Effective parameter inference for a mathematical model of the left ventricle

RSS Glasgow

Alan Lazarus
Joint with: Dirk Husmeier, Hao Gao and Xiaoyu Luo

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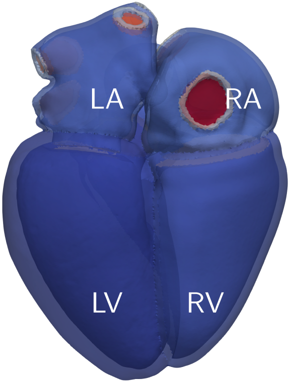
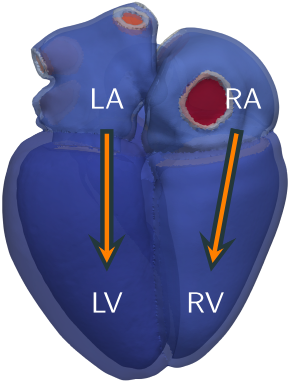
University of Glasgow

Plan

Heart function

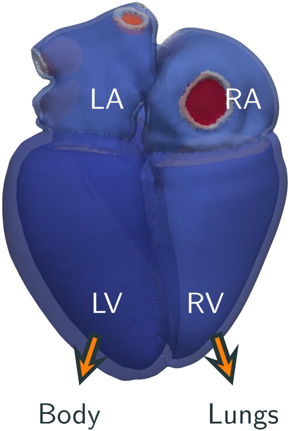


Heart function



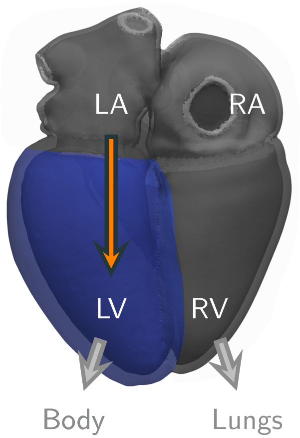
Diastole

Heart function



Systole

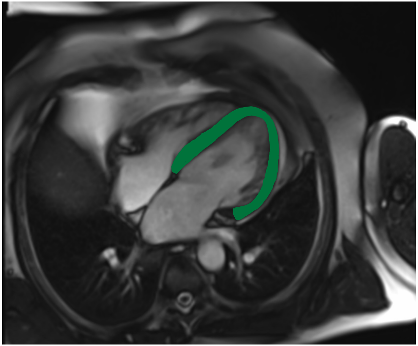
Heart function



Our interest: left ventricle in diastole

Left ventricle function

- Left ventricle function is guided by the myocardium.
- Relaxation of the muscle—passive behaviour— allows filling in diastole.
- With diastolic heart failure this filling reduces.
- Inferring the stiffness properties of the myocardium could help identify disease.



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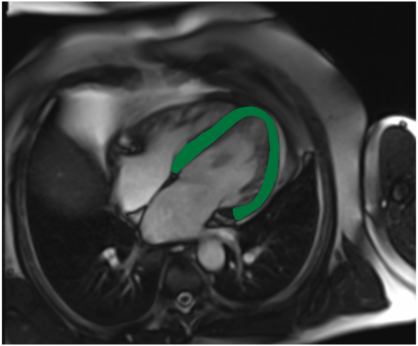

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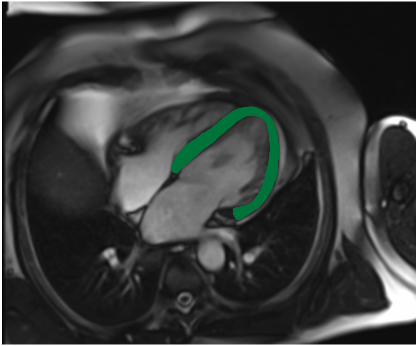

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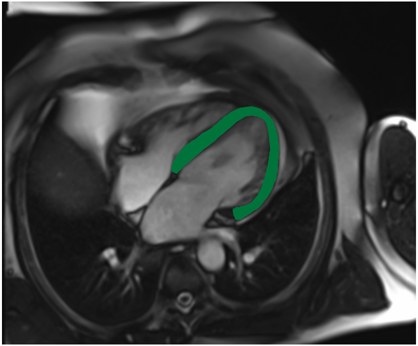

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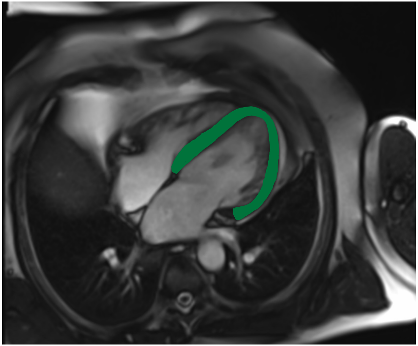
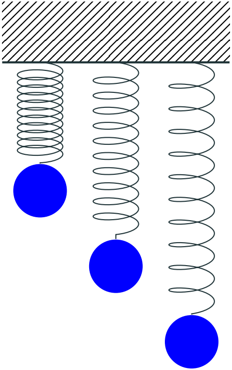
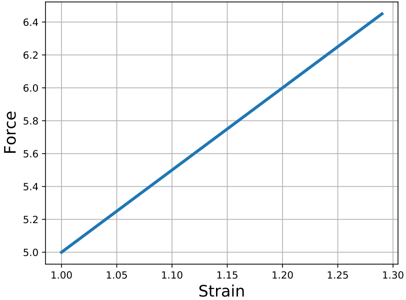


Describing material behaviour



$$F = kx$$

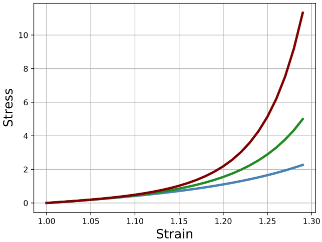
- Hooke's law is the stress-strain relation for linear materials.
- Describes the behaviour of the spring under external force.
- k is the material property—stiffness of the spring



Parameterized description of left ventricle passive behaviour

- Stress strain relation for myocardium provided by the Holzapfel Ogden law.
- A parameterized description of the myocardium.
- Parameters give us the stiffness properties!

$$\mathbf{\Psi} = \frac{a}{2b}\left[\exp\left\{b\left(I_1 - 3\right)\right\} - 1\right] + \sum_{i \in \{\mathrm{f},\mathrm{s}\}} \frac{a_i}{2b_i}\left[\exp\left\{b_i\left(I_{4i} - 1\right)^2\right\} - 1\right] + \frac{a_{\mathrm{fs}}}{2b_{\mathrm{fs}}}\left\{\exp\left(b_{\mathrm{fs}} I_{8\mathrm{fs}}^2\right) - 1\right\}$$



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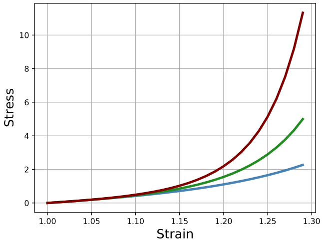

