Patient Specific Computational Modeling of Cardiac Mechanics

Henrik Nicolay Topnes Finsberg

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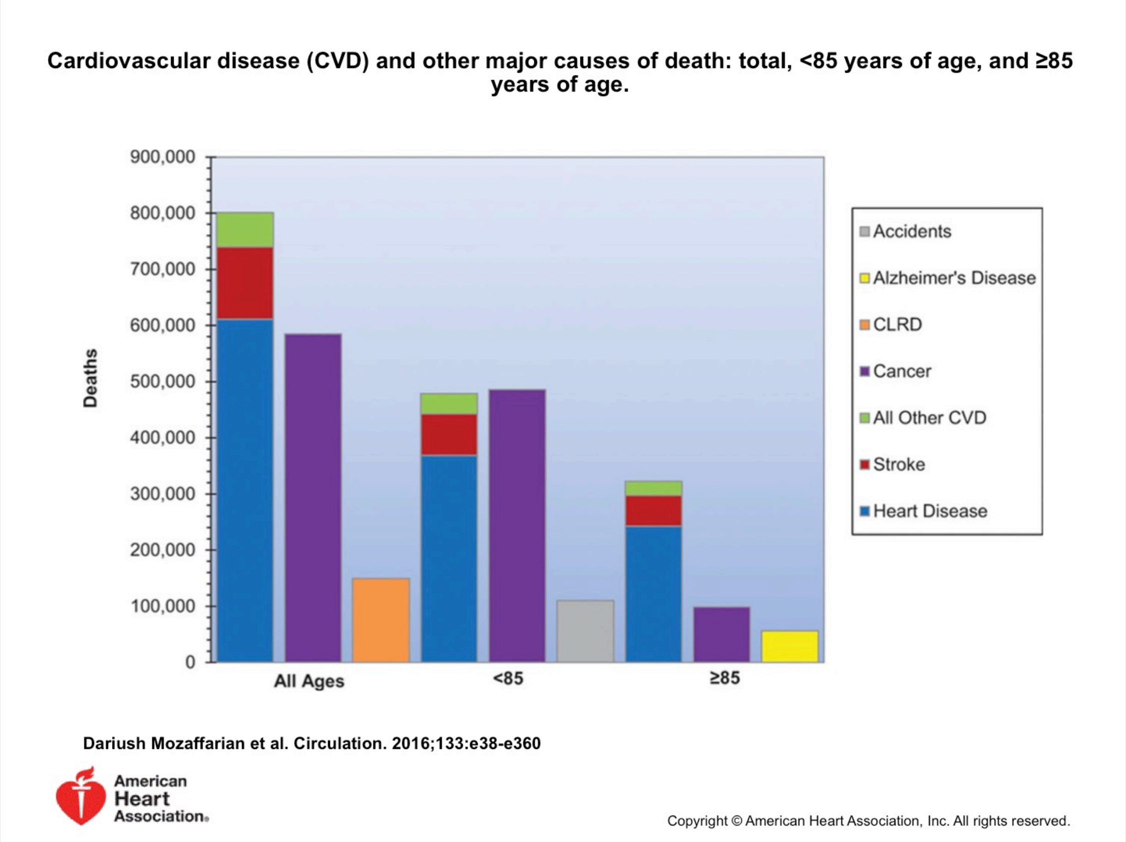
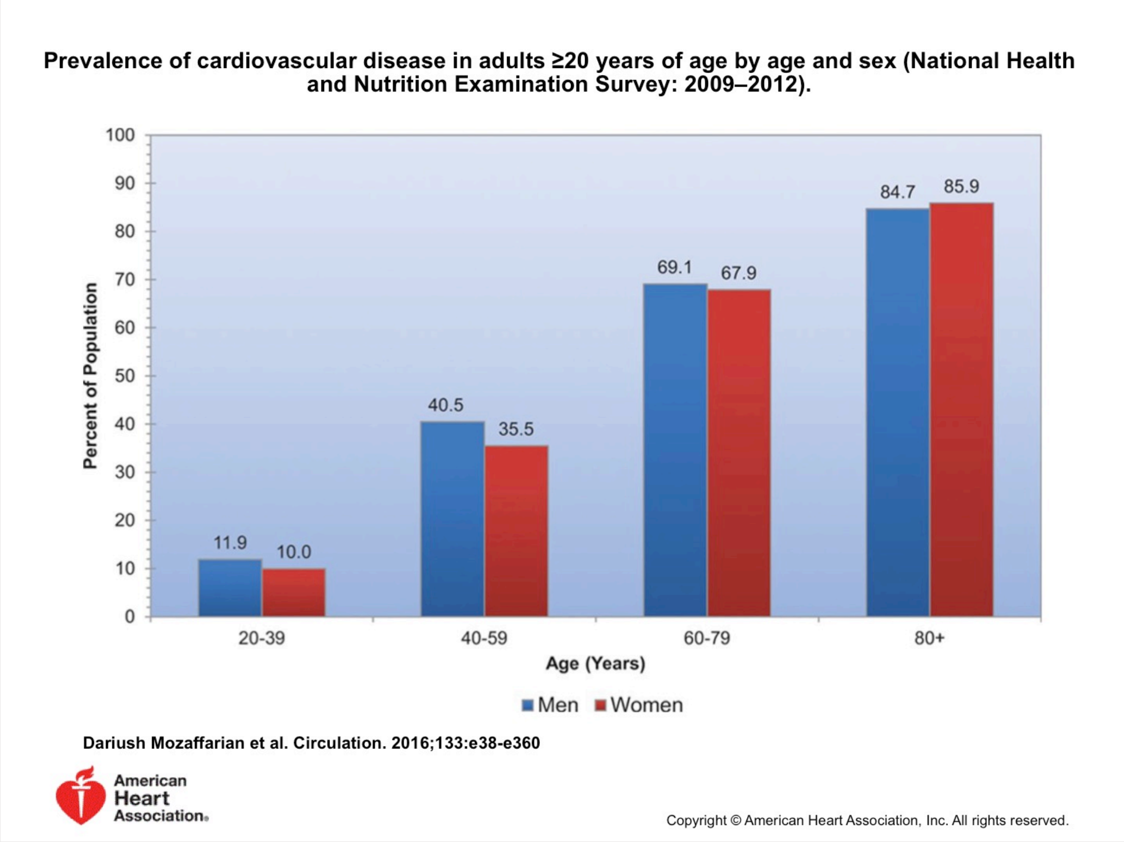
CENTER FOR CARDIOLOGICAL INNOVATION

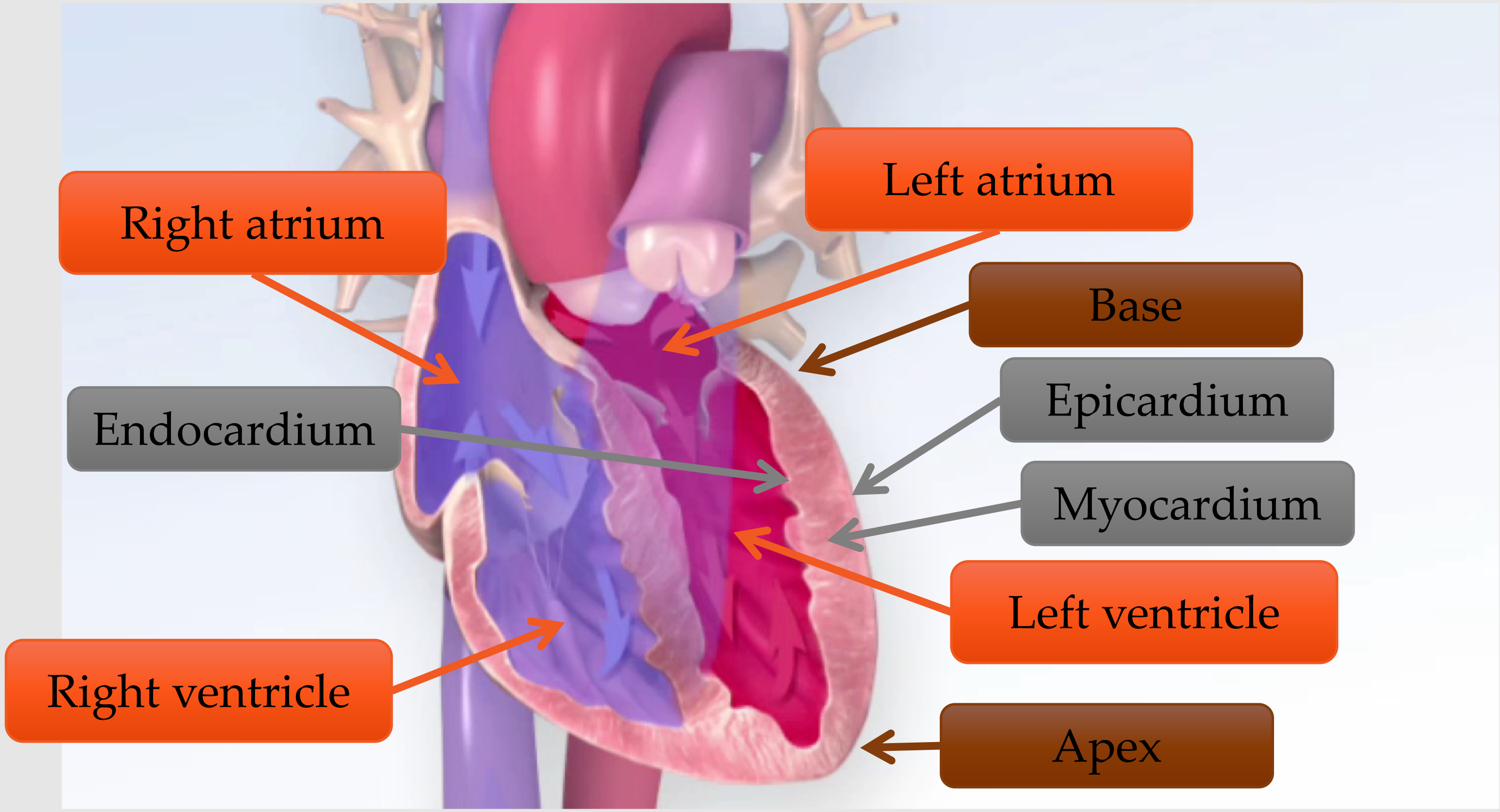
simula

Cardiovascular diseases are the number one cause of death in the western world

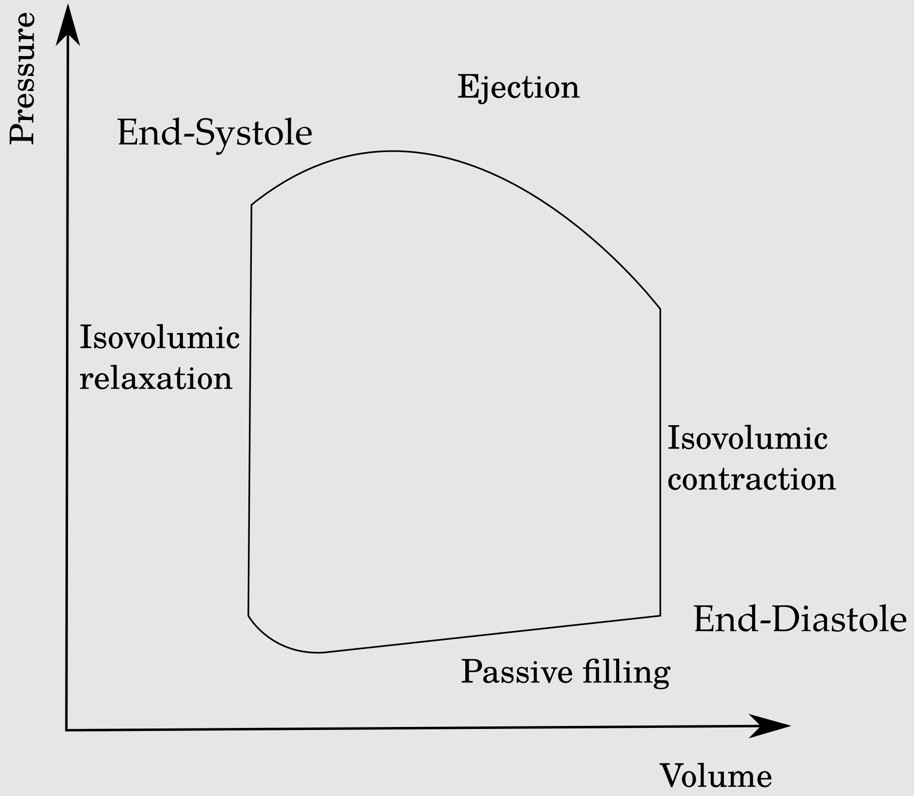




A cardiac cycle can be visualized using the pressure-volume loop



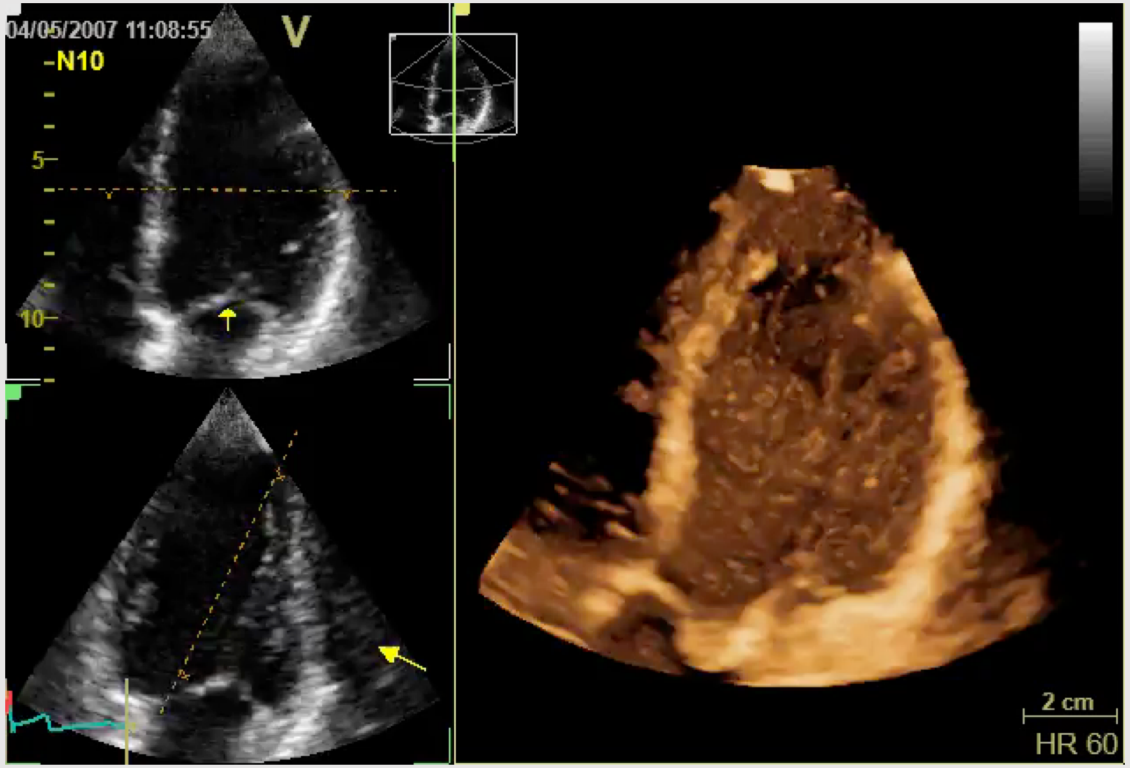
Pressure-Volume (PV) loop



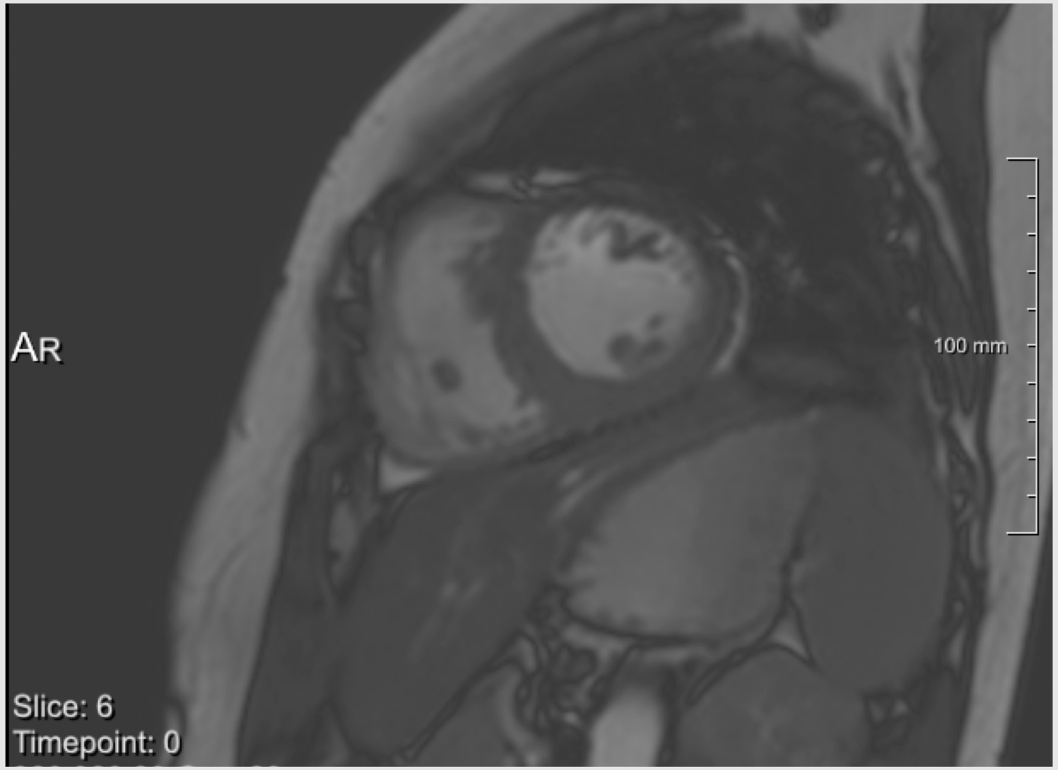
Source: American Heart Association

Cardiac structure and kinematics can be assessed through medical imaging techniques

Echocardiography (ultrasound)

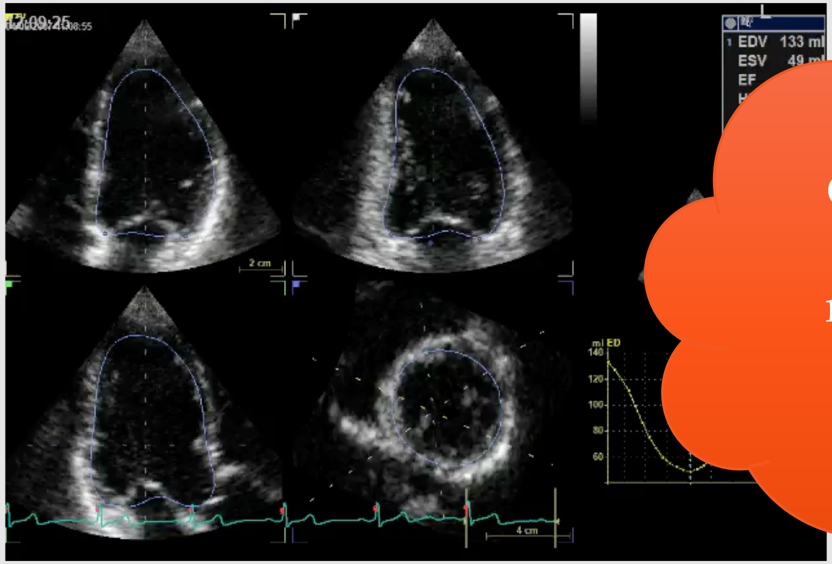


Magnetic Resonance Imaging (MRI)

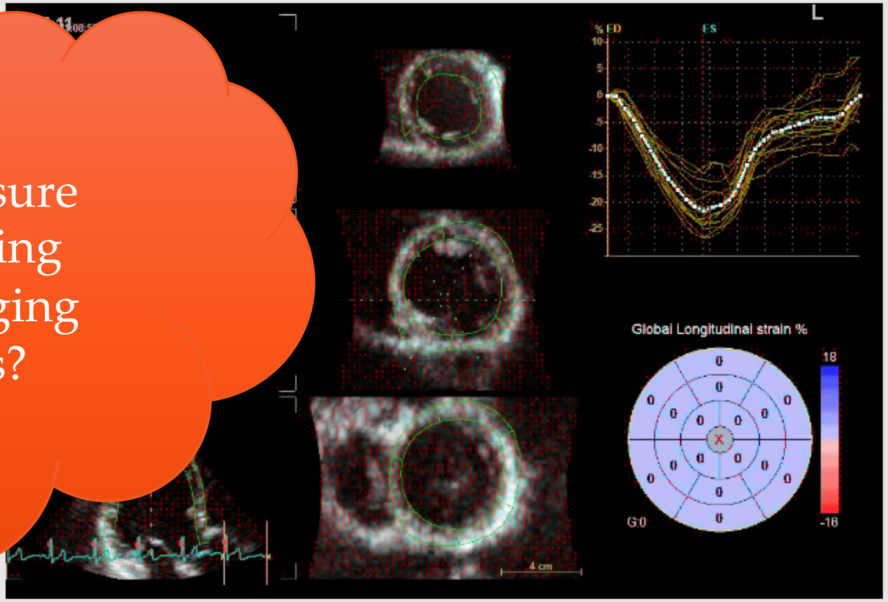


Cardiac structure and kinematics can be assessed through medical imaging techniques

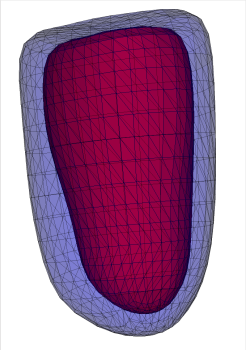
Volume and geometry

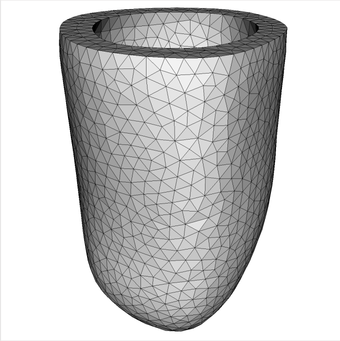


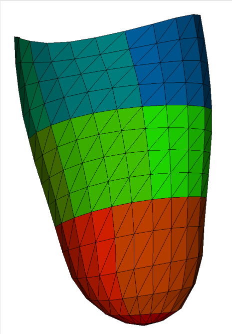
Regional strain

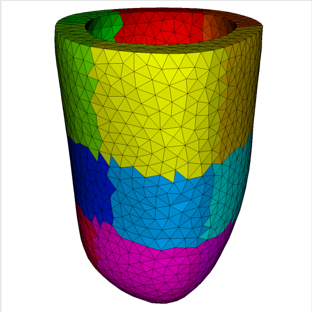


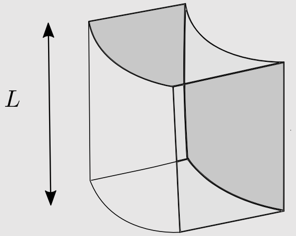
Can we measure anything using medical imaging techniques?











