Mathematical Modelling and its physiological applications

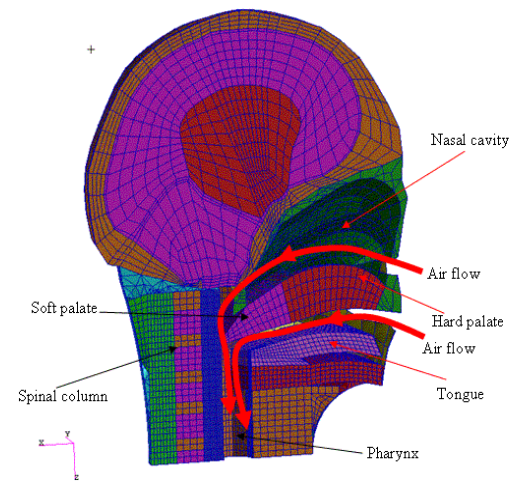
罗小玉　Xiaoyu Luo
School of Mathematics and Statistics,
University of Glasgow, UK.

University of Glasgow

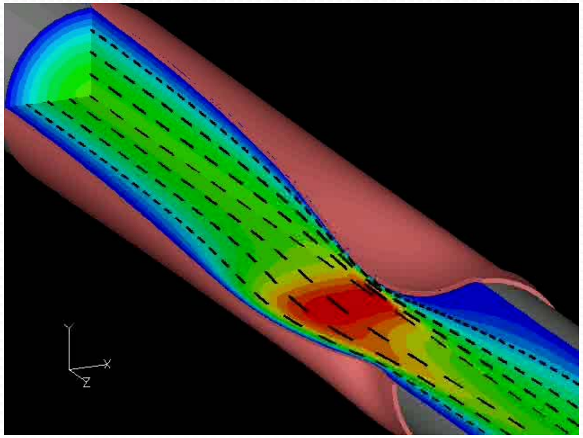
The University of Glasgow is the fourth oldest University in the English speaking world. It dates from 1451. Today it is one of the UK's largest universities with almost 16,000 undergraduate and 4000 postgraduate students, and over 5000 staff.

My current research:

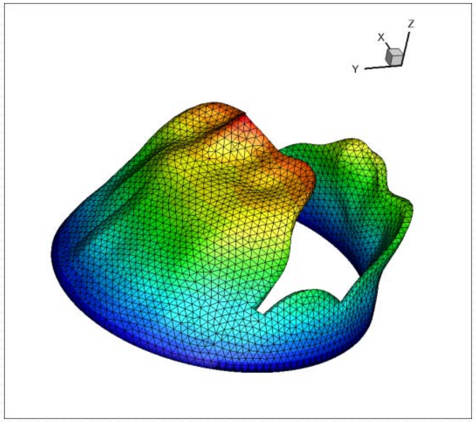
www.maths.gla.ac.uk/~xl



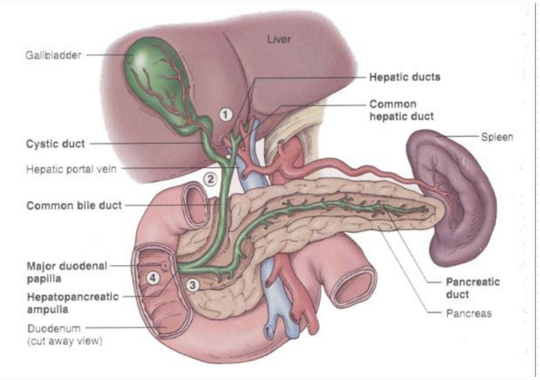
Snore and vocal folds (Royal Society)



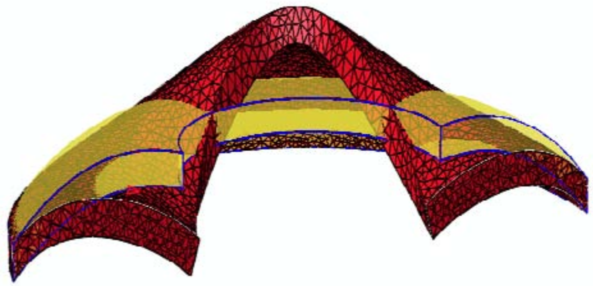
Flow in vessels (EPSRC)



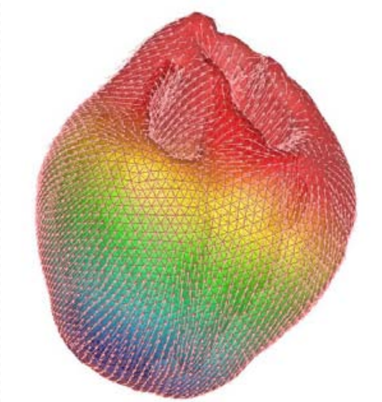
Heart valves (BHF)



Gallbladder pain (EPSRC)



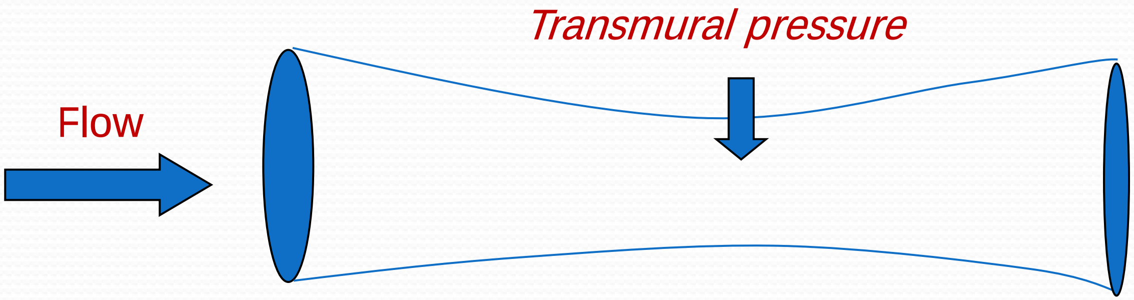
Buckling of eye iris



Multi-scale modelling of Heart (MRS)

The problem

An elastic tube conveying fluid can
oscillate self-excitedly when compressed:



Applications:

Blood flow in arteries and veins, urine flow in the urethra, flow in the airway, medical devices…

Motivation: mechanisms of self-excited oscillations

The governing equations:

Fluids Mechanics: Navier-Stokes

Solids Mechanics: Elastic beam equilibrium

↓

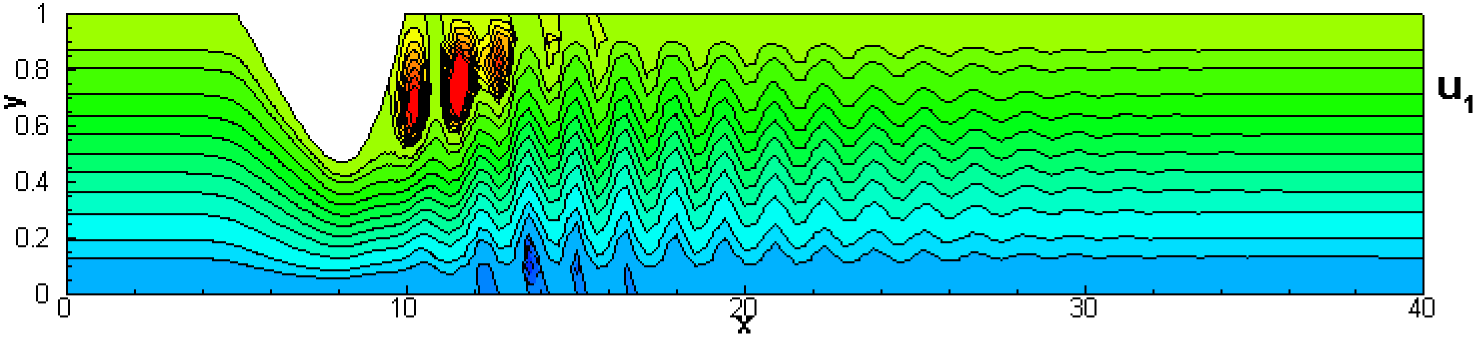
PDEs

↓ (FEM)

$$\boxed{M\frac{dU}{dt}+KU=F}$$

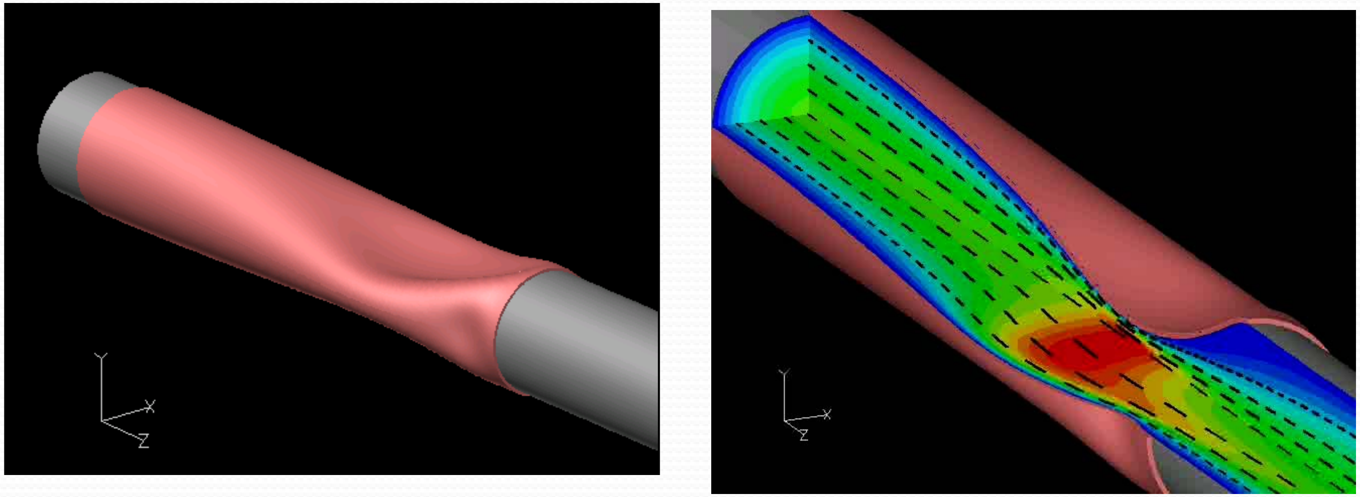
Cai & Luo (2003)

Collapsible tube flows in 2D

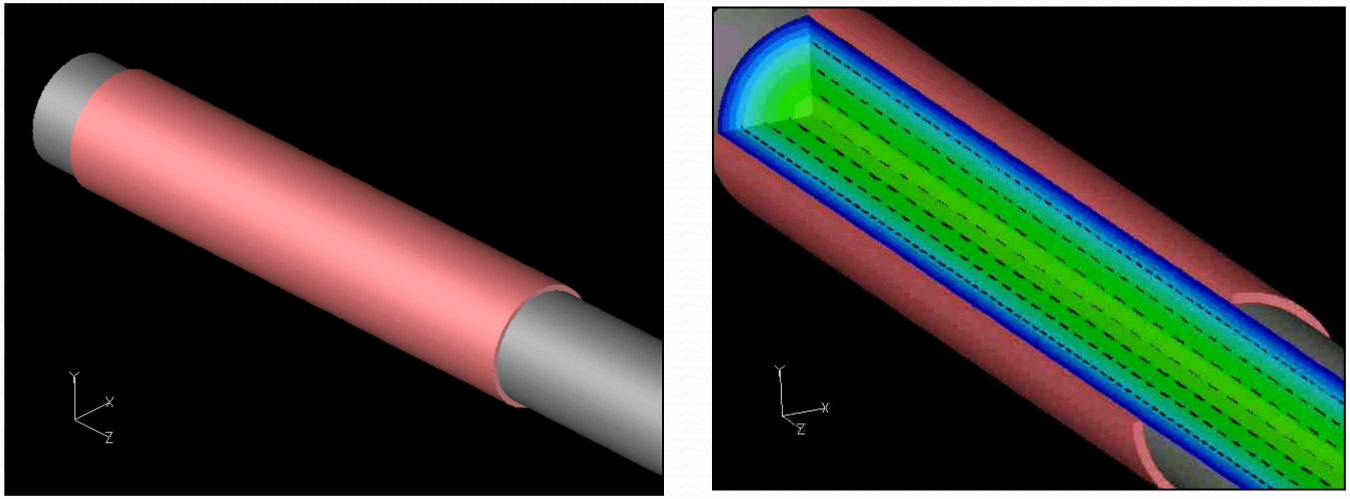


Collapsible tube flows in 3D

A: $\frac{h}{R} = \frac{1}{20}$



B: $\frac{h}{R} = \frac{2}{20}$

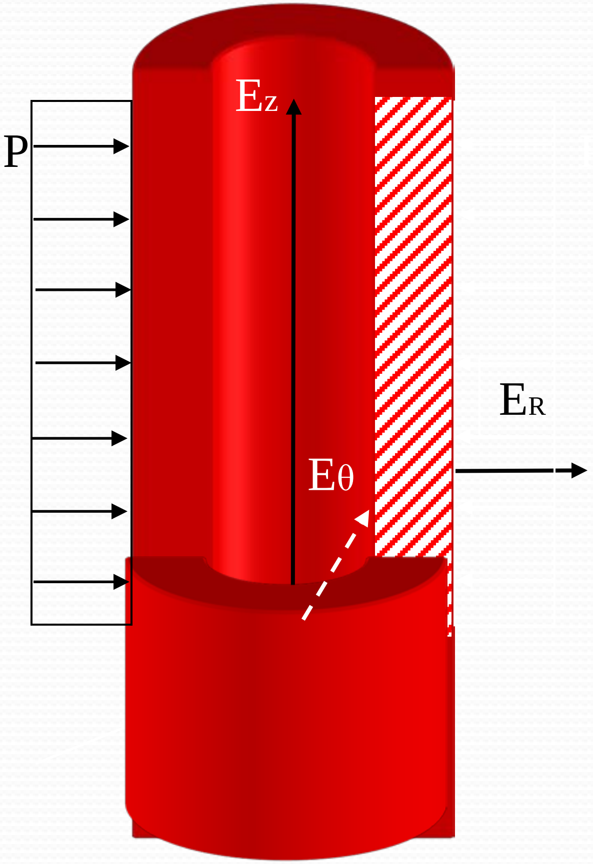


h=wall thickness

R=radius

Material Nonlinearity

- Isotropic
- Incompressible
- Hyperelastic



u=0; w=0

Axis-symmetric

Neo-hookean Material

$$W(\lambda_1, \lambda_2, \lambda_3) = \frac{1}{2}(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3)$$