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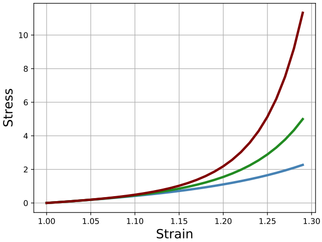
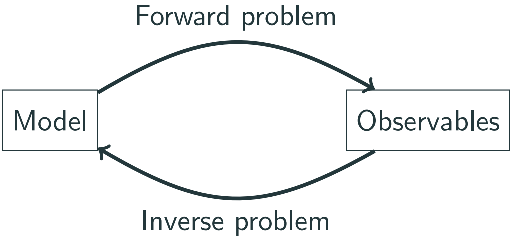


Forward and inverse problems



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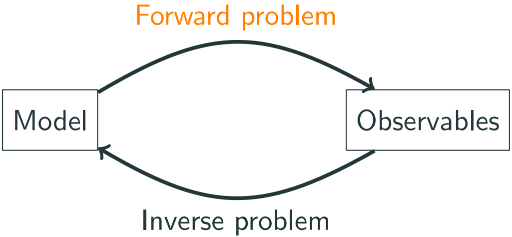


Plan

Background

The mathematical model

Statistical emulation

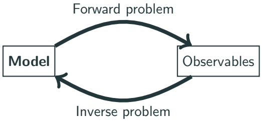
Emulation for multiple geometries

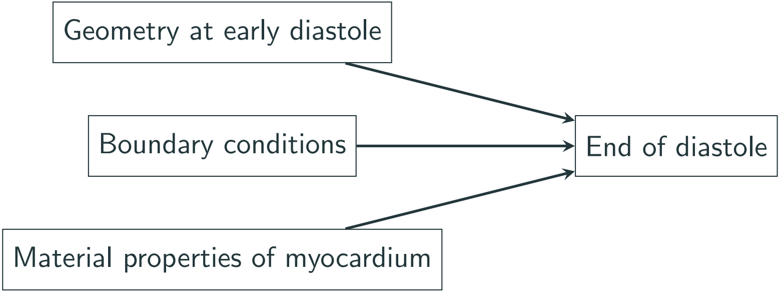
Parameter inference for different geometries

Using ex-vivo information

Ongoing work

The mathematical model as a black box





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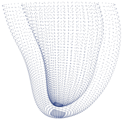
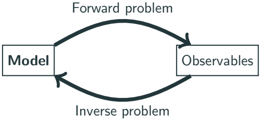




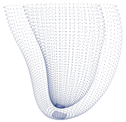
Geometry at early diastole

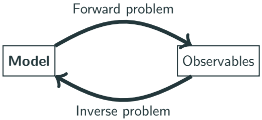
Boundary conditions

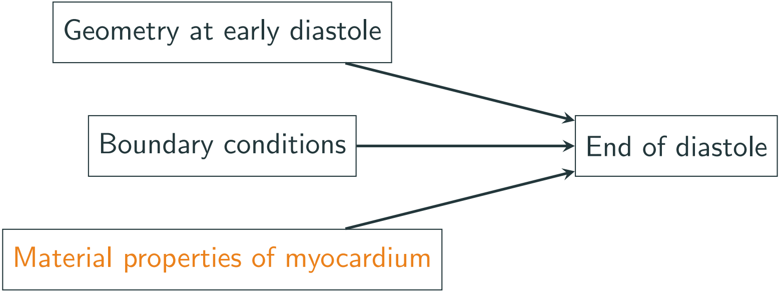
Material properties of myocardium

→ End of diastole

The mathematical model as a black box







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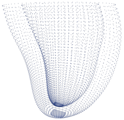

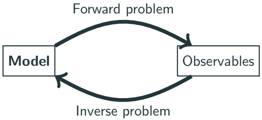

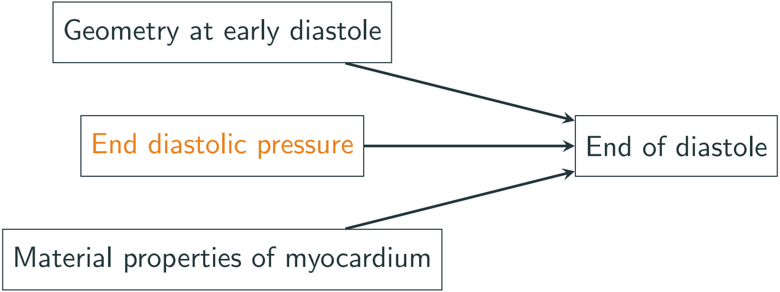

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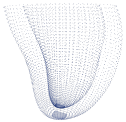

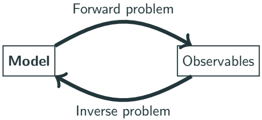

Geometry at early diastole

End diastolic pressure

Material properties of myocardium

End of diastole

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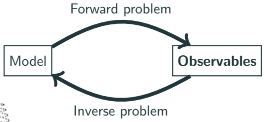
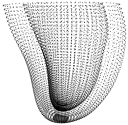
$$

What do we get from the model?

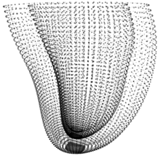
We have two reference points:



Early diastole



End of diastole



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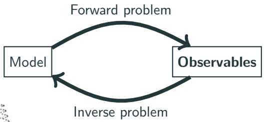

Early diastole

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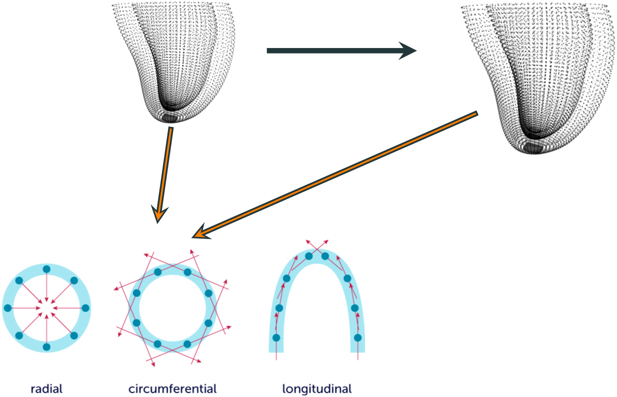

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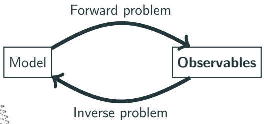

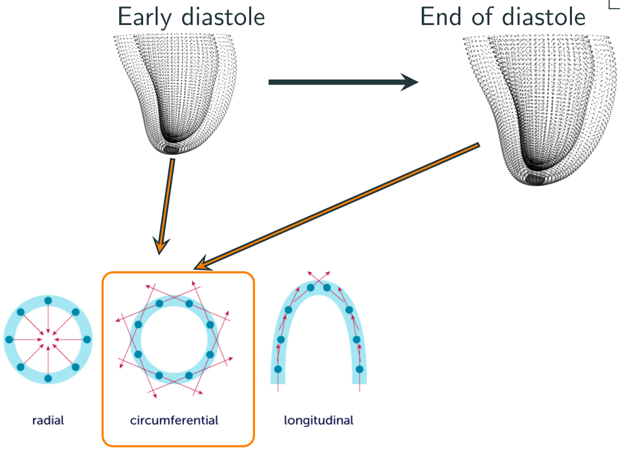

Currently, only circumferential strains can be accurately measured.