We cannot measure the forces in a beating heart

Law of Laplace (Woods 1892)

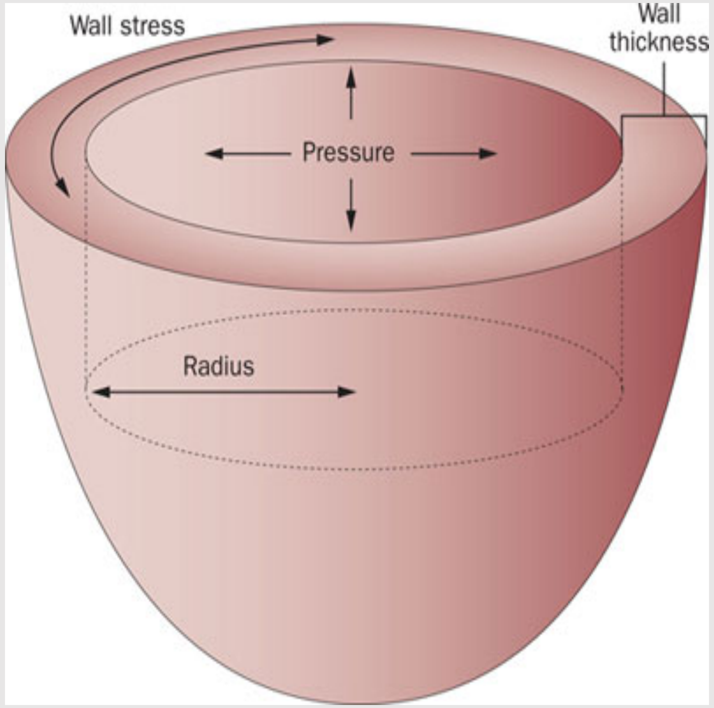
$$\text{wall stress} = \frac{P \times r}{2 \times w}$$

P : pressure

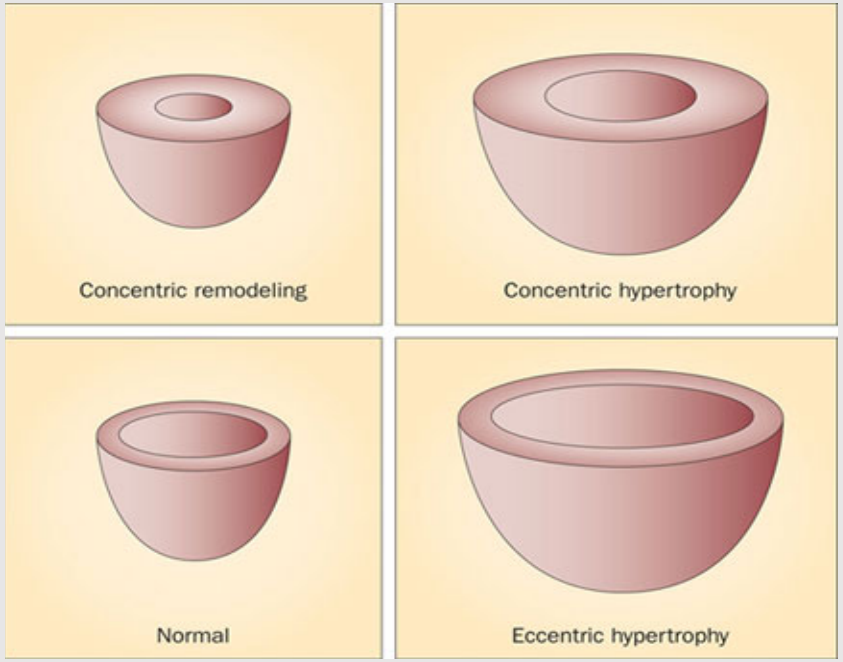
r : radius

w : wall thickness

One of the first examples of a **mathematical model** used to understand cardiac physiology

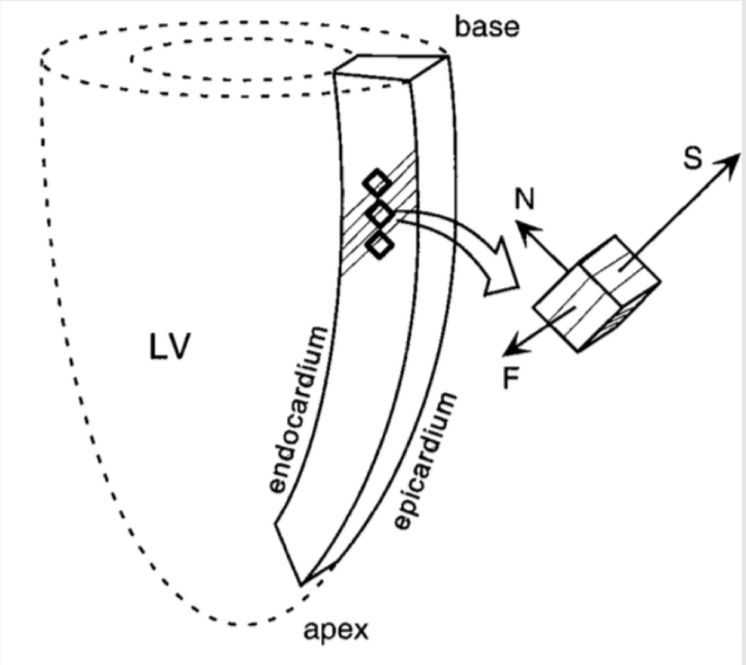


Gjesdal, 2011

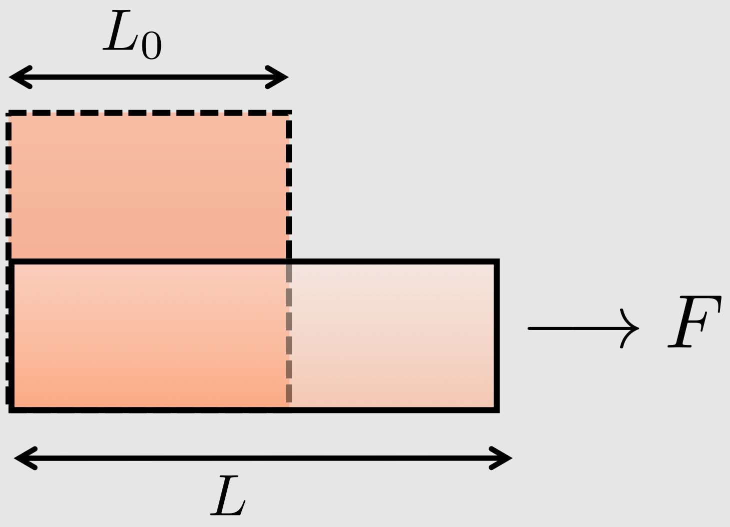


Gjesdal, 2011

A mathematical model is a simplification of the reality realized through equations



Dokos, 2002

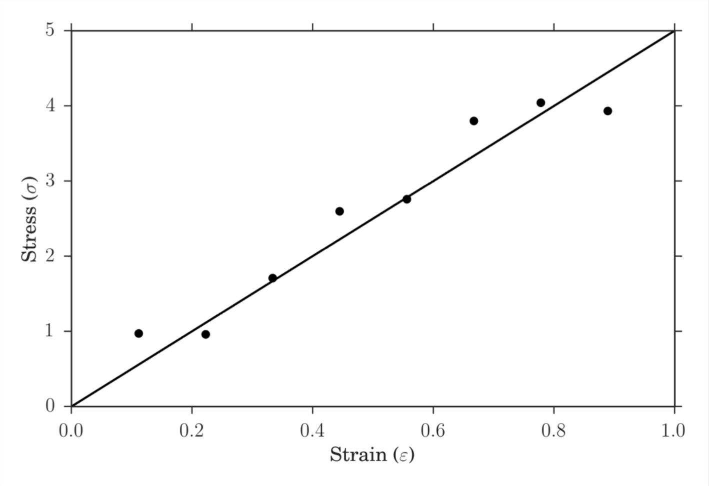


Observation:

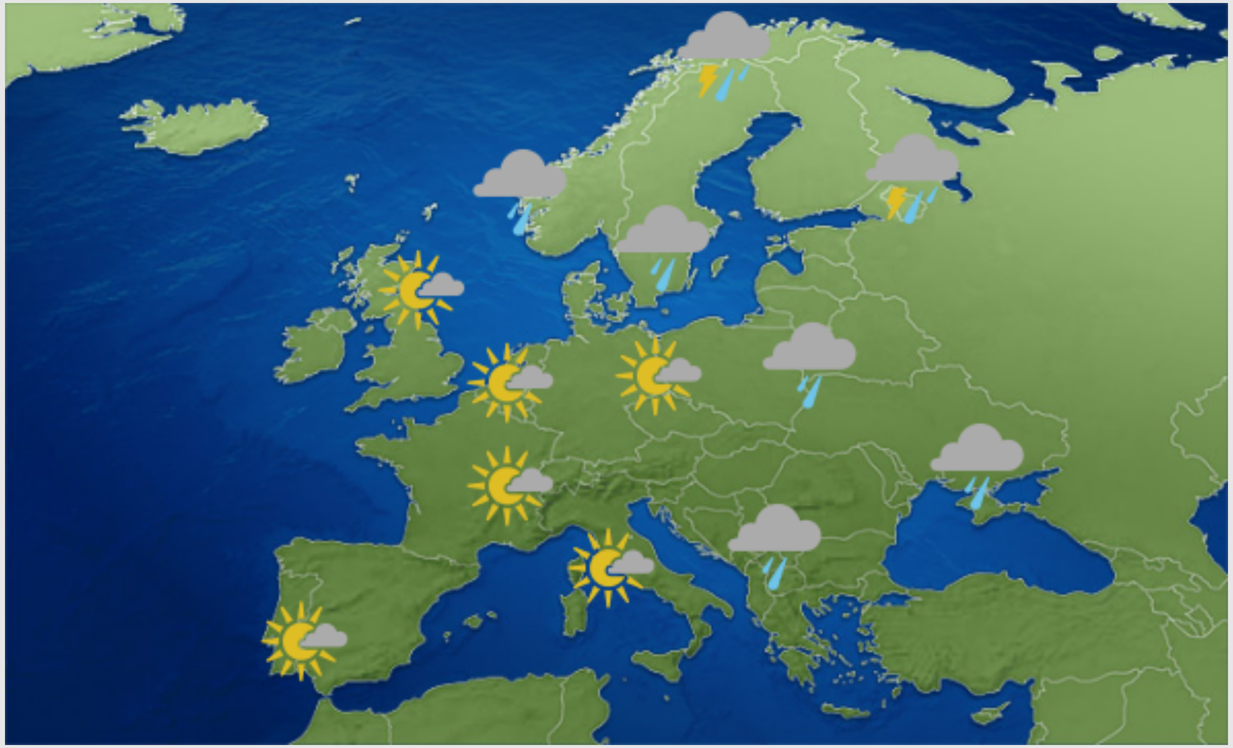
$$\sigma = \frac{F}{A} \qquad \varepsilon = \frac{L - L_0}{L_0}$$

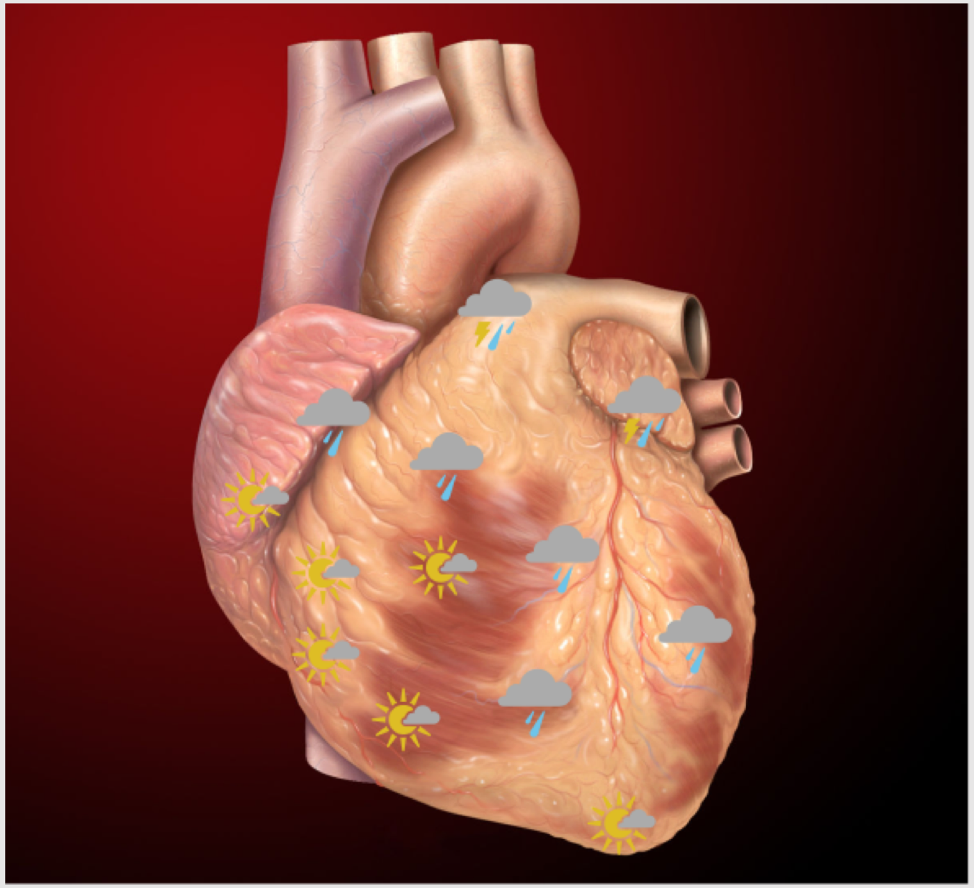
Assumption:

$$\sigma = D\varepsilon$$

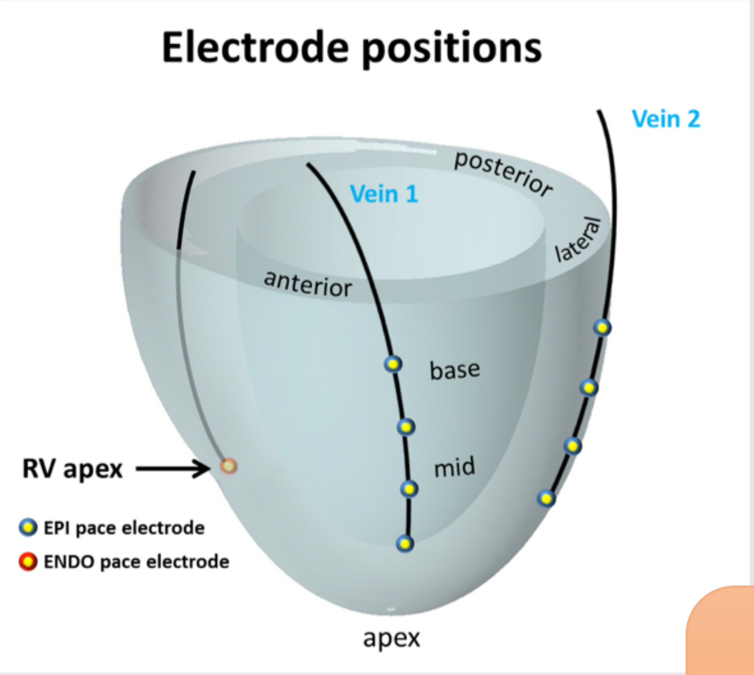


We can forecast the weather, but can we predict the outcome of a specific treatment of the heart?

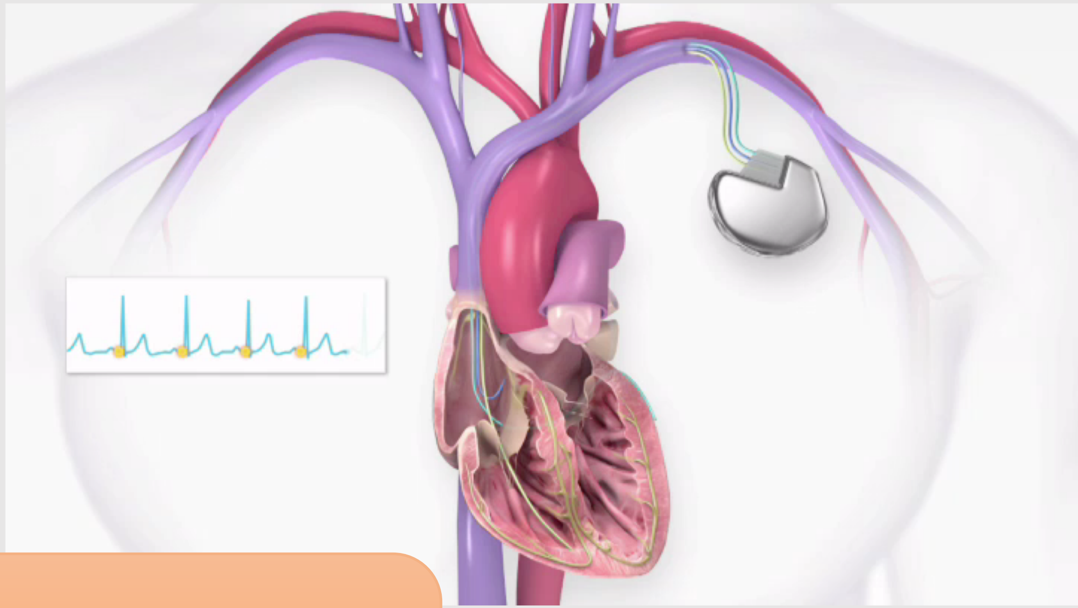




Clinicians want to improve responder rates of cardiac resynchronization therapy (CRT)



Left bundle branch block (LBBB)

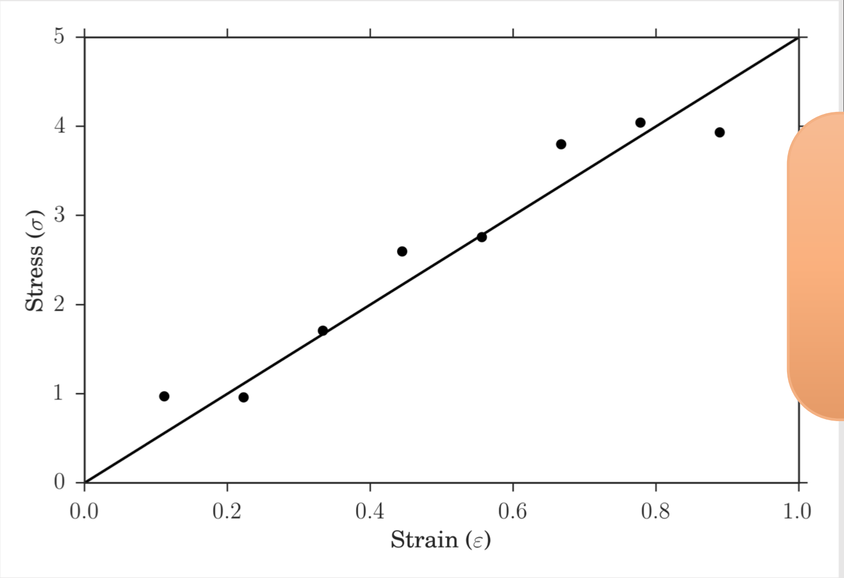


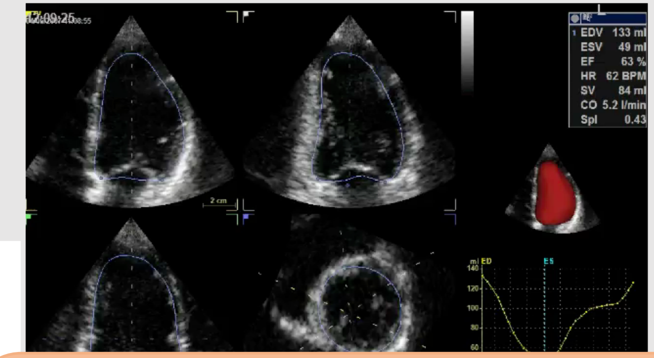
Source: American Heart Association

30-40 % do not respond!

