^2_{J_p})/2)}{r^2_{J_p}}$$

$\varepsilon_{11}, \varepsilon_{22}, \varepsilon_{12}$ = Green's strain for elastin.

β_{J_p} = Pitch of Collagen Fibres to azimuthal axis

r_{J_p} = Recruitment Variables

$\varepsilon_{C_{J_p}}$ = Green's strain for collagen.

Remodelling of Collagen

For simplicity, linear functions are used:

$$\frac{dr_{J_p}(x^1,x^2,t)}{dt}=\alpha(\varepsilon_{J_p}(x^1,x^2,t)-\varepsilon_A),\qquad \frac{dn_J(x^1,x^2,t)}{dt}=\beta(\varepsilon_{C_J}(x^1,x^2,t)-\varepsilon_A)$$
$$\alpha,\beta>0.$$

• Given a half-life of the collagen fibres a corresponding value for α can be determined.

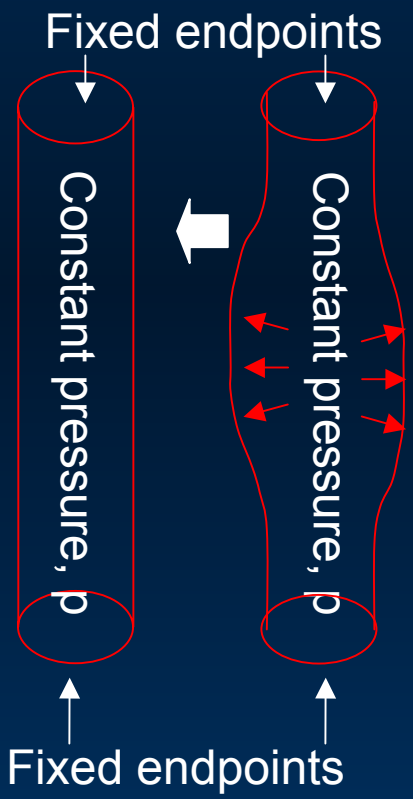
• β is then numerically determined by requiring that the dilation of the aneurysm is physiologically consistent.

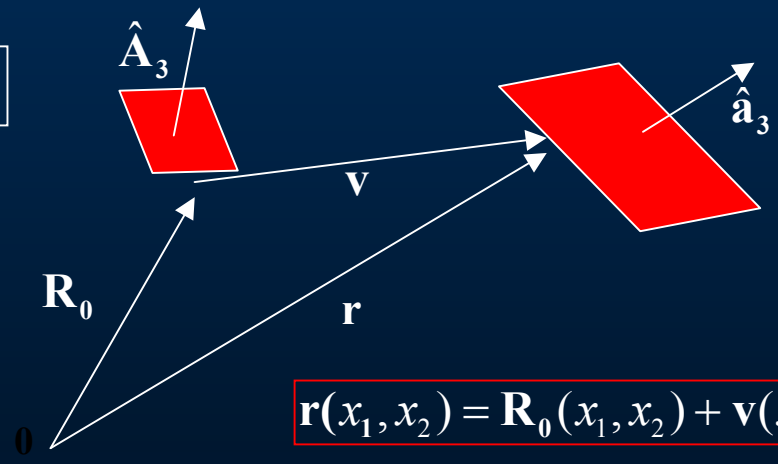
Note: if only r remodels and $n_{J_p}(x^1,x^2,t)=1$

total mass of collagen in the arterial wall remains constant.

Membrane Analysis

Mid-plane Deformation





$$\mathbf{r}(x_1, x_2) = \mathbf{R}_0(x_1, x_2) + \mathbf{v}(x_1, x_2)$$

$$\int_{volume} \delta W dV - \oint_{surface} p(\hat{\mathbf{a}}_3 \cdot \delta\mathbf{v}) dS = 0$$

$$\iint ((\varphi_i - p_i)\delta v^i + \varphi_{i1}\delta v^i_{,1}) dx^1 dx^2 = 0$$

$$\varphi_i = \varphi_i(v^i, v^i_{,1}, c_E(x_1, x_2, t), r_{J_p}(x_1, x_2, t), n_{J_p}(x_1, x_2, t))$$

VARIATIONAL EQUATION SOLVED BY FEM

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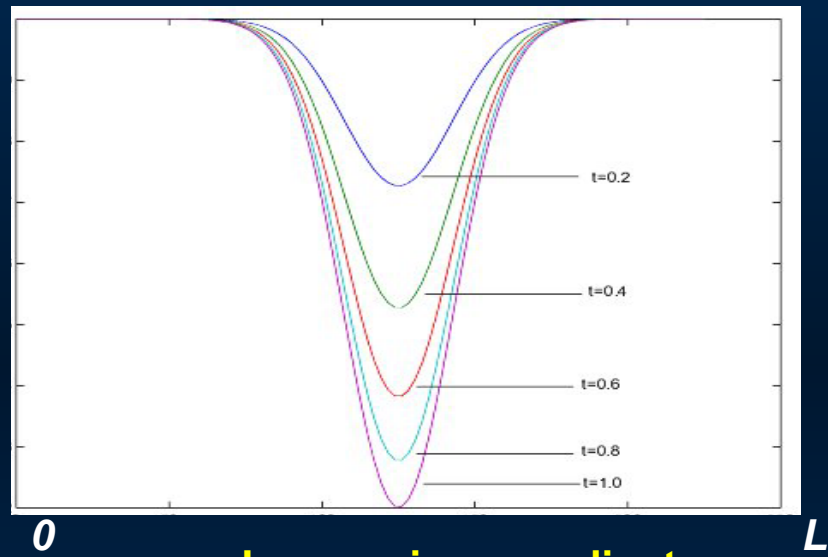
Modelling Elastin Degradation

- Assume:

- minimum point of concentration of elastin that decays exponentially

- elastin does not degrade at end points where aneurysm does not form

- elastin is degraded using a Gaussian profile



$$c_E(x^1, x^2, t) = 1 - (1 - c_{\min}^{t/T})(\exp[-4a(x^1 - L/2)^2 / L^2])$$

where

$c_{\min}$ = minimum concentration of elastin at $t = T$.

Here c_{min}=0.2, T=10 years.