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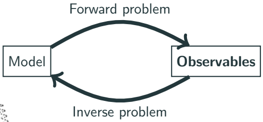

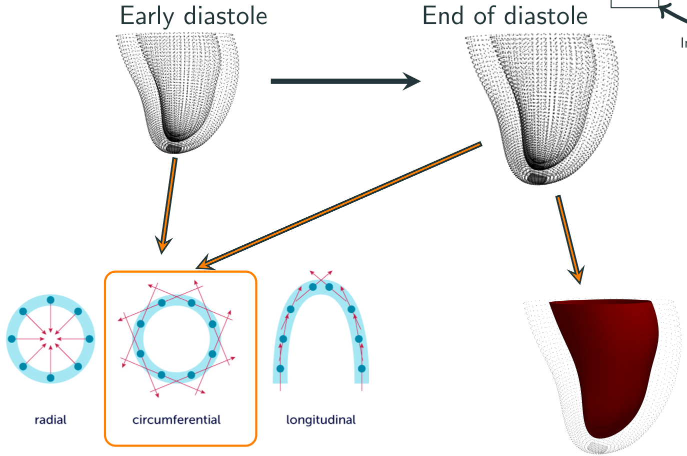

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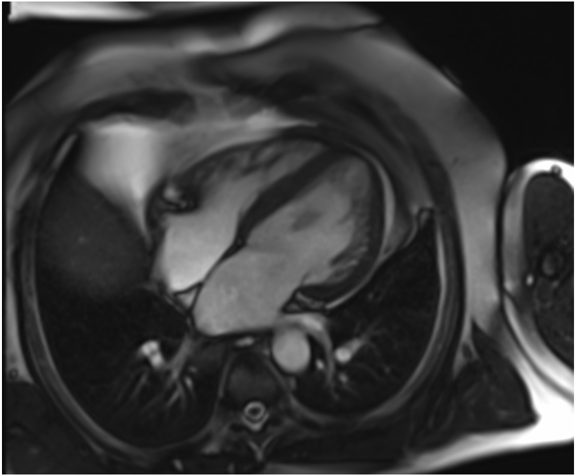
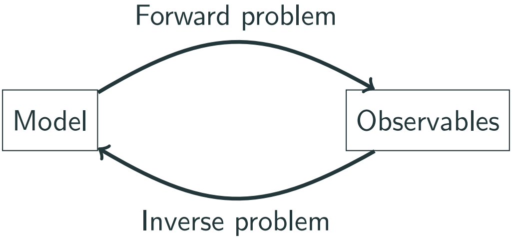
End diastolic volume of the cavity.

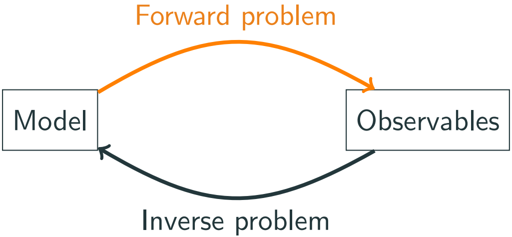
How are strains and volume measured?



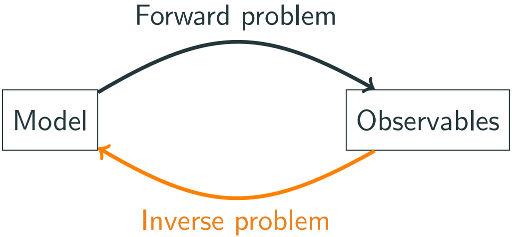
Can we now solve the inverse problem?



Expensive!



Very expensive!

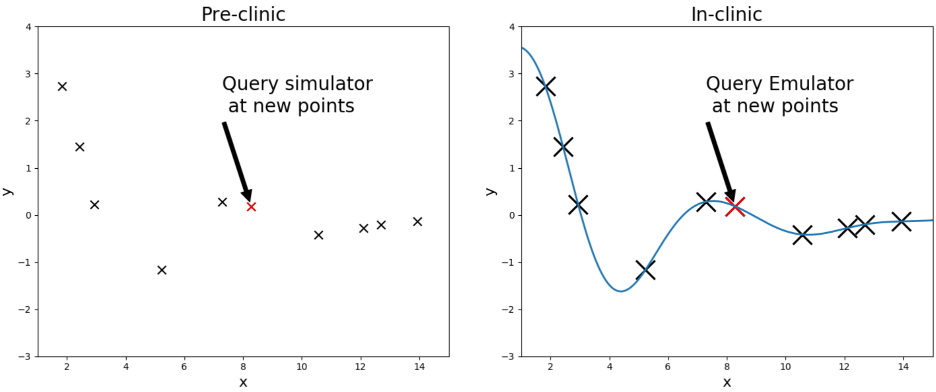


We can solve if the patient can wait 2 days and we ignore our uncertainty...

Plan

Emulation

Move the expensive simulations to the pre-clinic phase.



Two questions: what is our input space and how do we obtain our emulator?

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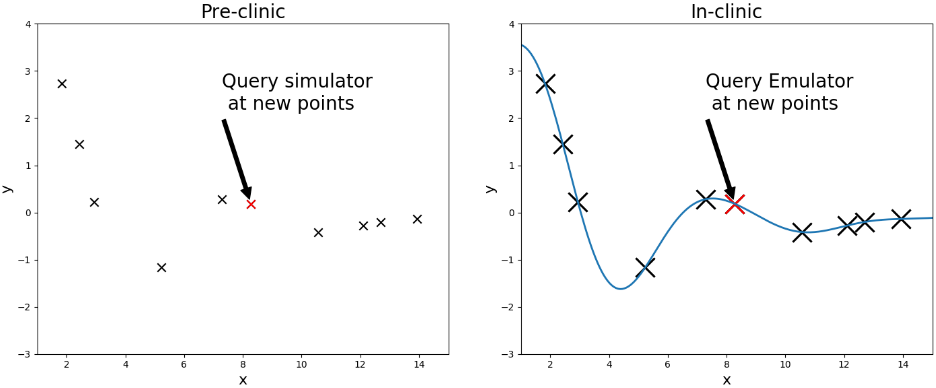

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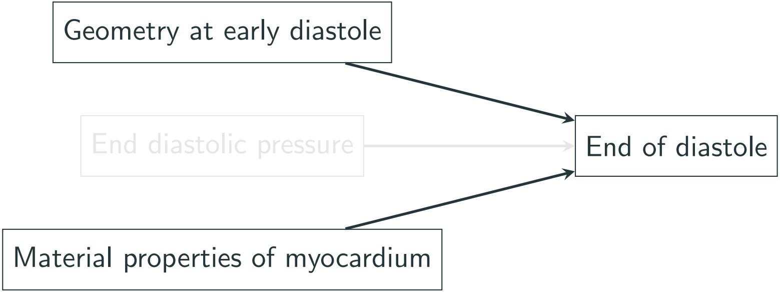