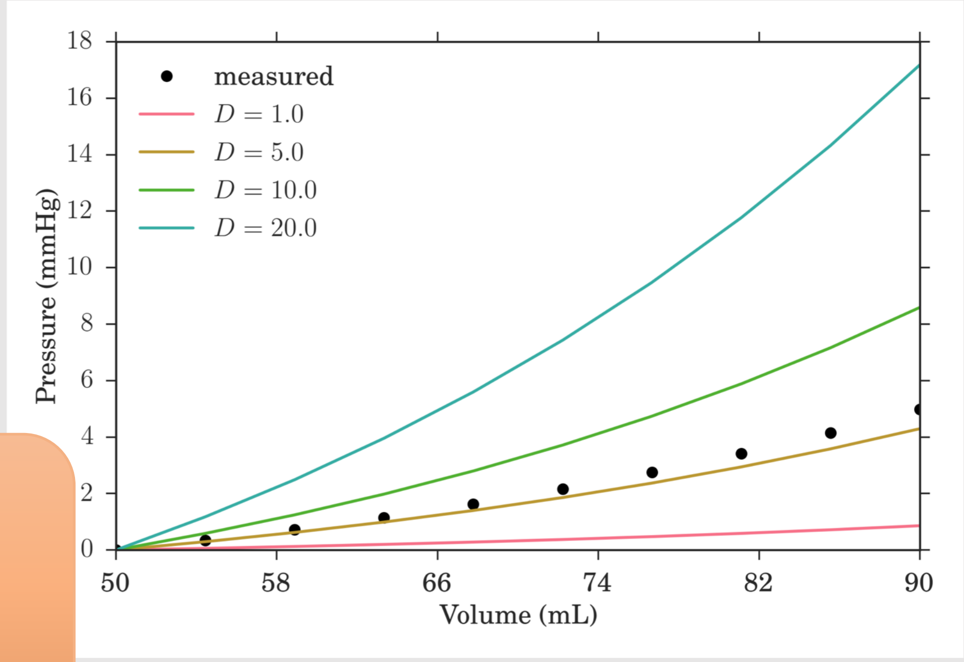
Models depend on parameters that have to be determined, but we might not have access to the data that we want

$$\sigma = D\varepsilon$$





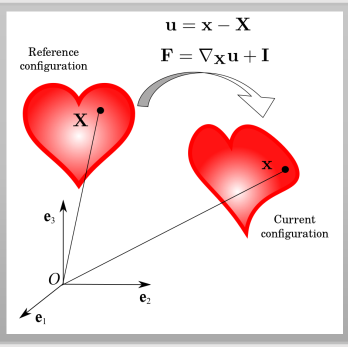
Data assimilation

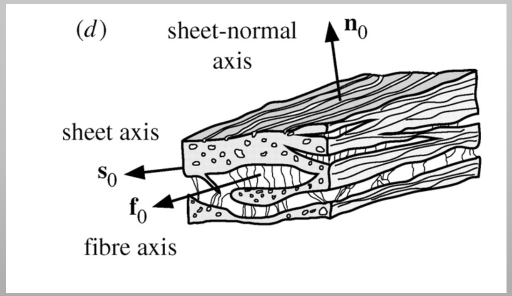


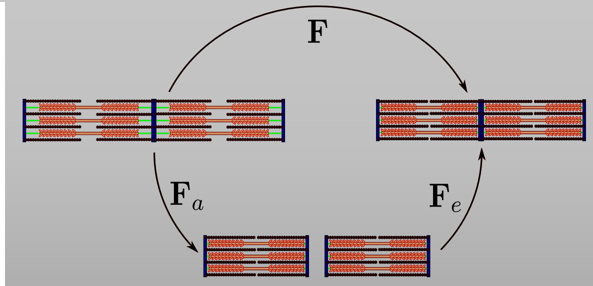
$$\text{minimize} : (\text{observations} - \text{simulations})^2$$
$$\text{subject to} : \text{Newton's laws should hold}$$

Outline

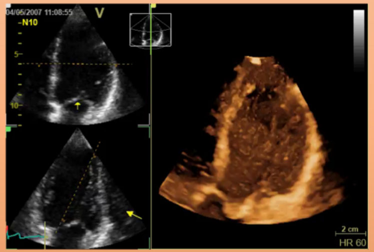
Mathematical modeling

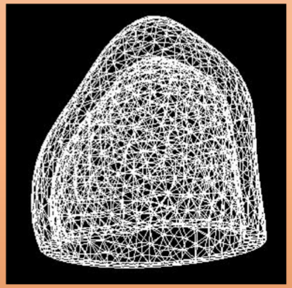






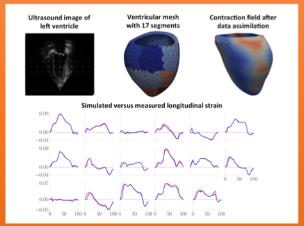
Model Personalization





Summary of papers

Paper 1



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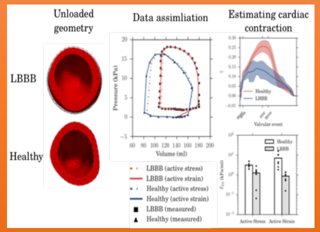
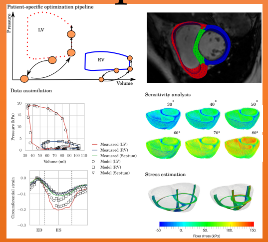
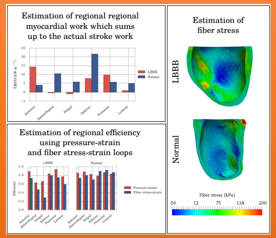


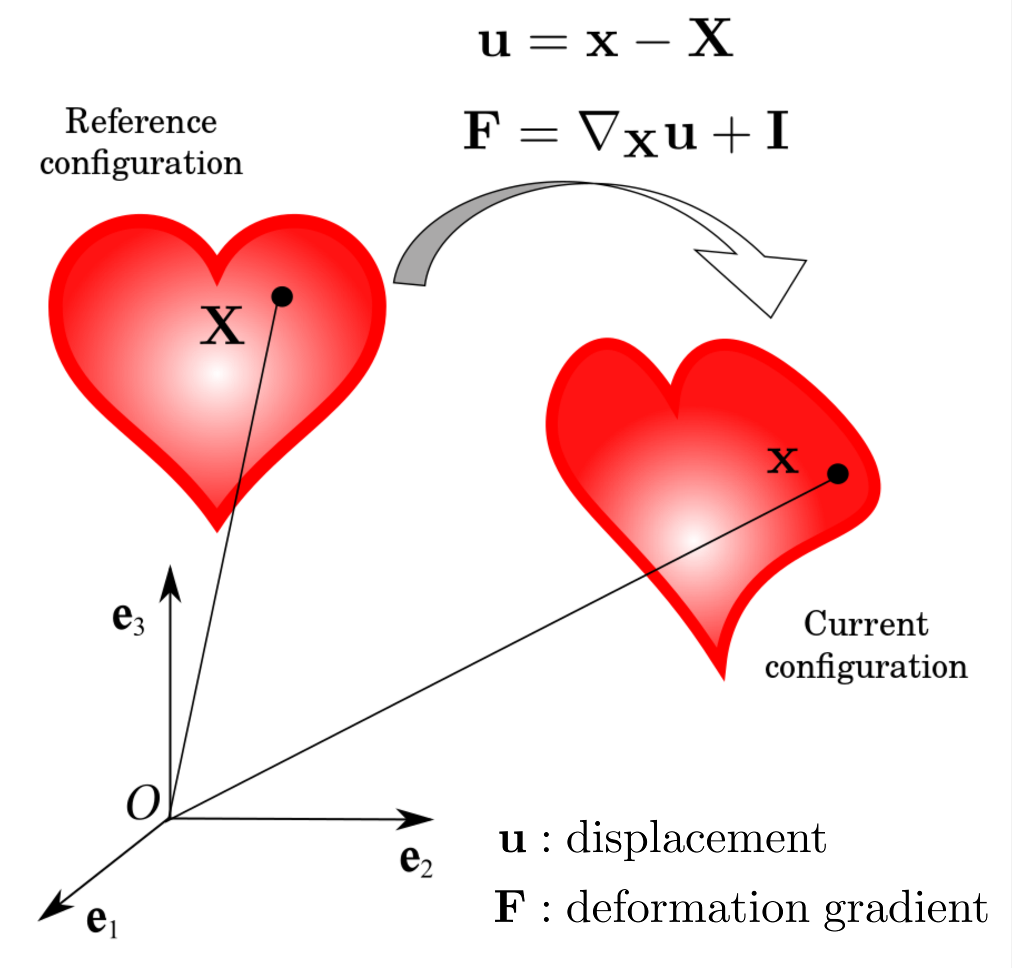
Paper 3



Paper 4



We represent the heart as a continuum body in the Lagrangian description



Mapping of vectors: $$\mathrm{d}\mathbf{x} = \mathbf{F}\mathrm{d}\mathbf{X}$$

Mapping volumes: $$\mathrm{d}v = \det(\mathbf{F})\mathrm{d}V = J\mathrm{d}V$$

Right Cauchy Green deformation tensor: $$\mathbf{C} = \mathbf{F}^T\mathbf{F}$$

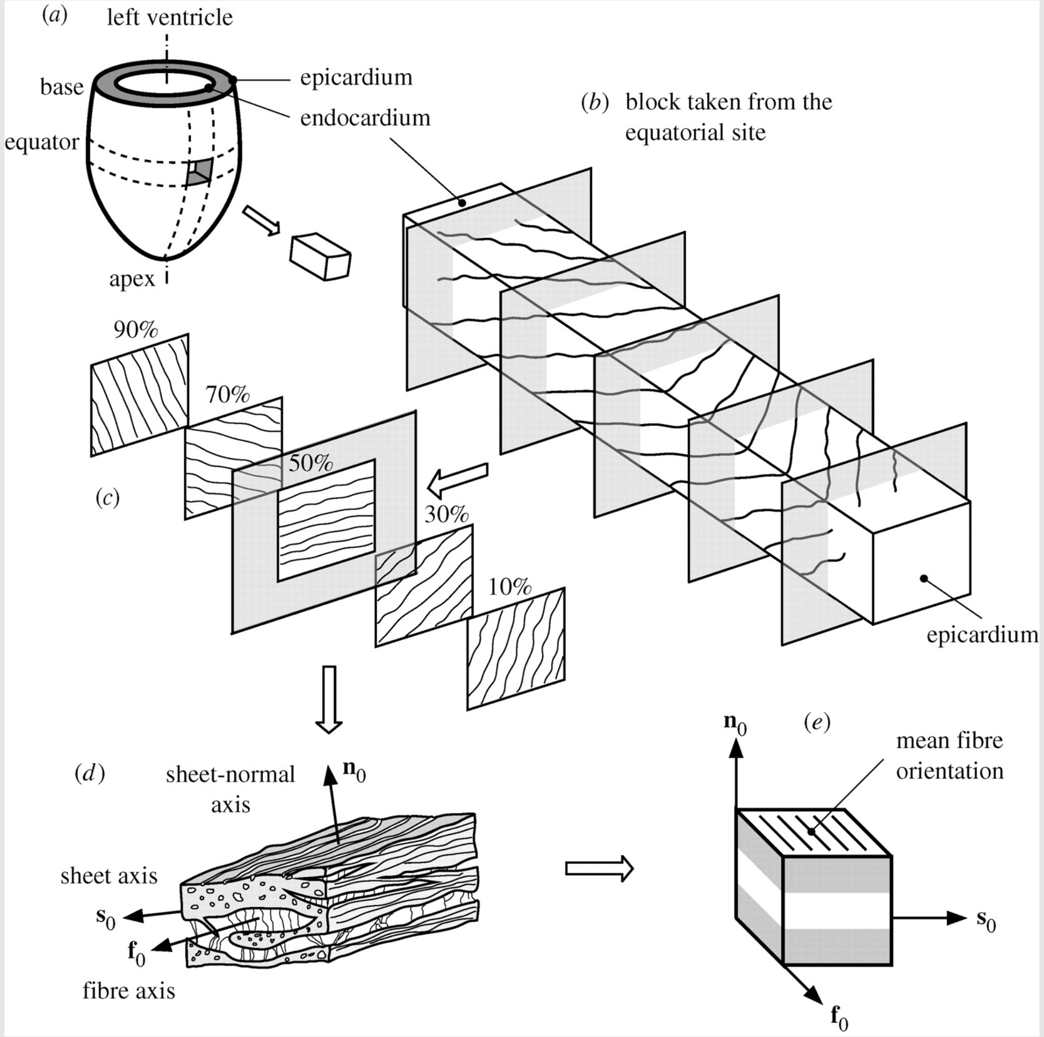
Green-Lagrange strain tensor $$\mathbf{E} = \frac{1}{2}(\mathbf{C} - \mathbf{I})$$

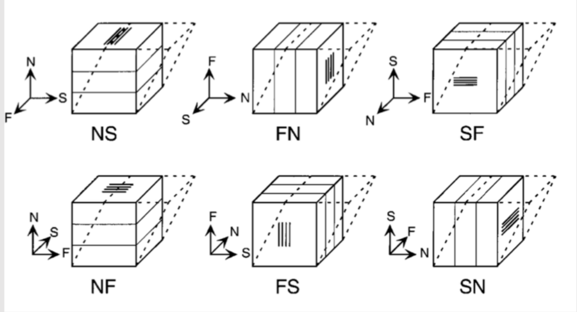
We assume that the myocardium is a hyperelastic material

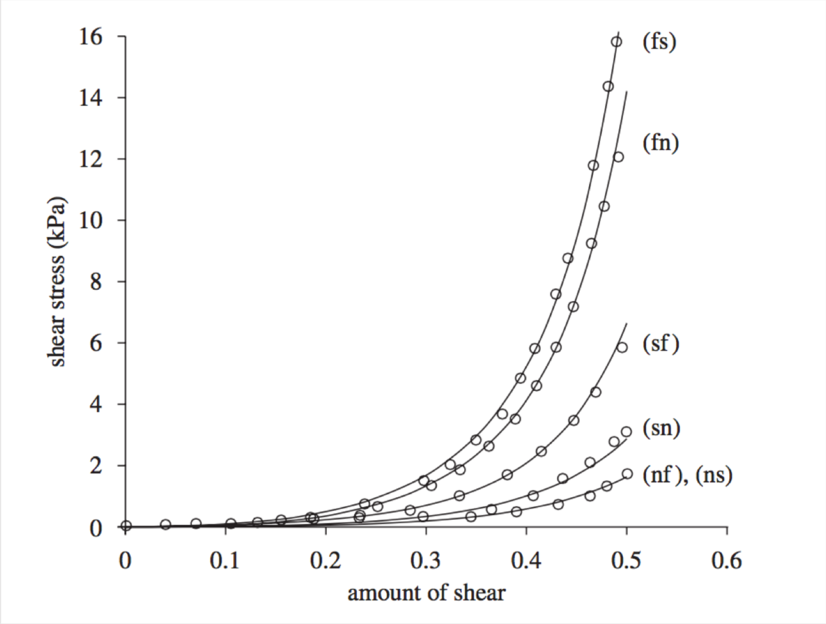
Stress is related to strain via a strain-energy density function

$$\mathbf{P} = \frac{\partial \Psi(\mathbf{F})}{\partial \mathbf{F}}$$

Myocardium is in general considered to be an orthotropic material







Dokos, 2002
Holzapfel and Ogden, 2009

We make a further assumption that the myocardium is transversally isotropic

$$\Psi =$$

$$\frac{a}{2b}\left(e^{b(I_1-3)}-1\right)$$ Extracellular matrix

$$+\frac{a_f}{2b_f}\left(e^{b_f(I_{4f}-1)^2}-1\right)$$ Fibers

$$+\frac{a_s}{2b_s}\left(e^{b_s(I_{4s}-1)^2}-1\right)$$ Sheets

$$+\frac{a_{fs}}{2b_{fs}}\left(e^{b_{fs}I_{8fs}^2}-1\right)$$ Angle between fibers and sheets

Transversally isotropic

Orthotropic

$$I_1 = \mathrm{tr}\mathbf{C}$$

$$I_2 = \frac{1}{2}\left[I_1^2 - \mathrm{tr}(\mathbf{C}^2)\right]$$

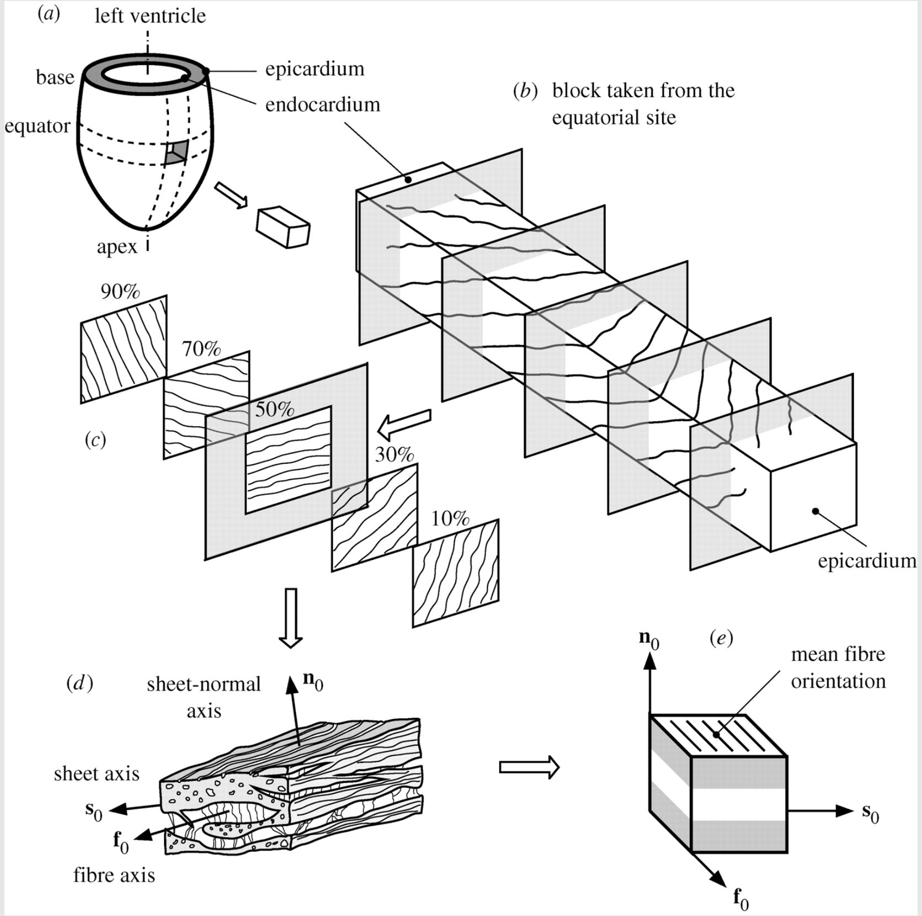
$$I_3 = \det\mathbf{C}$$

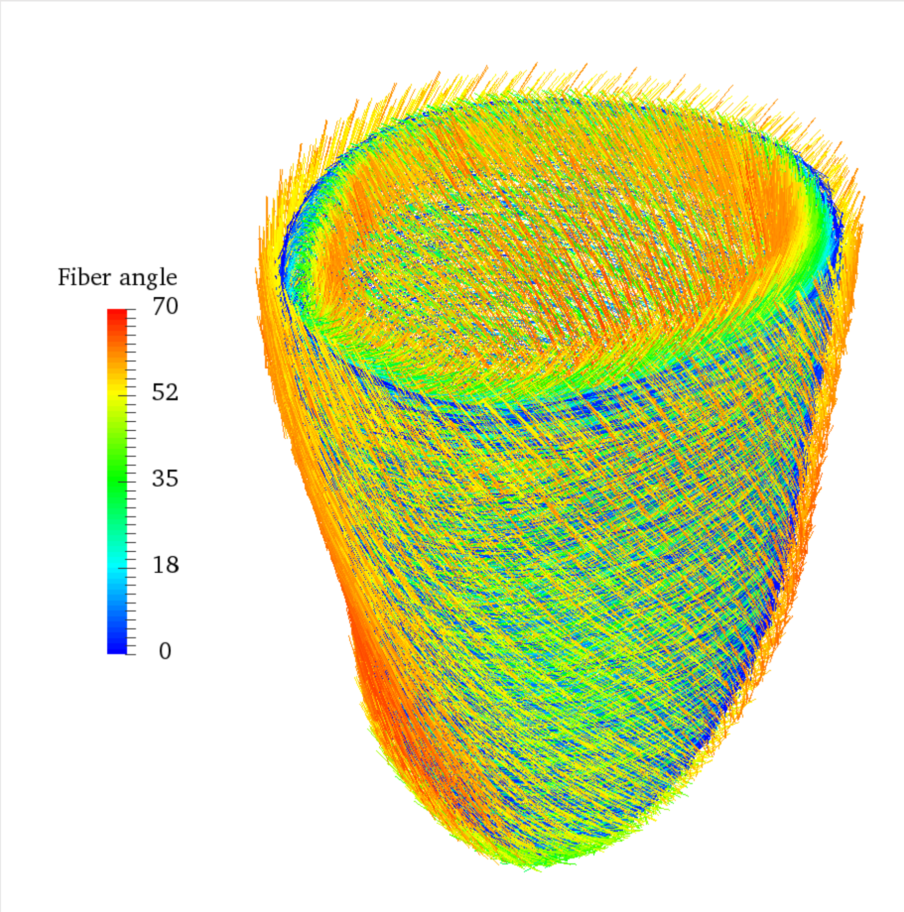
$$I_{4\mathbf{a}_0} = \mathbf{a}_0 \cdot (\mathbf{C}\mathbf{a}_0)$$

$$I_{8\mathbf{a}_0\mathbf{b}_0} = \mathbf{a}_0 \cdot (\mathbf{C}\mathbf{b}_0)$$

Holzapfel and Ogden, 2009

Myocardial fiber orientations are assigned using a rule-based algorithm





Bayer et al, 2012

We assume that the myocardium is incompressible

Constraint:

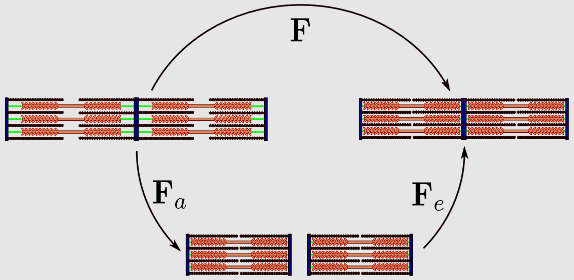
$$J = \det(\mathbf{F}) = 1$$

Enforce constraint using Lagrange multiplier:

$$\Psi = \Psi(\mathbf{F}) + p(J - 1)$$

There are two main approaches to model the active contraction – the active strain and the active stress approach

Active strain



$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_a$$

$$\Psi = \Psi(\mathbf{F}_e)$$

$$\mathbf{F}_a = (1-\gamma)\mathbf{f} \otimes \mathbf{f} + \frac{1}{\sqrt{1-\gamma}}(\mathbf{I} - \mathbf{f} \otimes \mathbf{f})$$

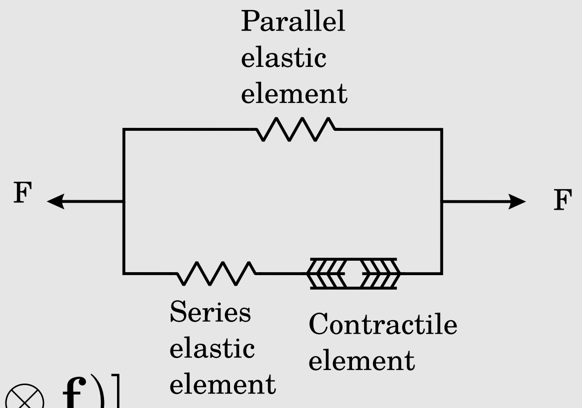
$\mathbf{f}$: fiber field in the current configuration

Mathematical properties are inherited from the strain-energy density

Active stress

$$\sigma = \frac{1}{J}\frac{\partial \Psi(\mathbf{F})}{\partial \mathbf{F}}\mathbf{F}^T + \sigma_a$$

$$\sigma_a = T_a\left[\mathbf{f} \otimes \mathbf{f} + \eta(\mathbf{I} - \mathbf{f} \otimes \mathbf{f})\right]$$



Well established and physiologically inspired

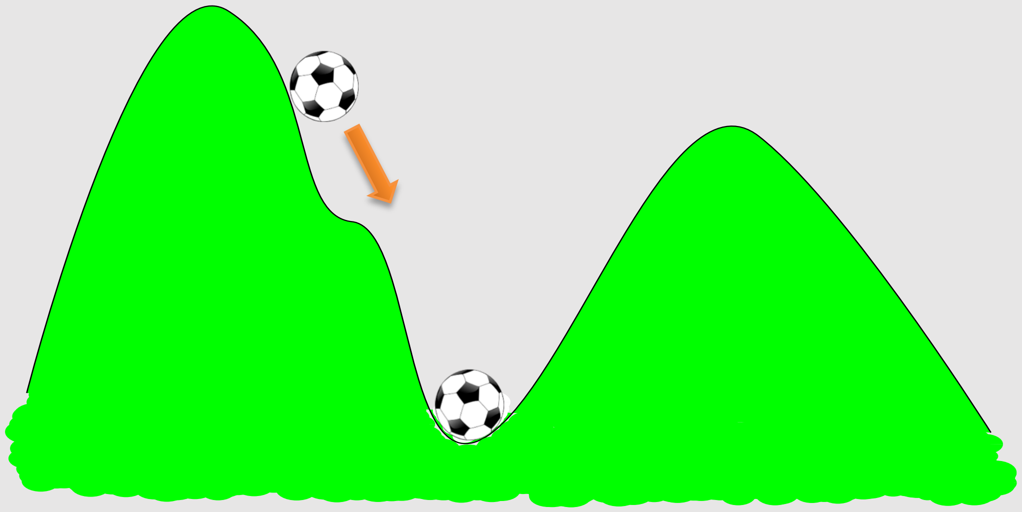
Balance of forces can be obtained through minimization of the total potential energy