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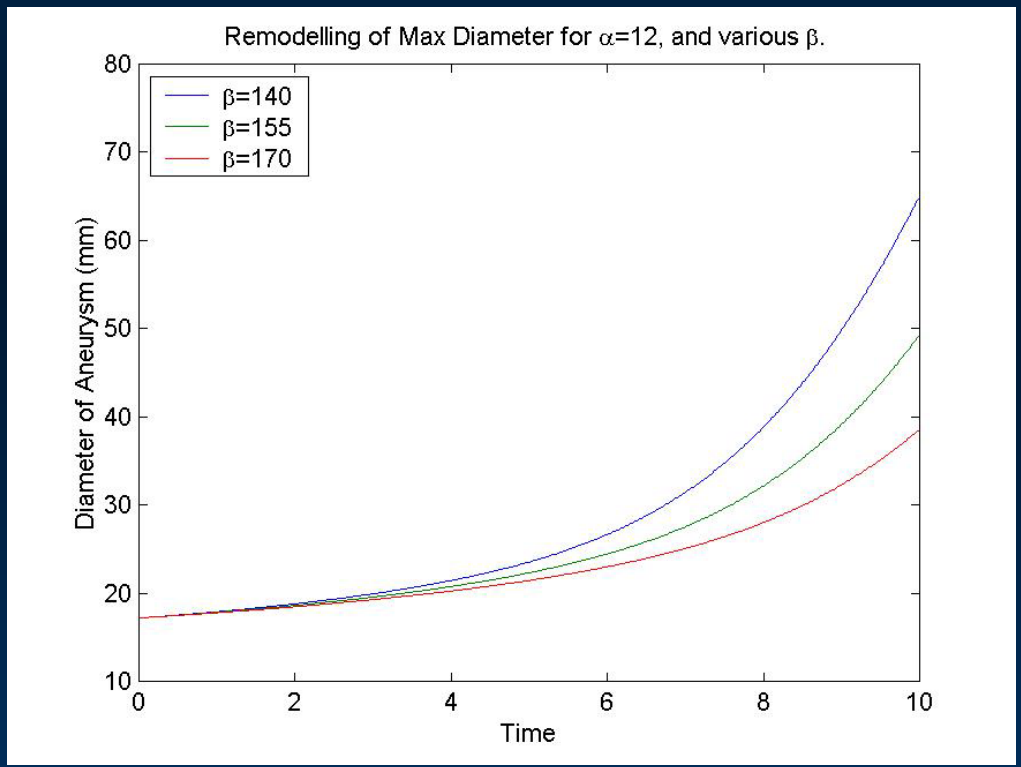
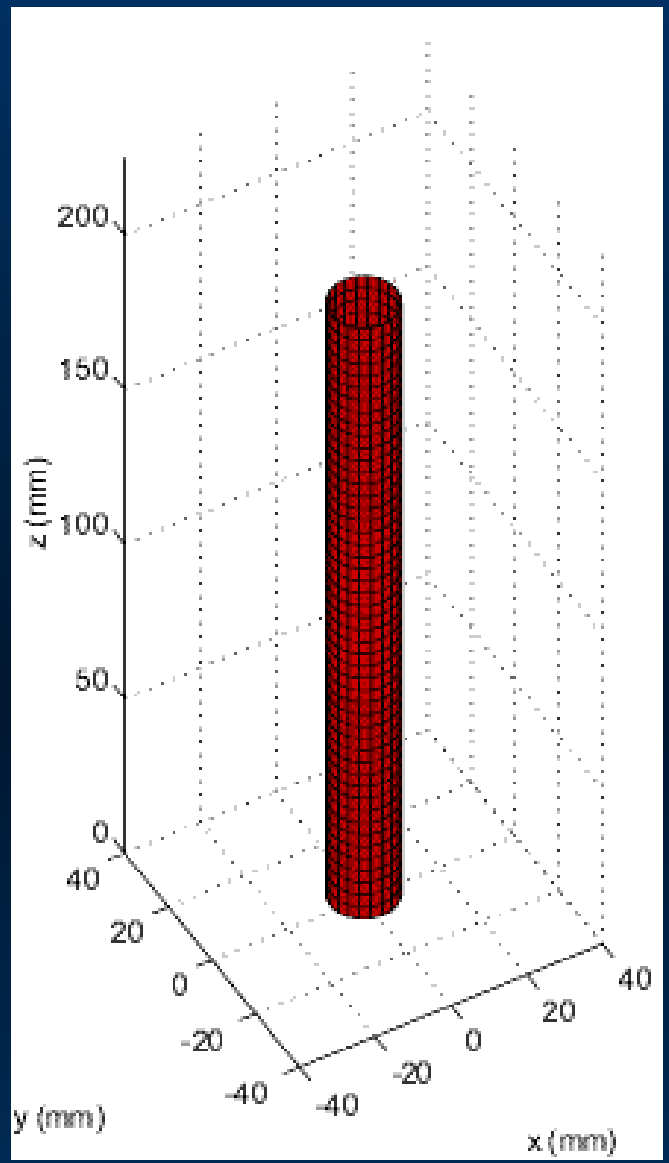
Axisymmetric Solution





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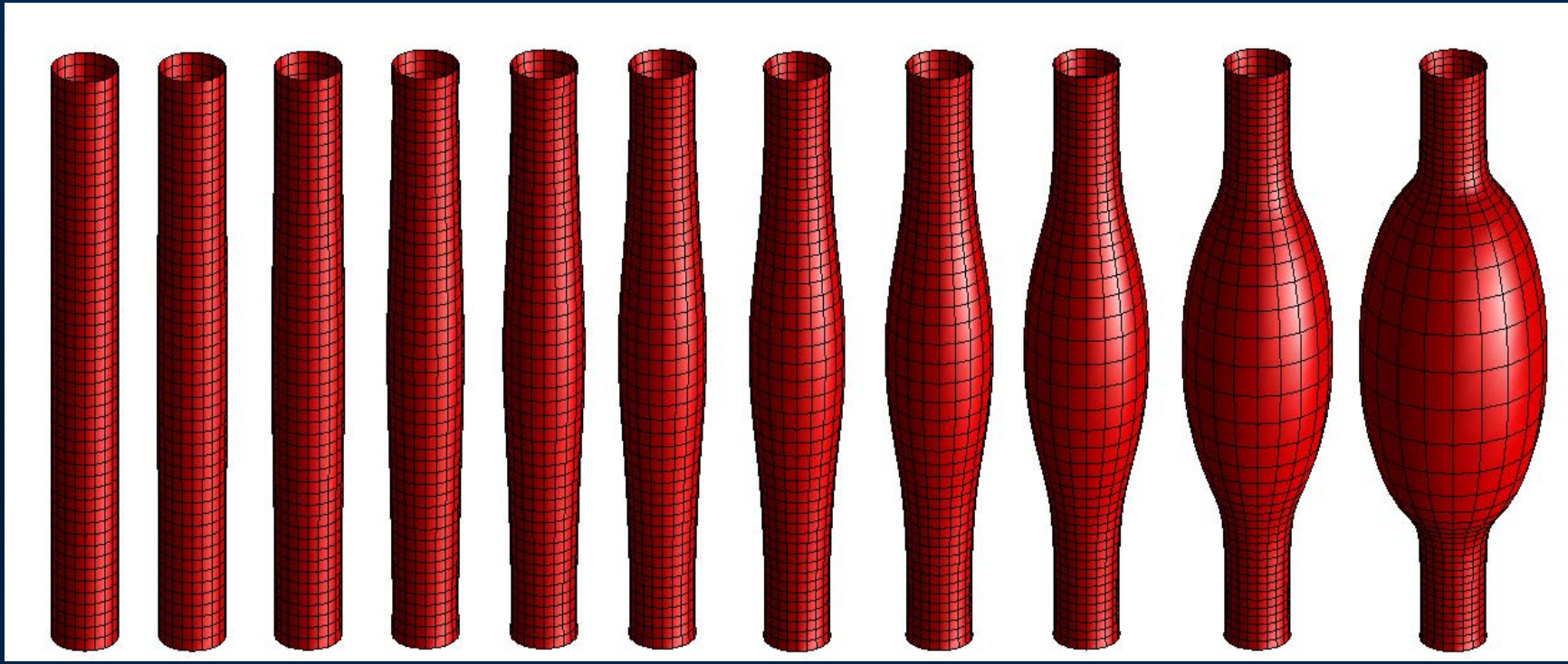
Axisymmetric Solution



A developing axisymmetric aneurysm at 0,1,2,3,4,5,6,7,8,9 &10 years from left to right.

