Uncertainty Quantification in Prospective and Predictive Patient Specific Cardiac Models

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University of Sheffield
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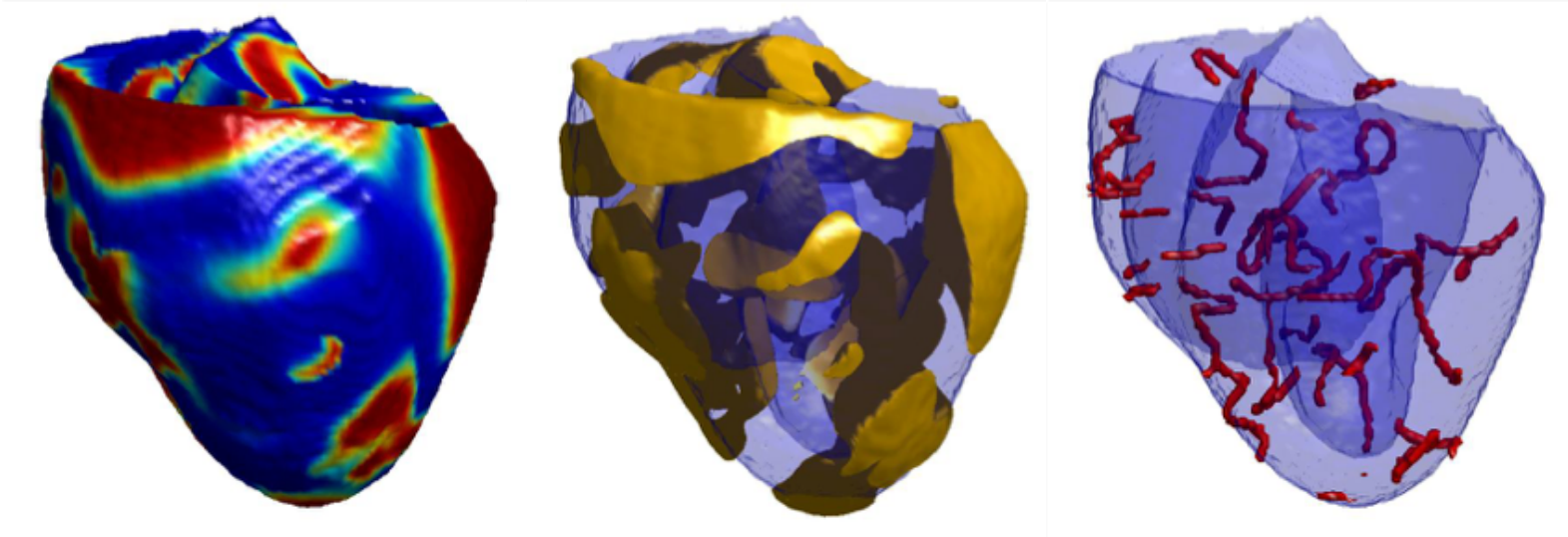
EPSRC
Engineering and Physical Sciences Research Council