Total energy:

$$\Pi(\mathbf{u}, p) = \Pi_{\text{int}}(\mathbf{u}, p) + \Pi_{\text{ext}}(\mathbf{u}).$$

$$\Pi_{\text{int}}(\mathbf{u}, p) = \int_\Omega [p(J-1) + \Psi(\mathbf{F})]\, \mathrm{d}V$$

$$\Pi_{\text{ext}}(\mathbf{u}) = -\int_\Omega \mathbf{B}\cdot\mathbf{u}\mathrm{d}V - \int_{\partial\Omega_N} \mathbf{T}\cdot\mathbf{u}\mathrm{d}S$$

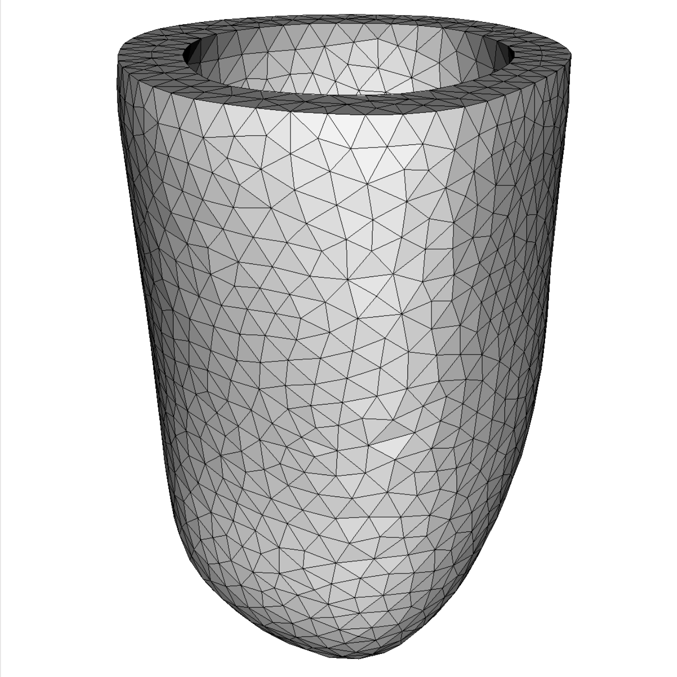


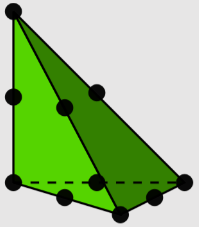
Minimization of energy:

$$0 = D_{\delta p}\Pi(\mathbf{u}, p) = \int_\Omega \delta p(J(\mathbf{u}) - 1)\mathrm{d}V$$

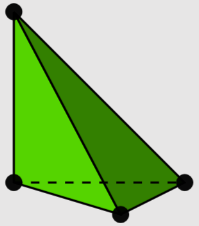
$$0 = D_{\delta\mathbf{u}}\Pi(\mathbf{u}, p) = \int_\Omega \left[pJ\mathbf{F}^{-T} + \mathbf{P}\right] : \mathrm{Grad}\,\delta\mathbf{u}\mathrm{d}V - \int_\Omega \mathbf{B}\cdot\delta\mathbf{u}\mathrm{d}V$$

Equations are discretized and solved using the finite element method





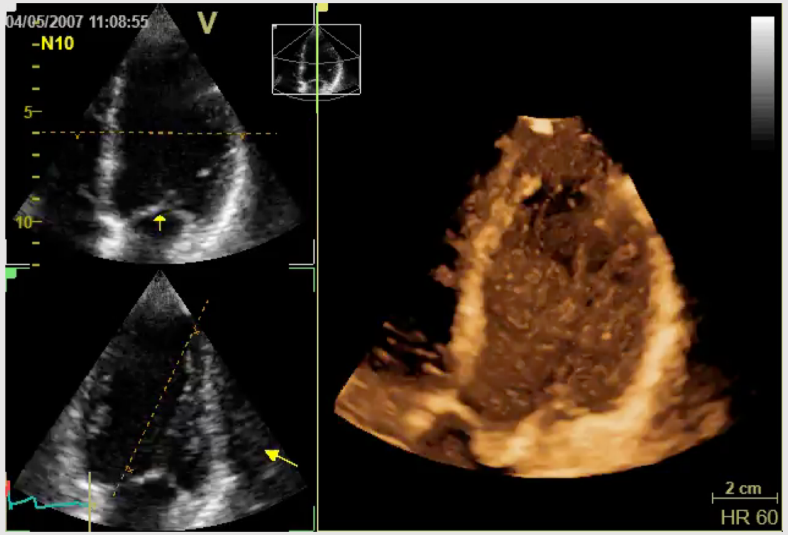
Piecewise quadratic Lagrange elements for displacement



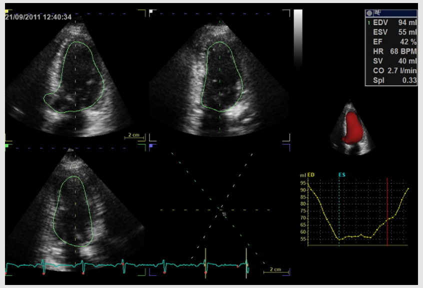
Piecewise linear Lagrange elements for hydrostatic pressure

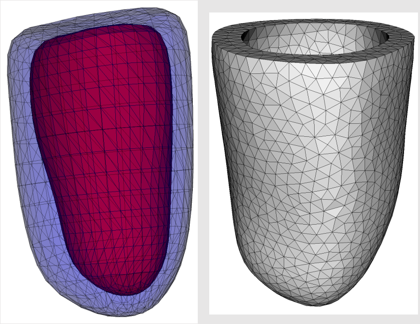
Taylor-Hood finite elements

We want to make models specific at the level of the individual

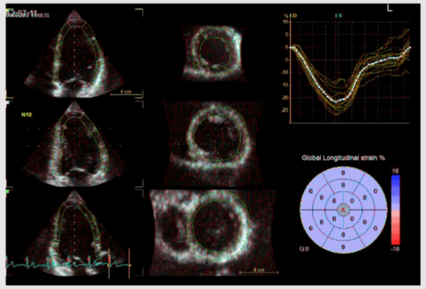


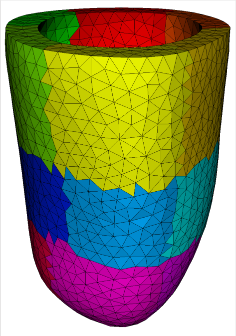
Volume

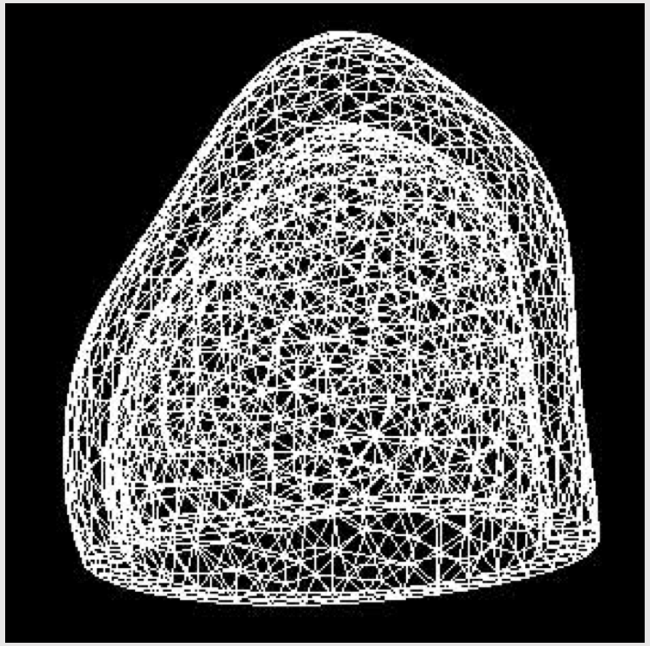




Regional strain







Models contain model parameters that can be tuned in order to obtain patient specificity

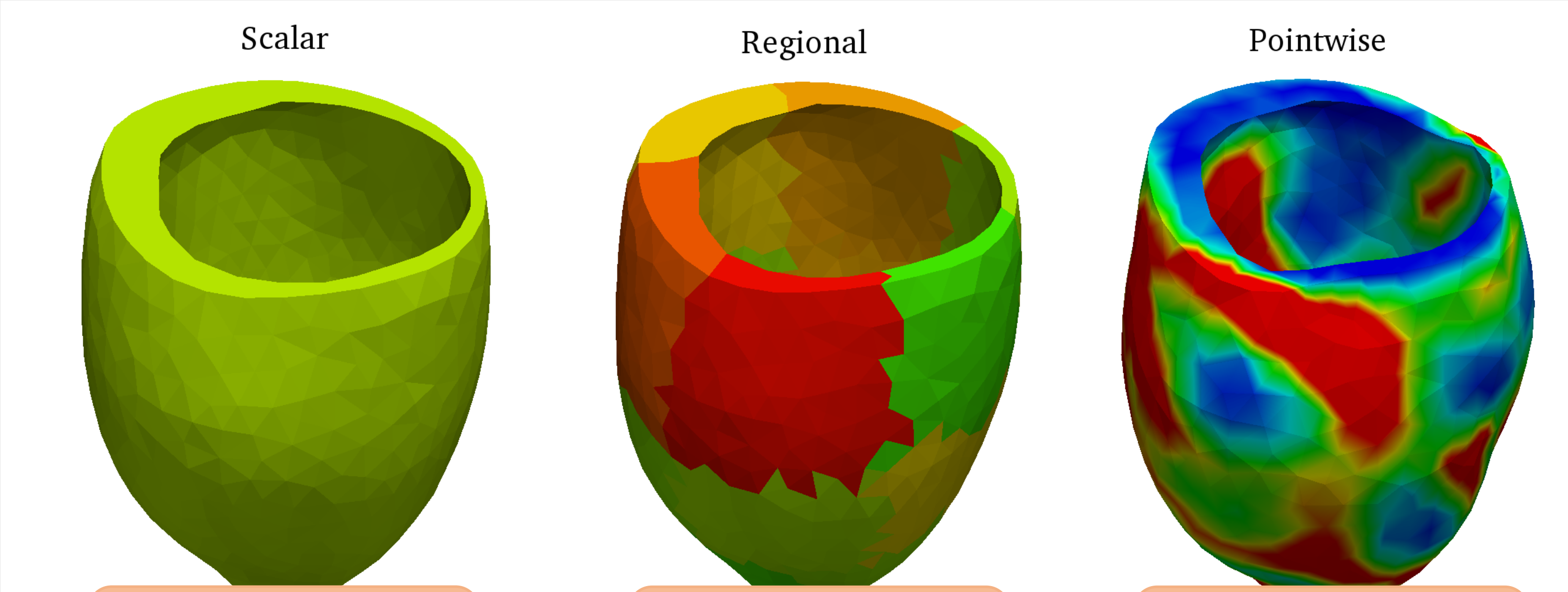
Parameters in the **passive** model

$$\Psi = \frac{a}{2b}\left(e^{b(I_1-3)} - 1\right) + \frac{a_f}{2b_f}\left(e^{b_f(I_{4f}-1)^2} - 1\right)$$

Parameters in the **active** model

$$\mathbf{F}_a = (1-\gamma)\mathbf{f}\otimes\mathbf{f} + \frac{1}{\sqrt{1-\gamma}}(\mathbf{I} - \mathbf{f}\otimes\mathbf{f})$$

Spatial resolution:

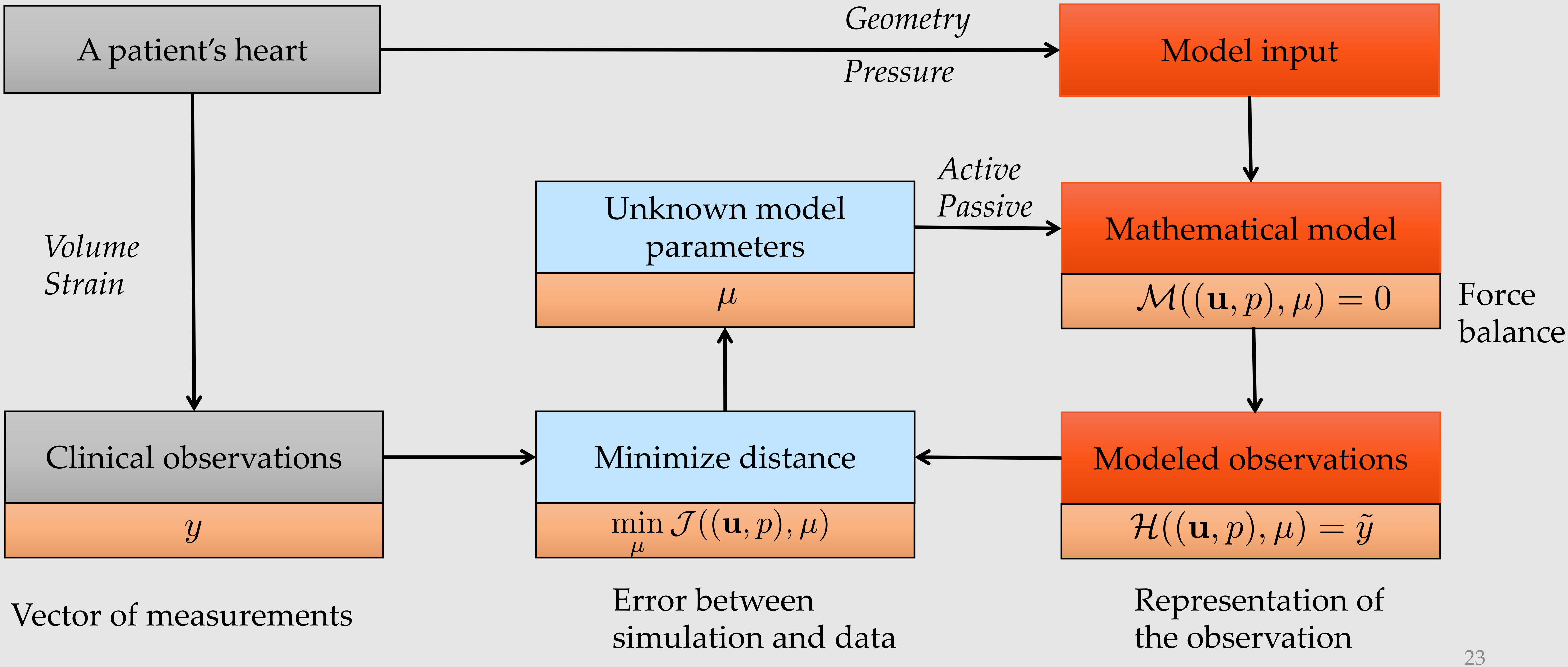


1 parameter

17 parameters

1262 parameters

Clinical observations can be fitted to the model by minimizing the difference between model and data



Minimization of model-data mismatch is formulated as a PDE-constrained optimization problem

Data assimilation

Minimize difference between model and observations by tuning parameters in the model

Mismatch functional

$$\min_{\mu} \mathcal{J}((\mathbf{u}, p), \mu)$$

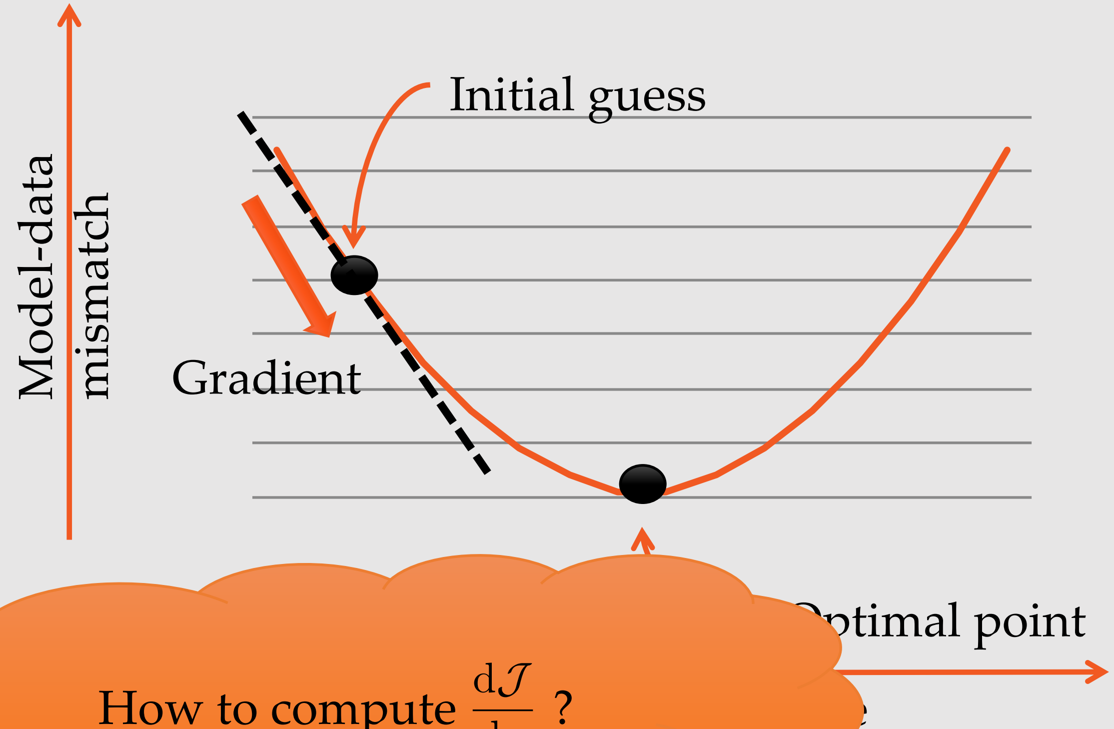
$$\text{subject to } \mathcal{M}((\mathbf{u}, p), \mu) = 0$$

Force balance equation

Expensive to evaluate functional

Keep number of functional evaluation at a minimum

Gradient-based optimization

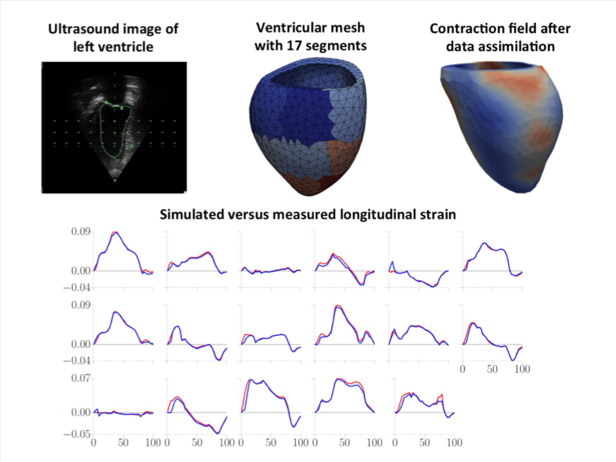


How to compute $\frac{\mathrm{d}\mathcal{J}}{\mathrm{d}\mu}$?