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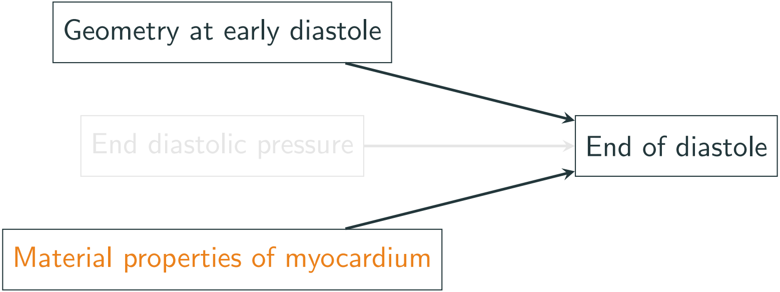

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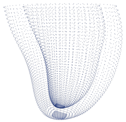

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Geometry at early diastole

End diastolic pressure

End of diastole

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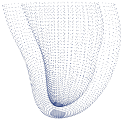

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Need to fill a 17k+8 dimensional space...

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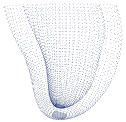

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INTRACTABLE

Plan

Dimensionality reduction for statistical emulation

- Dimensionality reduction allows us to find a low dimensional representation of the LV geometry from n training left ventricles.
- Design in the low dimensional space and run the simulator on the reconstructed geometries
- These can be fully represented by the m dimensional projection.
- For our data (**small n**) PCA outperforms more sophisticated methods.

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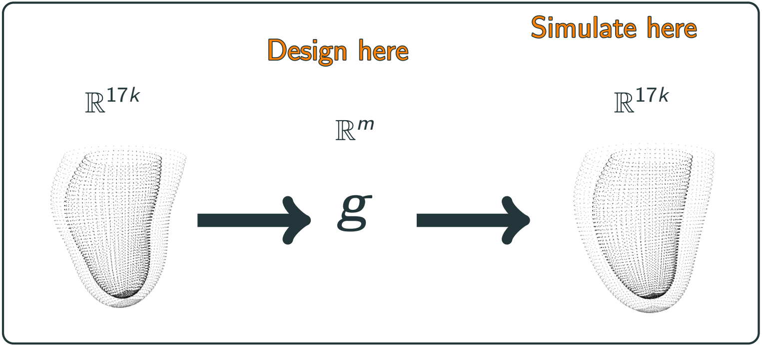

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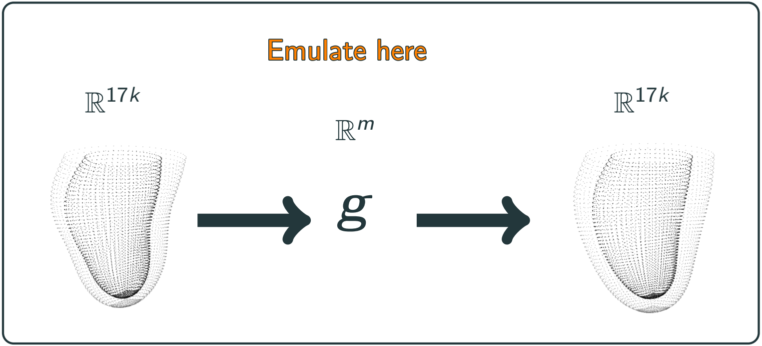


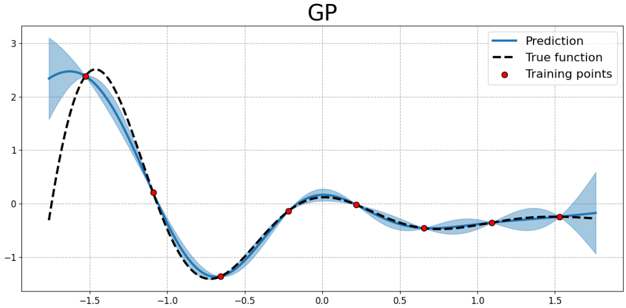
Dimensionality reduction for statistical emulation

- Dimensionality reduction allows us to find a low dimensional representation of the LV geometry from n training left ventricles.
- Design in the low dimensional space and run the simulator on the reconstructed geometries
- These can be fully represented by the m dimensional projection.
- For our data (**small n**) PCA outperforms more sophisticated methods.

Two questions: what is our input space and how do we obtain our emulator?

The problem with GPs

- Gaussian processes are the standard models used for emulation.
- With large datasets they rely on approximations.
- Computational costs are only as low as the number of inducement points.
- Neural networks are parametric: prediction costs do not grow with training set size.



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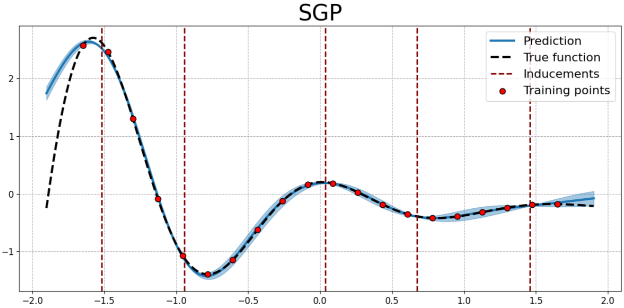
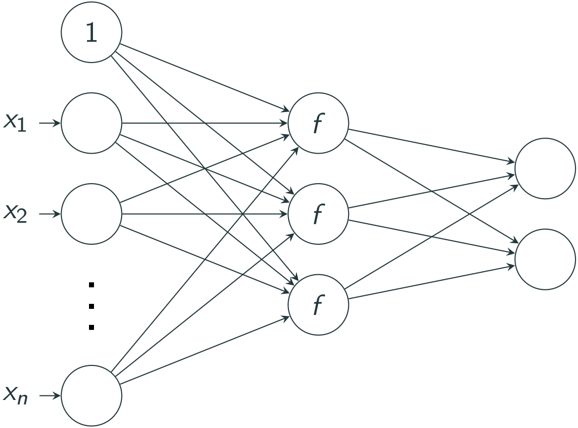


Neural Networks

Standard network architecture.