Equilibrium Equation

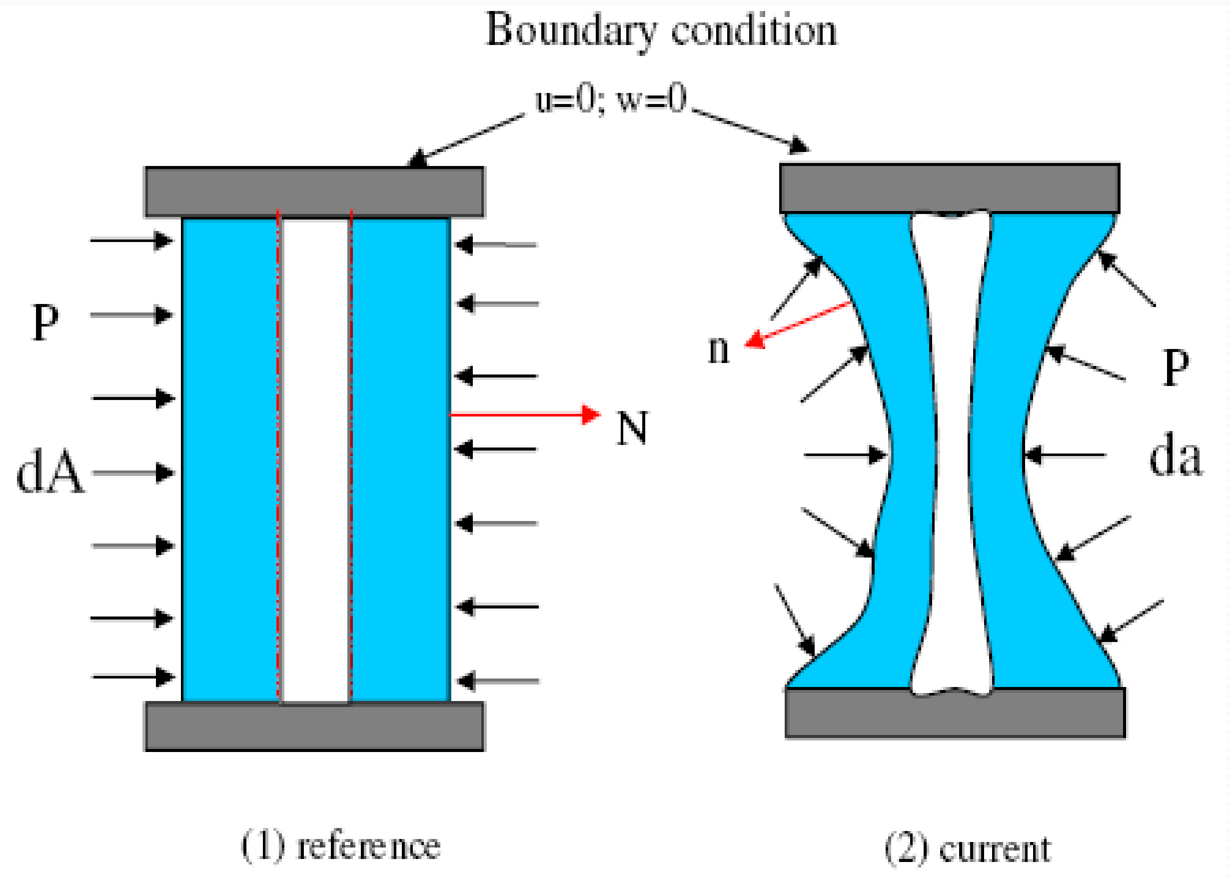
$$\begin{cases} S_{Rr,R} + S_{Zr,Z} + \frac{1}{R}(S_{Rr} - S_{\Theta\theta}) = 0 \\ S_{Rz,R} + S_{Zz,Z} + \frac{1}{R}S_{Rz} = 0 \end{cases}$$

Boundary Condition

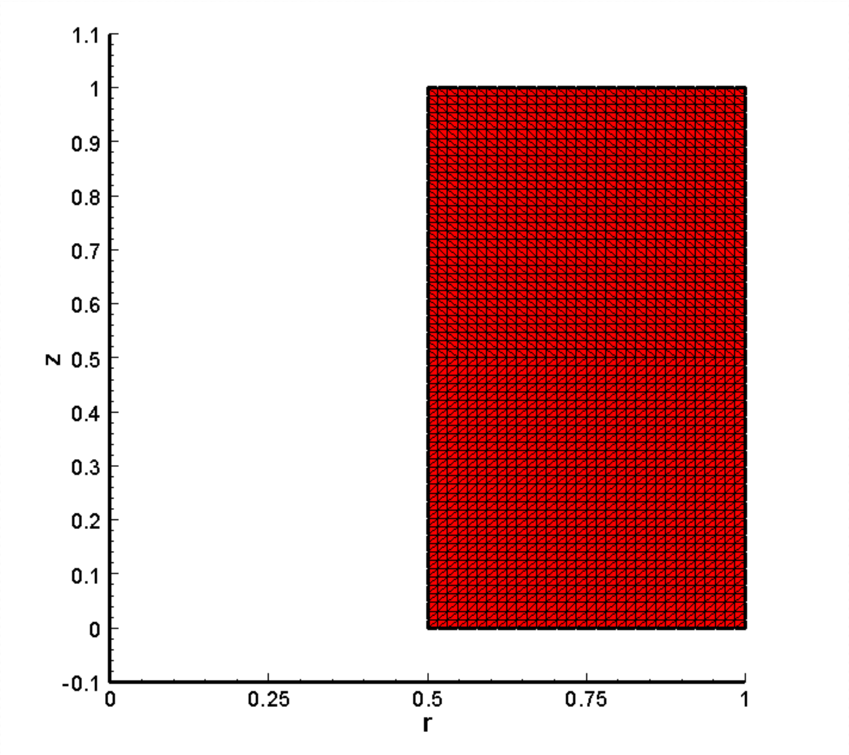
$$-P\mathbf{n}da = -PJ\mathbf{F}^{-\mathbf{T}}\mathbf{N}dA = \mathbf{S}^{\mathbf{T}}\mathbf{N}dA$$

$$\begin{cases} u = 0 & \text{at Z=0,L} \\ w = 0 & \text{at Z=0,L} \end{cases}$$

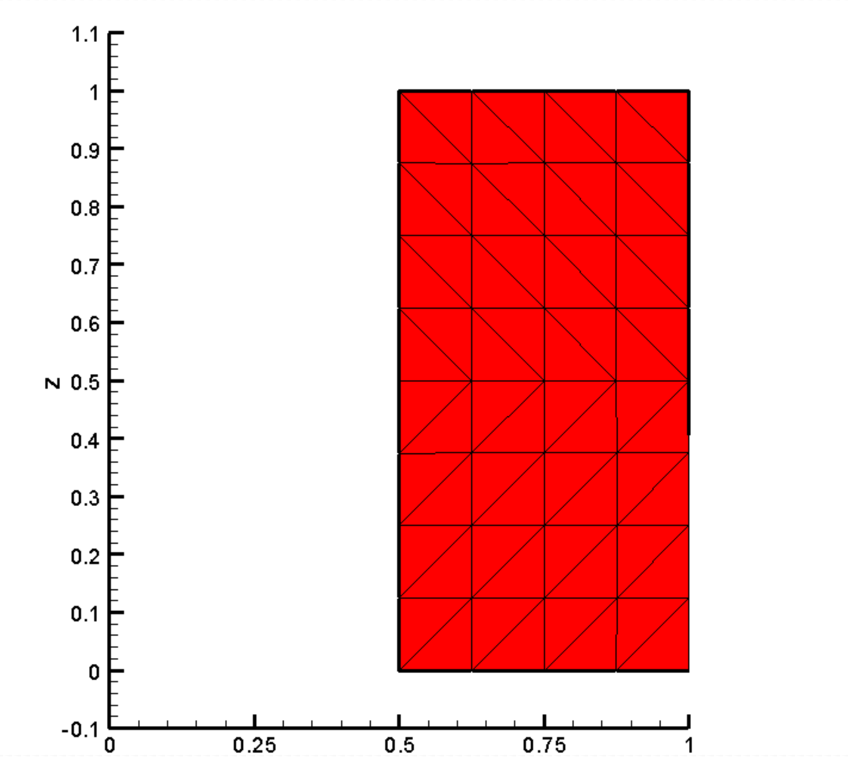
3D nonlinear analysis



Linear

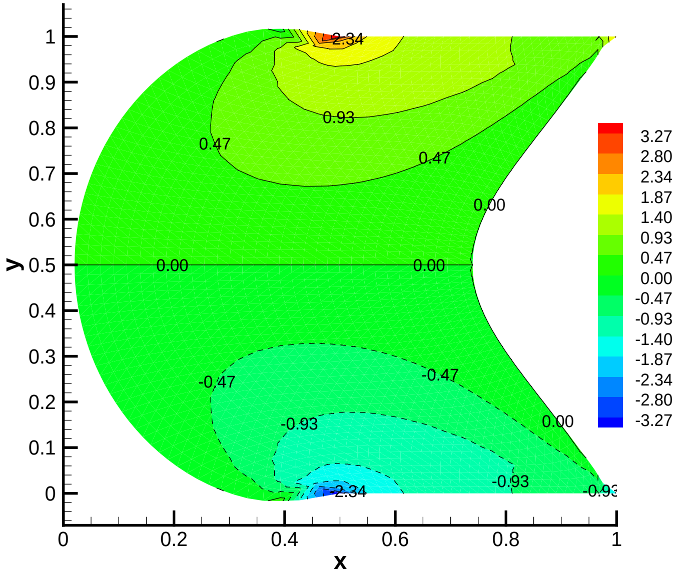


Nonlinear

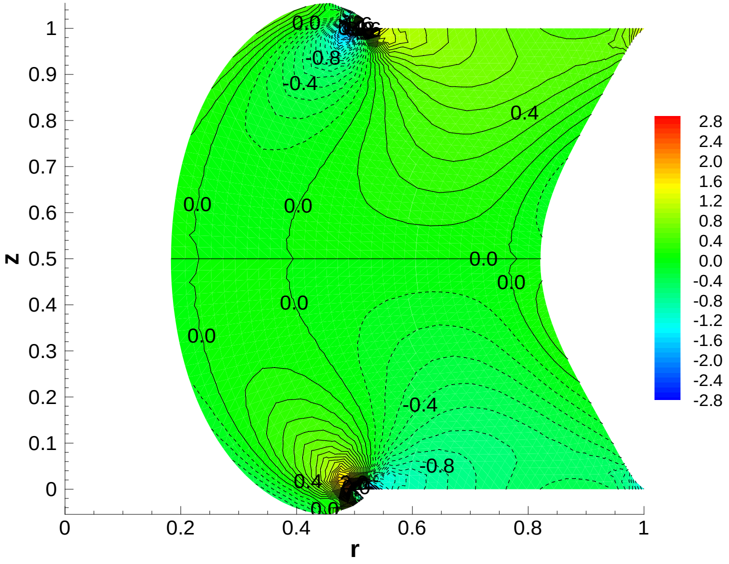


Stress Pattern

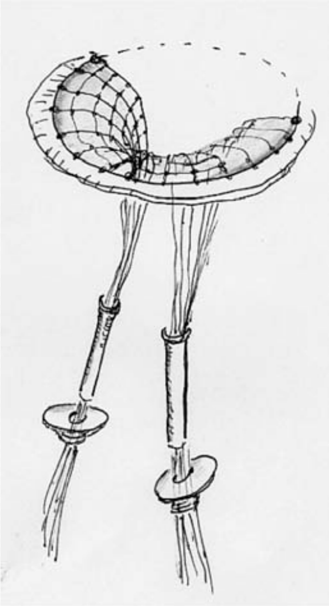
Linear



Nonlinear

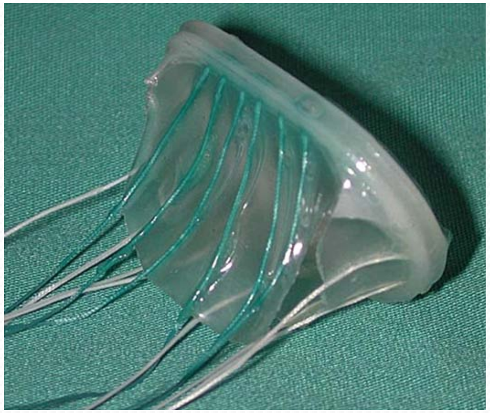


A New Bioprosthetic Mitral Valve (MV)



D. J. Wheatley (2002)
Mitral valve prosthesis
Pat. no. WO01/30277

A new bioprosthesis (polyurethane) design developed by Dept. of Cardiac Surgery, University of Glasgow



Benefits:

- durable
- no need for anticoagulation therapy,
- biostable (tested on sheep)
- based on real MV geometry, “similar” mechanical properties
- with chordae !