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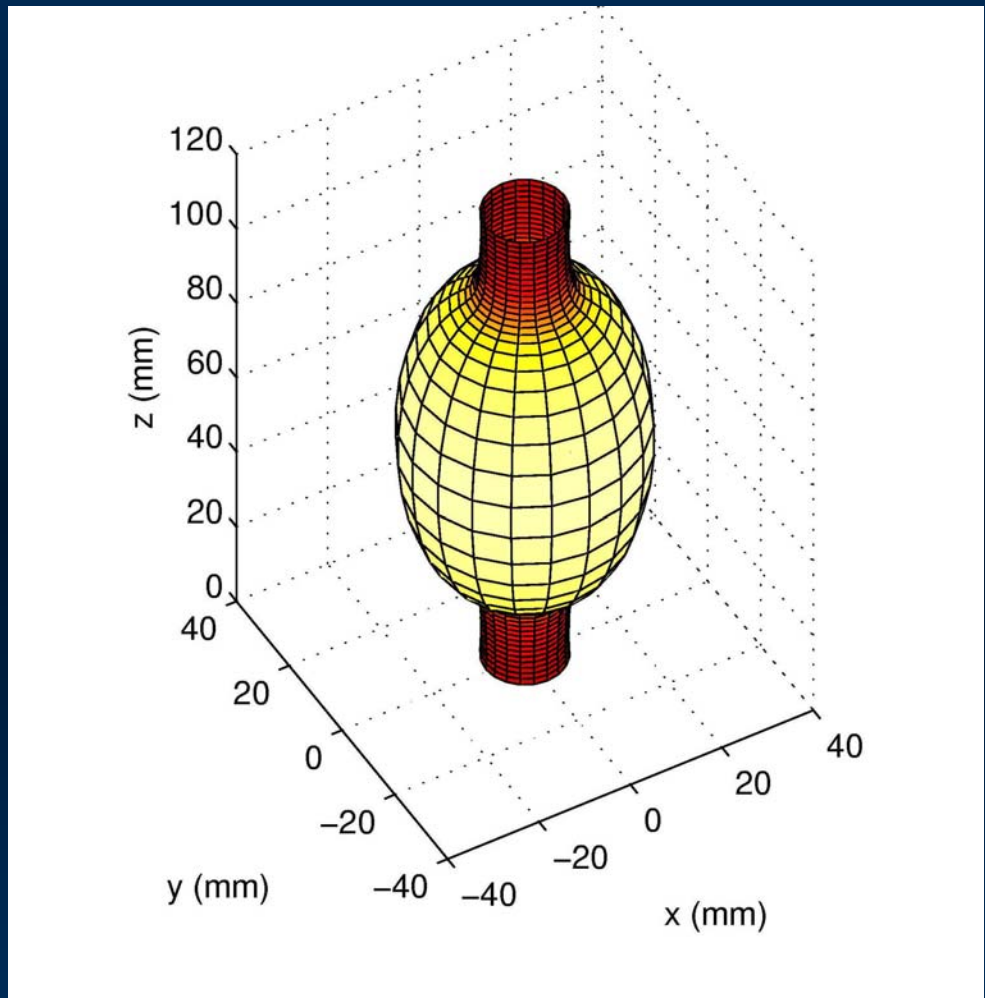
Axisymmetric Solution

Axisymmetric solution at 10 years.

Note the axial stretch in the middle region and retraction near the ends.



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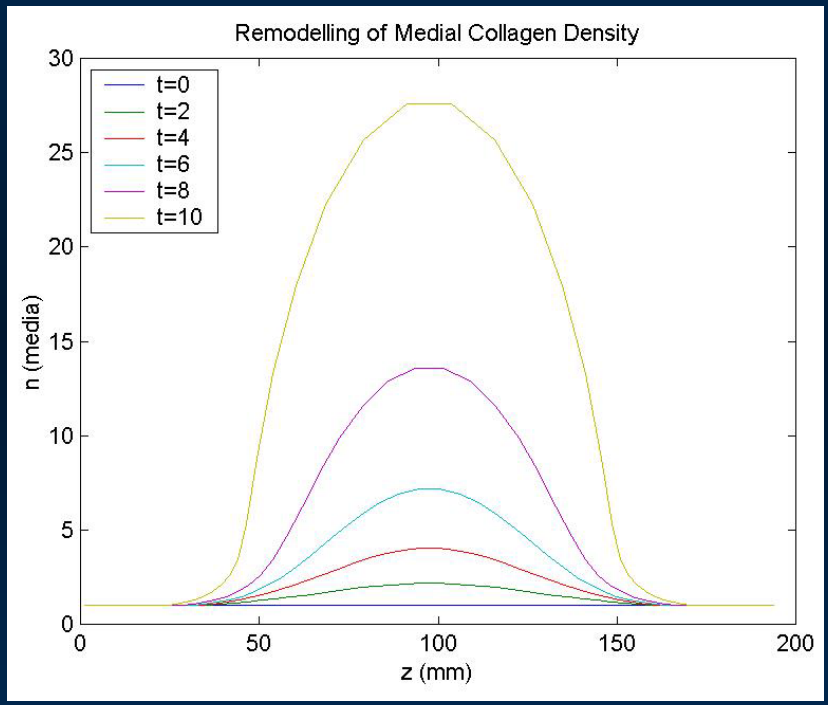
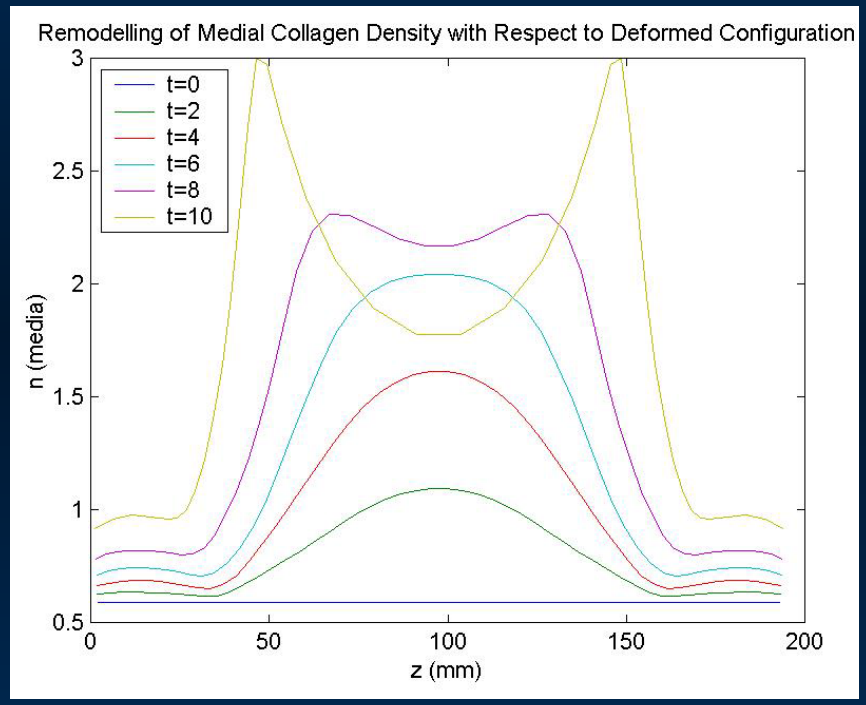
Remodelling of Medial Collagen Density





Note: Longitudinal tension stretches the central region. Remodelling of adventitial collagen density is similar.