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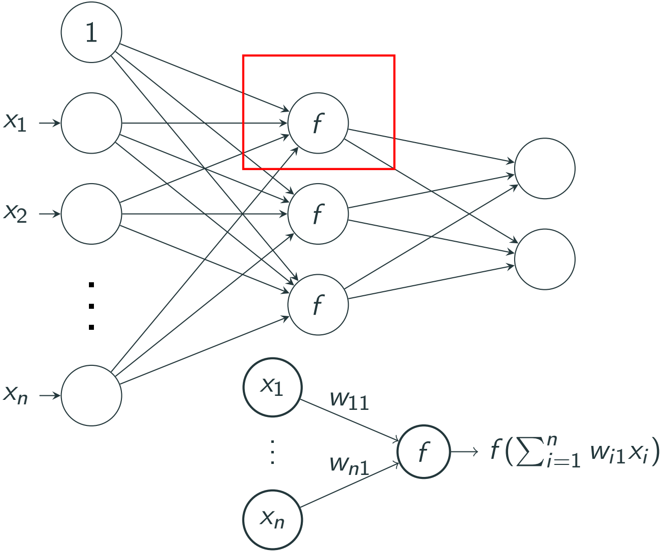
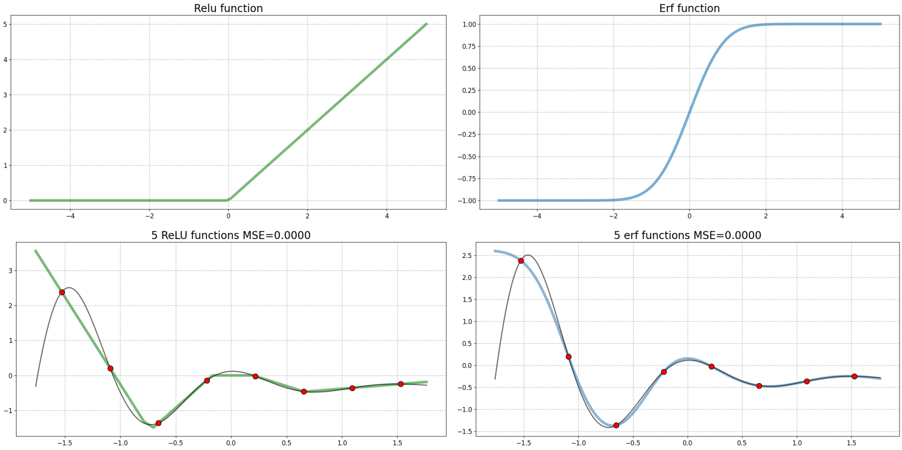


Effect of activation function



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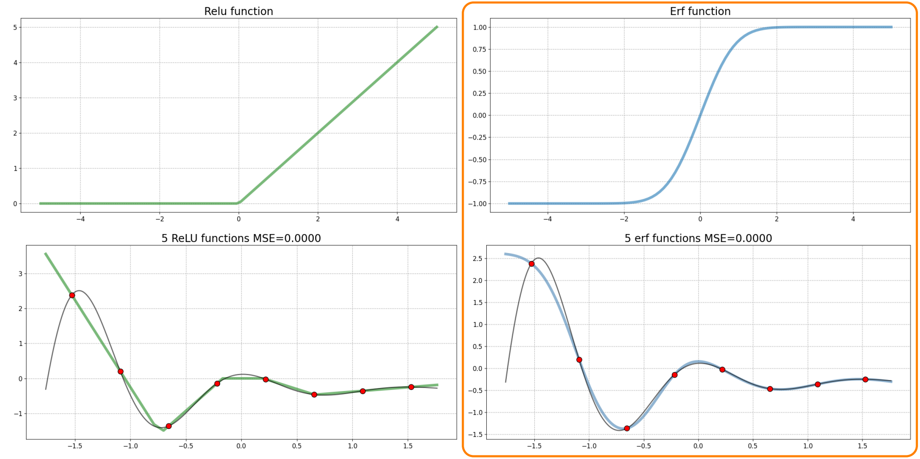
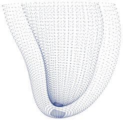


Plan

Recall: the simulator model



$\in \mathbb{R}^{17376}$

Geometry at early diastole

End diastolic pressure

End of diastole

Material properties of myocardium

$$\begin{aligned}\boldsymbol{\Psi} &= \frac{a}{2b}\left[\exp\left\{b\left(I_1 - 3\right)\right\} - 1\right] \\ &+ \sum_{i\in\{\mathrm{f},\mathrm{s}\}} \frac{a_i}{2b_i}\left[\exp\left\{b_i\left(I_{4i} - 1\right)^2\right\} - 1\right] \qquad \in \mathbb{R}^8 \\ &+ \frac{a_{\mathrm{fs}}}{2b_{\mathrm{fs}}}\left\{\exp\left(b_{\mathrm{fs}} I_{8\mathrm{fs}}^2\right) - 1\right\}\end{aligned}$$

$\boldsymbol{g} \in \mathbb{R}^m$ $\in \mathbb{R}^{17376}$

Geometry at early diastole → End of diastole

End diastolic pressure → End of diastole

Material properties of myocardium → End of diastole

$$\Psi = \frac{a}{2b}\left[\exp\left\{b\left(I_1 - 3\right)\right\} - 1\right] + \sum_{i \in \{\mathrm{f},\mathrm{s}\}} \frac{a_i}{2b_i}\left[\exp\left\{b_i\left(I_{4i} - 1\right)^2\right\} - 1\right] + \frac{a_{\mathrm{fs}}}{2b_{\mathrm{fs}}}\left\{\exp\left(b_{\mathrm{fs}} I_{8\mathrm{fs}}^2\right) - 1\right\} \quad \in \mathbb{R}^8$$

Recall: the simulator model

$\boldsymbol{g} \in \mathbb{R}^m$ ($\in \mathbb{R}^{17376}$)

Geometry at early diastole → End of diastole

End diastolic pressure → End of diastole

Material properties of myocardium → End of diastole

$$\Psi = \frac{a}{2b}\left[\exp\left\{b\left(I_1 - 3\right)\right\} - 1\right] + \sum_{i \in \{\mathrm{f},\mathrm{s}\}} \frac{a_i}{2b_i}\left[\exp\left\{b_i\left(I_{4i} - 1\right)^2\right\} - 1\right] + \frac{a_{\mathrm{fs}}}{2b_{\mathrm{fs}}}\left\{\exp\left(b_{\mathrm{fs}} I_{8\mathrm{fs}}^2\right) - 1\right\} \quad \in \mathbb{R}^8$$

Need to fill an $m + 8$ dimensional space...

Recall: the simulator model

$\boldsymbol{g} \in \mathbb{R}^m$

Geometry at early diastole

End diastolic pressure

End of diastole

Material properties of myocardium

$$\Psi = \frac{a}{2b}\left[\exp\{b(I_1 - 3)\} - 1\right] + \sum_{i \in \{\mathrm{f},\mathrm{s}\}} \frac{a_i}{2b_i}\left[\exp\left\{b_i (I_{4i} - 1)^2\right\} - 1\right] + \frac{a_{\mathrm{fs}}}{2b_{\mathrm{fs}}}\left\{\exp\left(b_{\mathrm{fs}} I_{8\mathrm{fs}}^2\right) - 1\right\} \quad \in \mathbb{R}^8$$

Tractable, but can we do better?