Project overview

Atrial fibrillation



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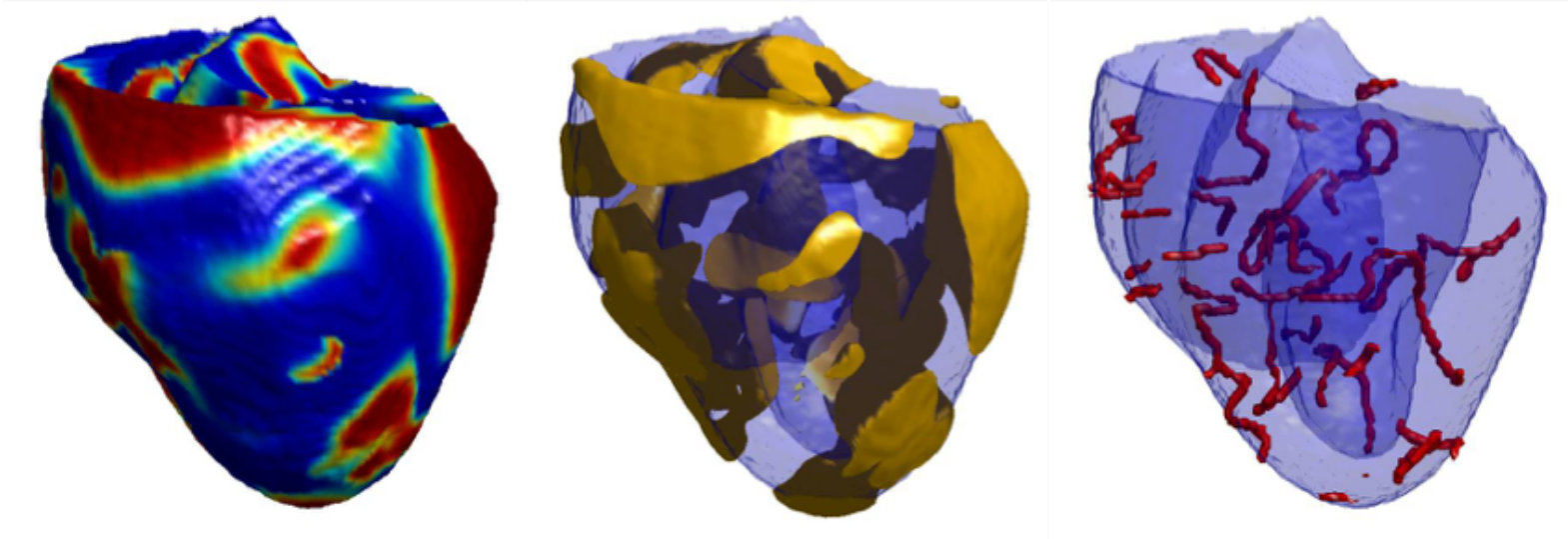


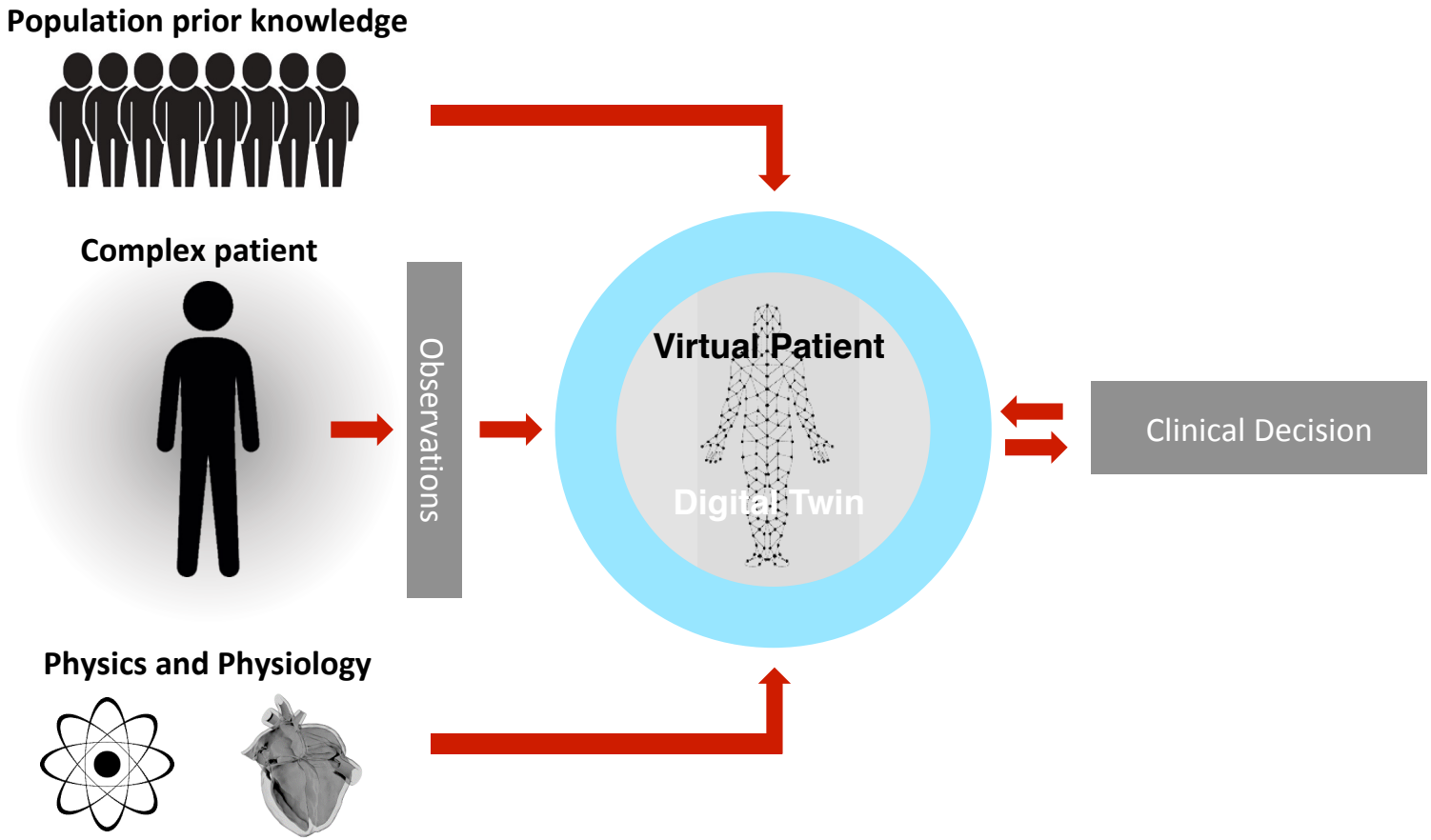
Atrial fibrillation (AF) - rapid and uncoordinated electrical activation (arrhythmia) leading to poor mechanical function.