The mitral valve (MV) mesh

GAMBIT

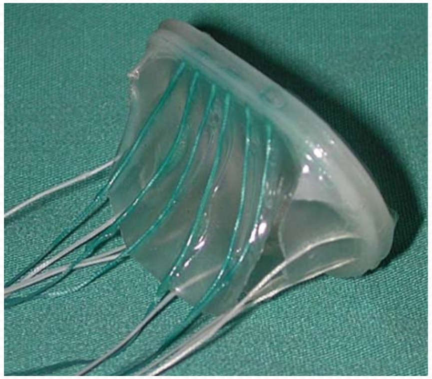
FEM model

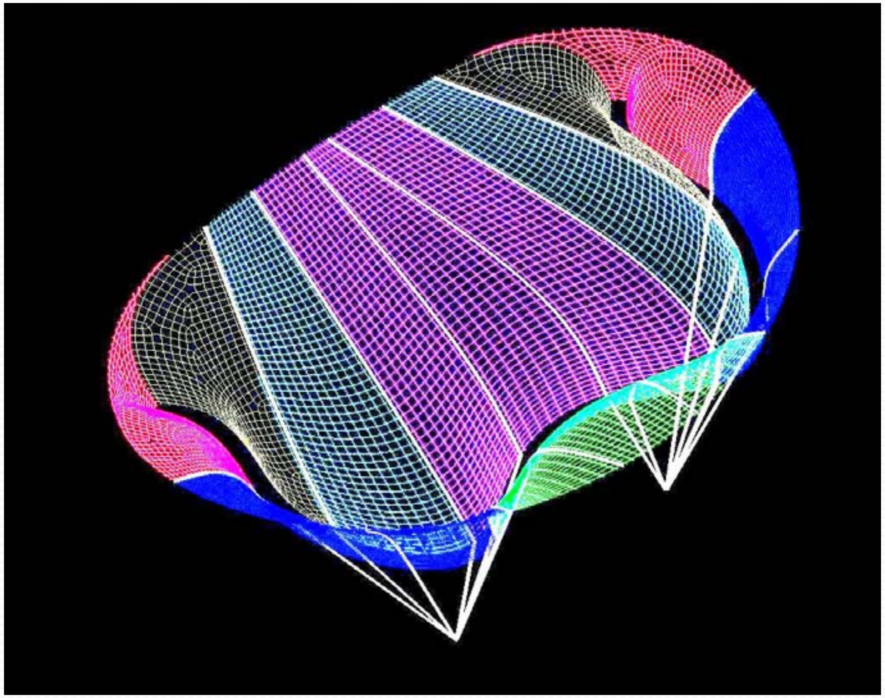
FIBRE GENERATOR

IB Solver

SOLIDWORKS
(Valve Design)
IGES file

Tecplot
(graphics)



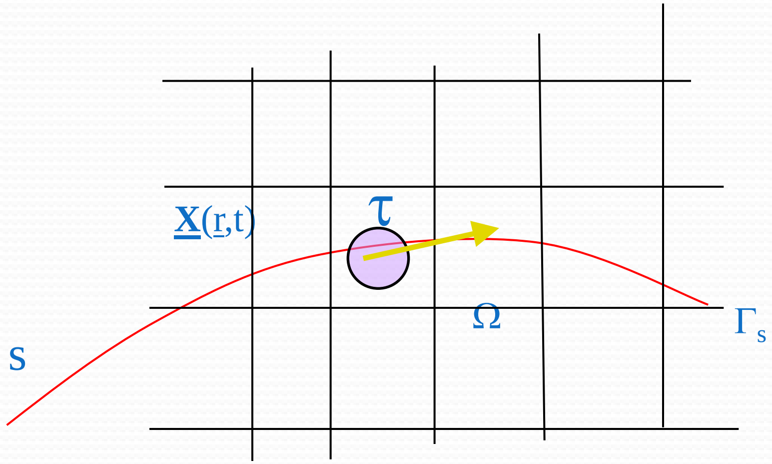


Polyurethane leaflets:
E = 5MPa,
h = 0.125mm
Chordae: E =30MPa,
Area = 0.4mm^2

Immersed Boundary Method (IB)

Fluid: N-S, $\underline{\boldsymbol{x}}$ Solid: Fibres, $\underline{X}$

Fluid-Structure Interactions:



$$f = \int_{\Gamma_s} F(\underline{r},t)\delta(\underline{x}-\underline{X}(\underline{r},t))ds,$$

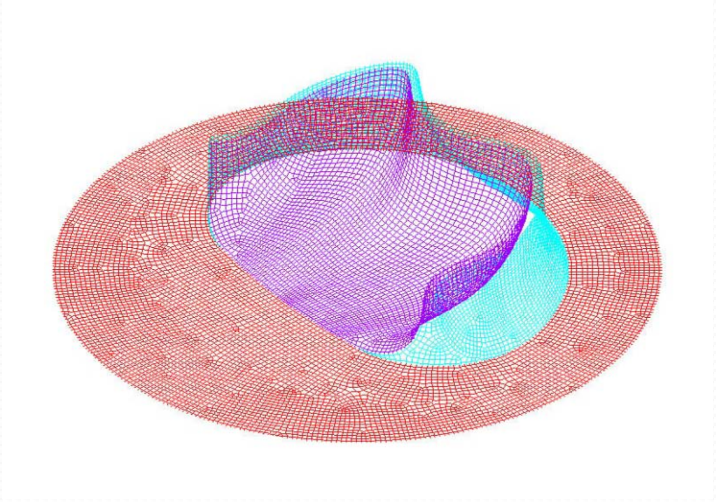
$$\frac{\partial \underline{X}}{\partial t}(\underline{r},t) = \int \underline{u}(\underline{x},t)\delta(\underline{x}-\underline{X}(\underline{r},t))d\underline{x},$$

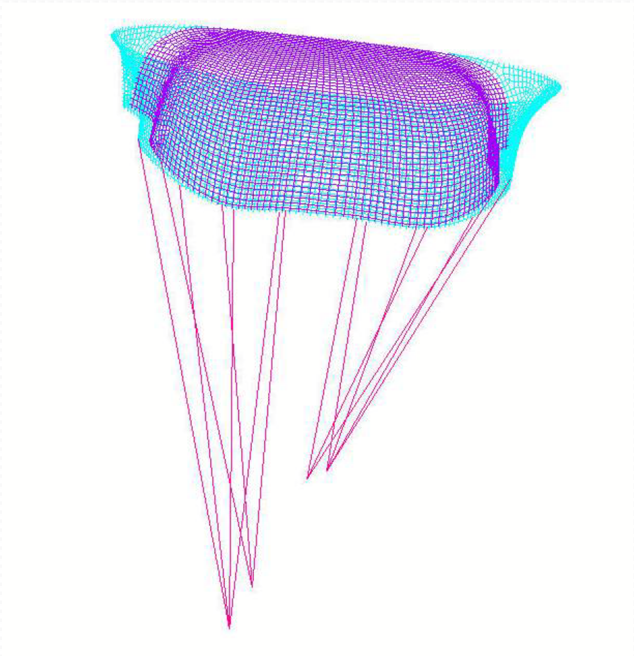
$\underline{x}$: fluid coordinates
$\underline{X}(\underline{\mathbf{r}},t)$: fibre point coordinates

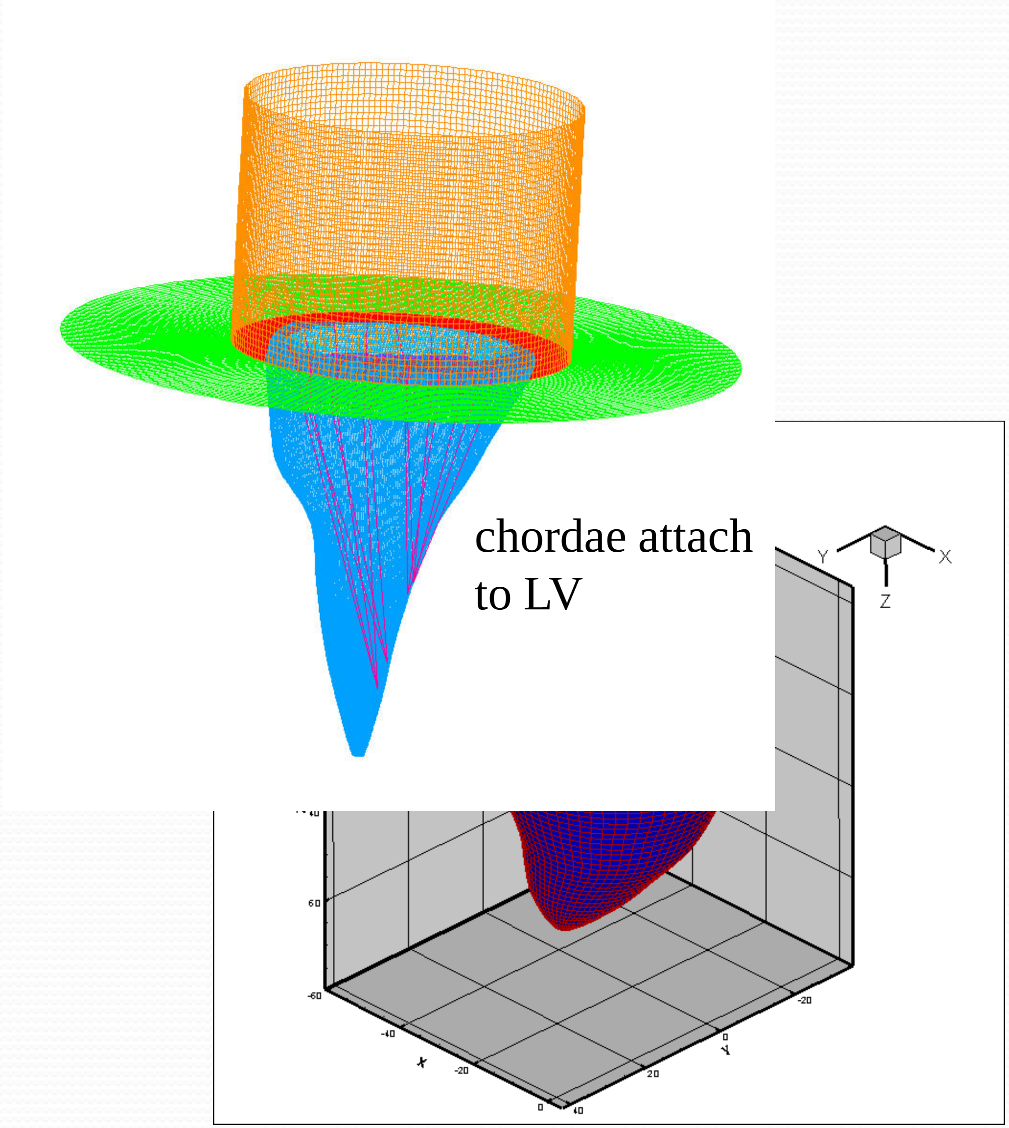
The immersed fibre imposes force $F = \frac{\partial}{\partial s}(T\tau) \rightarrow f$ on the fluid, and is moved by the fluid $\boldsymbol{u} \longrightarrow \frac{\partial \underline{\boldsymbol{X}}}{\partial \boldsymbol{t}}$.

Anisotropy (fibre) and geometric non-linearity modelled naturally.