A further reduction in complexity

$$\Psi = \frac{a}{2b}\{\exp[b(I_1 - 3)] - 1\} + \sum_{i \in \{f,s\}} \frac{a_i}{2b_i}\{\exp[b_i(I_{4i} - 1)^2] - 1\}$$
$$+ \frac{a_{\mathrm{fs}}}{2b_{\mathrm{fs}}}[\exp(b_{\mathrm{fs}} I_{8\mathrm{fs}}^2) - 1] + \frac{1}{2}$$

$$\begin{aligned} a &= \theta_1\, a_0, & b &= \theta_1\, b_0 \\ a_{\mathrm{f}} &= \theta_2\, a_{\mathrm{f}0}, & a_{\mathrm{s}} &= \theta_2\, a_{\mathrm{s}0} \\ b_{\mathrm{f}} &= \theta_3\, b_{\mathrm{f}0}, & b_{\mathrm{s}} &= \theta_3\, b_{\mathrm{s}0} \\ a_{\mathrm{fs}} &= \theta_4\, a_{\mathrm{fs}0}, & b_{\mathrm{fs}} &= \theta_4\, b_{\mathrm{fs}0} \end{aligned}$$

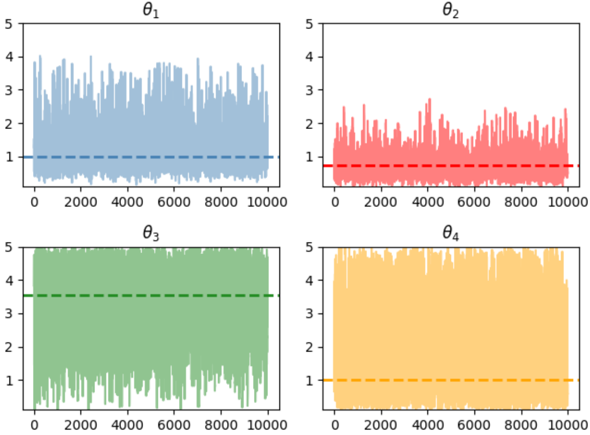
Infer $\theta_1, \theta_2, \theta_3$ and θ_4

Emulation problem is now $m + 4$ dimensional

Sampling with MCMC

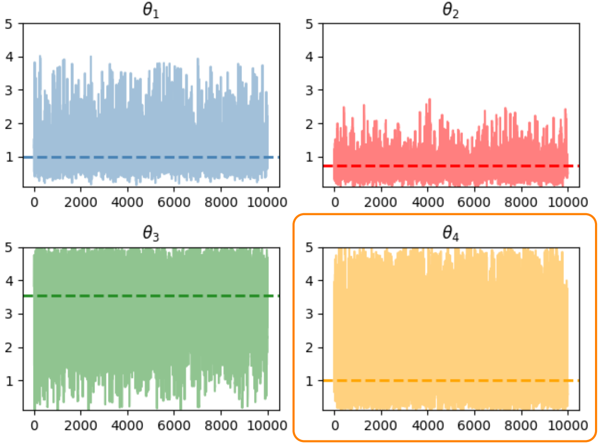
- We will use MCMC to quantify our uncertainty about the parameters.
- Two properties of the statistical emulator allow sampling with more sophisticated MCMC procedures:
    1. Efficiency: prediction in order of milliseconds instead of 8 minutes.
    2. Differentiability of the function
- However, we use an approximation (emulator) of the true function.
- Error is compounded by our approximation of the geometry.
- How does this affect our inference?

Inferring material parameters of a real geometry



Inference time: **15 seconds**

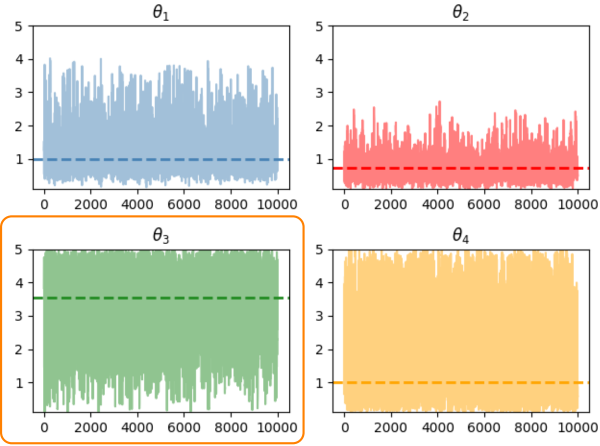
Inferring material parameters of a real geometry



Circumferential strains and volume are not sensitive to θ_4

Inference time: **15 seconds**

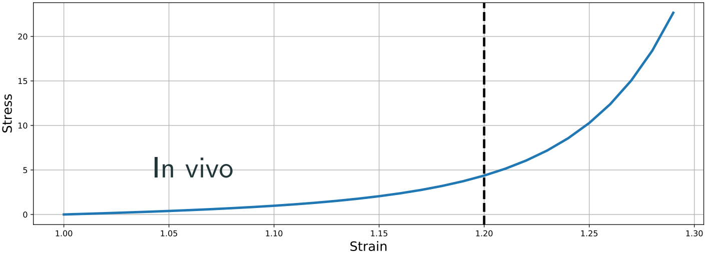
Inferring material parameters of a real geometry



Inference time: **15 seconds**

Problem with parameter identifiability

- Myocardium is a complicated material.
- Different components in material take effect at different stretches.
- Parameters of HO law reflect this changing behaviour.
- Observed data are only informative about small stretch regime.



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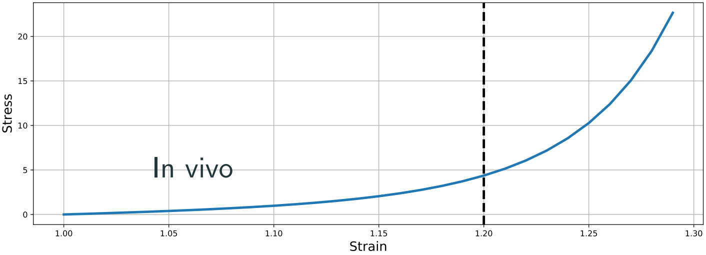

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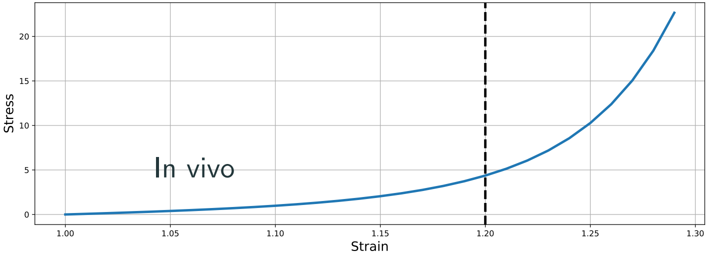