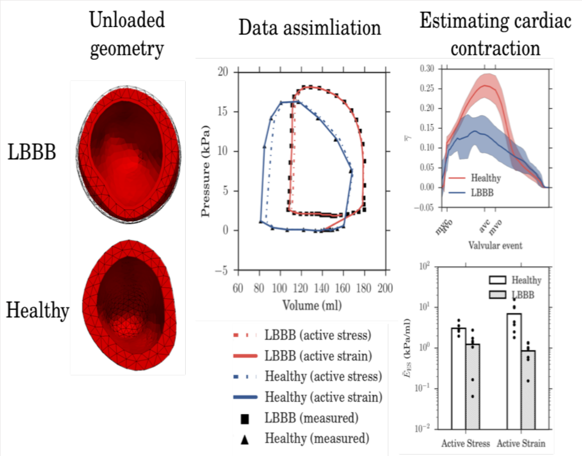
dolfin-adjoint

Summary of papers

Paper 1



Paper 2



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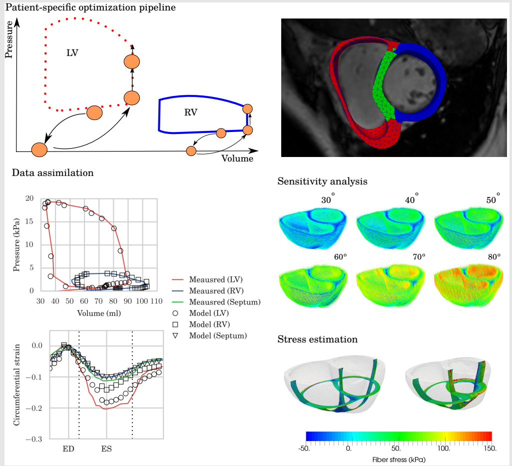
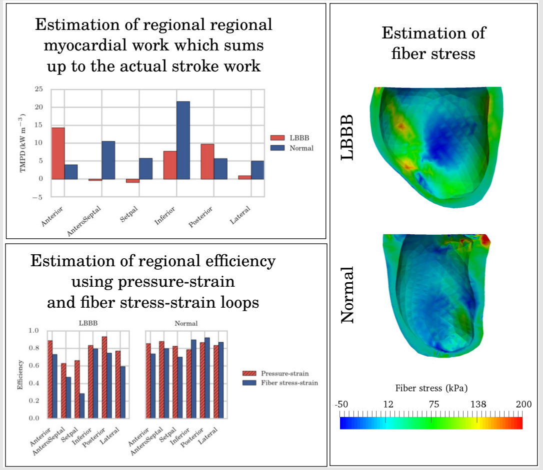


Paper 4

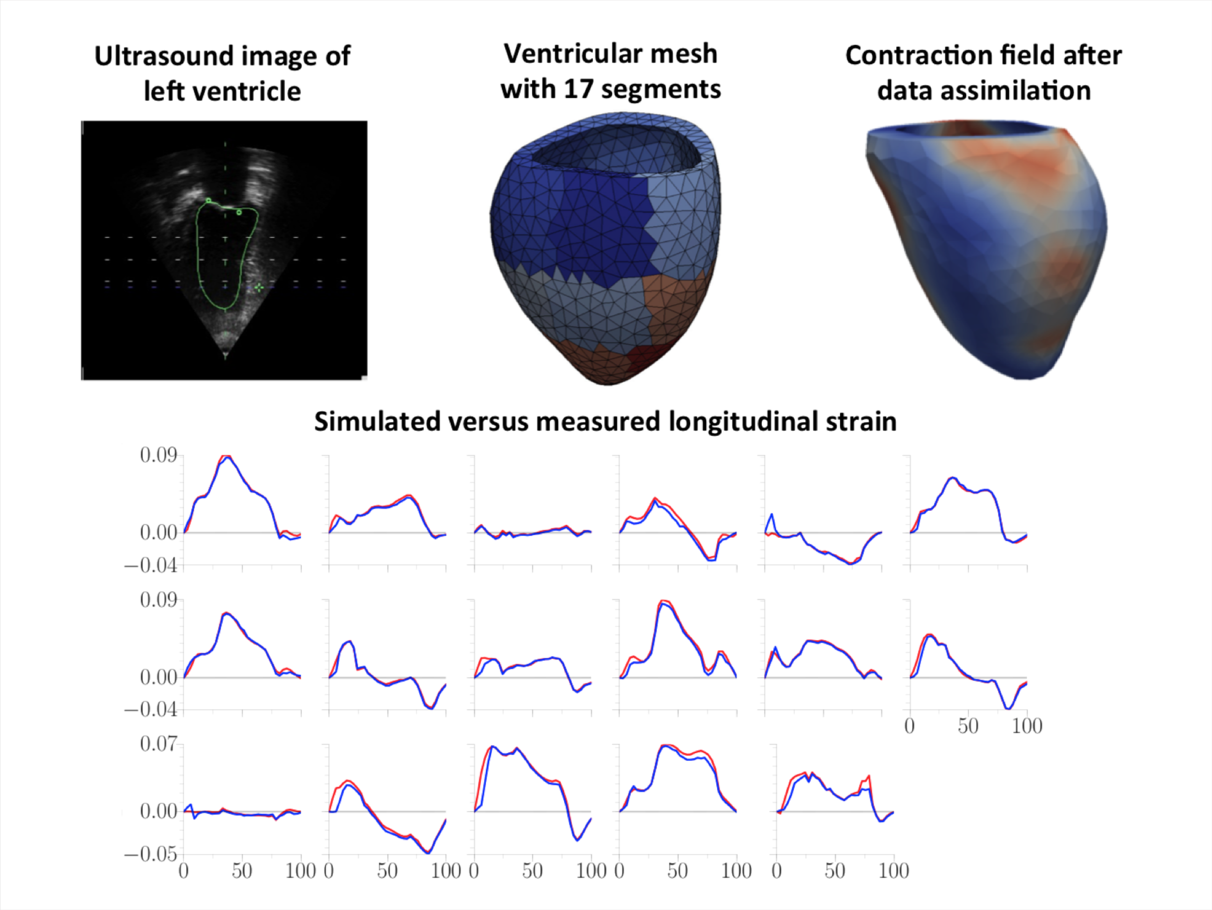


Paper 1

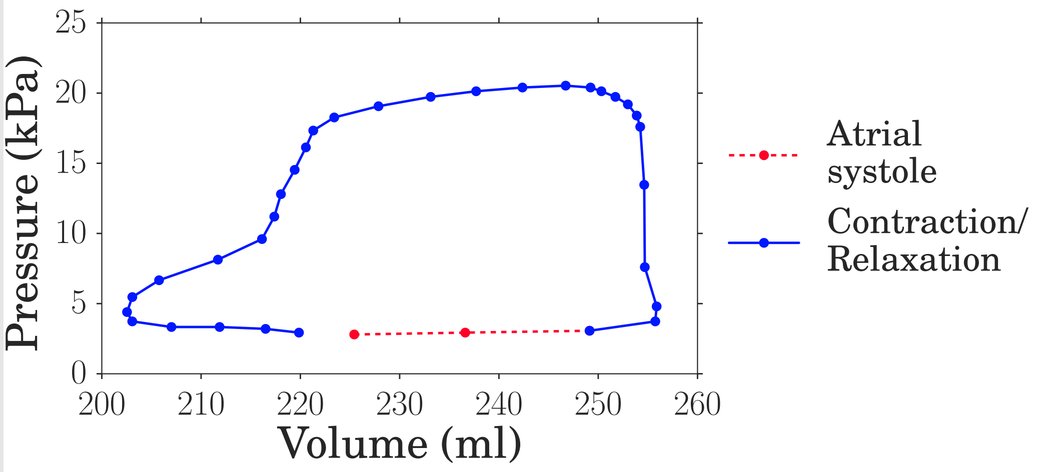
Title:
High-resolution data assimilation of cardiac mechanics applied to a dyssynchronous ventricle

Authors:
Gabriel Balban, Henrik Finsberg, Hans Henrik Odland, Marie E. Rognes, Stian Ross, Joakim Sundnes, and Samuel Wall

Status:
Published in International journal for numerical methods in biomedical engineering



We estimated model parameters to fit measured strain and volume



$$\mathcal{J}^i_{\text{vol}} = \left(\frac{V^i - \tilde{V}^i}{V^i}\right)^2$$

$$\mathcal{J}^i_{\text{strain}} = \sum_{j=1}^{17} \sum_{k\in\{c,r,l\}} \left(\varepsilon^i_{kj} - \tilde{\varepsilon}^i_{kj}\right)^2$$

$$\mathcal{J}^i_{\text{data}}(\alpha) = \alpha \mathcal{J}^i_{\text{vol}} + (1-\alpha)\mathcal{J}^i_{\text{strain}}$$

$$\mathcal{J}^i_{\text{smooth}}(\lambda) = \lambda \|\nabla \gamma^i\|^2$$

Passive

$$\Psi = \frac{a}{2b}\left(e^{b(I_1-3)} - 1\right) + \frac{a_f}{2b_f}\left(e^{b_f(I_{4f}-1)^2} - 1\right)$$

Scalar

$$\mathcal{J} = \sum \mathcal{J}^i_{\text{vol}}$$

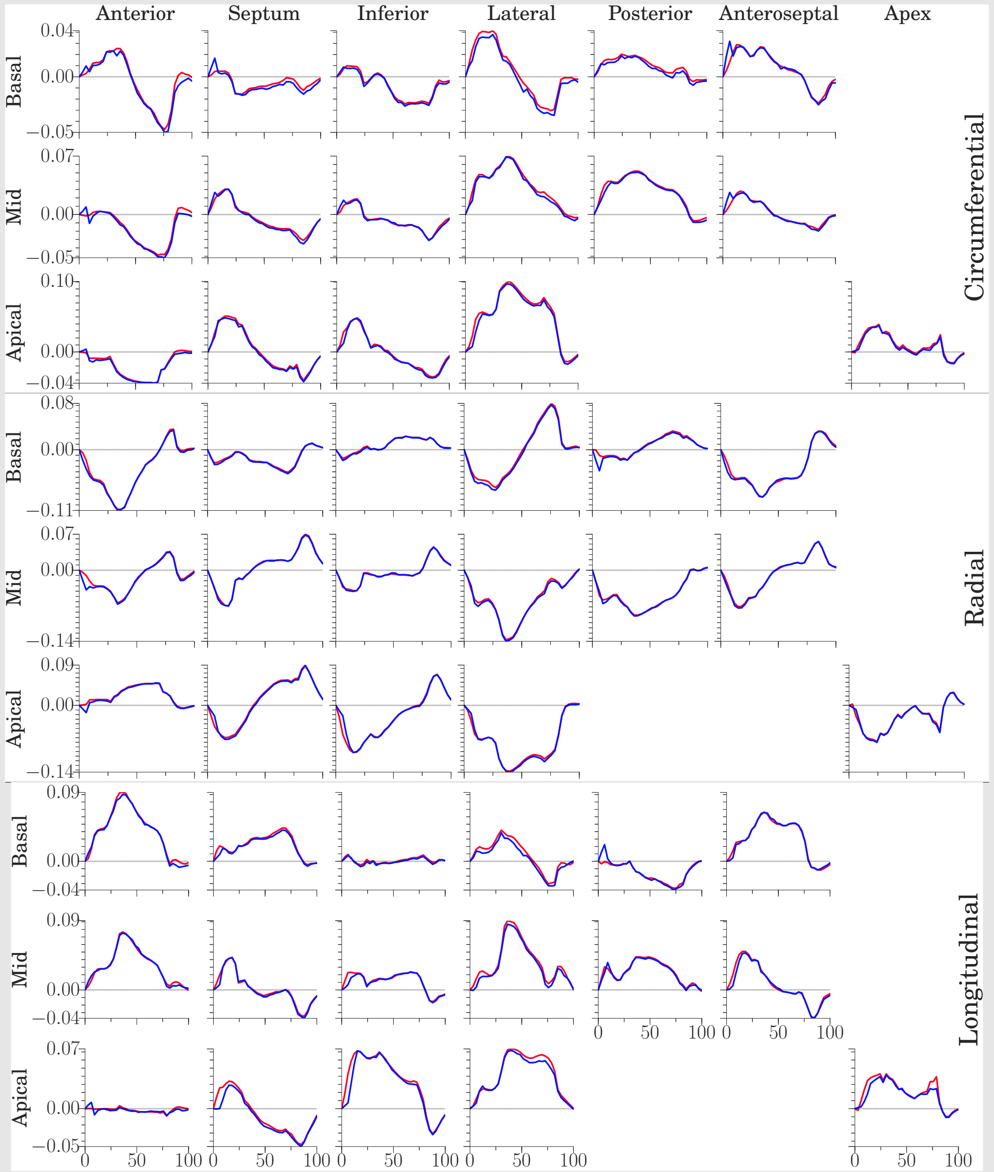
Active

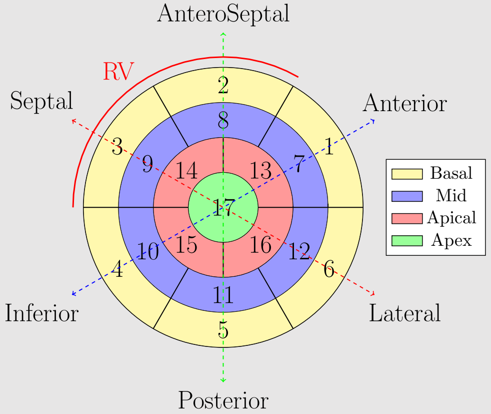
$$\mathbf{F}_a = (1-\gamma)\mathbf{f}\otimes\mathbf{f} + \frac{1}{\sqrt{1-\gamma}}(\mathbf{I} - \mathbf{f}\otimes\mathbf{f})$$

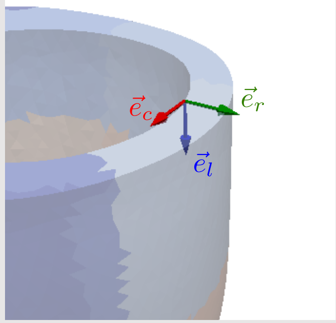
Scalar, Regional, Pointwise (P1)

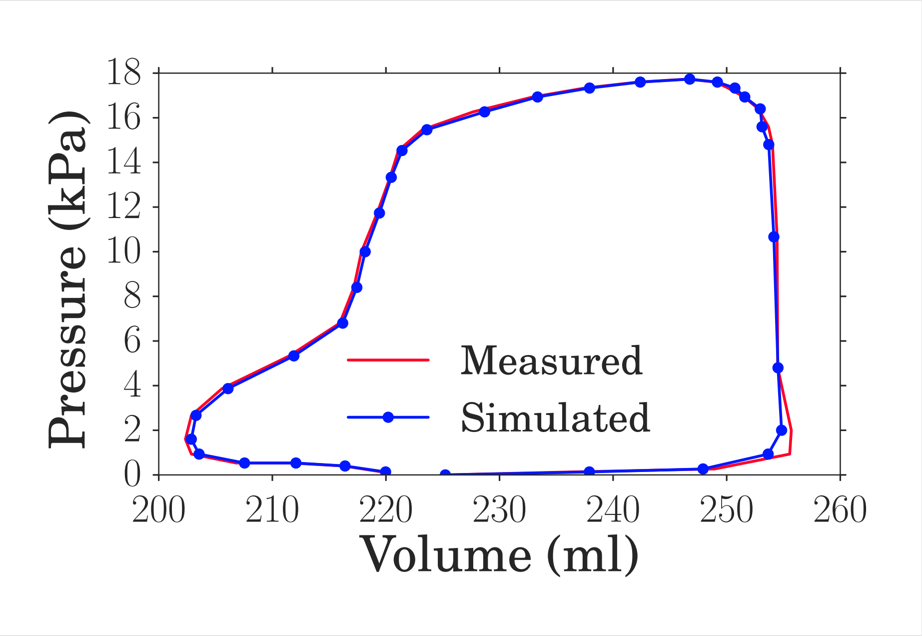
$$\mathcal{J} = \mathcal{J}^i_{\text{data}}(\alpha) + \mathcal{J}^i_{\text{smooth}}(\lambda)$$

It is possible to tune parameters to “almost perfectly” fit the data

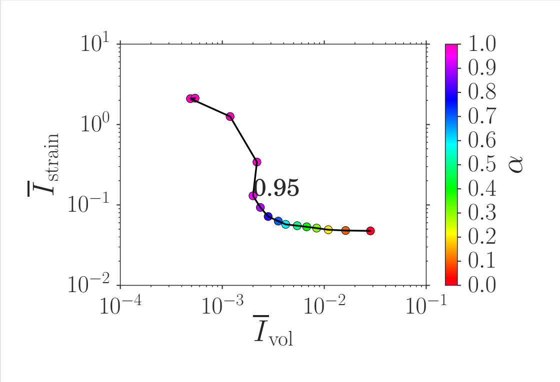




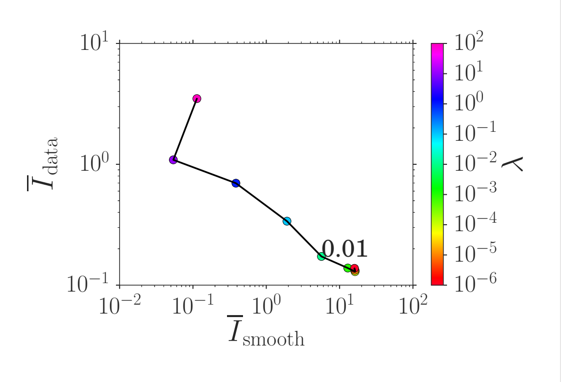




Choose α

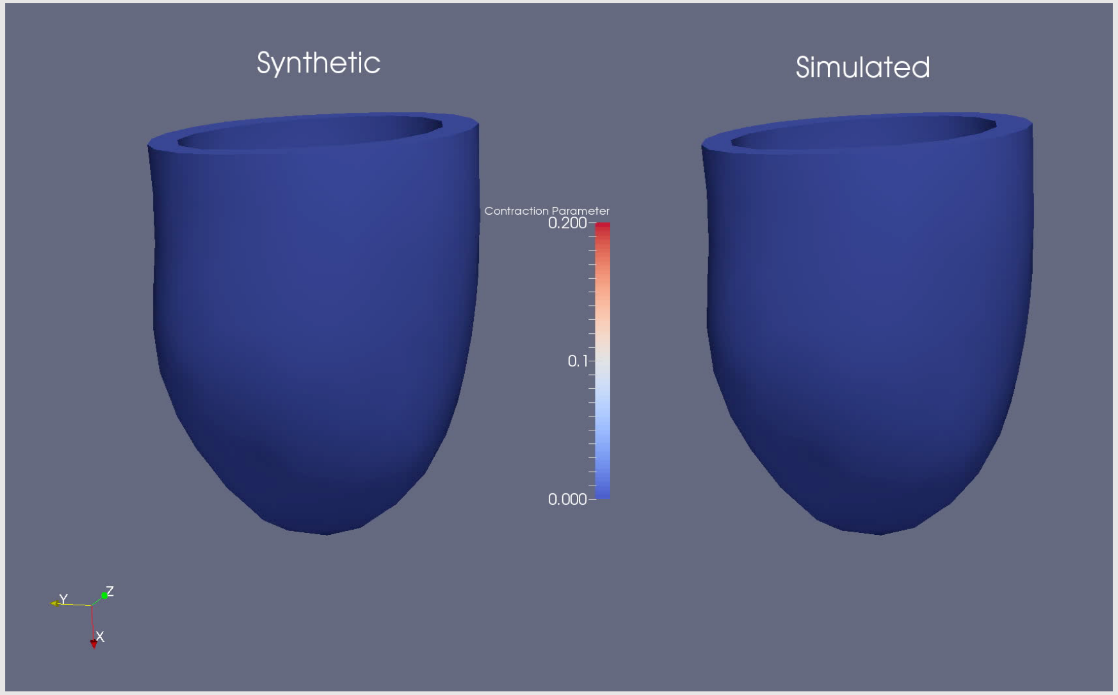


Choose λ

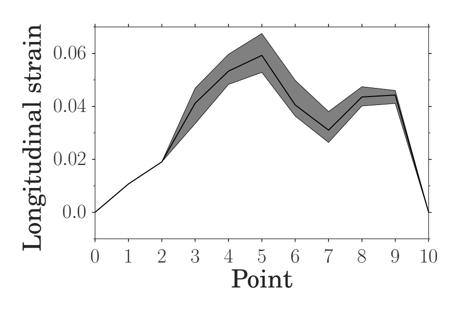


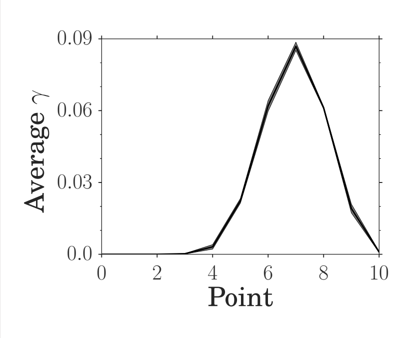
We verified identifiability of the contraction field using a synthetic data set

Noise-free

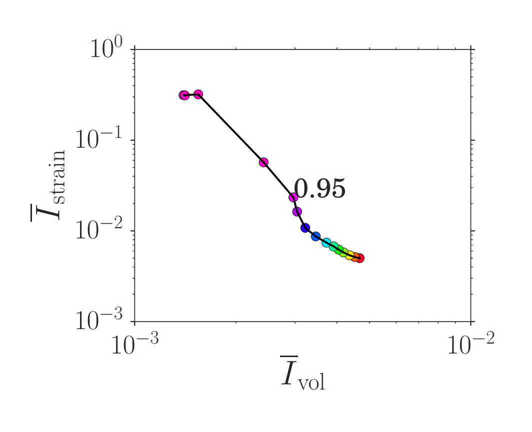


Effect of noise

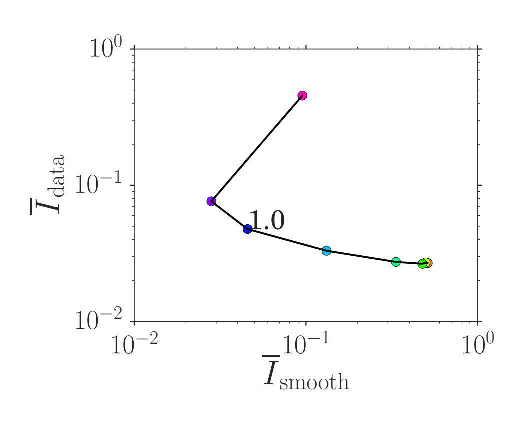




Choose α

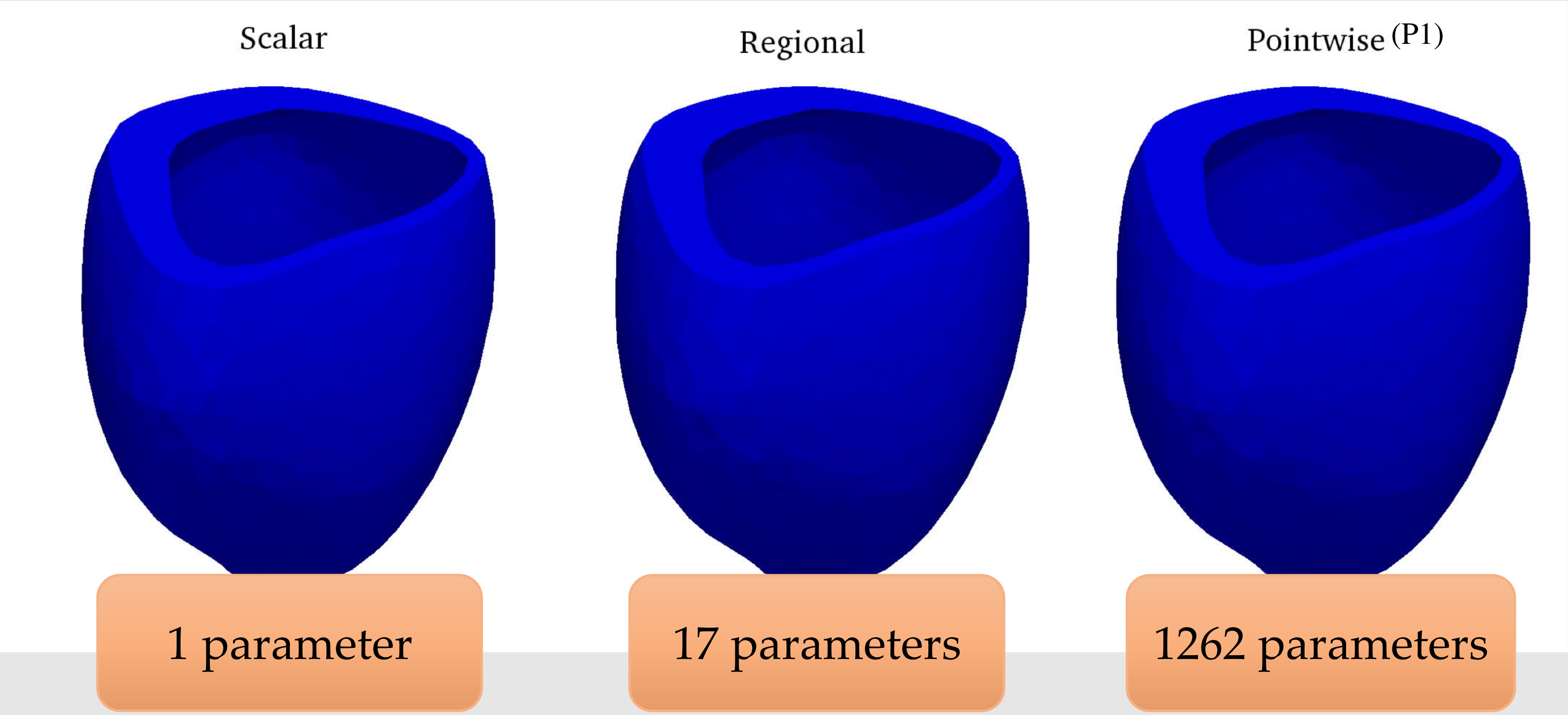


Choose λ



We tested different spatial resolution of the contraction parameter

resolution of γ	forward solves average	adjoint solves average	total run time (s)	adjoint evaluation average run time (s)
scalar	4.6	2.8	280	7.4
regional	12	6.5	210	19.3
P1	46	46	1100	7.9