- Affects around 610,000 people in UK.
- Catheter ablation removes/isolates pathological tissue that sustain/initiate AF.
- 40% of patients subsequently experience atrial tachycardia (AT).

Project overview II

Patient Specific Cardiac Models

Aim: predict whether an AF patient will develop AT following ablation, infer the reentry pathways, and then guide the surgical ablation to treat for both in a single procedure.



But how confident are we in our prediction

Project overview III

To infer reentry pathways we

- use a complex simulator (encoding scientific knowledge) to see whether AT can be maintained

This requires

- Left atrium geometry, spatially distributed tissue properties, fibre directions, etc for the individual patient

all of which are unknown.

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Workflow:

- MRI to build patient specific left atrium mesh, identify fibrosis.
- Electrophysiology study to learn electrical activation map, conduction velocities
- Interpolate to entire LA, allowing conduction velocity and restitution curves to be calculated
- Use these to inform the heterogeneity in our prior distribution of the tissue properties
- Build an emulator of the simulator
- Find our posterior distribution over tissue parameters etc
- Predict AT pathways, make clinical recommendations

Uncertainty quantification

Project aim is characterize and combine the uncertainties to make decisions that take our lack of knowledge into account.

- Noisy data, recorded at a small number of sparse, uncertain locations
- Large number of unknown parameters
- Complex simulator (limited computational resource)
- Misspecification/discrepancy

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$$\mathbb{P}(E\text{vent}|D\text{ata}) = \int \mathbb{P}(E|\theta, x, f)\pi(\theta, x, f|D)d\theta dxdf$$

where

$$\pi(\theta, x, f|D) \propto \pi(D|\theta, x, f)\pi(\theta)\pi(x)\pi(f)$$

We need to characterize variability at the

- population level $\pi(\theta), \pi(x)$ etc
- individual level $\pi(\theta, x, f, ...|D)$ – may need to be done online
- and the physics/simulator $\pi(D|\theta, x, f)$