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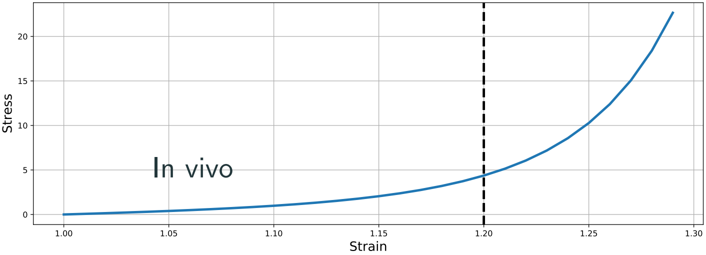


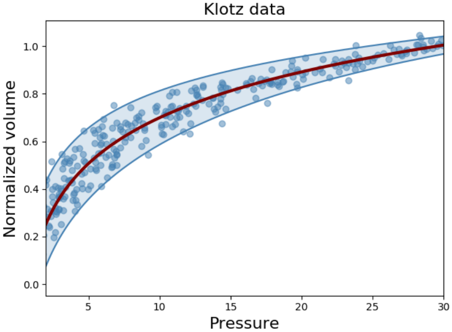
Plan

The Klotz curve

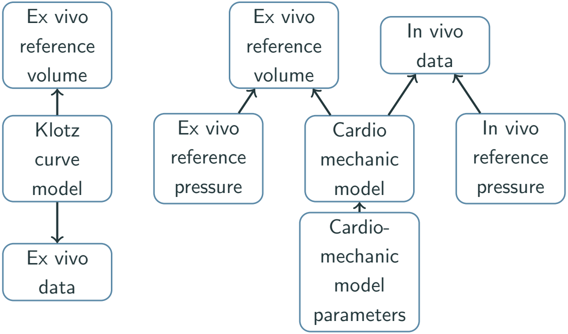
- Klotz et al inflated left ventricles (ex vivo) from volume V_0 at pressure 0 to volume V_{P} and pressure P.
- Measuring also the volume at pressure 30, V_{30}, they found a relationship between normalized volume $\tilde{V} = \frac{V_{\mathrm{P}} - V_0}{V_{30} - V_0}$ and pressure P :

$$\tilde{V} = \frac{\log \frac{P}{\alpha}}{\beta}$$

- Can we use this relationship to include the behaviour at high stretch?



A first attempt: the non empirical Klotz prior



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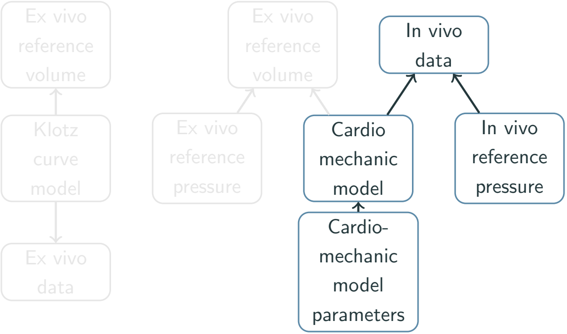
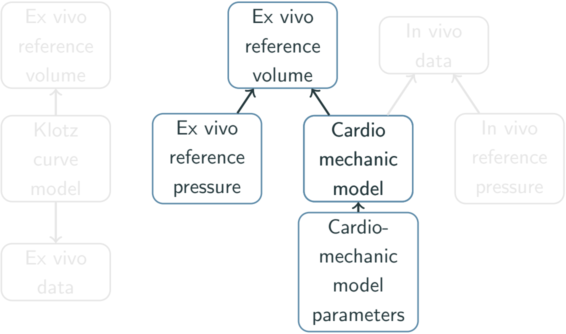


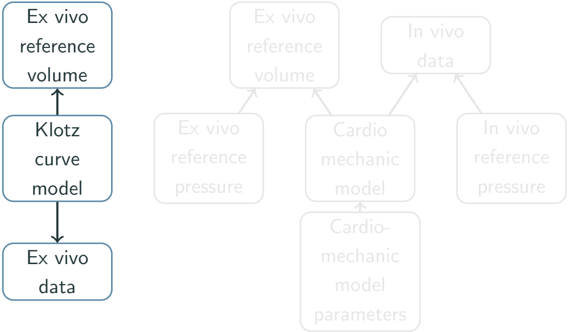
Our likelihood: this comes from our model of the in vivo left ventricle.

A first attempt: the non empirical Klotz prior



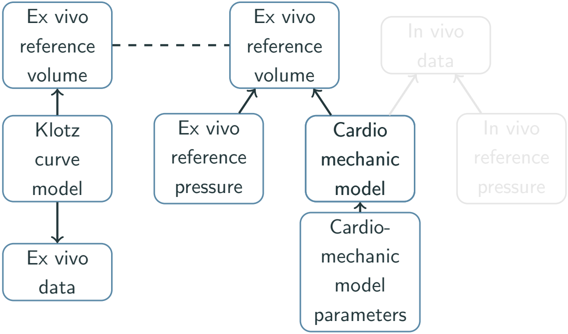
This distribution, $\pi_E(\tilde{V}_{20})$, comes from emulators trained to predict volume at pressure 20 and pressure 30 (with associated uncertainty).

A first attempt: the non empirical Klotz prior



This distribution,$\pi_{\mathrm{KL}}(\tilde{V}_{20})$, comes from enforcing the Klotz relationship on the left ventricle.

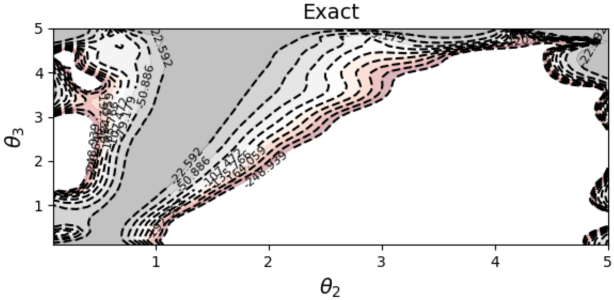
A first attempt: the non empirical Klotz prior



Match these with **product of experts**: $\mathcal{F} = \int \pi_E(\tilde{V}_{20})\pi_{\mathrm{KL}}(\tilde{V}_{20})d\tilde{V}_{20}$.

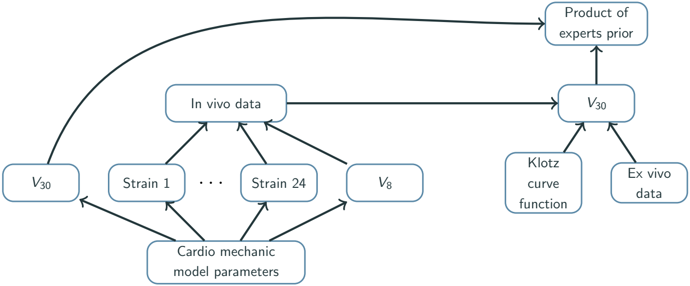
Problem with the non empirical Klotz prior

Ridge in θ_3 direction.



Let us try an alternative formulation...