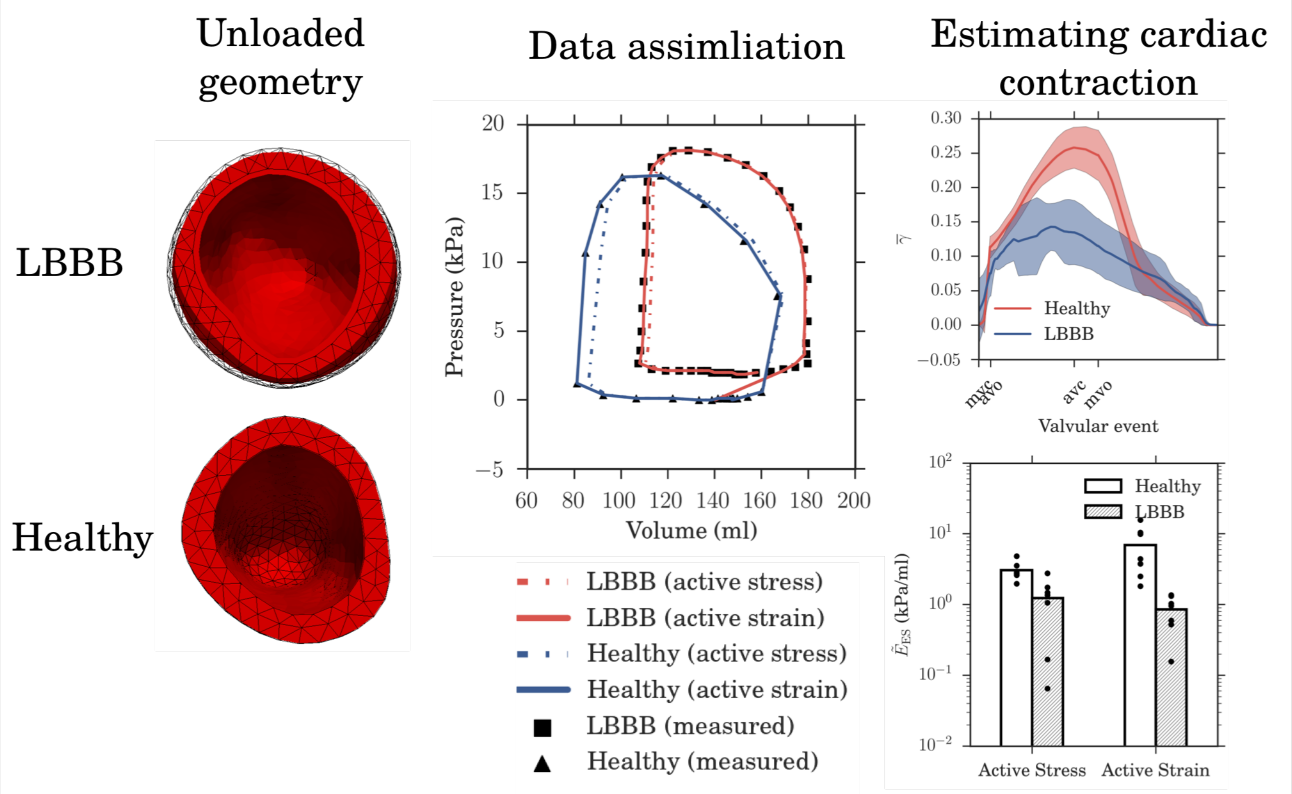
resolution of γ	$\overline{I}_{\mathrm{vol}}$	$\overline{I}_{\mathrm{strain}}$	$\overline{I}_{\mathrm{strain}}^{\mathrm{relmax}}$
scalar	0.044	1.5	0.27
regional	0.024	1.1	0.16
P1	0.0037	0.17	0.029

Paper 2

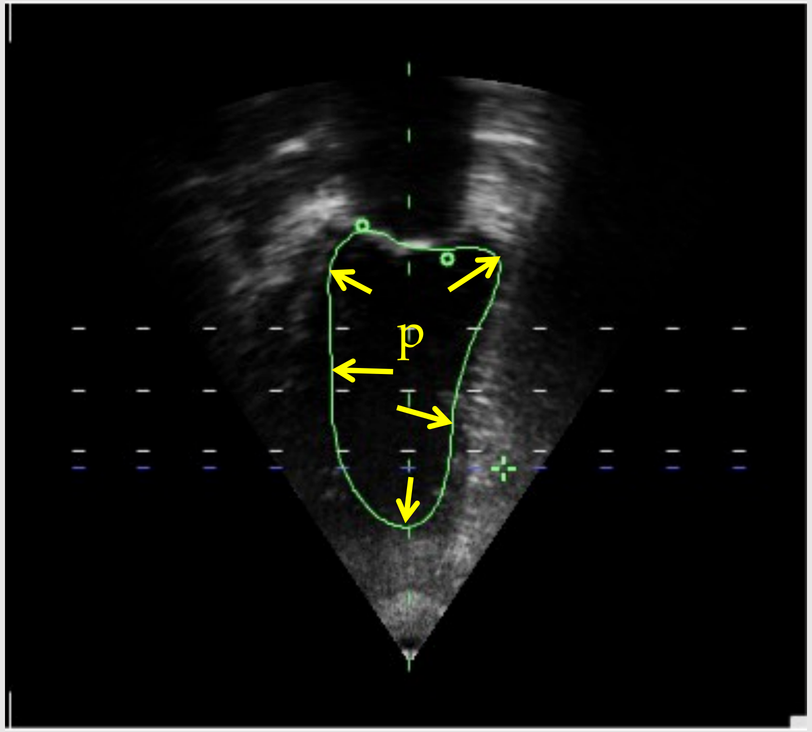
Title:
Estimating cardiac contraction through high resolution data assimilation of a personalized mechanical model

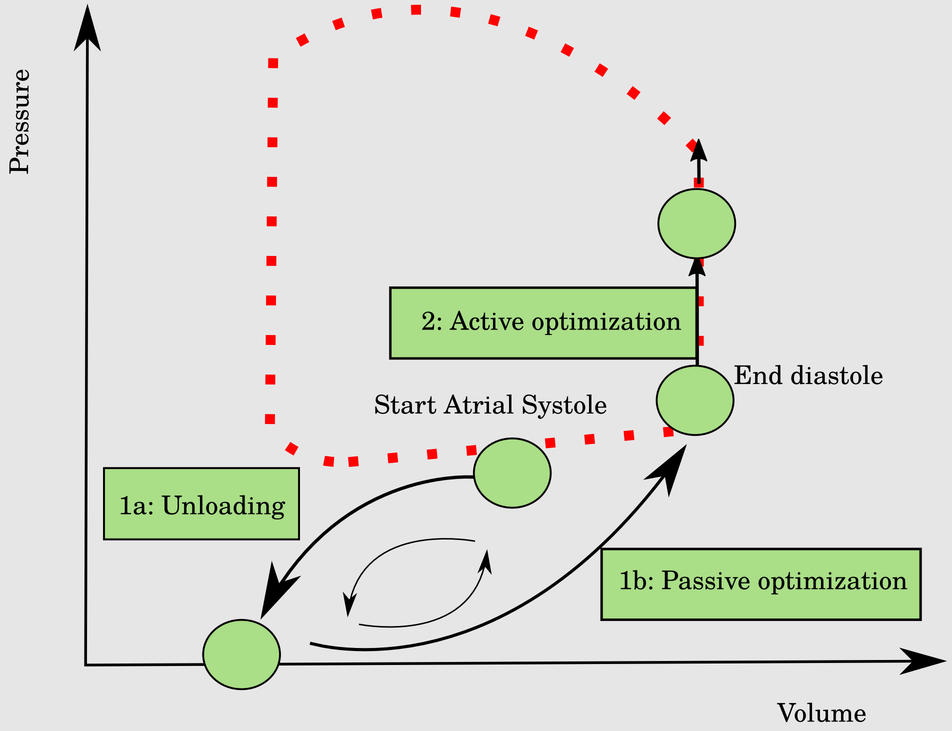
Authors:
Henrik Finsberg, Gabriel Balaban, Stian Ross, Trine F. Håland, Hans Henrik Odland, Joakim Sundnes, and Samuel Wall

Status:
Published in Journal of Computational Science



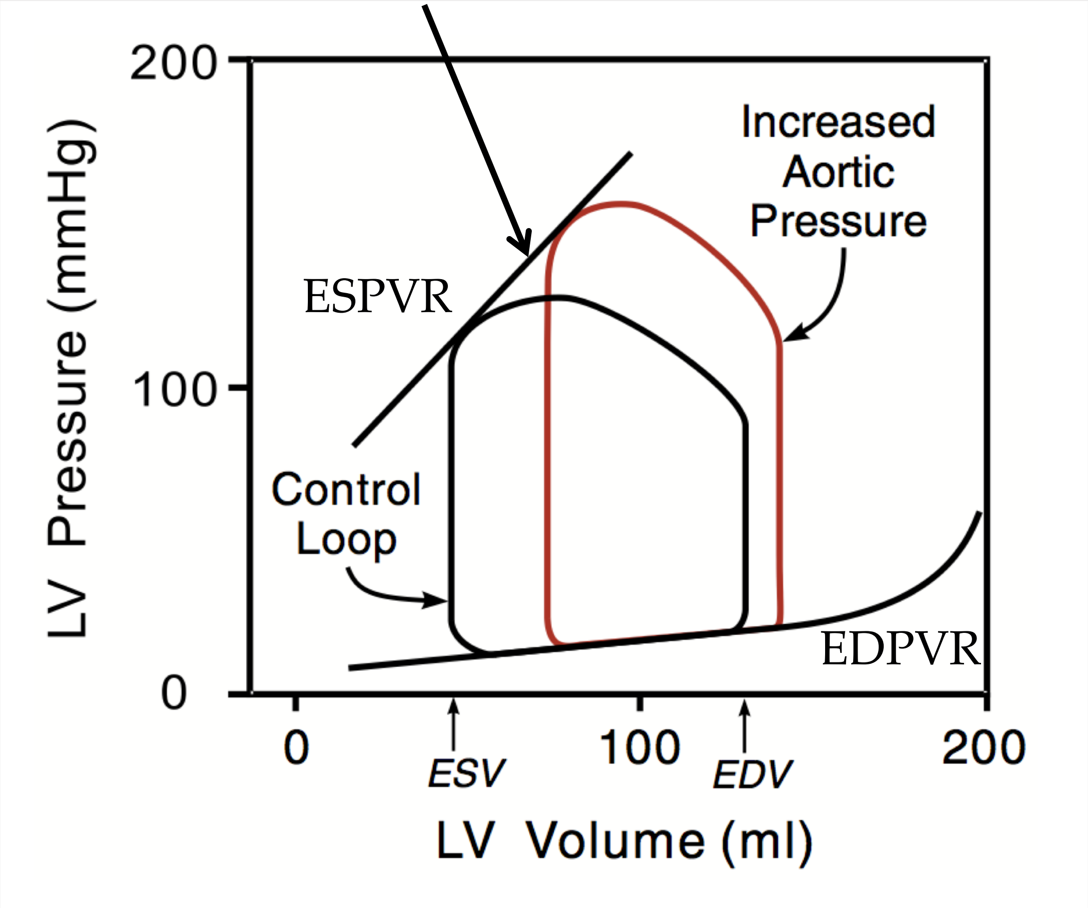
We improved the pipeline by also including an estimation of the unloaded configuration





The end-systolic elastance is an index of myocardial contractility

Slope = Contractility $= E_{\mathrm{ES}}$



$$P(t) = E(t)(V(t) - V_0)$$

$$E_{\mathrm{ES}} \approx \frac{P(t_{\mathrm{ES}})^{\Delta} - P(t_{\mathrm{ES}})}{V(t_{\mathrm{ES}})^{\Delta} - V(t_{\mathrm{ES}})}$$

Suga, 1974

Patients with heart failure showed reduced contractility compared to healthy subjects

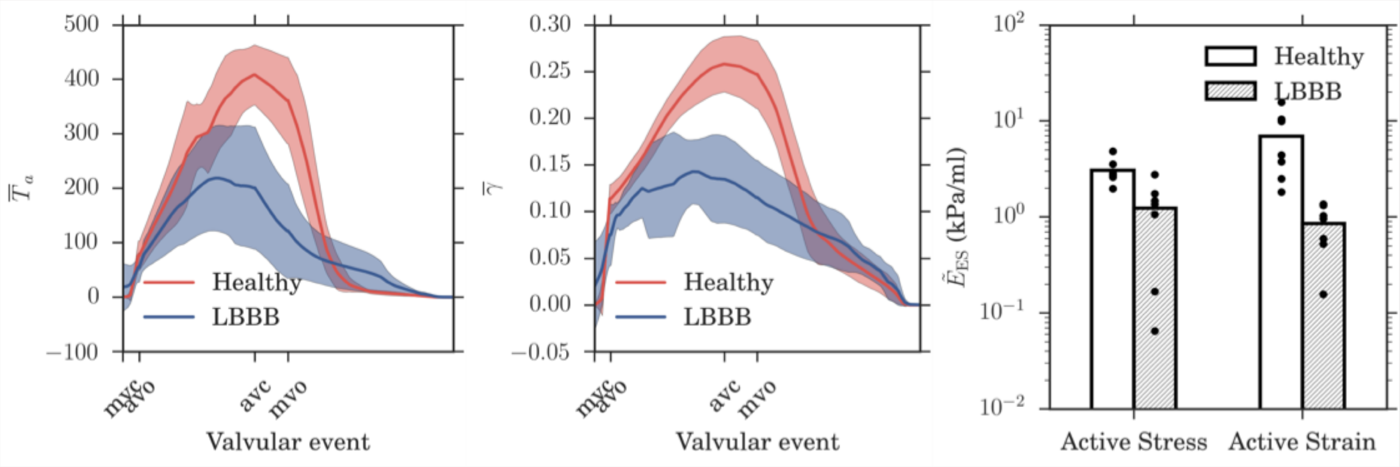
$$\mathbf{F}_a = (1-\gamma)\mathbf{f}\otimes\mathbf{f} + \frac{1}{\sqrt{1-\gamma}}(\mathbf{I}-\mathbf{f}\otimes\mathbf{f})$$

Average active strain: $\bar{\gamma} = \frac{1}{|\Omega|}\int_{\Omega}\gamma(\mathbf{X})\mathrm{d}\mathbf{X}$

$$\sigma_a = T_a\mathbf{f}\otimes\mathbf{f}$$

Average active stress: $\bar{T}_a = \frac{1}{|\Omega|}\int_{\Omega}T_a(\mathbf{X})\mathrm{d}\mathbf{X}$

Average active stress | Average active strain | Estimated End-systolic elastance

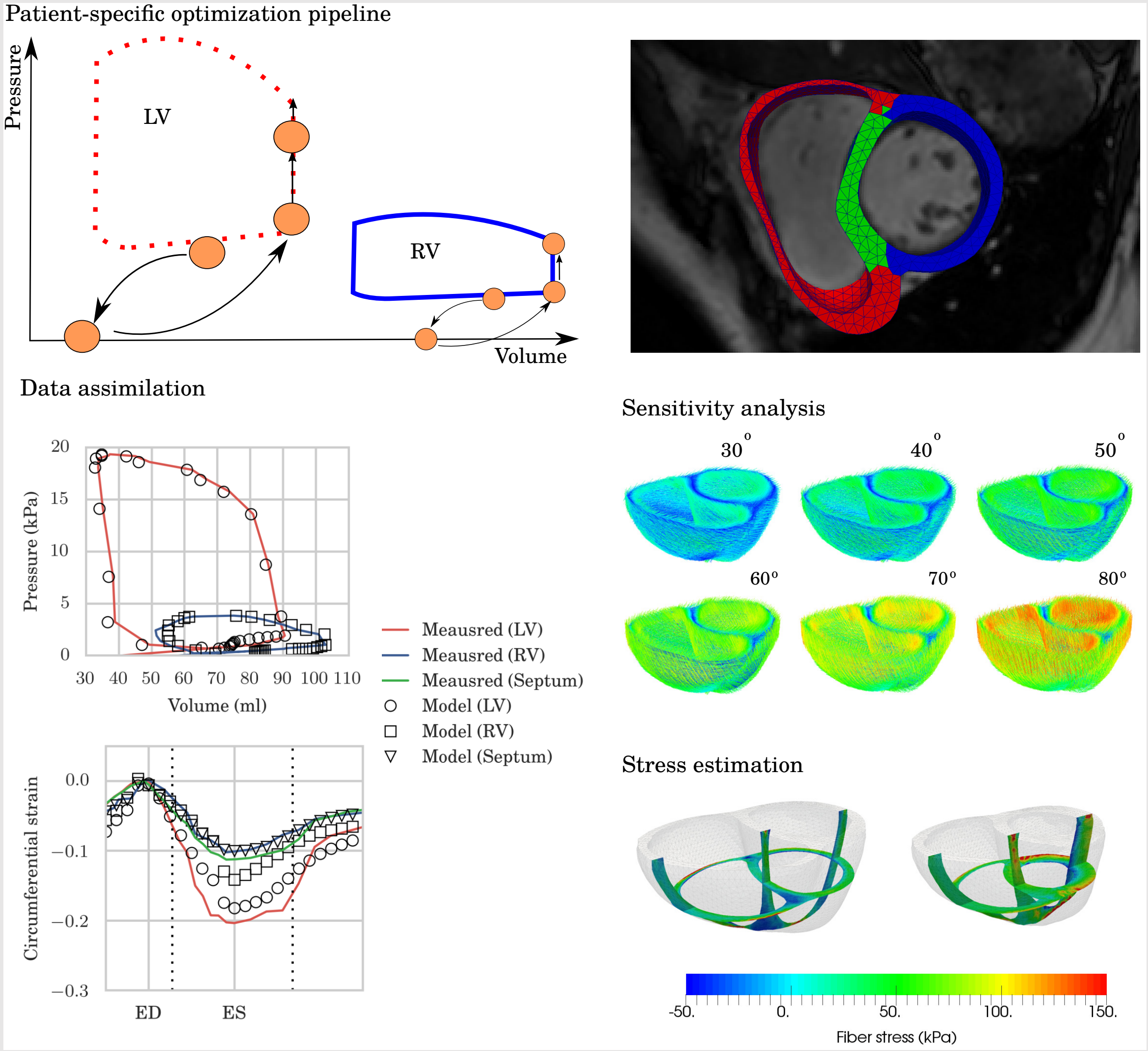


Paper 3

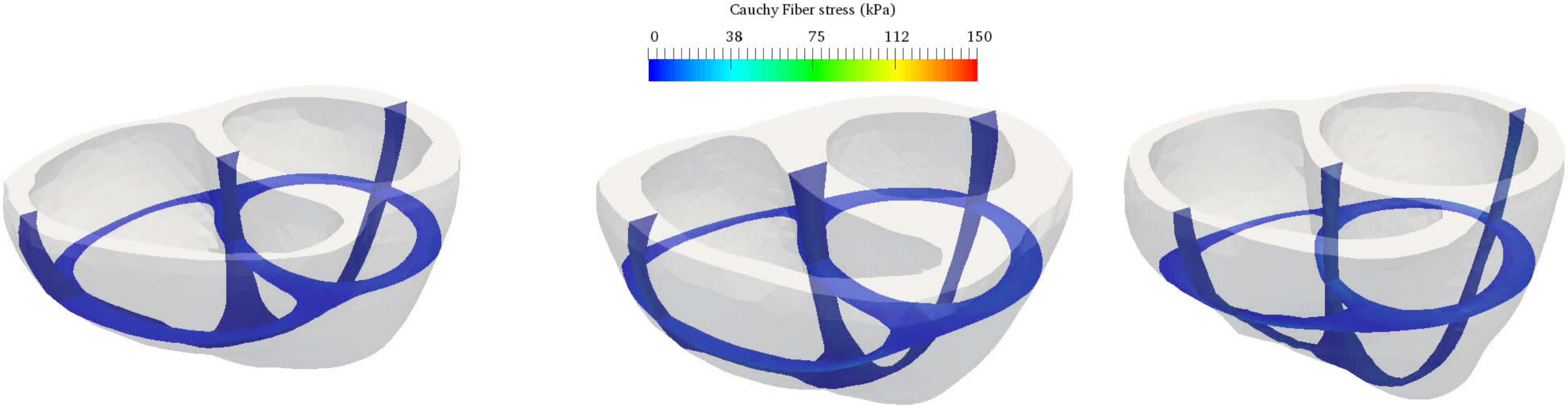
Title:
Efficient estimation of personalized biventricular mechanical function employing gradient-based optimization

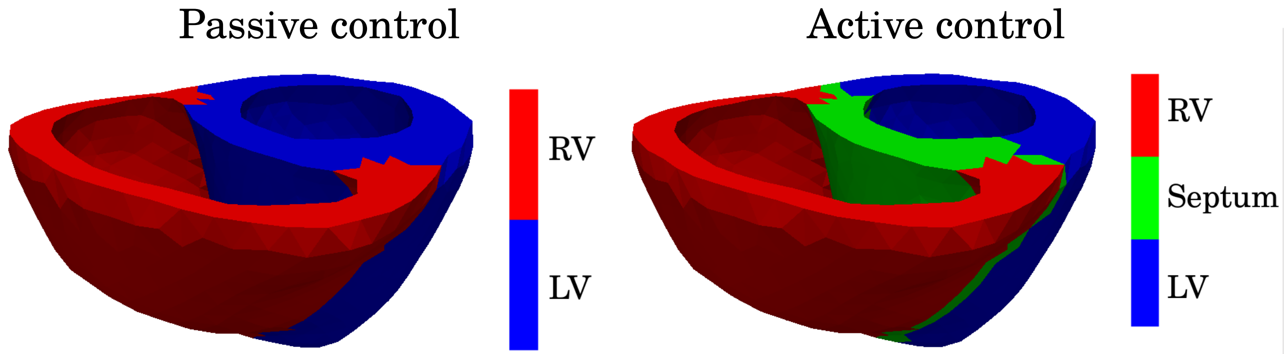
Authors:
Henrik Finsberg, Ce Xi, Ju Le Tan, Liang Zhong, Martin Genet, Joakim Sundnes, Lik Chuan Lee, and Samuel T. Wall

Status:
Submitted to International journal for numerical methods in biomedical engineering