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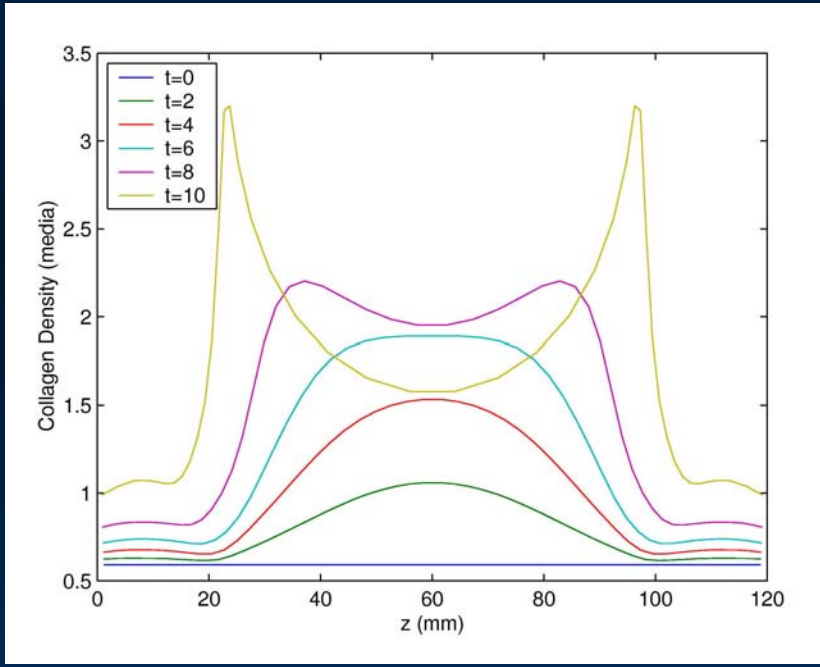
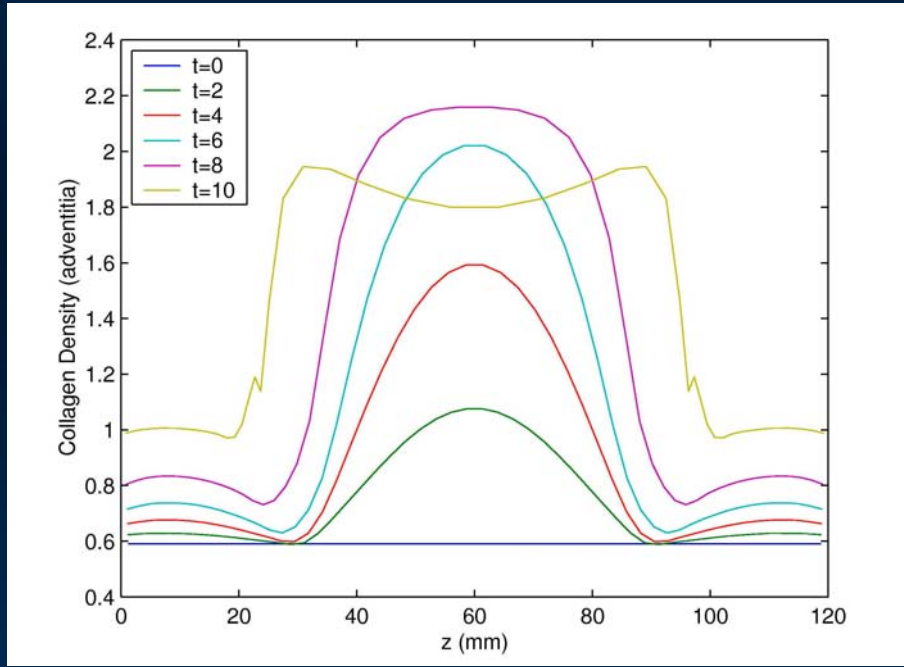
Comparison between medial and adventitial collagen density



media



adventitia

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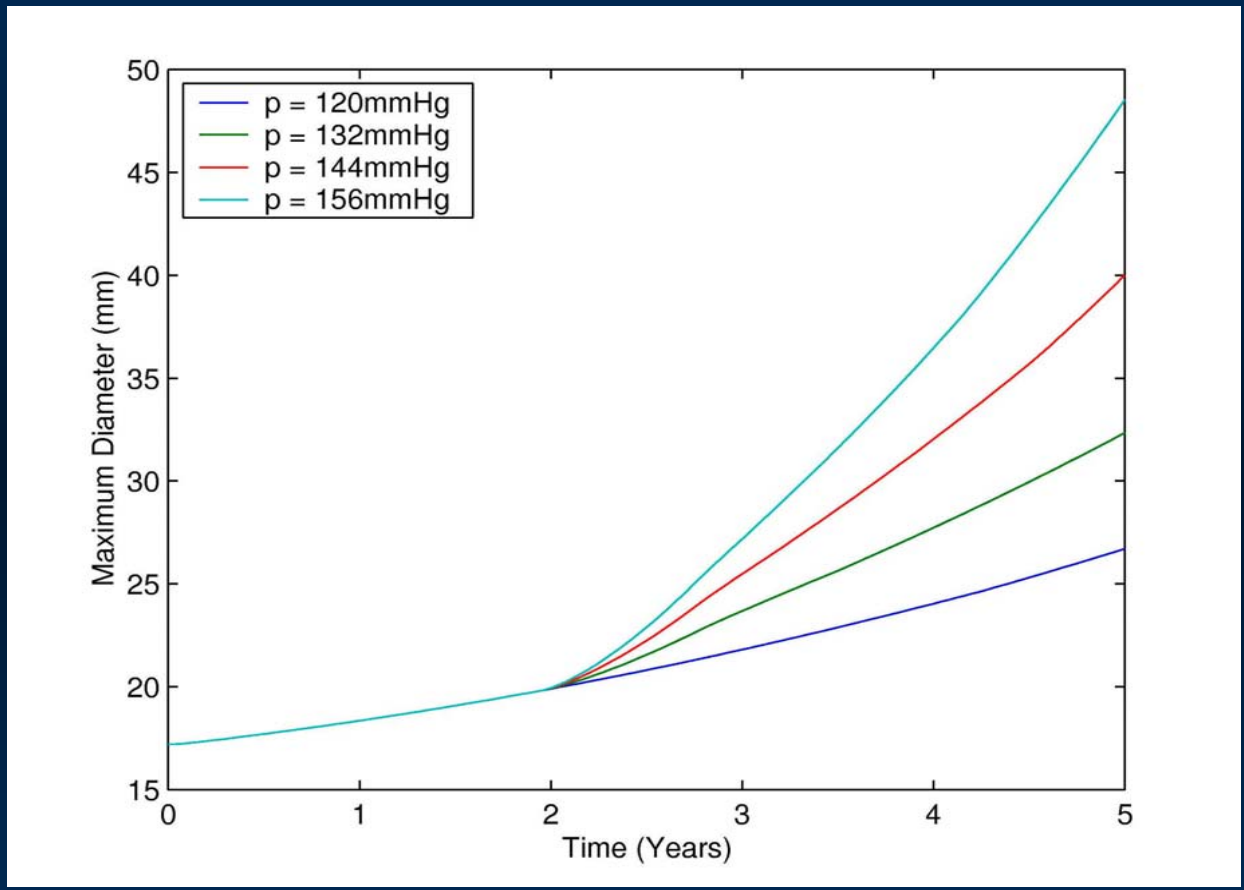
Hypertension Effects



Increasing the pressure leads to physiologically realistic increasing dilation rates

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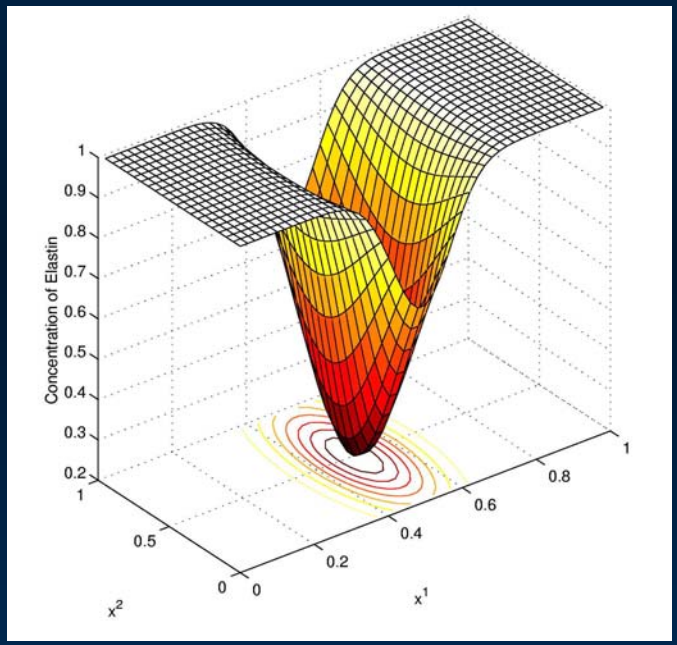
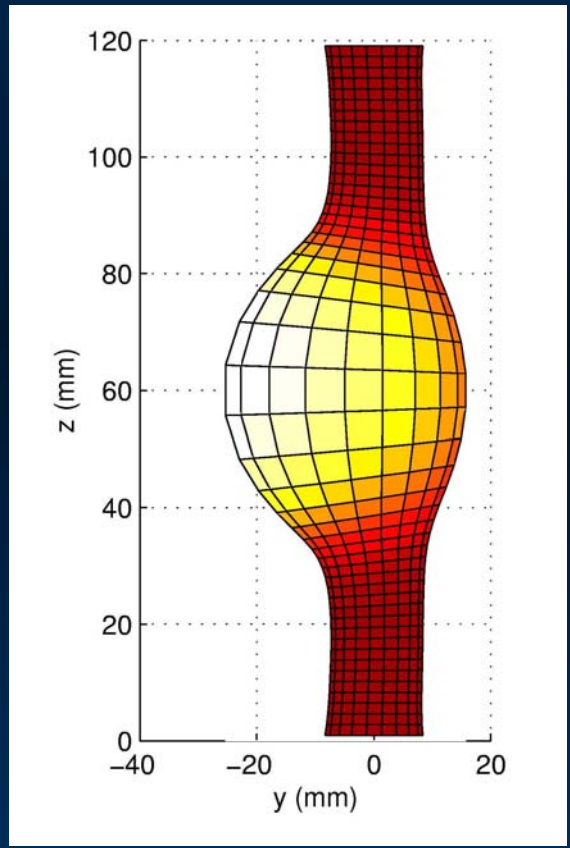
Asymmetric Elastin Degradation