The MV model is placed inside the moving LV

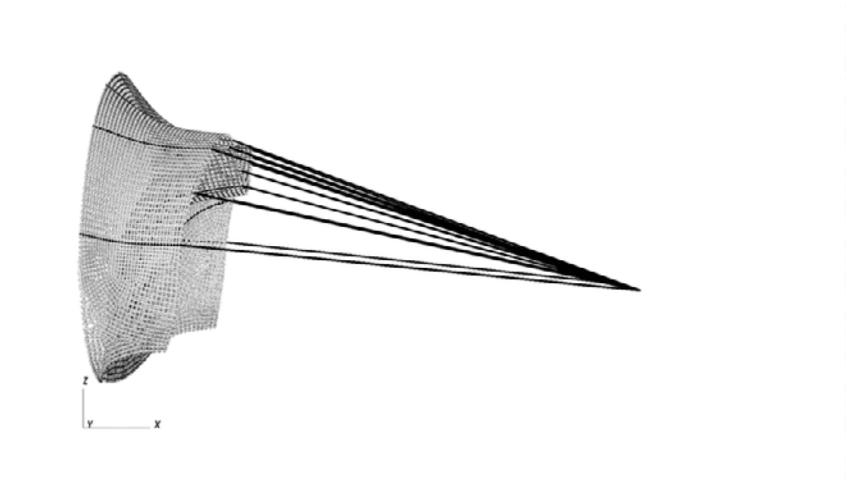




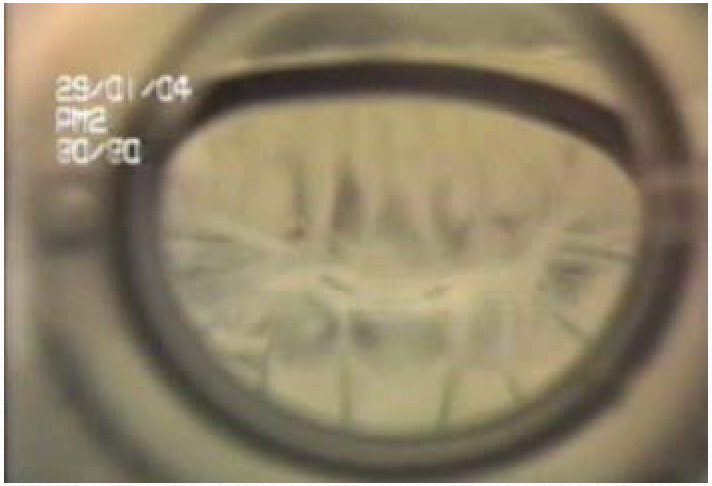


chordae attach to LV

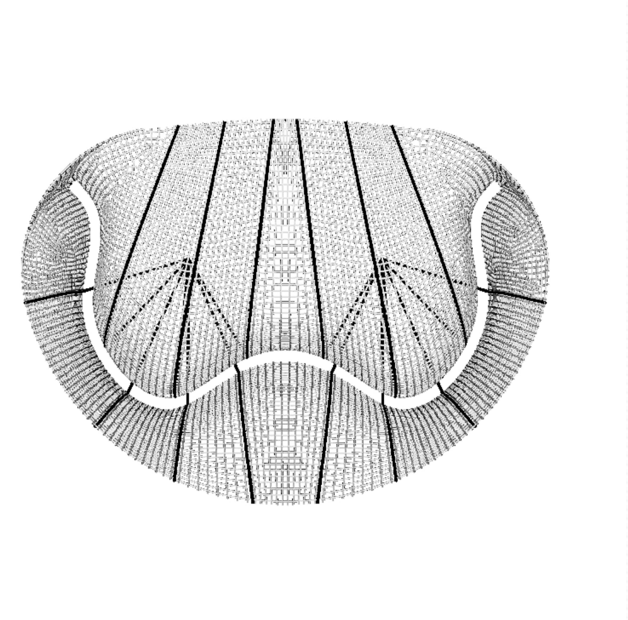
IBAMR: Valve closure

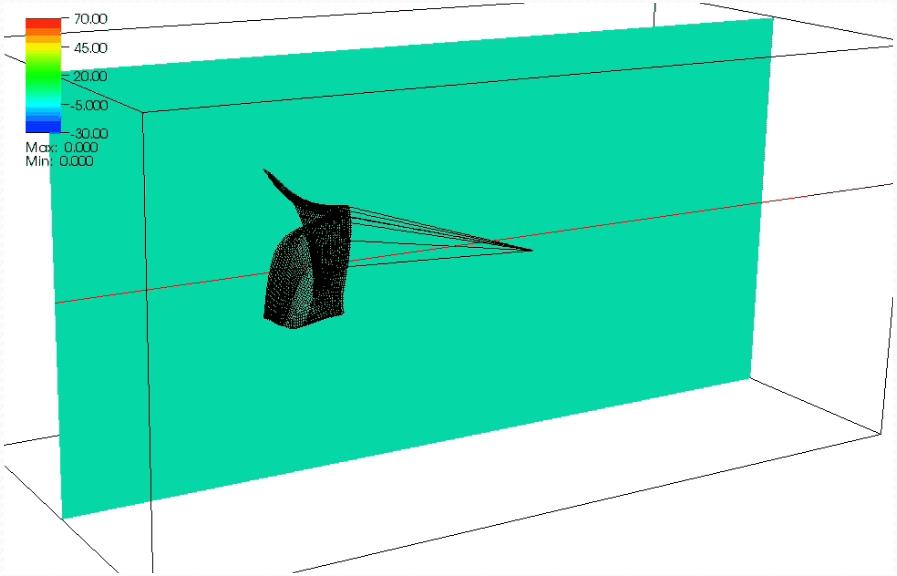


With chordae bending only: better closure, over-opening



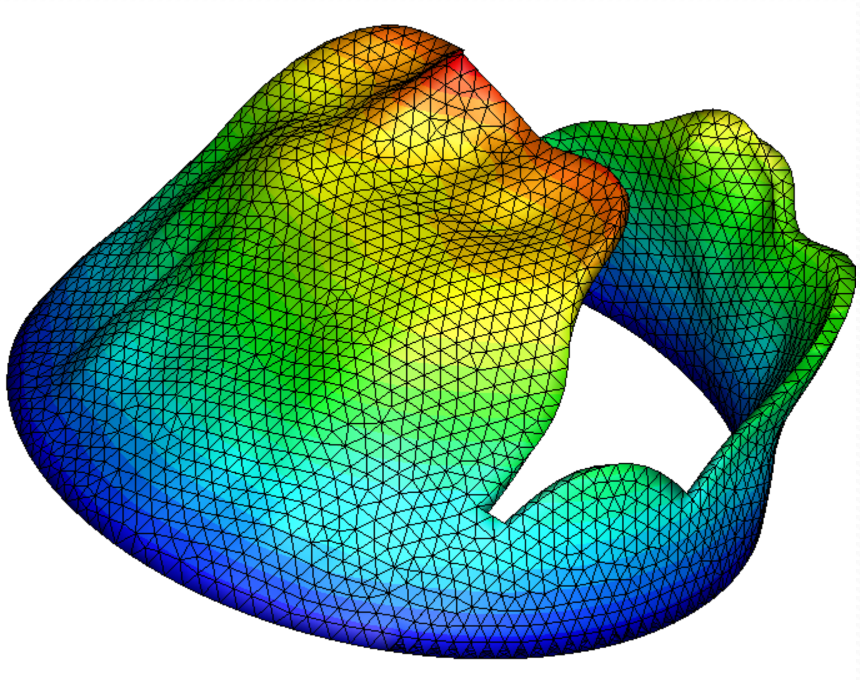
Experiments



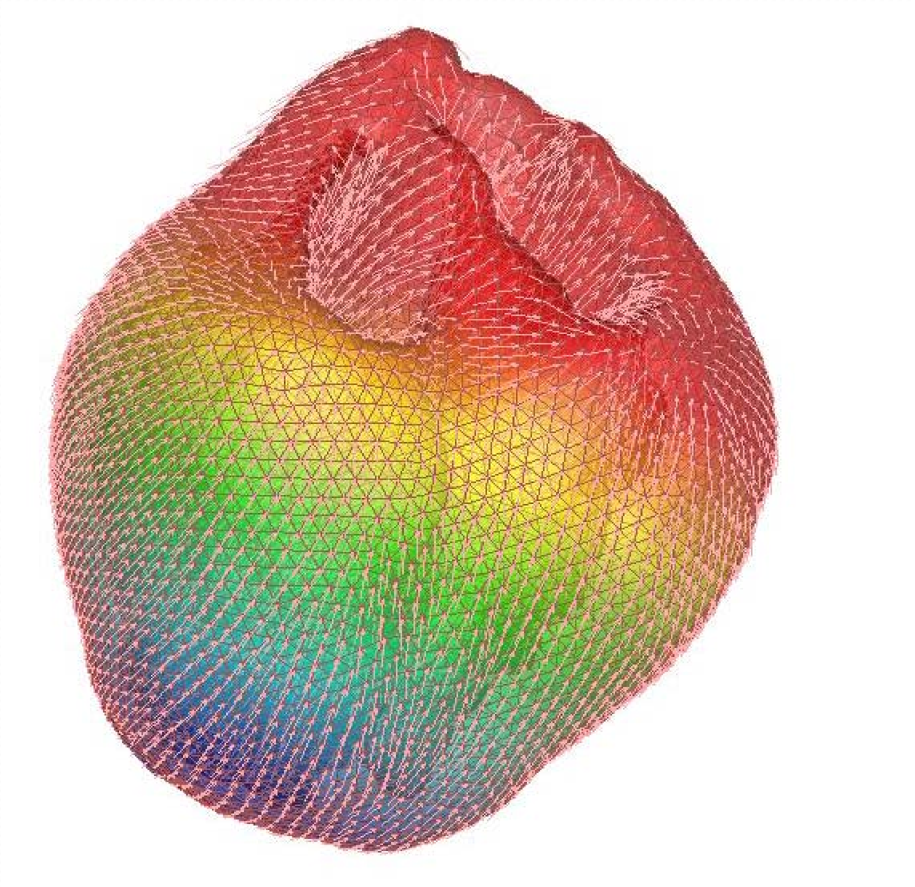


With valve bending as well

On going work:
Modelling of human mitral valve



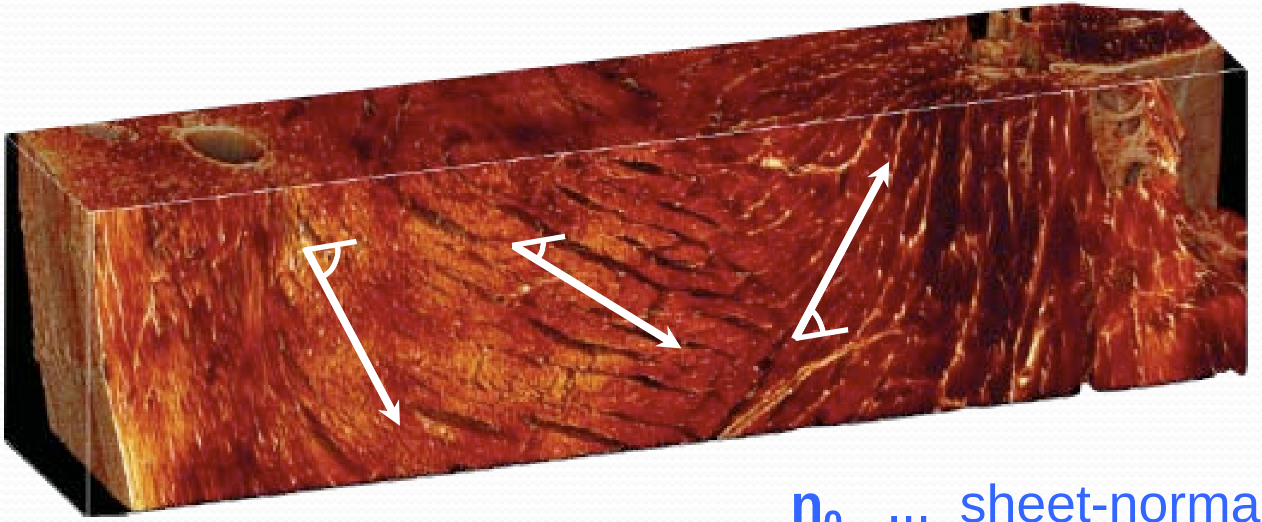
Multi-scale modelling of heart



Fibre Structure of the LV wall

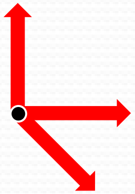
Change of the 3D layered organization of myocytes through the wall thickness

Epicardium (external)

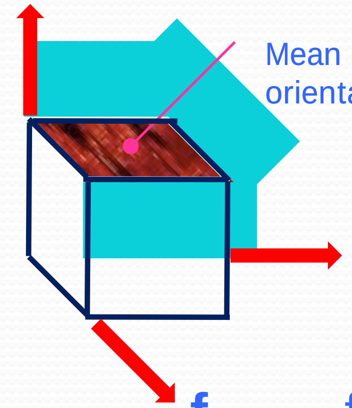


Endocardium (internal)

Basis vectors



$\mathbf{n}_0$ ... sheet-normal

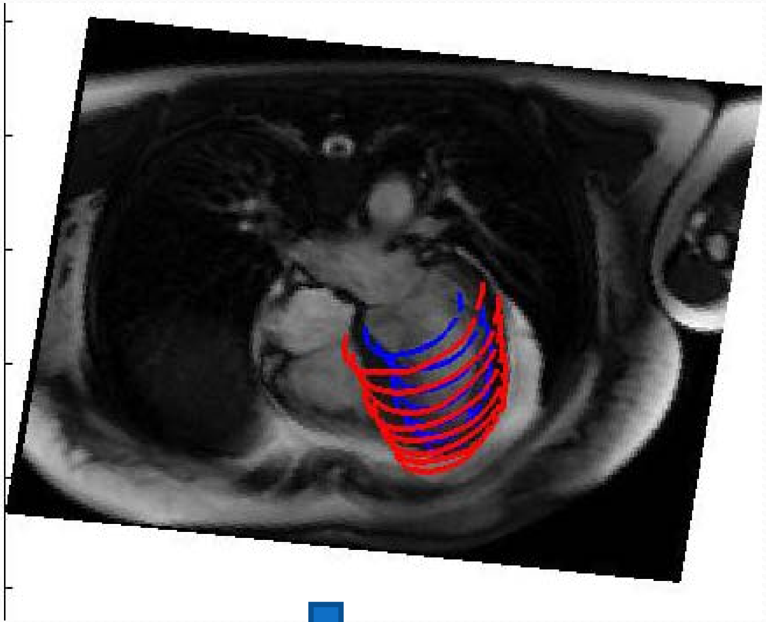


Mean fibre orientation

$\mathbf{s}_0$ ... sheet axis

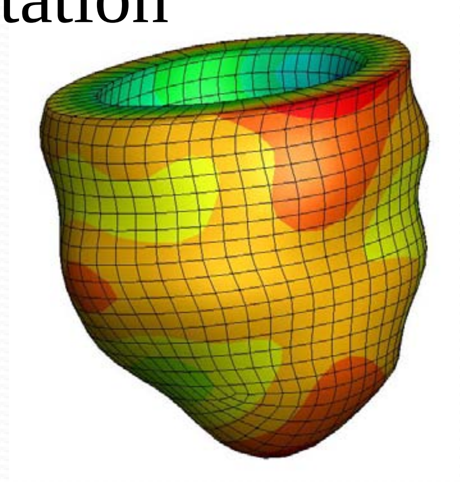
$\mathbf{f}_0$ ... fibre axis

MRI based left ventricle model

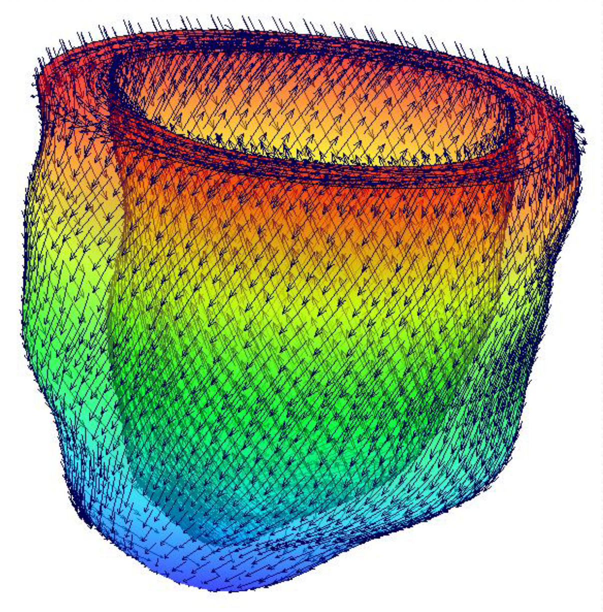


MRI

Segmentation



add fibres



For a fiven LV fibre structure $\mathbf{f}_0, \mathbf{n}, \mathbf{s}_0$

use a nonlinear anisotropic LV model:

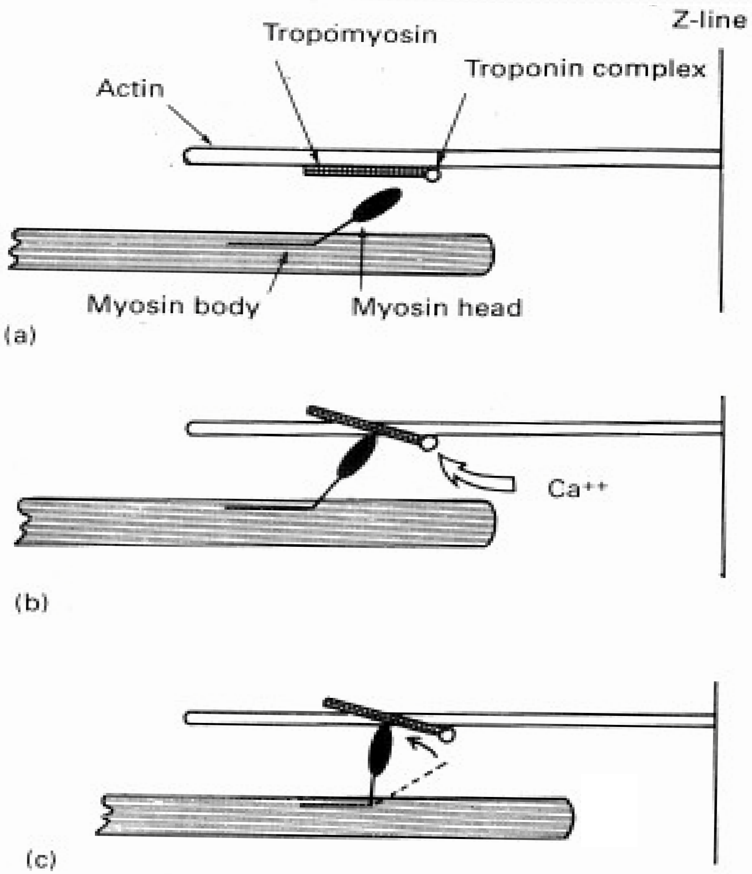
$$W = W(I_1, I_{4f}, I_{4s}, I_{8sf}, I_6)$$

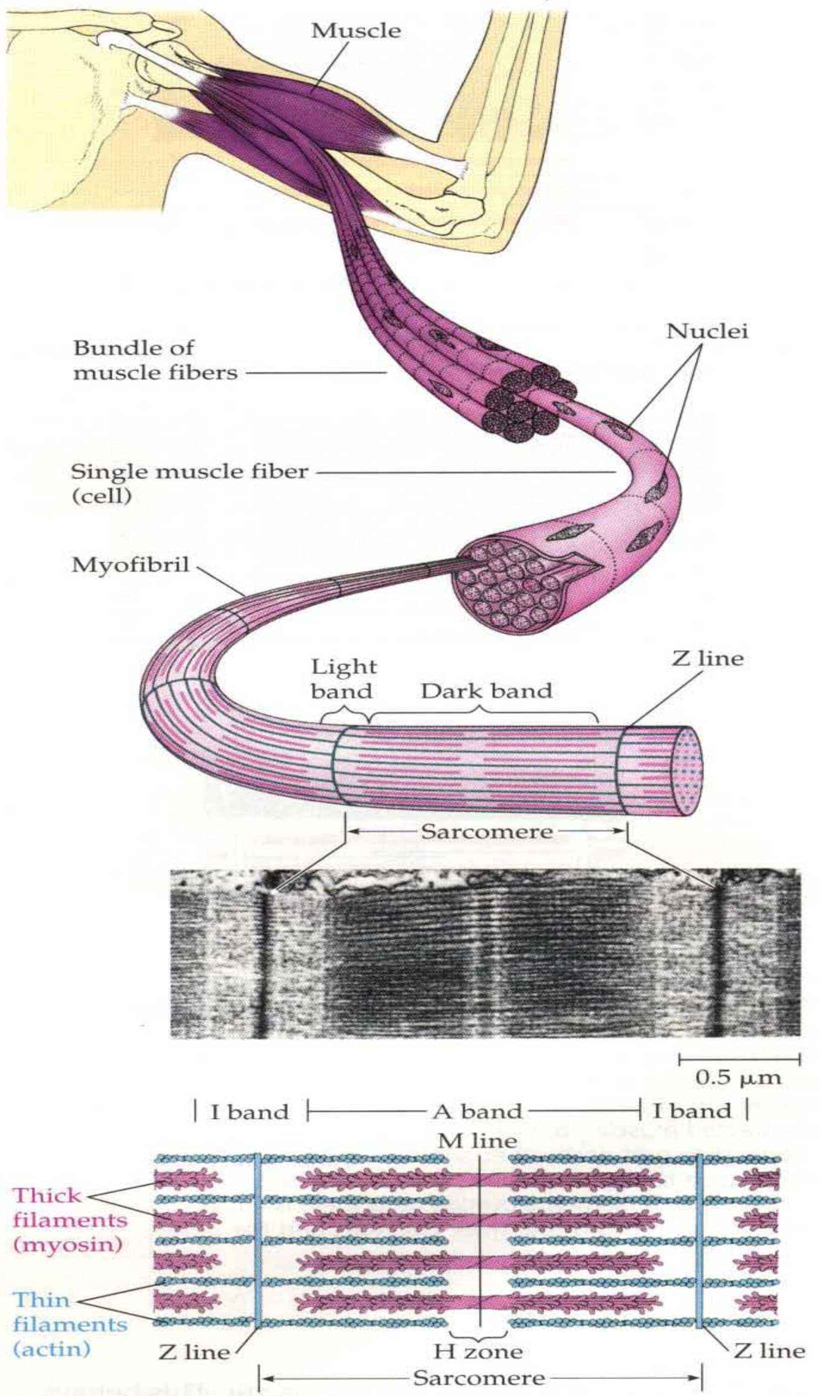
$$= \frac{a}{2b}\exp\{b(I_1 - 3)\} + \sum_{i=f,s} \frac{a_i}{2b_i}\exp\{b_i(I_{4i} - 1)^2\}$$

$$+ \frac{a_{fs}}{2b_{fs}}\exp\{b_{fs}(I_{8fs} - 1)^2\} + \frac{1}{2} I_6$$

- Construct the residual stress field at the zero-loading state
- Obtain he “true” dynamic strain through out the heart beat
- Estimate patient-specific material parameters

Active contraction





Active stress models

Hunter-McCullock-terKeurs (HMT) model:

$$\frac{d[C_a^{2+}]_b}{dt} = \rho_0[C_a^{2+}]_i([C_a^{2+}]_{b\max} - [C_a^{2+}]_b) - \rho_0(1 - \frac{T}{\gamma T_0})[C_a^{2+}]_i$$

$$\frac{dz}{dt} = \alpha_0 \left[\left(\frac{[C_a^{2+}]_b}{C_{50}} \right)^n (1 - z) - z \right]$$

$$T_0 = T_{ref}\left[1 + \beta_0(\lambda - 1)\right]z$$

$$T_a = f(T_0, \lambda, \mathrm{t}) \quad \text{(e.g. Hill's eq: } T_a = \frac{1 - aV}{1 + V} T_0 \text{)}$$

$[C_a^{2+}]_{i,}$ $[C_a^{2+}]_{b,}$: the input and bound (to Troponin C) calcium concentrations

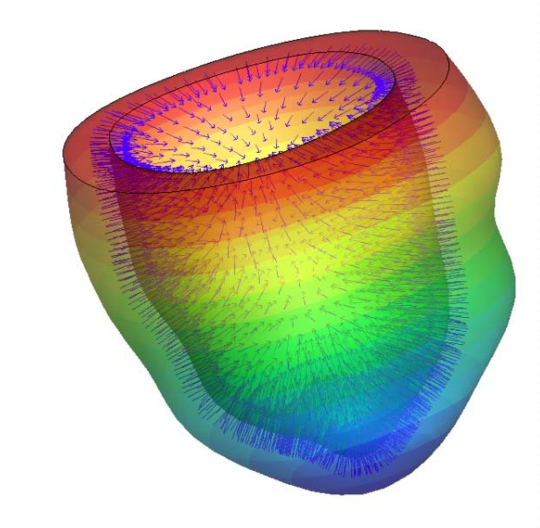
l : sarcomere length l.

T_0 : the isometric tension

λ : extension ratio

z : proportion of action sites available for cross-bridge binding.

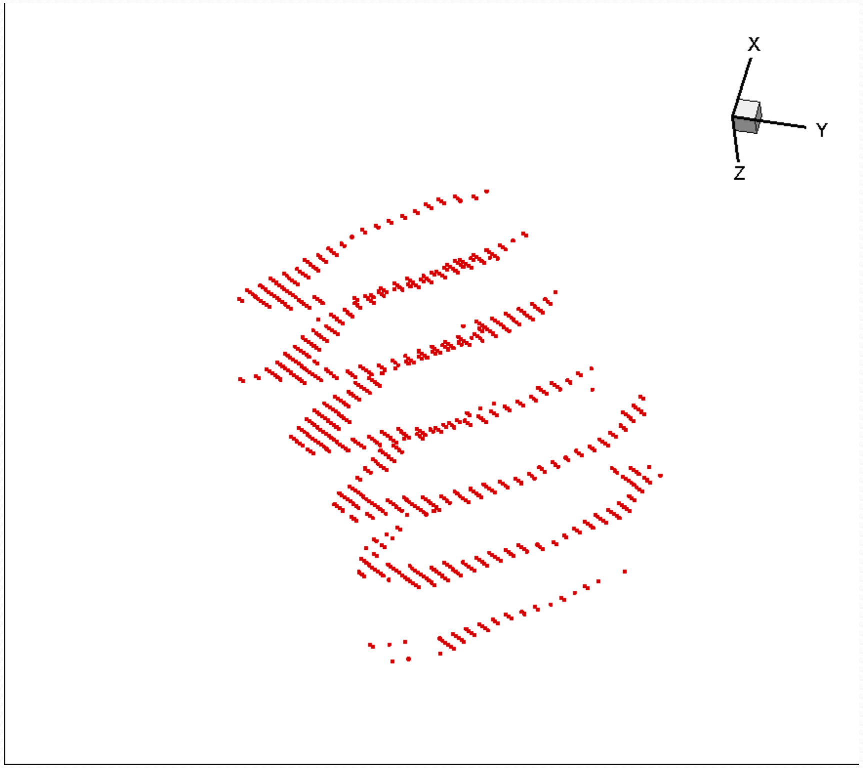
LV model and DENSE

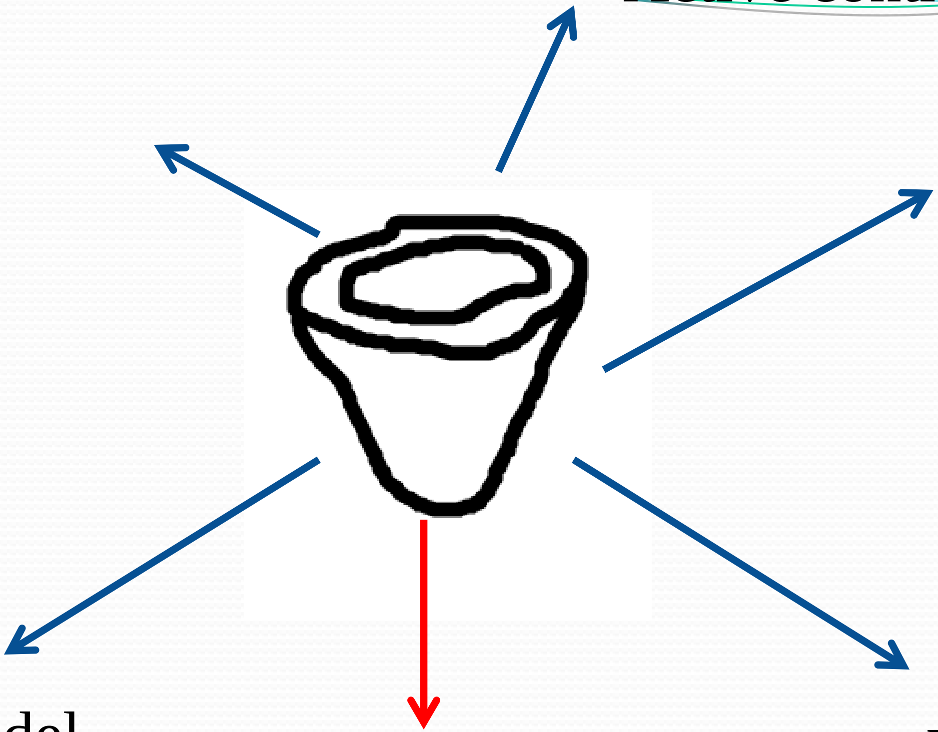


A LV model from MRI

Material parameters can obtained for animals.
What about patient-specific parameters?