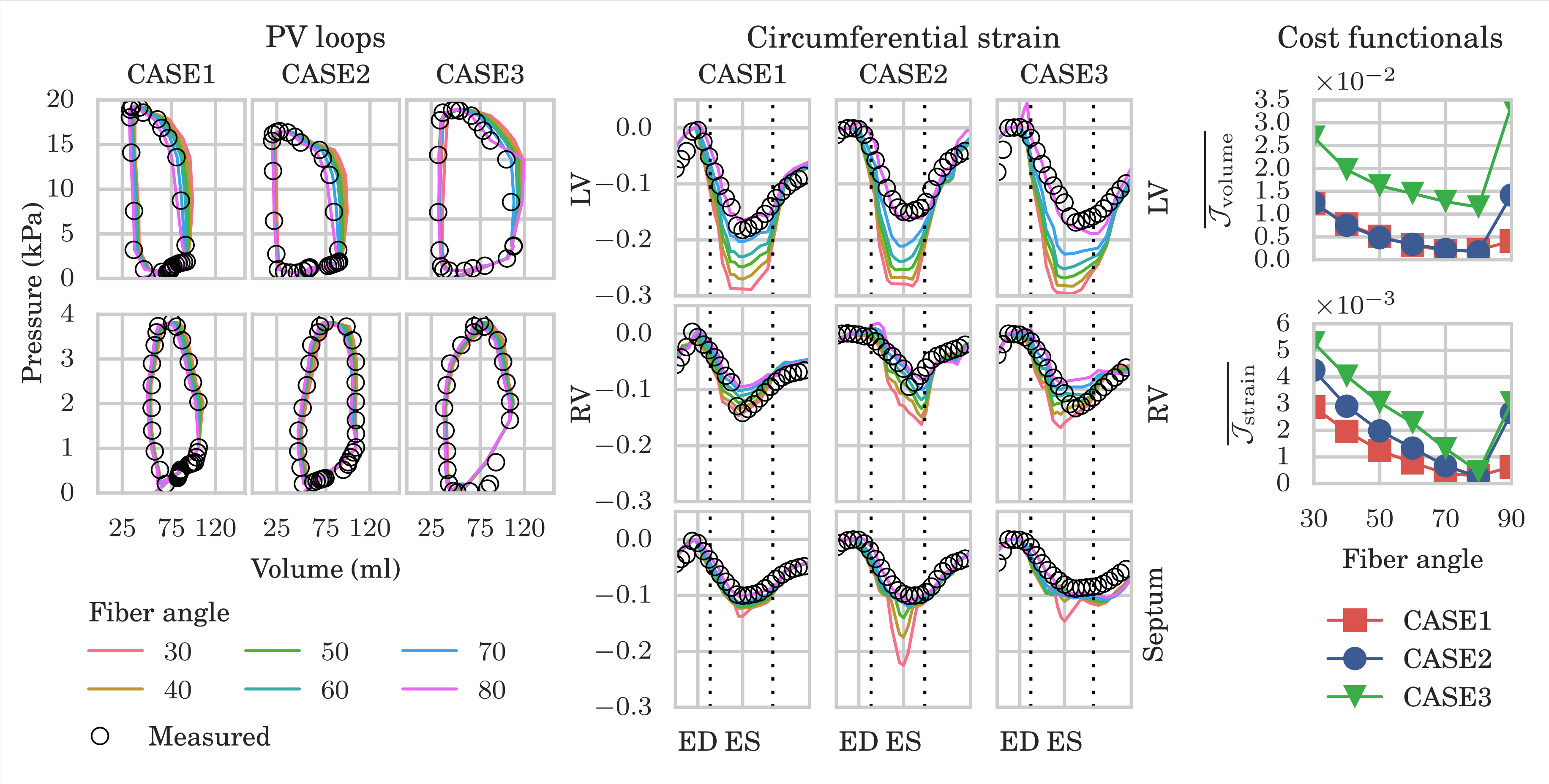


Data assimilation pipeline was tested on three healthy bi-ventricles

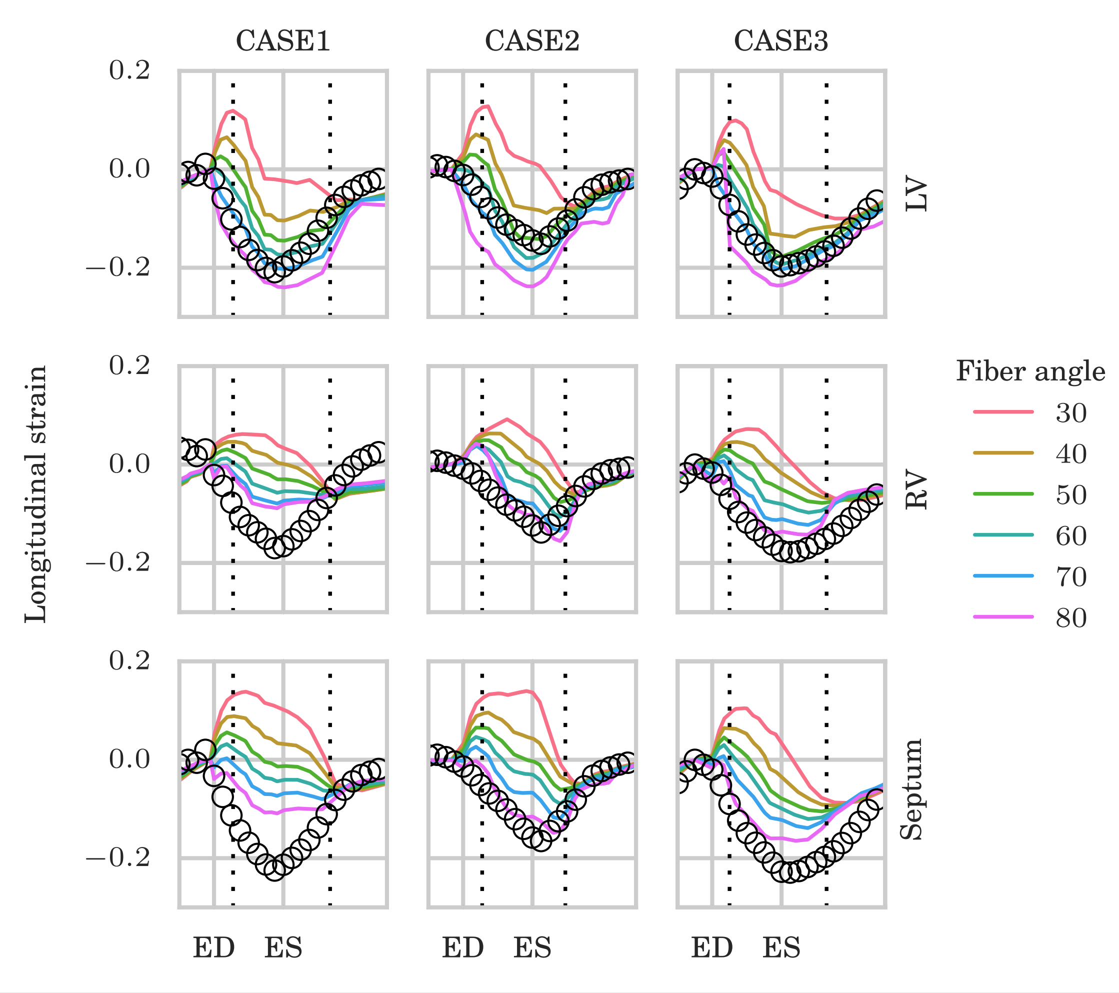




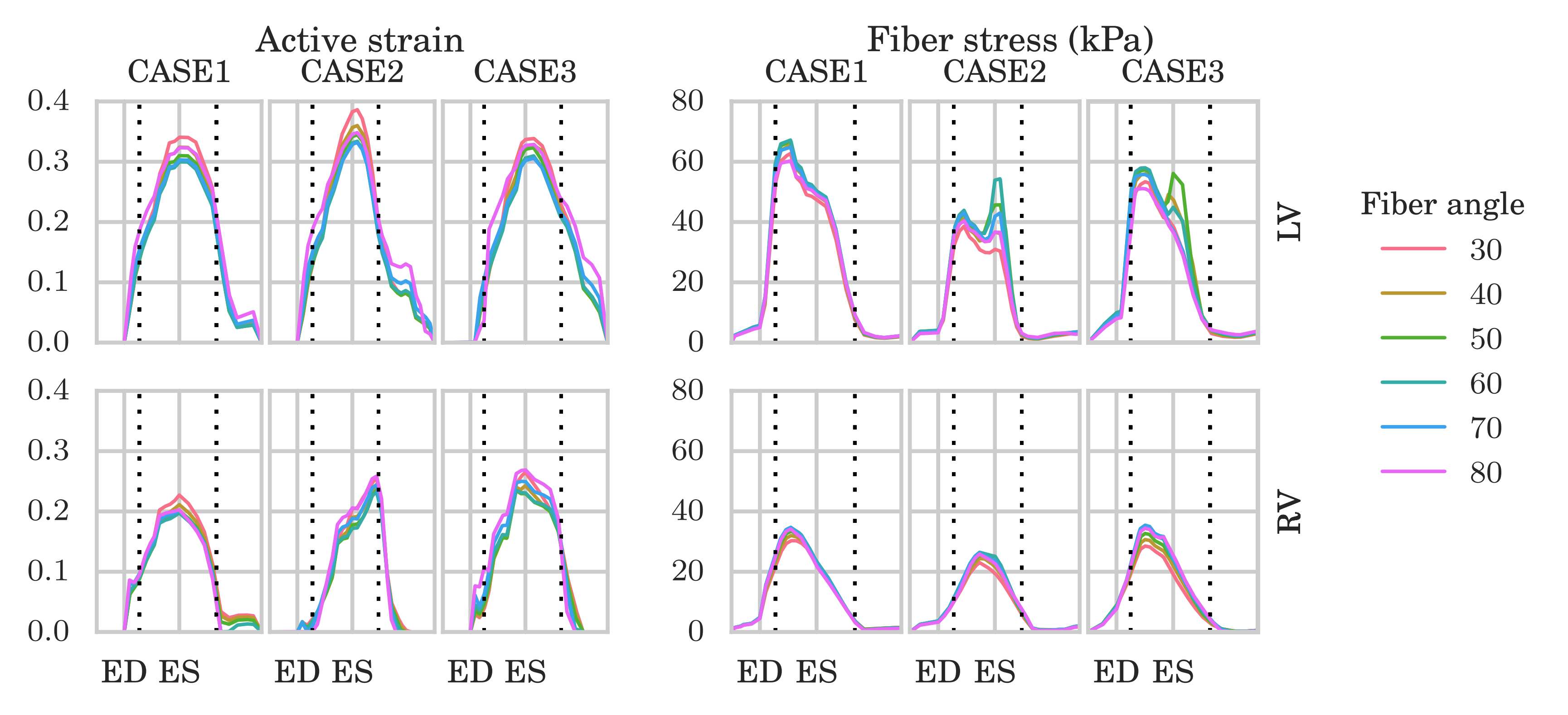
We tested a range of different fiber angles, and found large differences in optimal fit



Longitudinal strain traces were not used in the optimization, and serve as model validation



Active strain and fiber stress were not very sensitive to varying fiber angles

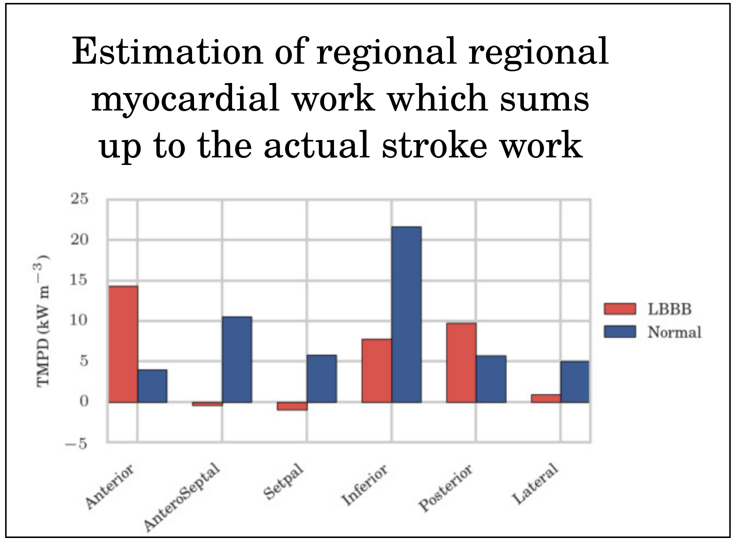


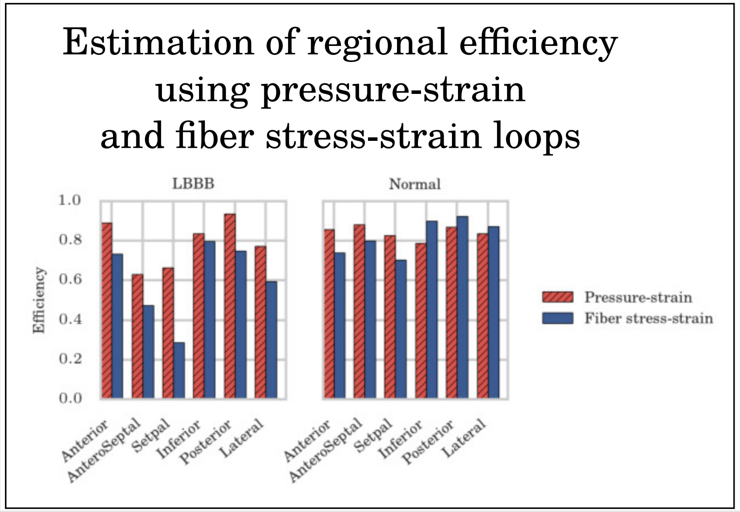
Paper 4

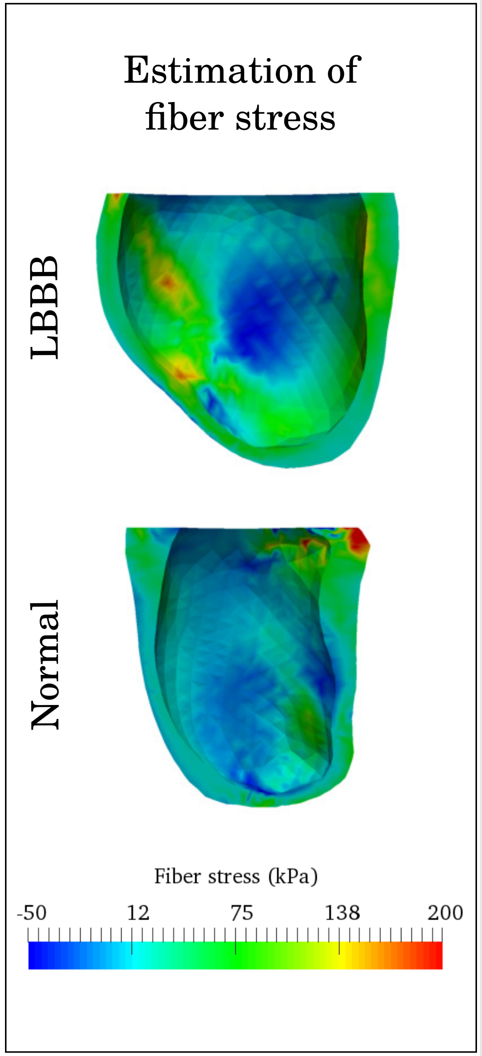
Title:
Assessment of regional myocardial work from a patient-specific cardiac mechanics model

Authors:
Henrik Finsberg, John Aalen, Camilla K. Larsen, Espen Remme, Joakim Sundnes, Otto A. Smiseth, and Samuel T. Wall.

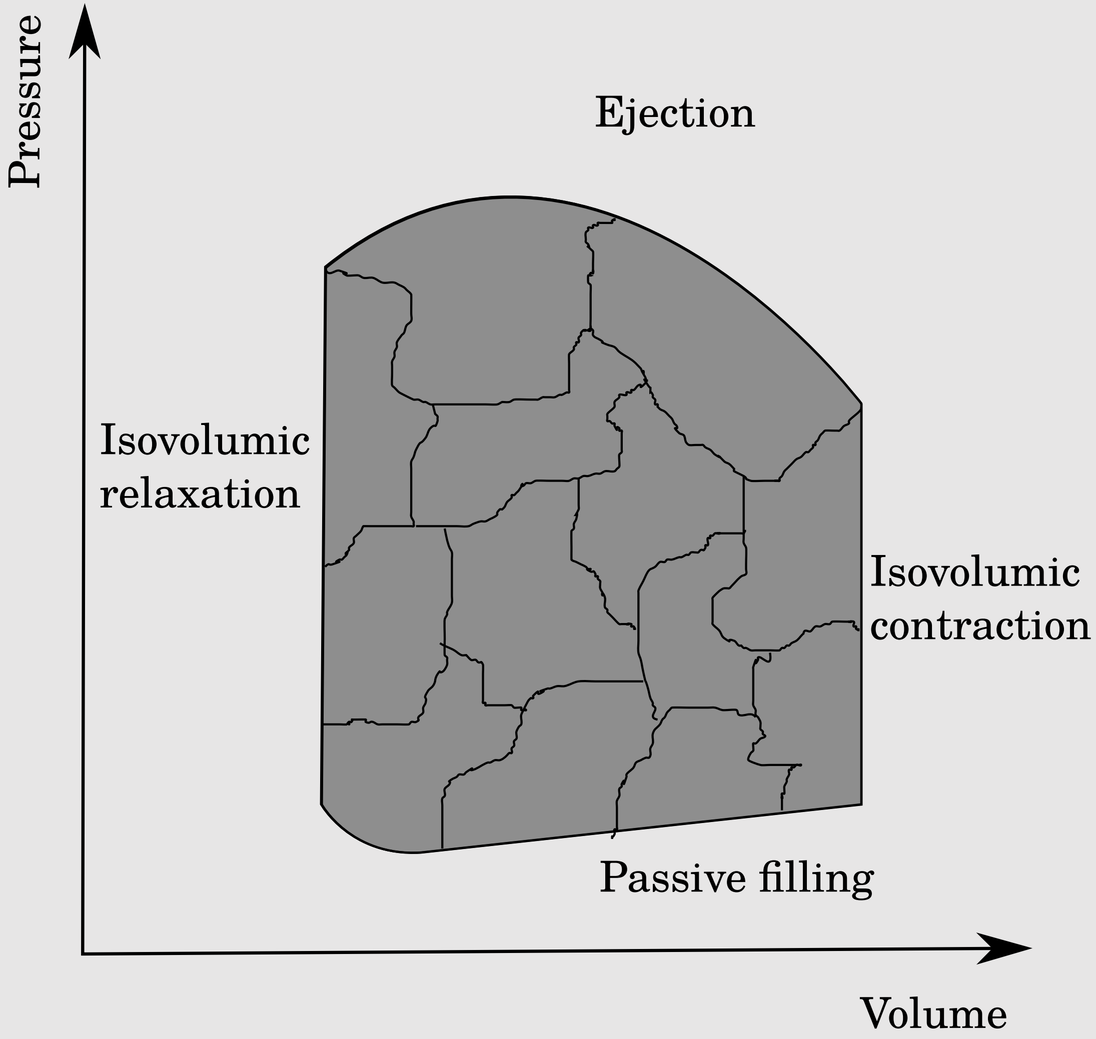
Status:
To be submitted





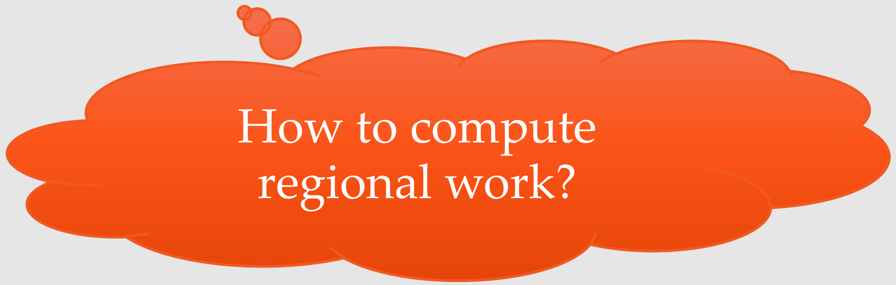


Total myocardial work in the left ventricle can be estimated by the area of the pressure-volume loop



$$\left[\frac{m^3}{t} \cdot \mathrm{Pa} \cdot t\right] = \left[\mathrm{Pa} \cdot m^3\right] = [\mathrm{Joule}]$$

$$\mathcal{W} = \int \frac{\mathrm{d}V}{\mathrm{d}t} P(t) \mathrm{d}t$$



The patient specific mechanics models can be used to estimate work

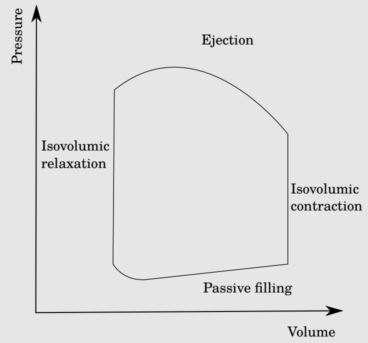
Work: $$\mathcal{W}(t_1, t_2)[\Omega_j] = -\int_{t_1}^{t_2} \int_{\Omega_j} \mathbf{S}(t, \mathbf{X}) : \dot{\mathbf{E}}(t, \mathbf{X}) \mathrm{d}\mathbf{X} \mathrm{d}t$$

Power density: $$\mathcal{W}(t_1, t_2)[\Omega_j] / |\Omega_j| \cdot (t_2 - t_1)$$

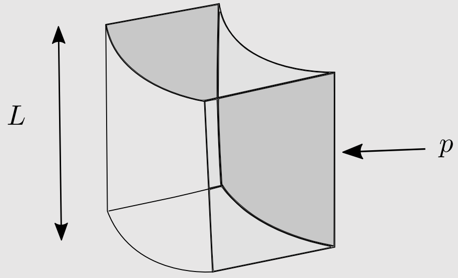
Second Piola-Kirchhoff stress tensor: $\mathbf{S}(t, \mathbf{X})$

Green-Lagrange strain tensor: $\mathbf{E}(t, \mathbf{X})$

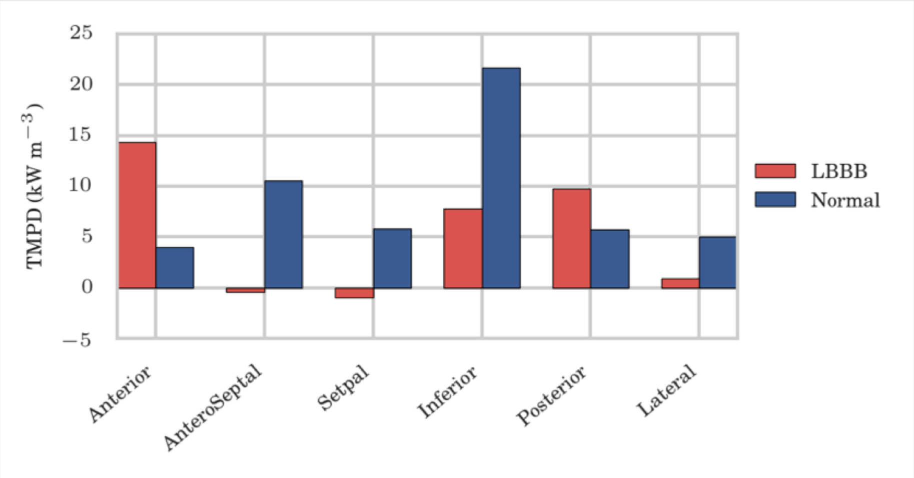
Case	PV area (kW m^{-3})	Full (kW m^{-3})	Fiber (kW m^{-3})	Pressure-GLS (kW m^{-3})
LBBB	8.41	10.60	6.42	1.02
Normal	15.79	16.35	9.59	1.59