Elastin concentration

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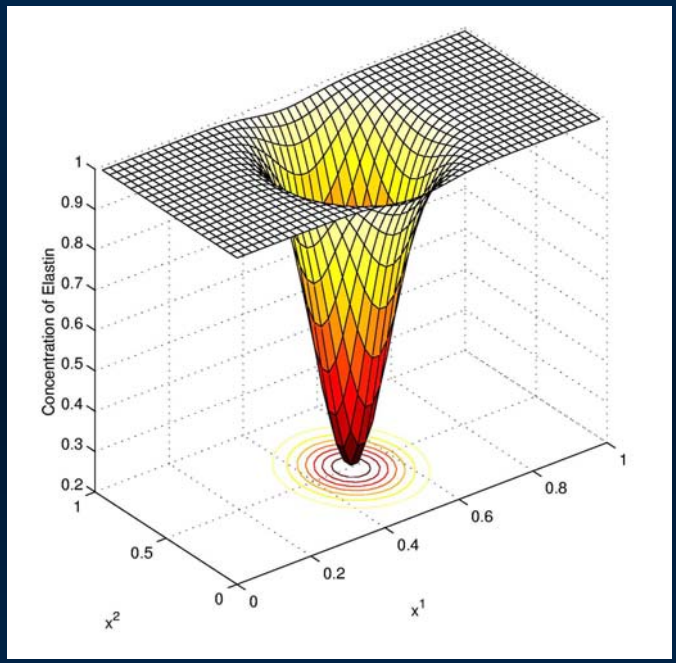
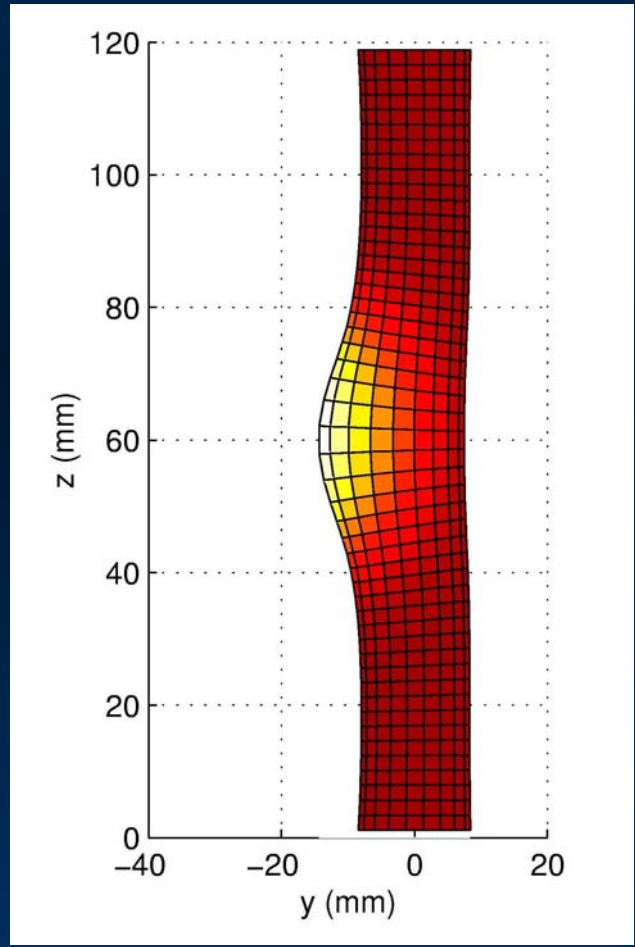
More-Localised Elastin Degradation





The asymmetry of the aneurysm is less when the elastin degradation is more localised.

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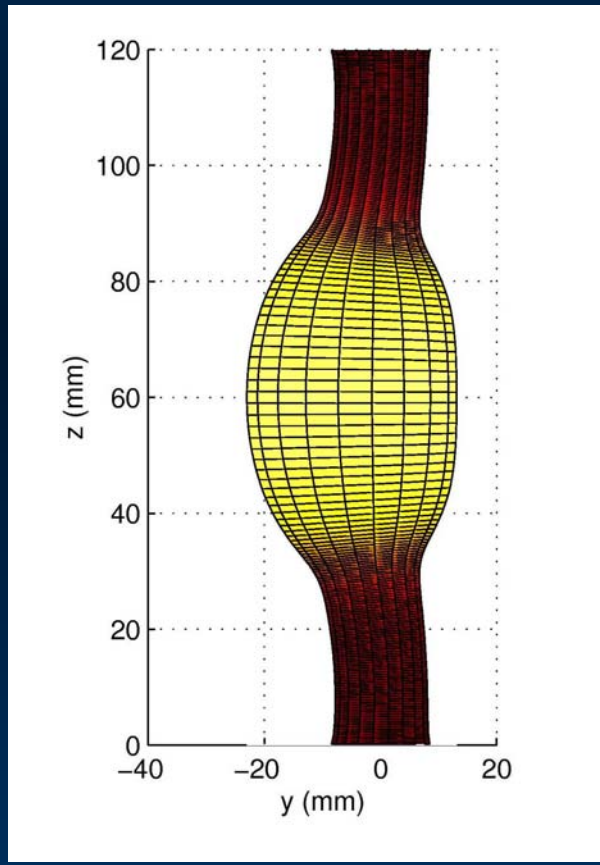
Spinal Contact

For large dilations spinal contact can occur.