Strain field from DENSE





Parameter estimation – (DENSE)

Active contraction

3D anisotropic nonlinear modelling

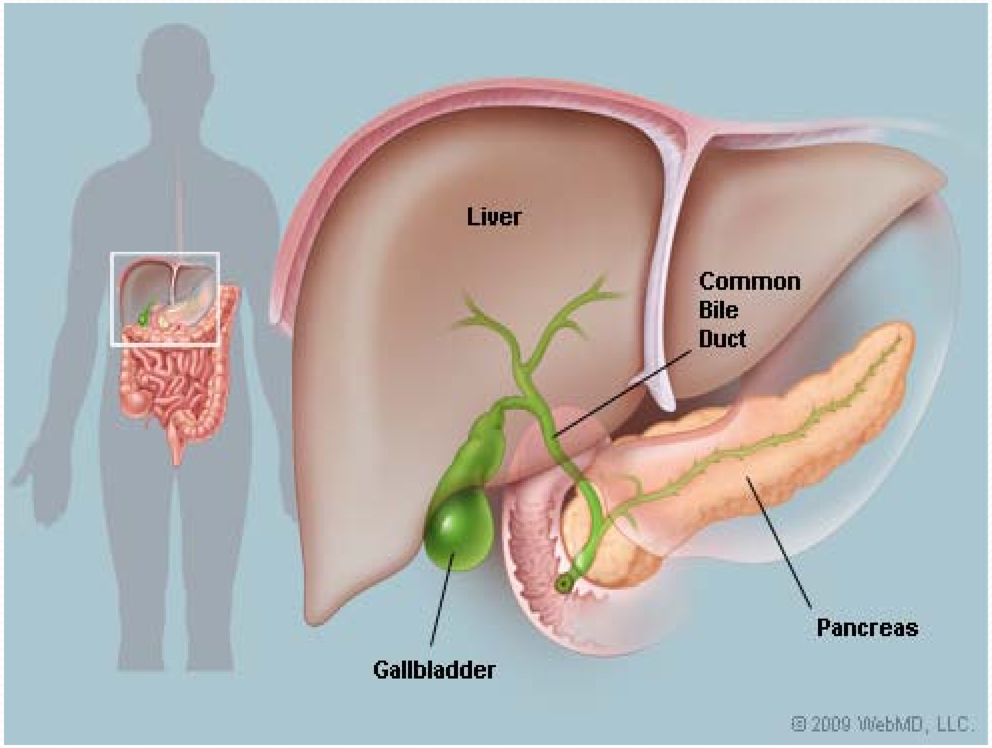
Phantom model

Residual stress

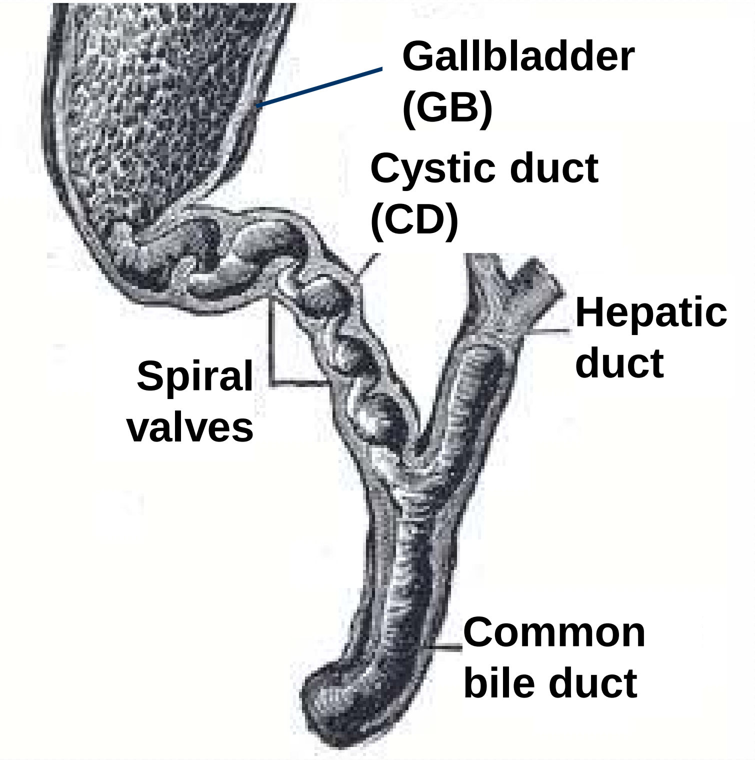
Fibre structure

LV modelling challenges

The human gallbladder



© 2009 WebMD, LLC.

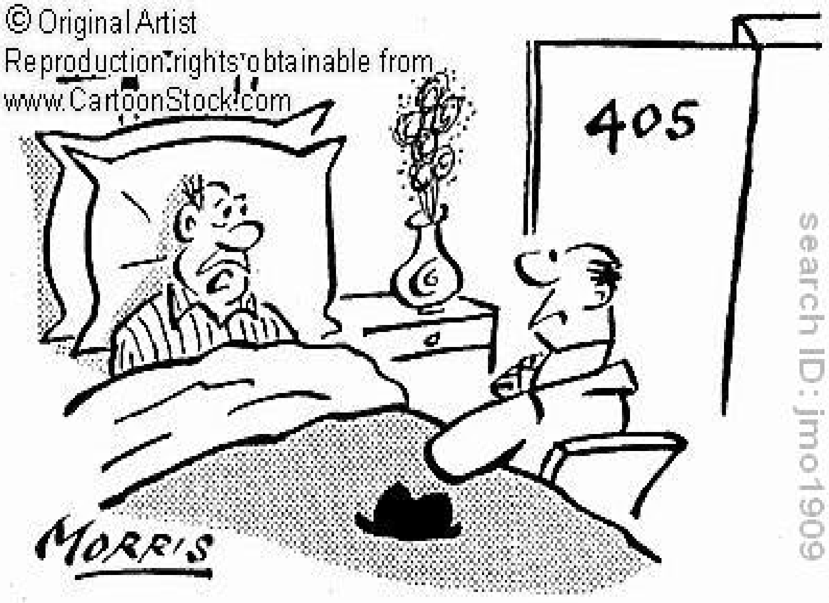


The biliary system creates, transports, stores, and releases bile into the duodenum to help in digestion.

The biliary system includes the gallbladder (a pear-shaped organ located directly below the liver), cystic ducts, and hepatic and common bile ducts.

Common biliary diseases

- Gallstones
  - — Super-saturation of bile with cholesterol
  - — Presence of calculi nucleating agents
  - — Reduction in gallbladder motility
- Inflammation of gallbladder
  - — often caused by obstruction of cystic duct
  - — impaired gallbladder emptying



"One minute I was Chairman and Chief Executive of Mammon Industries, the next I'm the gallbladder in room 405."

Gallbladder Pain (Li *at al.* 2008, 2010)

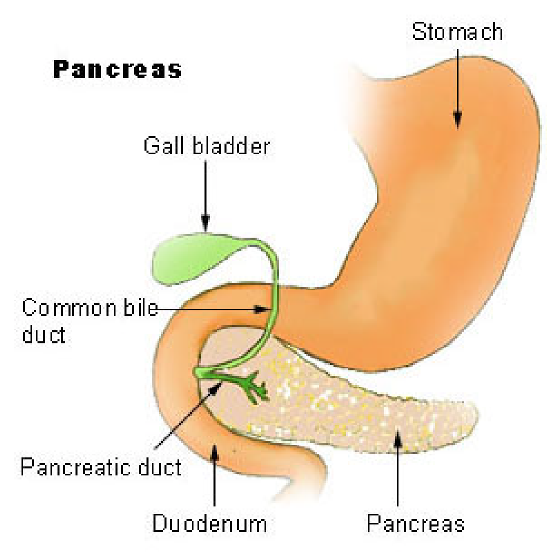
- Acalculus pain - occurs in patients without gallstones
  - 7.6% of men and 20.7% women.

- Clinical practice: If ejection fraction (*EF*) < 35%,
  GB is removed

- Outcome:
  - Pain relief for up to 50% patients only
  (Royal Hallamshire Hospital, Sheffield)

CCK test

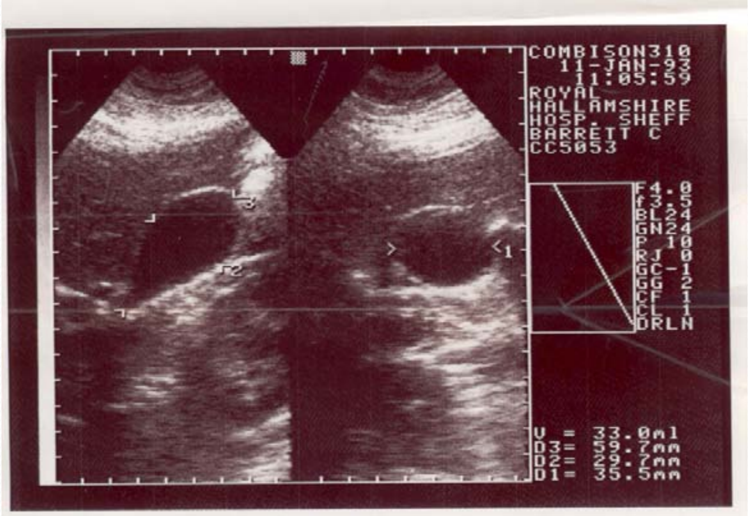
CCK injection

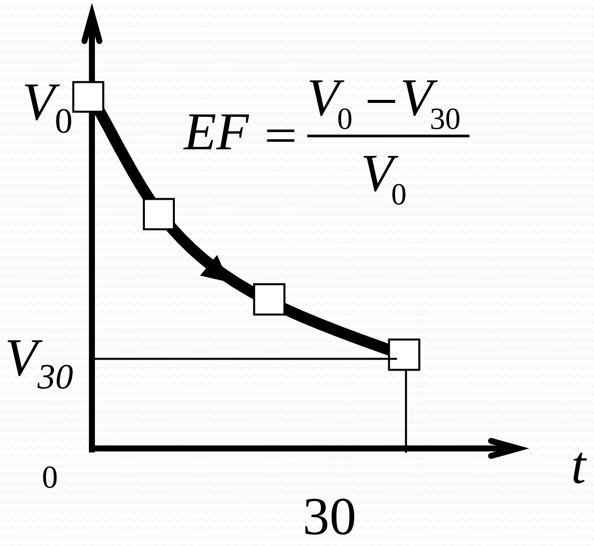


CCK Provocation Test

Induction of pain within 5 min of an CCK injection is used to diagnose GB pain

Ejection Fraction





$$EF = \frac{V_0 - V_{30}}{V_0}$$

A Windkessel model for emptying

$$-\frac{dV}{dt} = \frac{p - p_d}{R} \qquad (1)$$

where V is the GB volume, p is the GB pressure, R is the resistance

$$\frac{dV}{dt} = C\frac{dp}{dt} \qquad (2)$$

Hence

$$C\frac{dp}{dt} + \frac{p - p_d}{R} = 0 \qquad (3)$$

where C is the GB compliance, chosen to be 2.731ml/mmHg,

and pressure in duodenum is chosen to be p_d = 6mmHg.

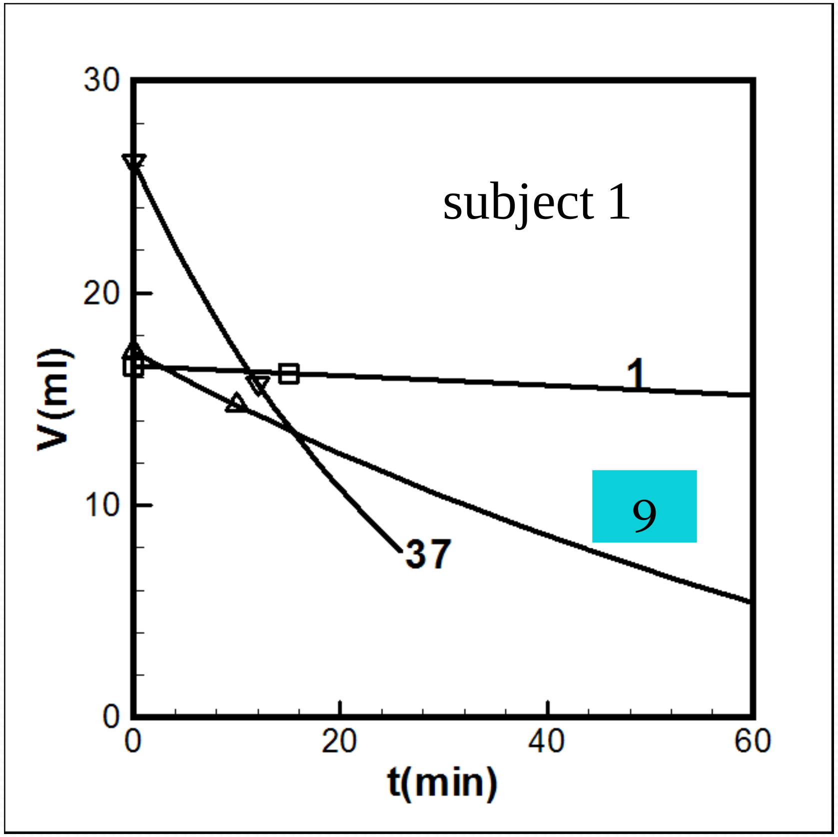
Model applied to 51 subjects

CCK followed by volume monitoring

Subject 1: EF=4.2%

9: EF=39.5%

37: EF >70%



GB removal for subject 1?