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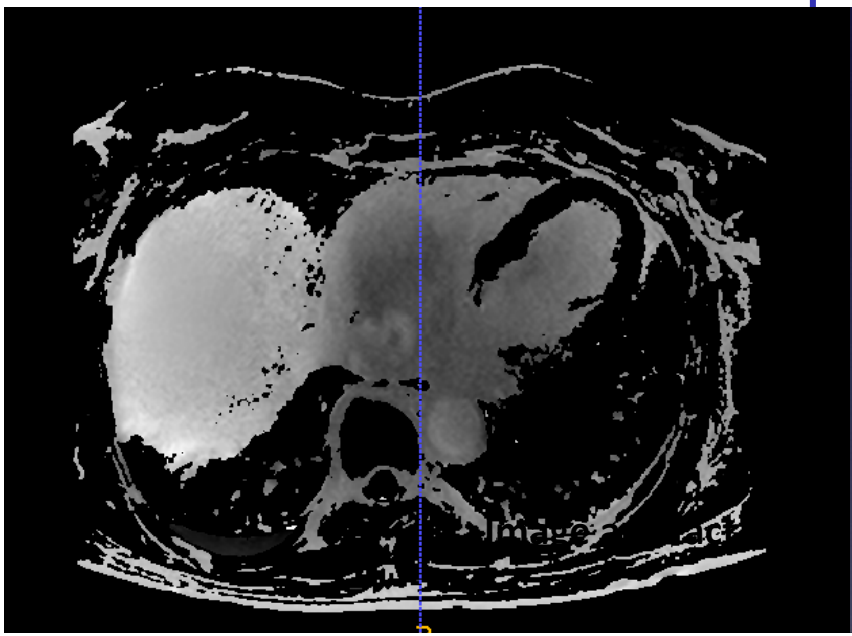
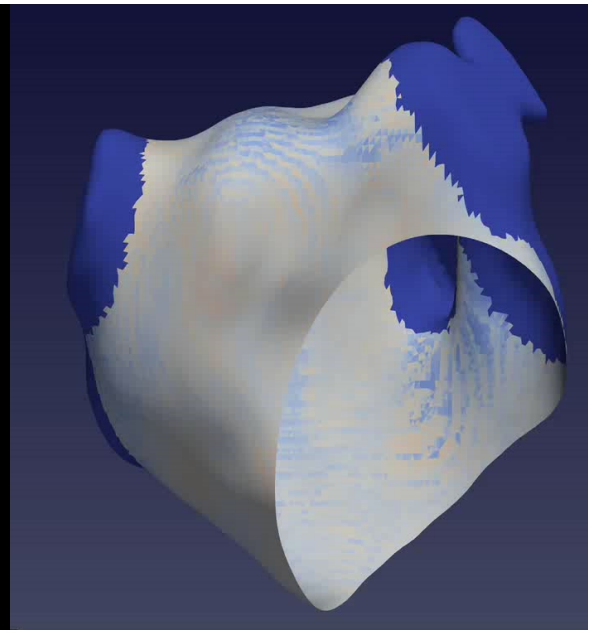
Pragmatic approach necessary.

Problem 1: Uncertain shape - Cesare Corrado





Measure shape $x_{obs} \in \mathbb{R}^D$ where $D \sim 10^5$

$$x_{obs} = x_{true} + e' \quad \text{where} \quad e' \sim N(0, \Sigma')$$

How can we parsimoniously describe the variation in atrial shapes in the populations $x^1_{true}, \ldots, x^n_{true}$?