Spine modelled as a plate with a stiff backed spring



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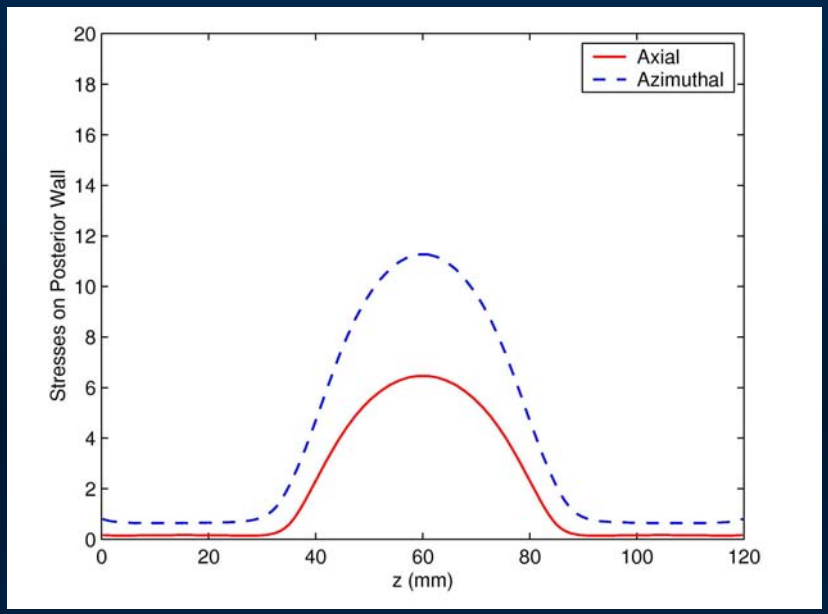
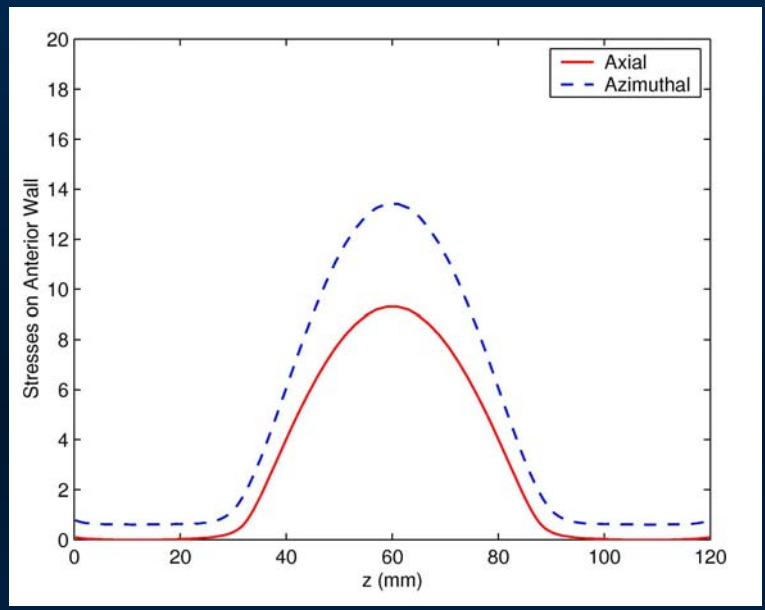
Spinal Contact Wall Stresses



Posterior wall



Anterior wall

Azimuthal stress are greater than axial stress on both walls, and the anterior wall stresses are about 20% greater then those on the posterior wall.

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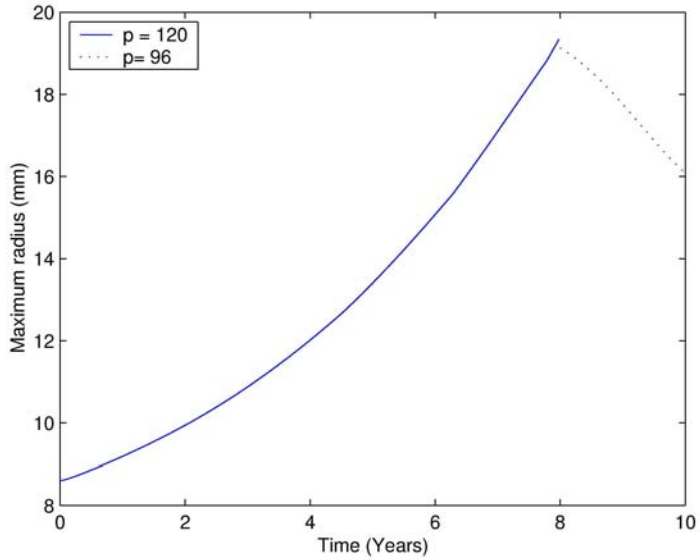
Post-Stent Retraction



After 8 years the pressure load acting on the aneurysm wall is reduced by 20%. This causes an initial small reduction in the size of the aneurysm. However, the aneurysm reduces in size yet further as the collagen remodels. This is a consequence of fibres having strains lower than the attachment strain following the initial pressure drop. Subsequently, the wall aneurysm retracts as fibres are replaced with fibres with greater strains.

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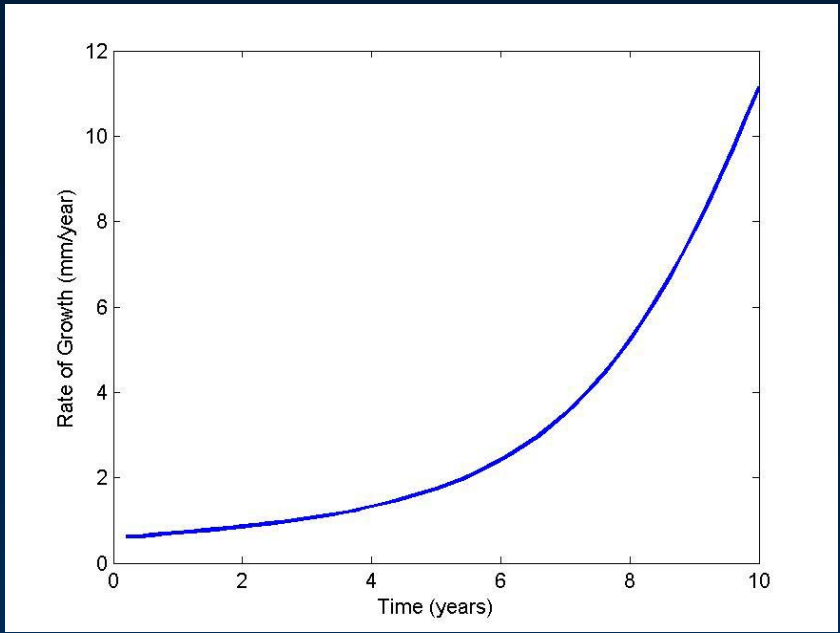
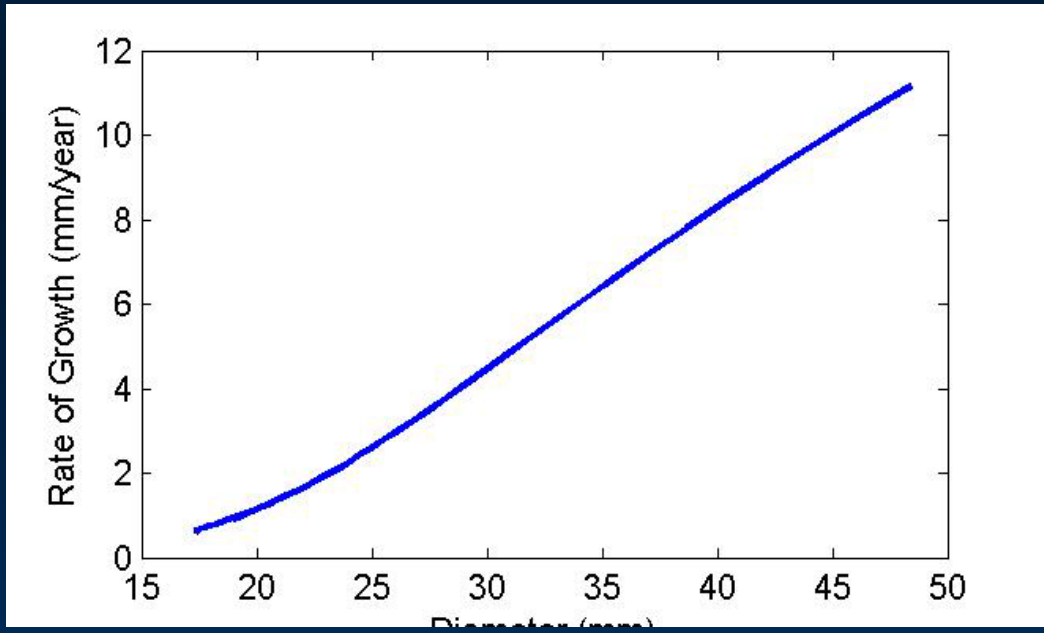
Growth rate