Pressure and resistance

Peak pressure (mmHg):

subject 1: P=15.2

9: P=15.4

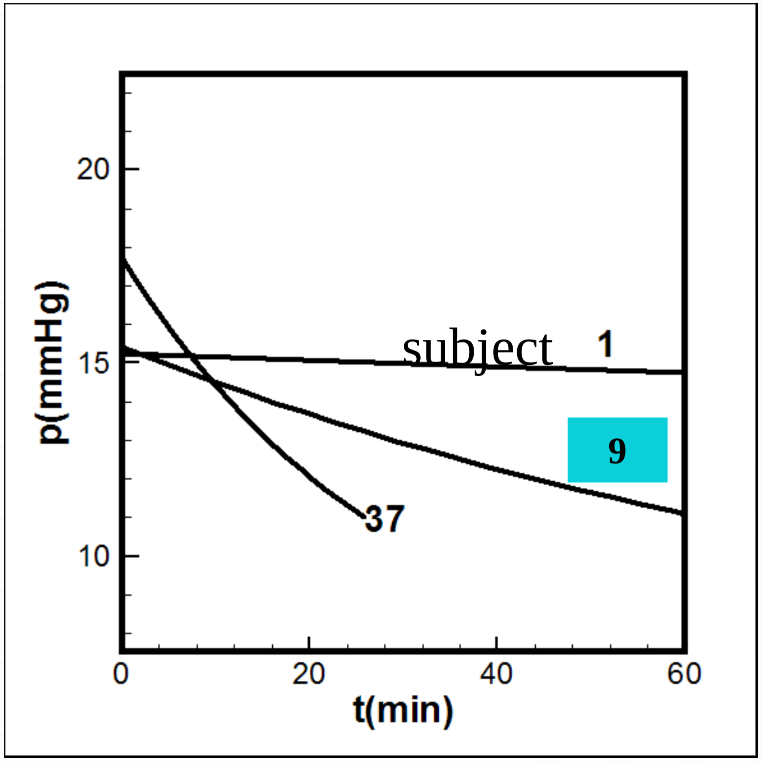
37: P=17.7

Resistance:

subject 1: R=392.6

9: R=35.7

37: R=11.1



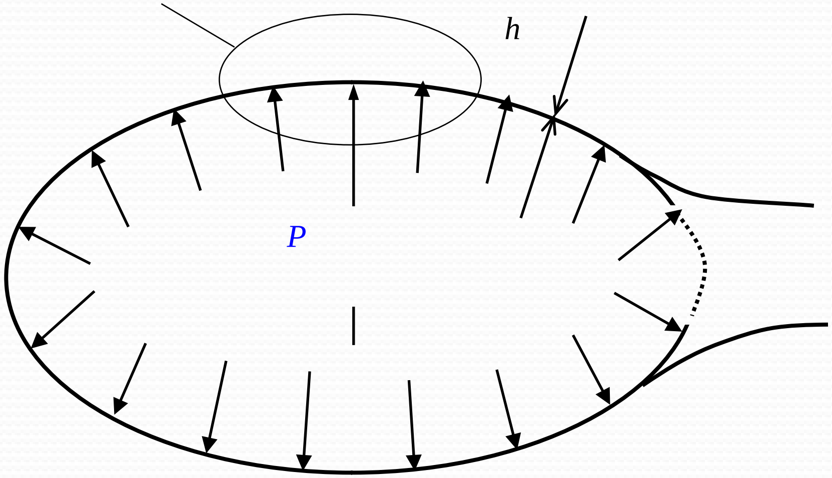
Subject 1 or 37?

Subject 9 is the one with pain!

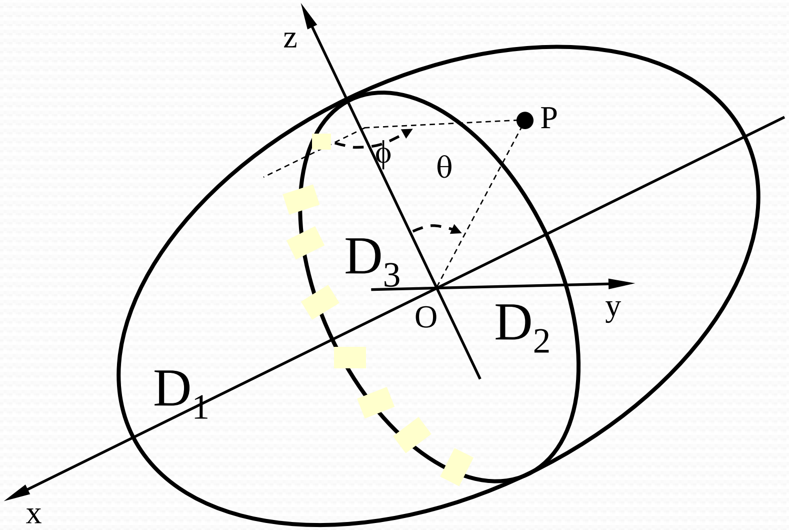
Stress distribution

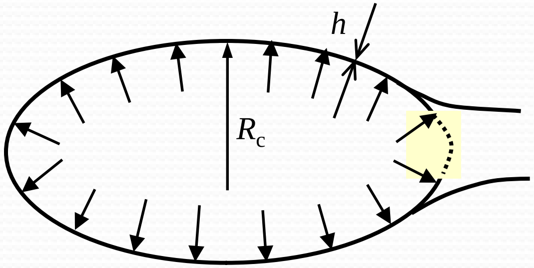
Stress (force/area) inside the GB changes even under uniform pressure

The highest stress zone



Model the GB as an ellipsoid





Gallbladder assumed to be ellipsoid under uniform pressure.

In this case, the stresses are known.

Stresses of a linear elastic ellipsoid

Novozhilov (1964)

$$\sigma_\theta = p\ F_\theta$$
$$\sigma_\phi = p\ F_\phi$$
$$\tau_{\theta\phi} = p\ F_\tau$$

where $k_1 = D_1/D_3 \qquad k_2 = D_2/D_3$

F_θ, F_ϕ, F_τ are the functions describing the instantaneous shape of a GB:

$$F_\theta = C\frac{D_3 k_1 k_2}{4h_{GB}}\left(1 - \frac{k_1^2 - k_2^2}{k_1^2 k_2^2}\cos 2\phi\right),\ F_\tau = \frac{D_3}{4k_1 k_2 h_{GB}}\left(k_1^2 - k_2^2\right)\cos\theta \sin 2\phi$$

$$F_\phi = \frac{D_3}{4k_1 k_2 h_{GB} C}\left[k_1^2 k_2^2 + \left(k_1^2 + k_2^2 - 2k_1^2 k_2^2\right)\sin^2\theta + \left(k_1^2 - k_2^2\right)\cos^2\theta \cos 2\phi\right]$$

$$C = \frac{\sqrt{k_1^2 \cos^2\theta \cos^2\phi + k_2^2 \cos^2\theta \sin^2\phi + \sin^2\theta}}{\sqrt{k_1^2 \sin^2\phi + k_2^2 \cos^2\phi}}$$

Pain threshold

We drive the stress threshold for pain based on experimental data of common bile duct (Gaensler 1951)

$$[\sigma] = \frac{pd}{2h} = 175\ mmHg$$

Hence the subject is in pain if:

$$\sigma_{\max} \geq [\sigma]$$

Pain prediction:

The maximum normal stress is

$$\sigma_{\max} = \max\left[\sigma_\theta, \sigma_\varphi\right]$$

The maximum normal stresses for subjects 1, 9, 37 are

92.9 mmHg, 300.8mmHg, 62.8 mmHg, respectively.

So subject 9 should feel pain – agreed with clinical recording.

Which pain indicator?

EF<35%:

21/51 agree with clinical observation (41.2%) ☹

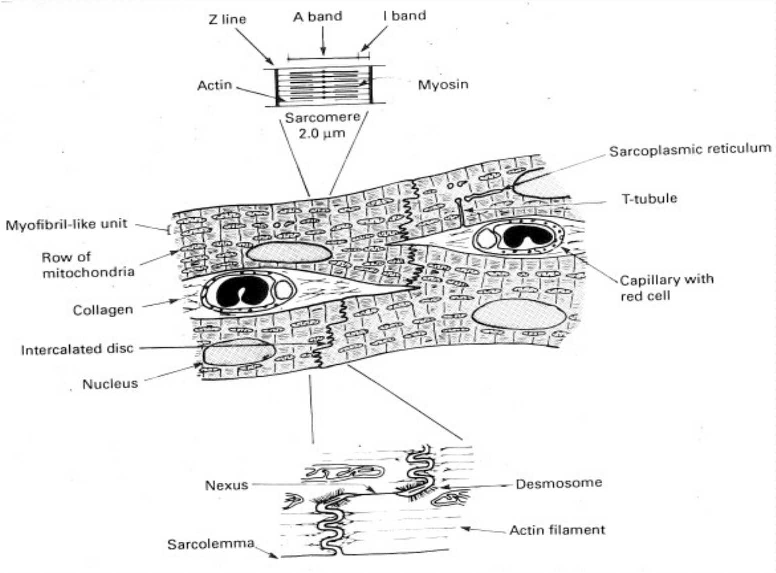
$P_{\max} > 15.4$ mmHg:

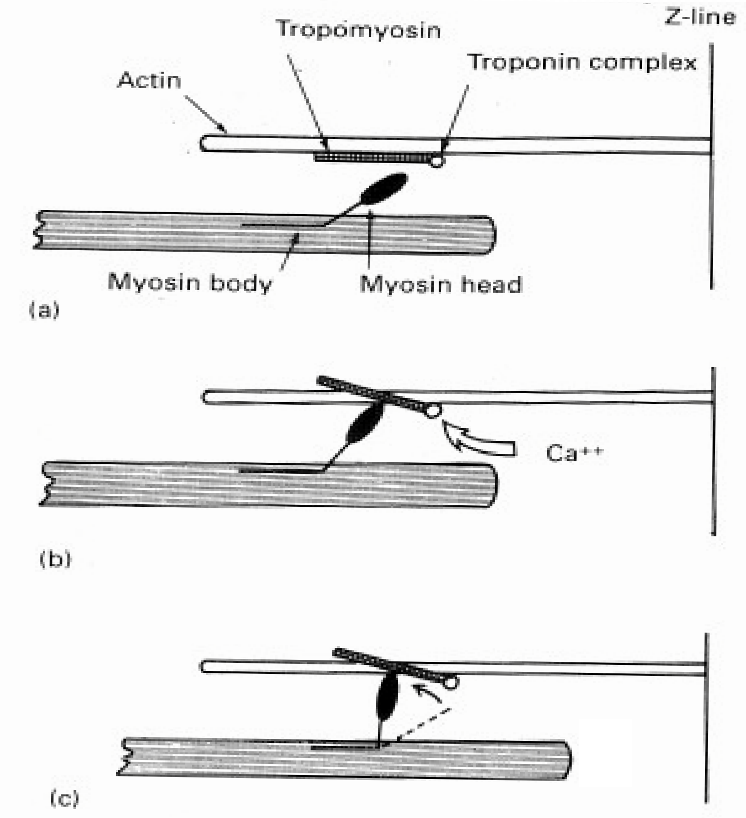
21/51 agree with clinical observation (41.2%) ☹

$\sigma_{\max} > 175$ mmHg:

39/51 agree with clinical observation (76.5%) ☺

Active stress (cross-bridge kinetics):





Cross-bridge trigged by Calcium ion binding to troponin C

Kinetics of cross-bridge

Attached *n* and detached (*1-n*) status:

$$n = [\mathrm{AMp}] + [\mathrm{AM}] \underset{g_{app}}{\overset{f_{app}}{\rightleftarrows}} (1-n) = [\mathrm{Mp}] + [\mathrm{M}]$$

$$\longrightarrow \quad \frac{dn(x,t)}{dt} = \left(1-n(x,t)\right) f_{app} - n(x,t)\, g_{app}$$

The model prediction

$$f_{app} = \left(\frac{r_{\max}}{\sigma^a_{\max}} \right) \left(\frac{\dfrac{d\sigma^a}{dt} - \sigma^a g_{app}}{1 - \left(\dfrac{r_{\max}}{\sigma^a_{\max}} \right) \sigma^a} \right), \quad g_{app} = \frac{g^{mean}_{app}}{\sigma^a_{mean}} \sigma^a$$

$$\left[\mathrm{Ca}^{2+} \right] = \frac{[\mathrm{Ca}^{2+}]^{mean}}{\sigma^a_{mean}} \sigma^a$$

σ^a_{mean} =59mmHg, $[\mathrm{Ca}^{2+}]^{mean}$=357mM, $r_{\max} = 0.5 - 0.75$

Interesting results

Smooth muscle	f_{app} (s^{-1})	g_{app}(s^{-1})
Swine carotid	0.2032	0.0575
Bovine tracheal	0.3455	0.1021
Guinea pig GB	0.0553	0.0154
Human GB	0.044-0.046	0.003-0.02