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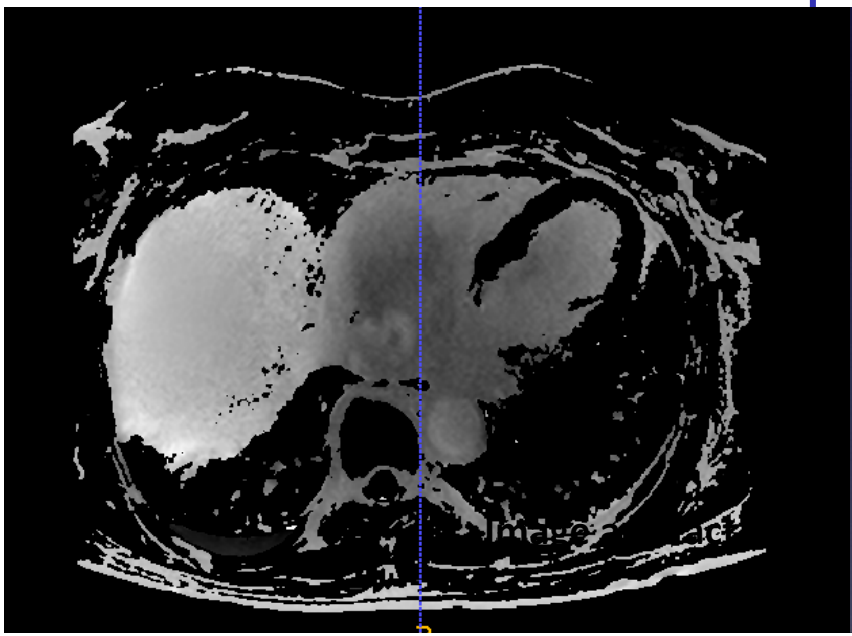

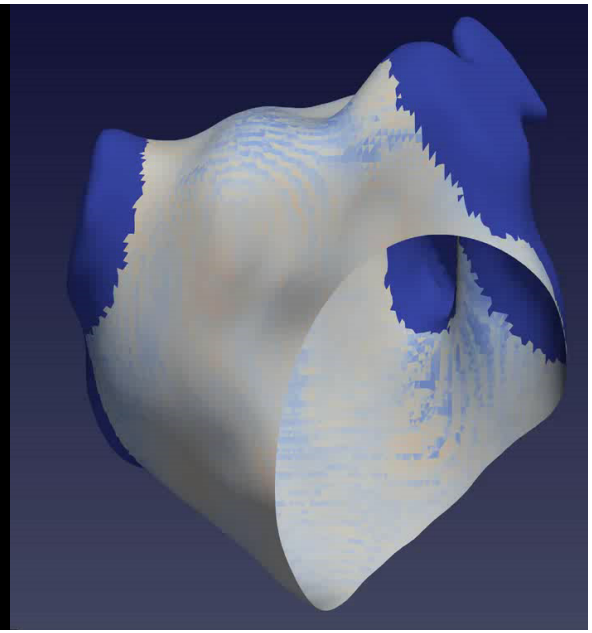

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How can we parsimoniously describe the variation in atrial shapes in the populations $x^1_{true}, \ldots, x^n_{true}$?
Working in the standard basis is infeasible

$$x_{obs} = \sum_i x_{obs,i} v_i \quad \text{where} \quad (v_i)_j = \delta_{ij}$$

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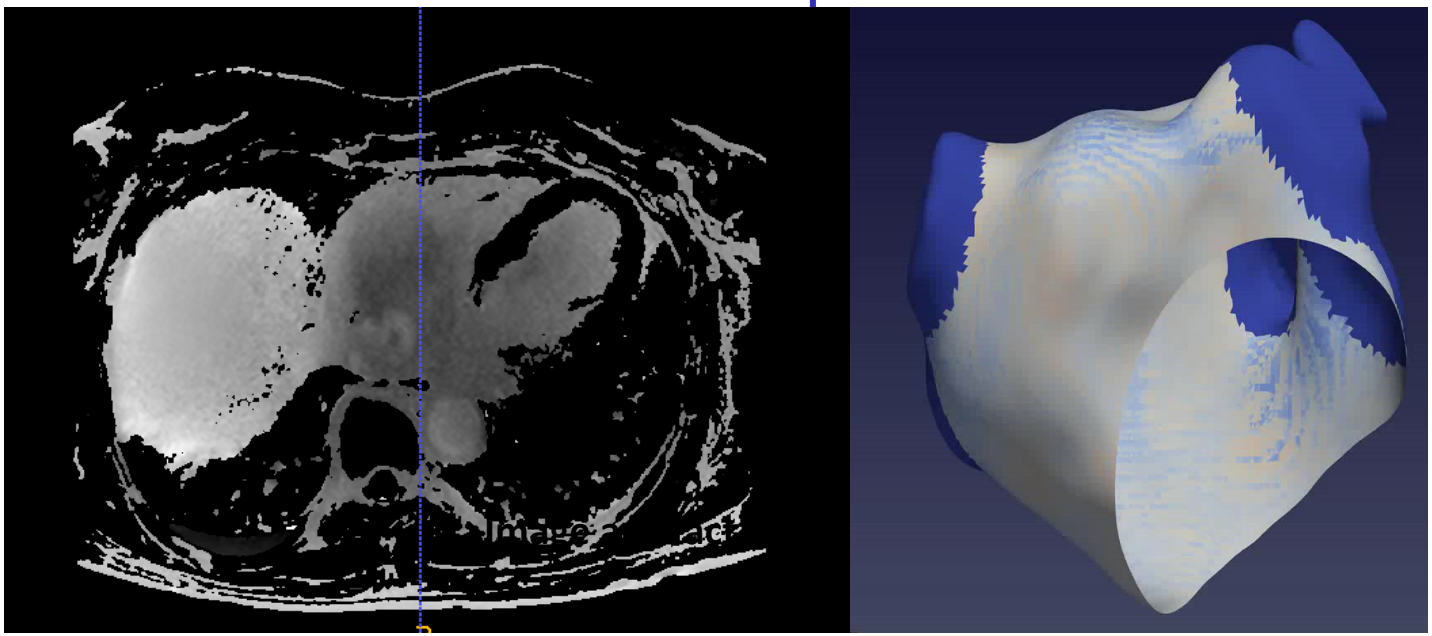