A second attempt: the empirical Klotz prior



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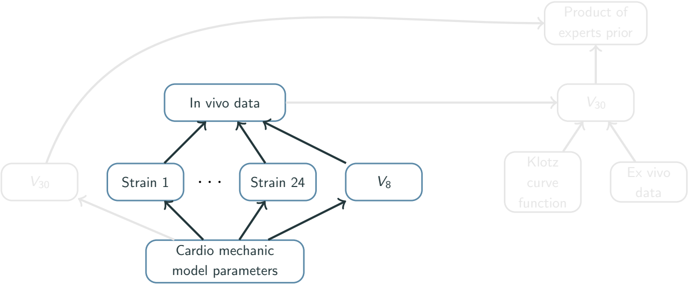
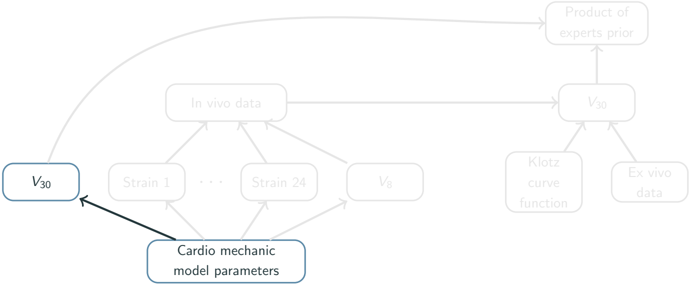


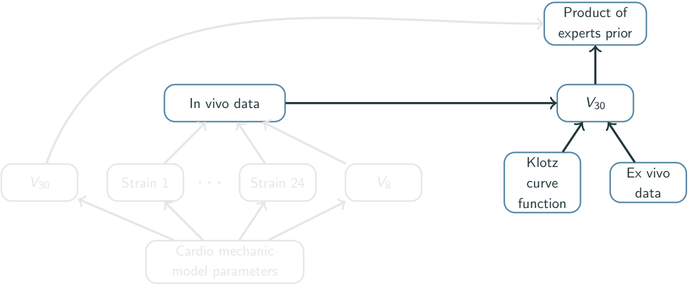
Likelihood function for in vivo data comes from emulated cardiac model.

A second attempt: the empirical Klotz prior



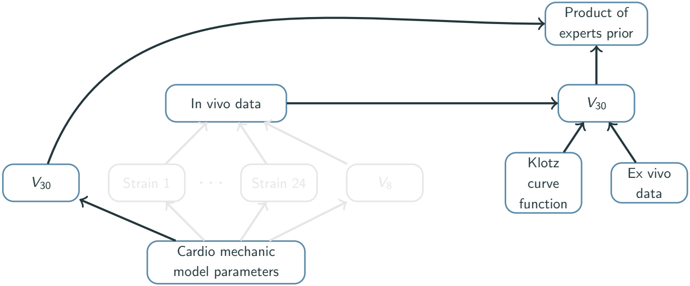
A prediction of V_{30} comes from a pressure 30 volume emulator.

A second attempt: the empirical Klotz prior



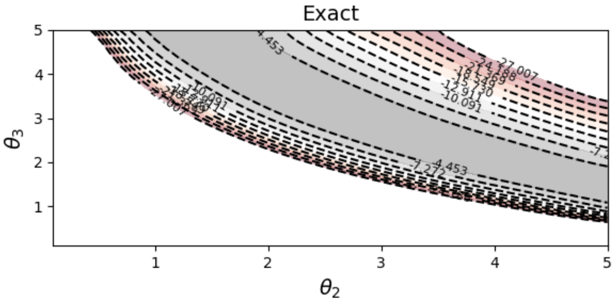
A prediction of volume at pressure 30 from Klotz function, this time related to the in vivo volume measurement.

A second attempt: the empirical Klotz prior



Match with product of experts: now we have an empirical Klotz prior (relies on the measured volume)

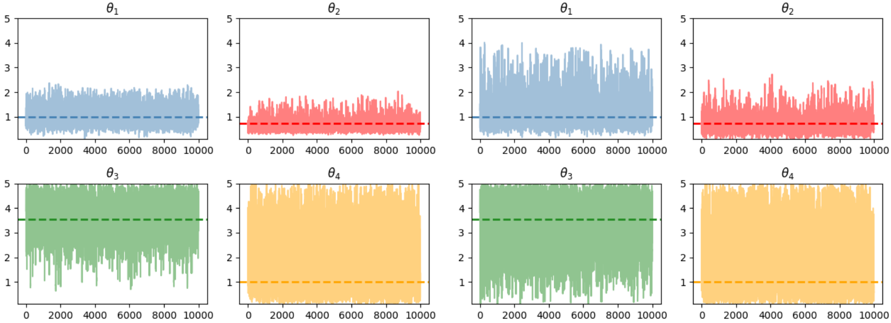
Assessing performance of the Klotz prior



Ridge in the prior is aligned with the θ_2 axis.

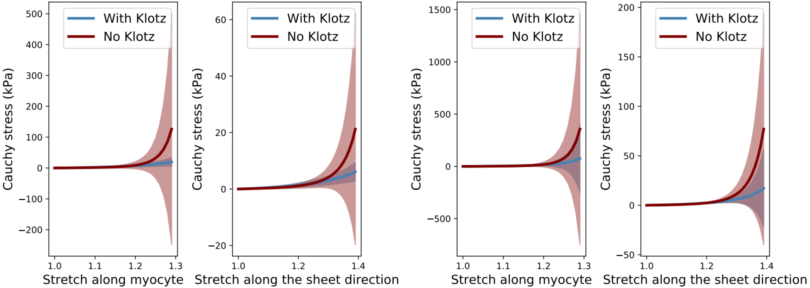
Does Empirical Klotz make a difference?

Yes, if our data are generated in line with the Klotz curve



But we do not know how closely the in vivo heart follows the Klotz curve

How about real data?



Summary so far

- The parameters from the reparameterized HO law are difficult to estimate
- Klotz is probably not the answer to the problem—do we really want to rely so heavily on ex vivo data?
- Instead, we should try new parameterizations
- Or accept lack of identifiability and try to use only those parameters we can learn

Plan

Alternative parameterization

$$
\begin{aligned}
\boldsymbol{\Psi} &= \frac{a}{2b}\left[\exp\left\{b\left(I_1 - 3\right)\right\} - 1\right] \\
&+ \sum_{i \in \{\mathrm{f},\mathrm{s}\}} \frac{a_i}{2b_i}\left[\exp\left\{b_i\left(I_{4i} - 1\right)^2\right\} - 1\right] \\
&+ \frac{a_{\mathrm{fs}}}{2b_{\mathrm{fs}}}\left\{\exp\left(b_{\mathrm{fs}} I_{8\mathrm{fs}}^2\right) - 1\right\}
\end{aligned}
$$

$a, b, a_{\mathrm{f}}, b_{\mathrm{f}}$ inferred, $a_{\mathrm{s}}, b_{\mathrm{s}}, a_{\mathrm{fs}}, b_{\mathrm{fs}}$ constant

a and a_f are more identifiable, can we use these for predicting tissue health?

Thank you!

PC performance