More accurate stress analysis

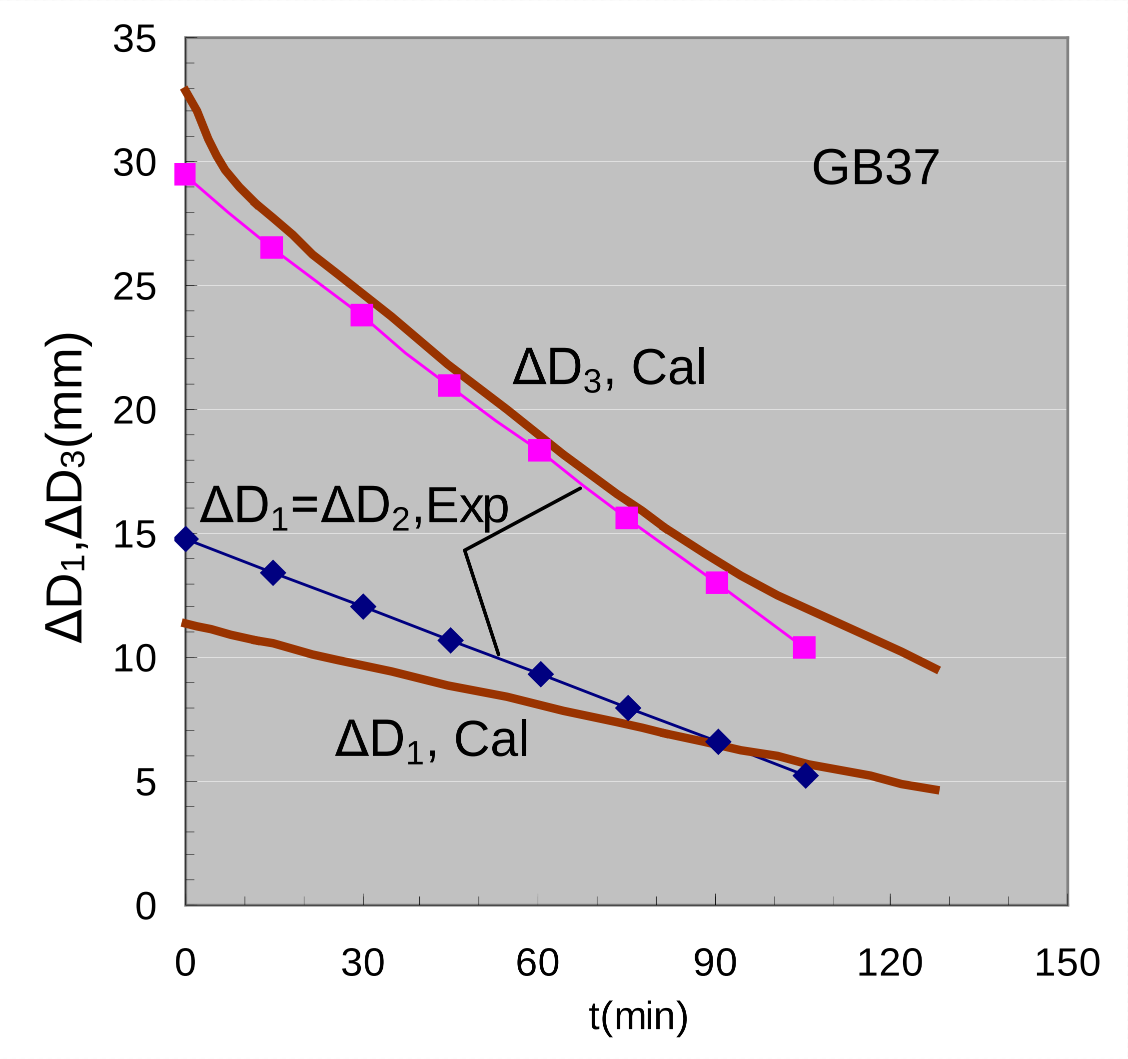
Nonlinear GB with fibres

Consider GB as Nonlinear, anisotropic tissues with circumferential fibres plus isotropic matrix layer.

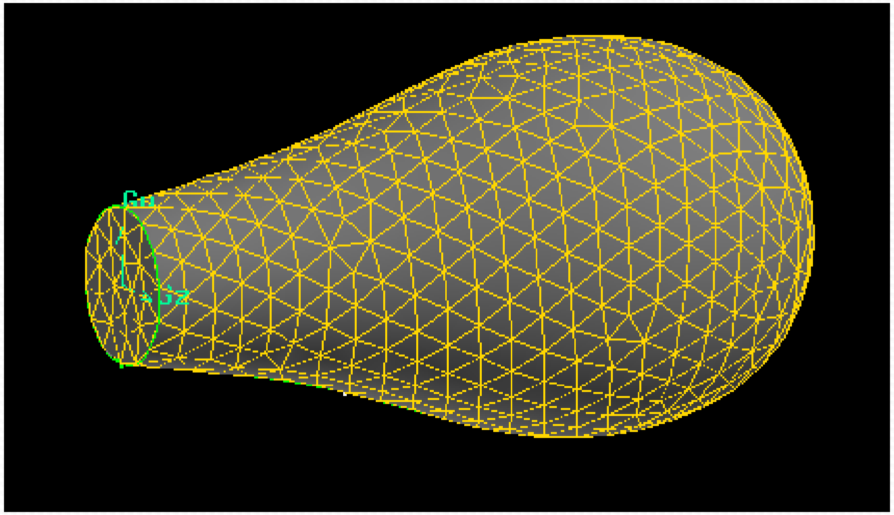
Strain energy density function:
(Holzapfel et al, 2000, J of Elasticity, 61, 1-48)

$$W\left(I_{1,},I_4\right)=C_{10}\left(I_1-3\right)+\frac{k_1}{2k_2}e^{k_2\left(I_4-1\right)^2-1}$$

Comparison with measurements

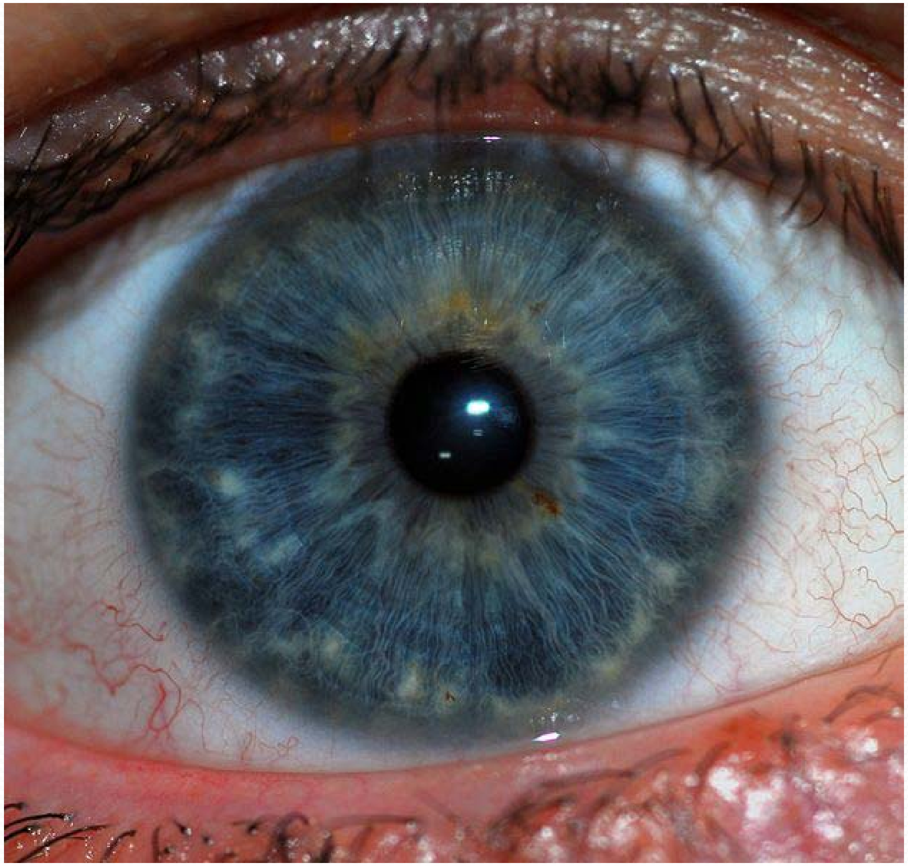


Future work



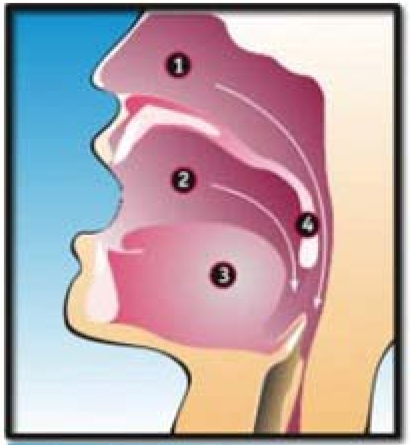
- Patient specific models
- GB remodelling – longer term?
- Drug tests

Buckling of the eye iris



Snoring

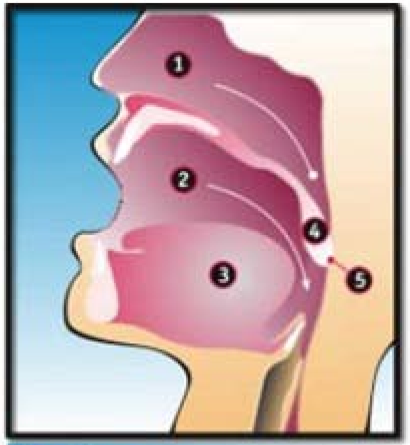
- Snoring during sleep is a common event in OSA patients



Normal Airway

upper airway anatomy

Nasal and Oral Airways are open.



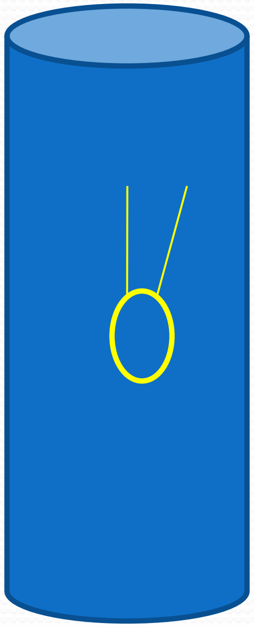
Snoring

caused by Uvula/Soft Palate blockage

Uvula and Soft Palate (4) collapse against rear wall of throat (5). Oral airway (2) remains open.

Arterial Dissection

Arterial dissection, in which a tear develops within the arterial wall, can occur in any branch of the human arterial tree. It is often a life-threatening event and is of significant interest to surgeons .

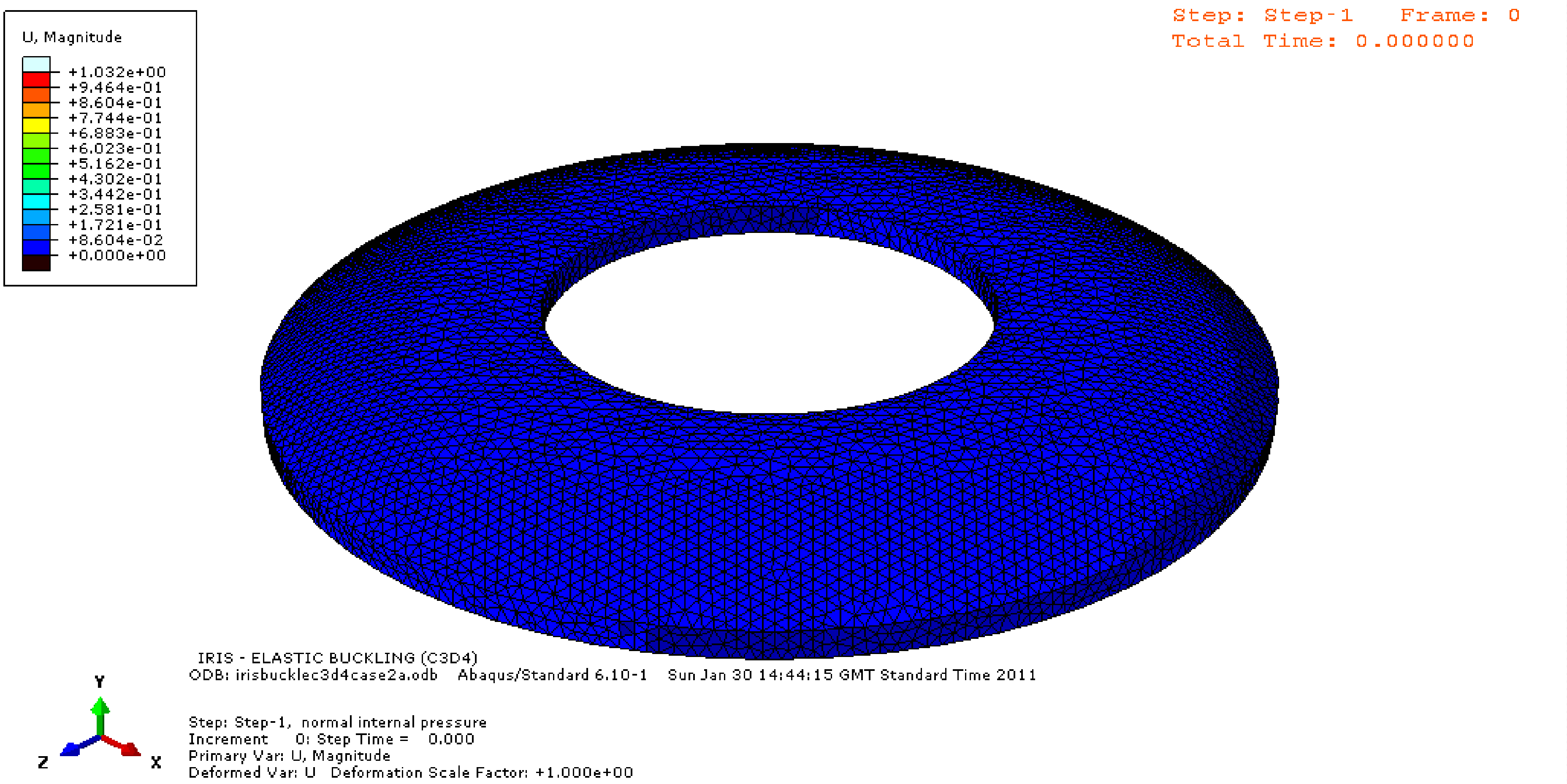


Crack propagation modelled using the cohesive zone

THANK YOU

"Let me not answer your question this way..."

Buckling of the eye iris



Step: Step-1 Frame: 0
Total Time: 0.000000

IRIS - ELASTIC BUCKLING (C3D4)
ODB: irisbucklec3d4case2a.odb Abaqus/Standard 6.10-1 Sun Jan 30 14:44:15 GMT Standard Time 2011

Step: Step-1, normal internal pressure
Increment 0: Step Time = 0.000
Primary Var: U, Magnitude
Deformed Var: U Deformation Scale Factor: +1.000e+00

The iris model