Aim: change into a basis that allows variation to be described in lower dimension

$$x_{obs} = \mu + \sum_{i=1}^{d} \lambda_i u_i + e \quad \text{where} \quad e \sim N(0, \Sigma)$$

where $\lambda = (\lambda_1, \ldots, \lambda_d)^\top$ is the new coordinate describing variation in $\mathbb{R}^d$ (where $d \ll D$) for the orthonormal basis $\{u_1, \ldots, u_d\}$.

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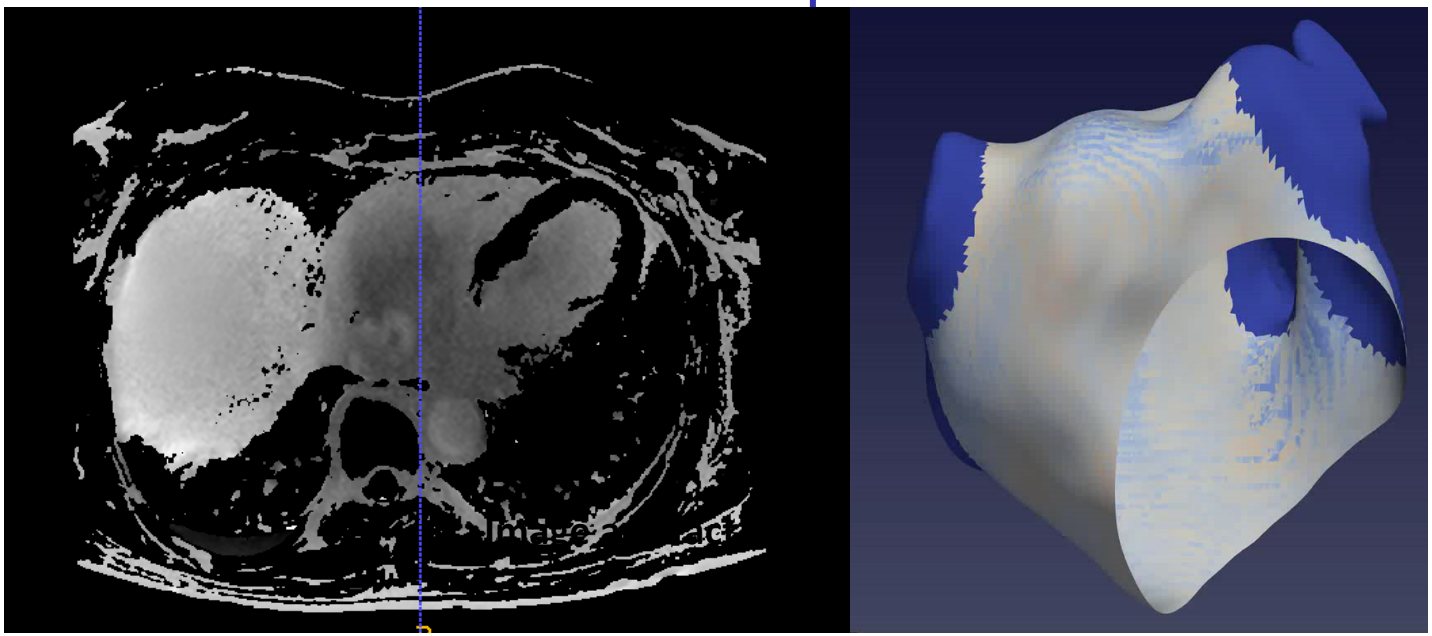