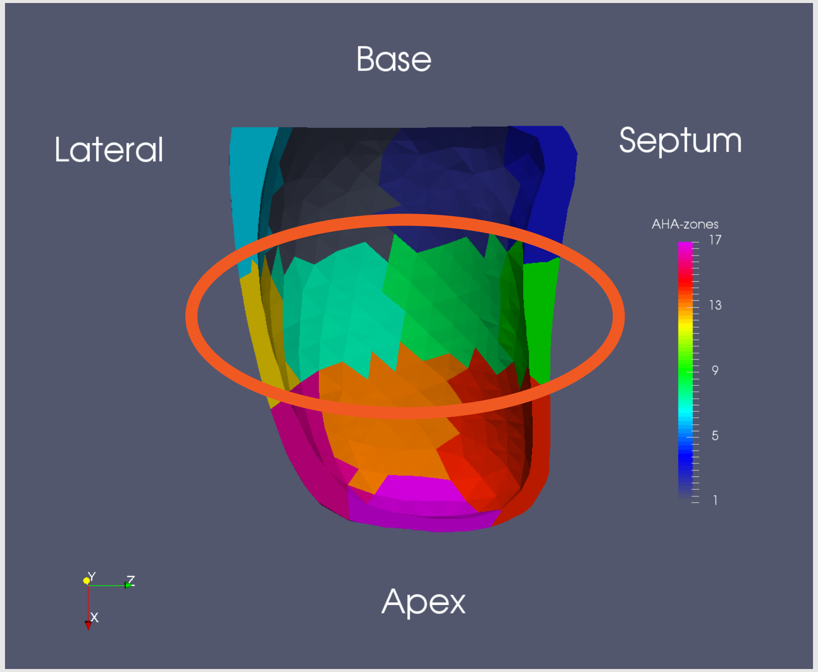
$$\begin{pmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{21} & \sigma_{22} & \sigma_{23} \\ \sigma_{31} & \sigma_{23} & \sigma_{33} \end{pmatrix} \qquad \begin{pmatrix} \sigma_{ff} & \cdot & \cdot \\ \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot \end{pmatrix}$$

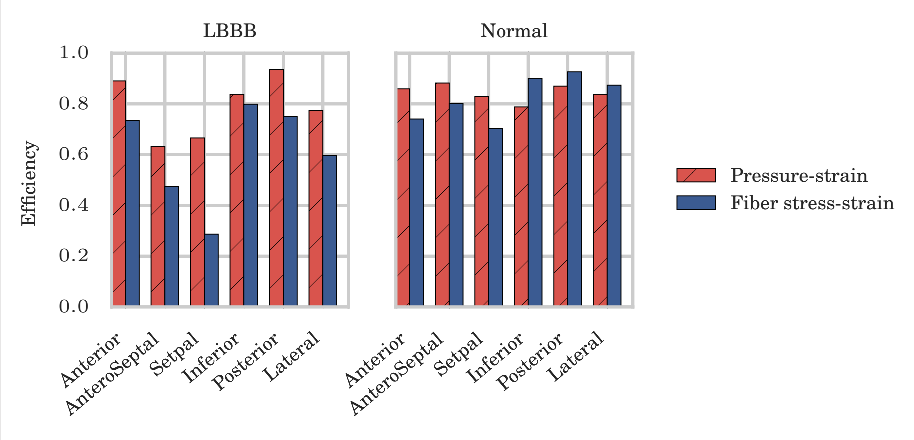


The regional efficiency of each segment show the same trend regardless of how work is estimated



Regional total power density
Positive values indicate generation of work
Negative values indicate work usage

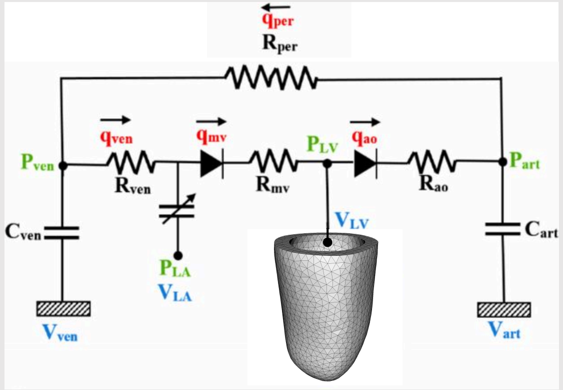




Regional efficiency
Higher values indicate higher efficiency

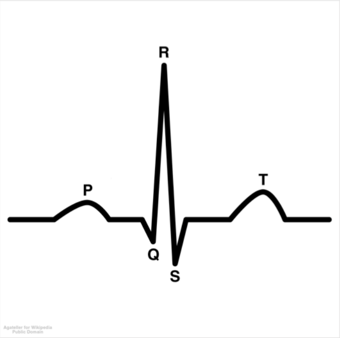
Next steps

Circulatory model

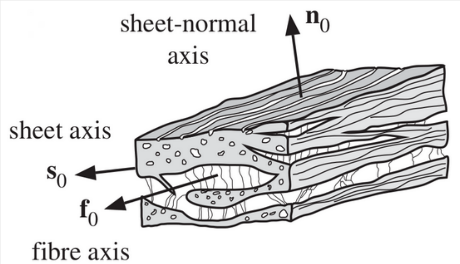


Shavik et. al, 2017

Electro-mechanical coupling

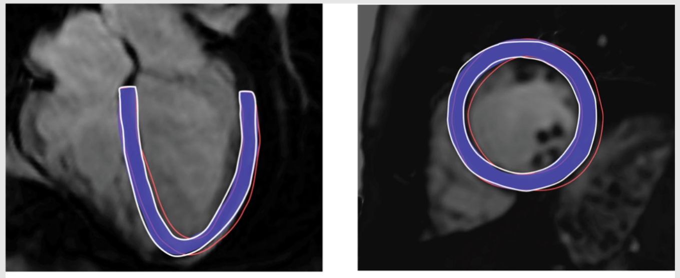


Realistic material properties



Holzapfel et. al, 2009

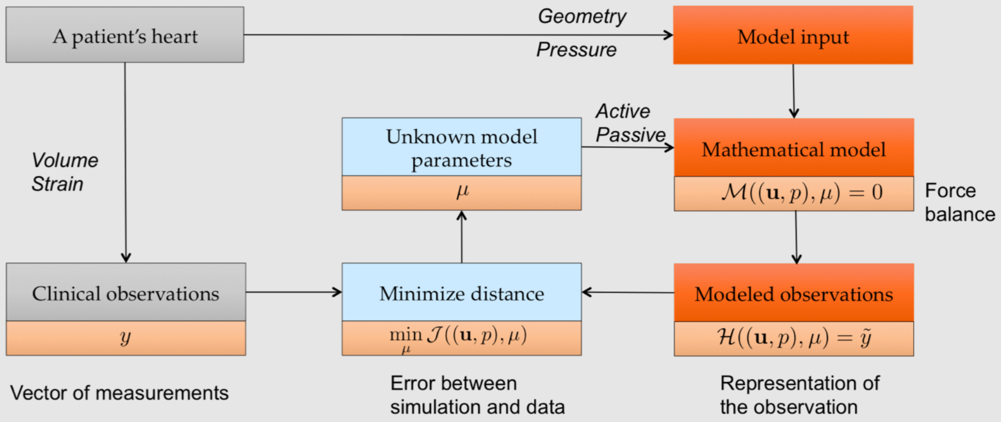
Realistic boundary conditions

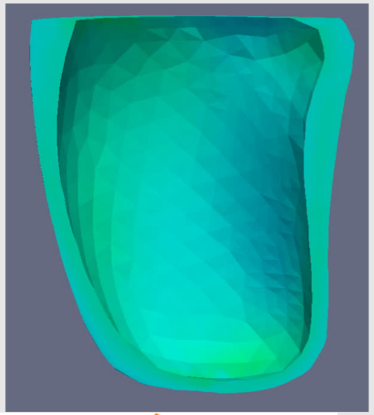


Asner, et. al, 2017

Model fidelity versus parameter identifiability

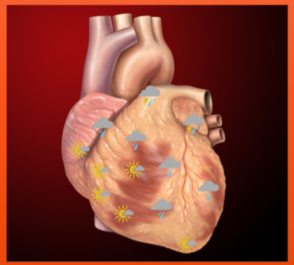
Summary and future directions





Diagnostic tool

Prediction



Thank you!

In silico medicine

Validation
is what matter most!

Acknowledgements:

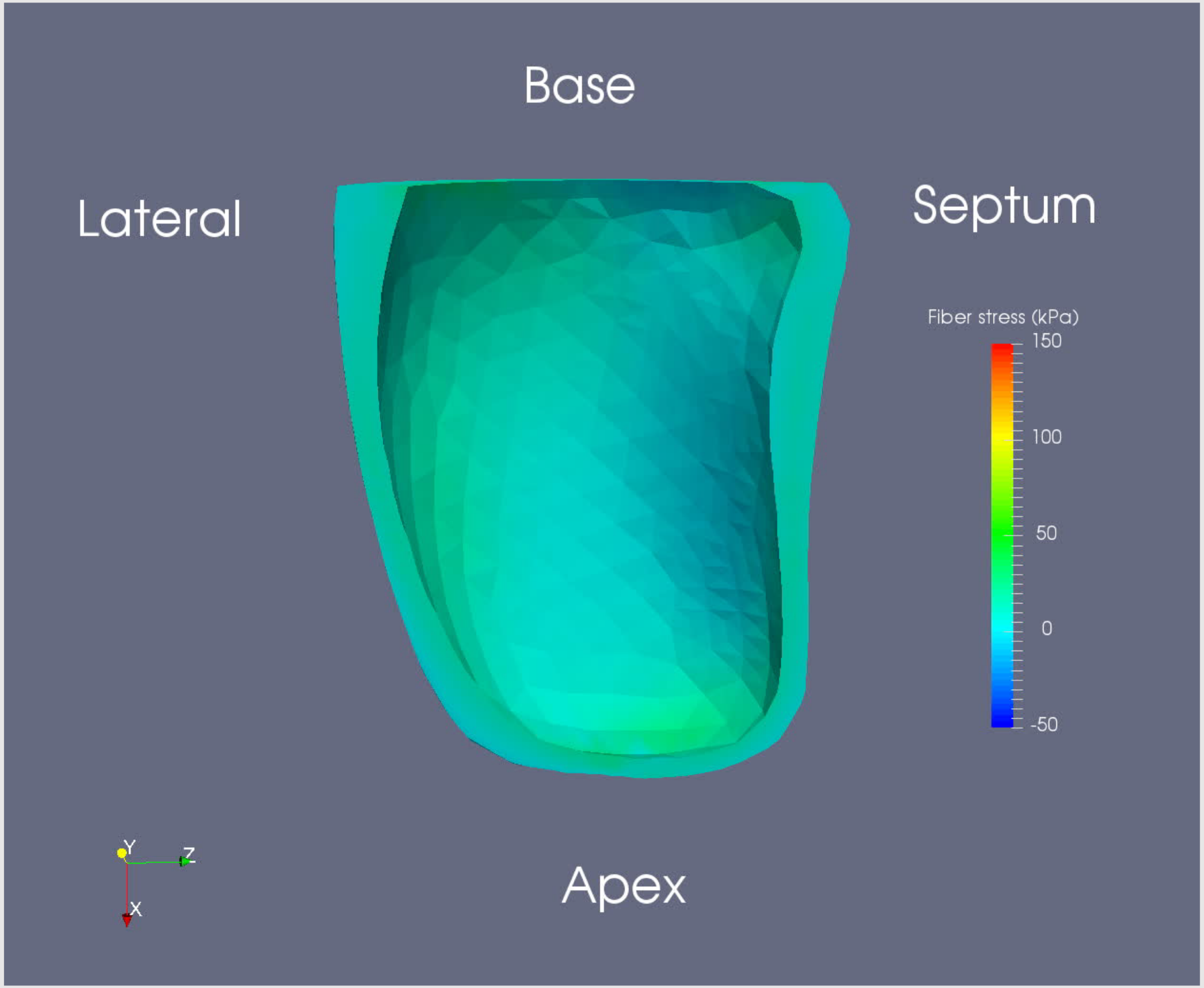
- Supervisors
- Simula
- CCI
- Family

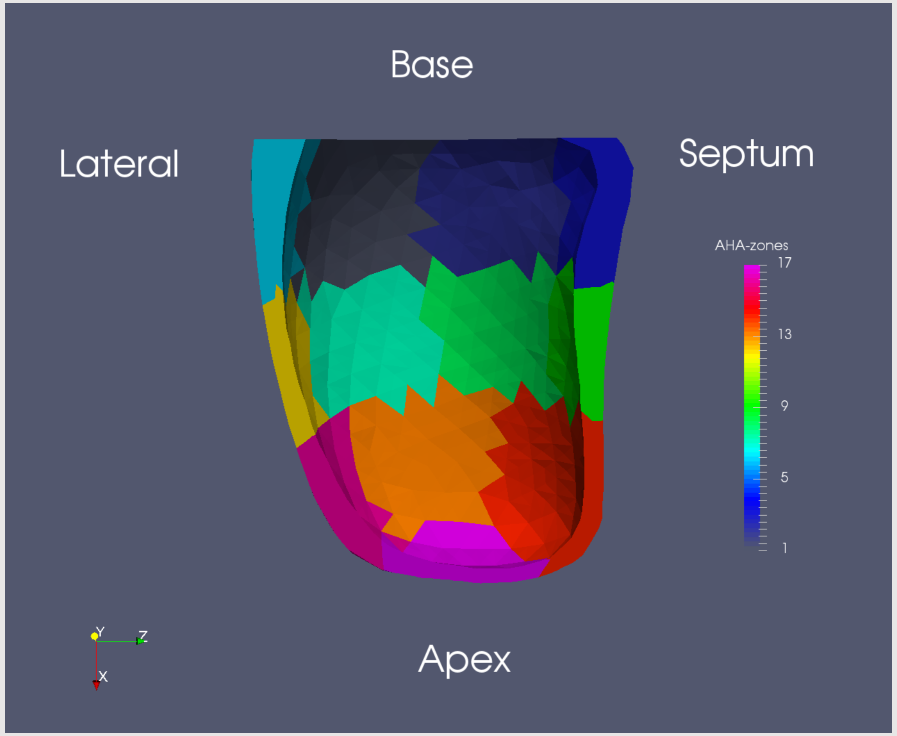
CENTER FOR CARDIOLOGICAL **INNOVATION**

simula

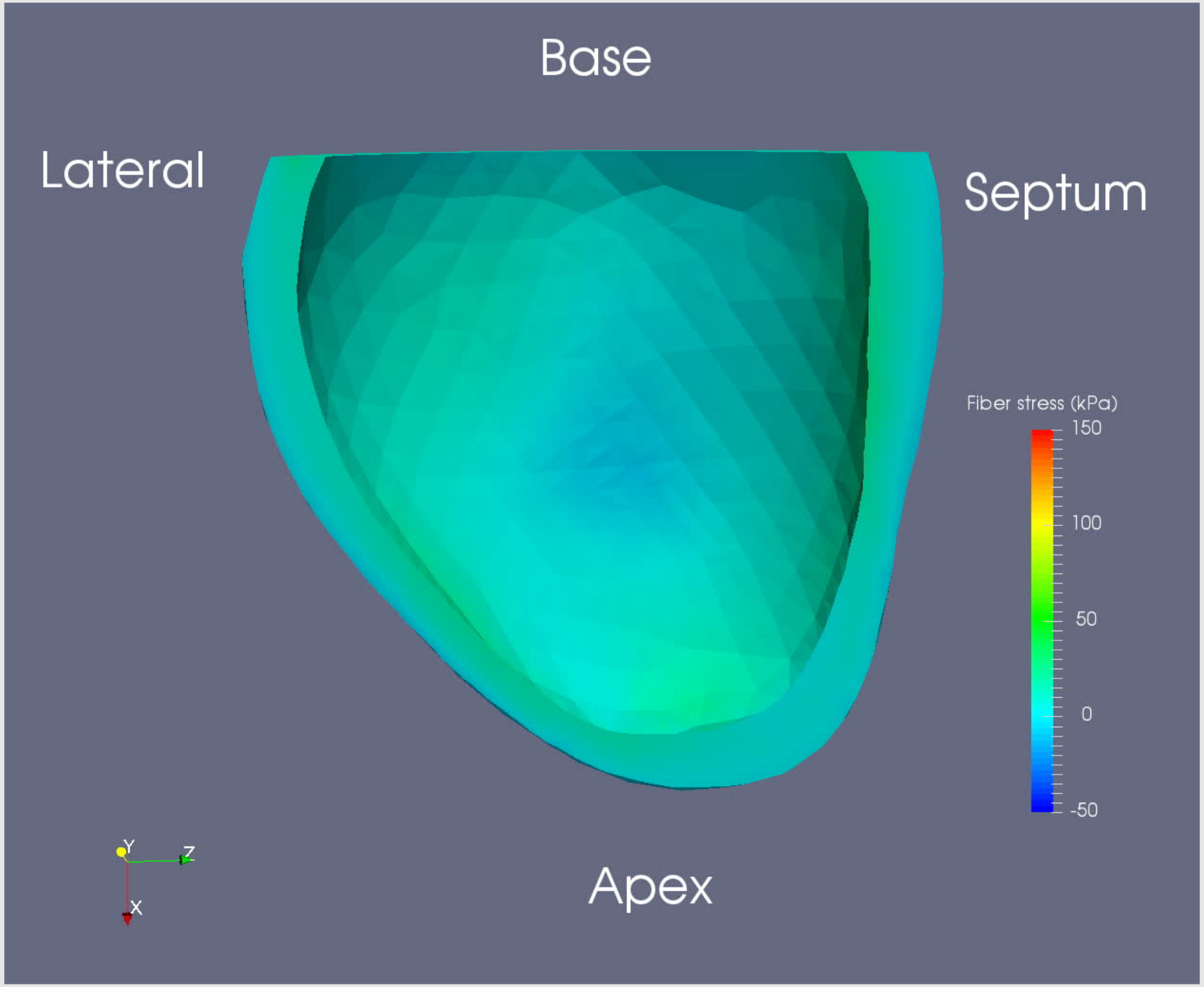
Extra slides

Normal


Base
Lateral
Septum
Fiber stress (kPa)
150
100
50
0
-50
Y
Z
X
Apex


Base
Lateral
Septum
AHA-zones
17
13
9
5
1
Apex

LBBB


Base
Lateral
Septum
Fiber stress (kPa)
150
100
50
0
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X
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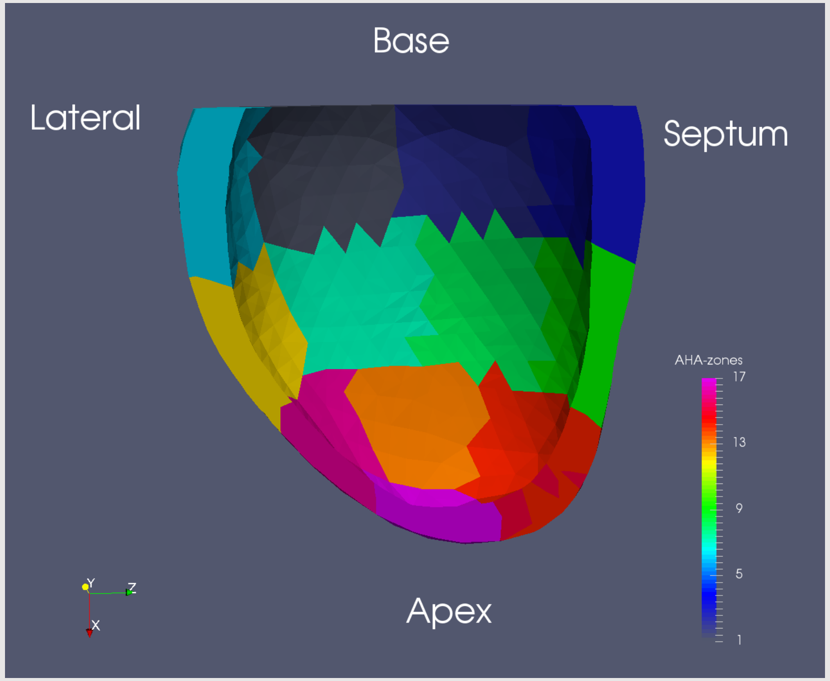
Base
Lateral
Septum
AHA-zones
17
13
9
5
1
Y
Z
X
Apex

For high dimensional parameter spaces, the gradient is most efficiently computed by considering the adjoint problem.

Chain rule:

$$\frac{\mathrm{d}}{\mathrm{d}\mu}\mathcal{J} = \frac{\partial}{\partial \mu}\mathcal{J}(\mathbf{w}(\mu),\mu) + \frac{\partial}{\partial \mathbf{w}}\mathcal{J}(\mathbf{w}(\mu),\mu)\frac{\mathrm{d}}{\mathrm{d}\mu}\mathbf{w}(\mu) \qquad \mathbf{w} = (\mathbf{u}, p)$$

Differentiate the force balance equation:

$$\frac{\mathrm{d}}{\mathrm{d}\mu}\mathcal{M}(\mathbf{w}(\mu),\mu) = \frac{\partial}{\partial \mathbf{w}}\mathcal{M}(\mathbf{w}(\mu),\mu)\frac{\mathrm{d}}{\mathrm{d}\mu}\mathbf{w}(\mu) + \frac{\partial}{\partial \mu}\mathcal{M}(\mathbf{w}(\mu),\mu) = 0$$

Rewrite terms:

$$\frac{\partial}{\partial \mathbf{w}}\mathcal{J}(\mathbf{w}(\mu),\mu)\frac{\mathrm{d}}{\mathrm{d}\mu}\mathbf{w}(\mu) = -z^*\frac{\partial}{\partial \mu}\mathcal{M}(\mathbf{w}(\mu),\mu) \qquad z^*\frac{\partial}{\partial \mathbf{w}}\mathcal{M}(\mathbf{w}(\mu),\mu) = \frac{\partial}{\partial \mathbf{w}}\mathcal{J}(\mathbf{w}(\mu),\mu)$$

Take the adjoint!

$$\frac{\partial}{\partial \mathbf{w}}\mathcal{M}(\mathbf{w}(\mu),\mu)^* z = \frac{\partial}{\partial \mathbf{w}}\mathcal{J}(\mathbf{w}(\mu),\mu)^*$$

dolfin-adjoint