The rate of growth increases steeply with time and is linearly related to the diameter of the AAA. This implies that the diameter increases exponentially with time ***in agreement with the clinical observations*** of Vardulaki *et al*. (1998) .





time (years)

diameter (mm)

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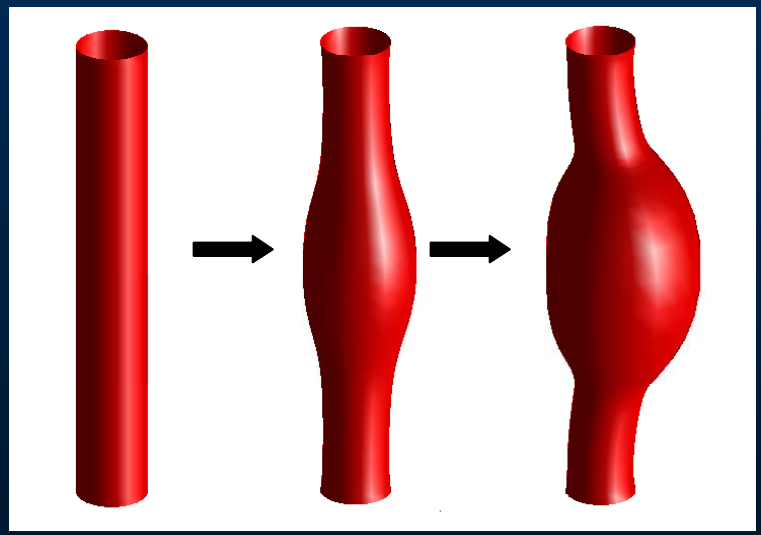
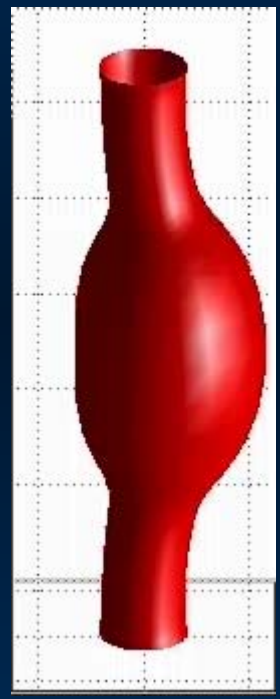
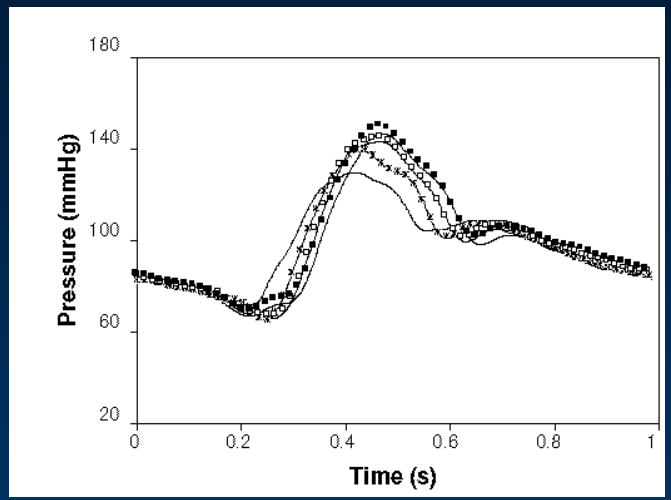
A Pulsating Aneurysm Simulation



Stage 1: grow the aneurysm



Stage 3: study the dynamic stresses and strains



Stage 2: apply a dynamic pressure pulse

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Change in Elastic Properties

For a pulsating AAA, the strain ε_{max}, elastic modulus E_p and stiffness β are defined in terms of the diameter D and pressure P (Lanne *et al* 1992) as

$$\varepsilon_{max} = \frac{D_{systolic} - D_{diastolic}}{D_{diastolic}}$$

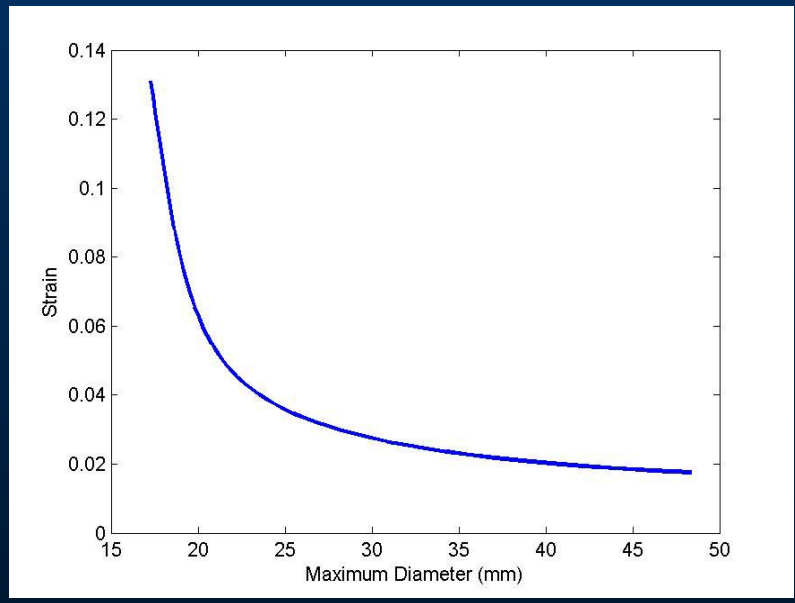
$$E_p = k \frac{P_{systolic} - P_{diastolic}}{(D_{systolic} - D_{diastolic})/D_{diastolic}}$$

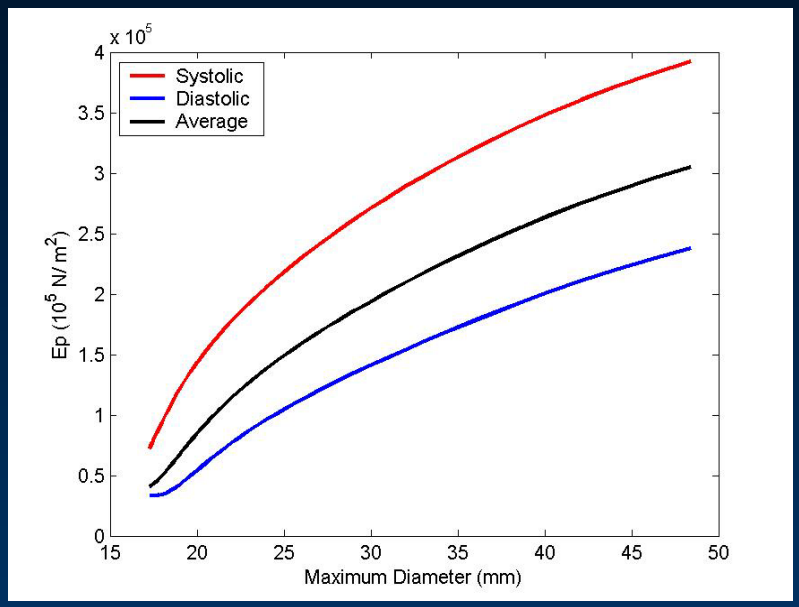
$$\beta = \frac{\ln(P_{systolic}/P_{diastolic})}{(D_{systolic} - D_{diastolic})/D_{diastolic}}$$

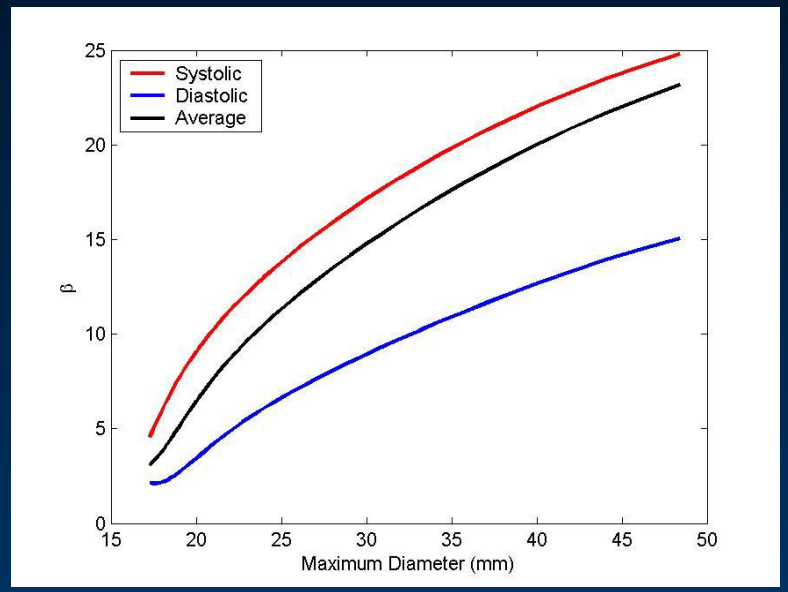
ε_{max} decreases exponentially with time; E_p and β increase exponentially.

Strain falls exponentially manner as diameter increases, and rates of increase of E_p and β decrease, because the diameter increases exponentially with time.

Values consistent with Lanne et al's (1992) clinical study.







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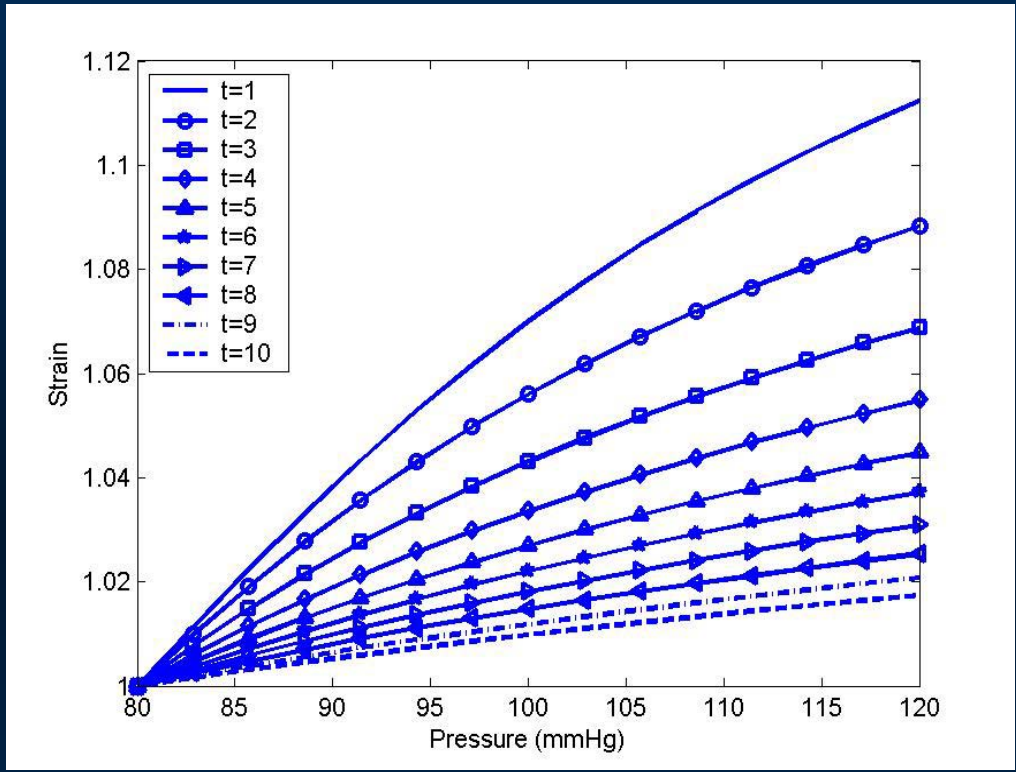
Dynamic Pressure Wave Simulation



The aneurysm becomes stiffer as the AAA develops.

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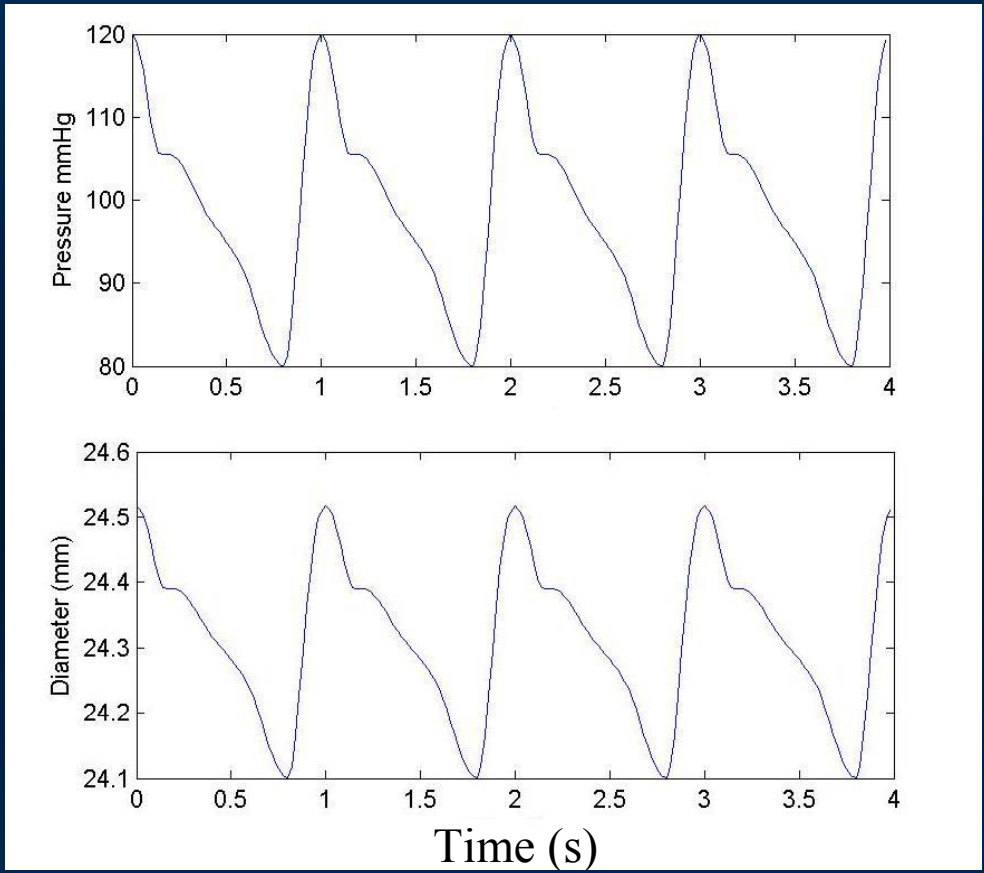
Dynamic Pressure Wave Simulation



Consequently the diameter waveform looks identical to the pressure waveform after time t = 10 years because ***the stiffer aneurysm has an almost linear pressure-diameter response***

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Summary

• This is a new microstructurally based model which accounts for the waviness and density of collagen fibres. There are two key remodelling variables:

n_J - the collagen fibre density

r_J - onset of collagen recruitment.

• Remodelling Hypothesis

Fibres attach to the e.c.m. independent of configuration of tissue.

Peak attachment strain for the fibres occurs at systole.

• Applications: Predicting future dilation, Stress/strain distributions, Dilation in hypertension, Post-stent retraction.

• Novel continuum mechanics is needed to account for behaviour of soft tissue.

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Future Work

- Better remodelling functions
- Taper and tortuosity of the aorta
- External supporting structures
- Internal structures - calcification, intramural thrombus
- Predicition of thickening of the wall
- Rupture criteria
- Predicition of growth rates
- Comparison with clinical data

Acknowledgements

Mr S. Dodds, Good Hope Hospital, Sutton Coldfield, Birmingham

Mr J. Scott, St. James's Hospital, Leeds.

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