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Determine the reduced basis, error variance Σ and prior $\lambda \sim N(0, \Sigma_\lambda)$ from the population. cf Andrew McCulloch's talk

Use Bayesian approach to characterize uncertainty about individual anatomy via

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- PCA basis is optimal
  - ie let $U = [u_1, \ldots, u_d] \in \mathbb{R}^{D \times d}$ be the first d eigenvectors of $Var_p(x)$. Then $\lambda = U^\top x = (\langle u_1, X \rangle, \ldots, \langle u_d, X \rangle)^\top$.
  - u_i maximizes $u_i^\top Var_p(x) u_i$ s.t. $\langle u_i, u_j \rangle = \delta_{ij}$
  - Equivalently, $UU^\top X$ is the best rank d approximation to X (in the Frobenius norm $\sim L_2$).

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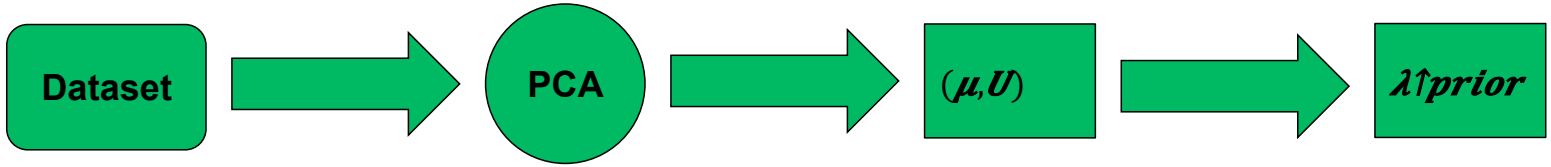
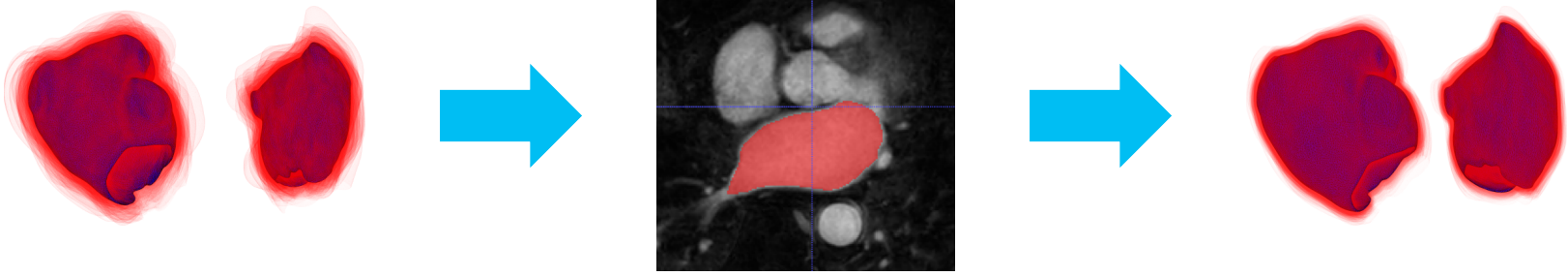
But for other purposes (eg in supervised problems) PCA can give poor dimension reduction.

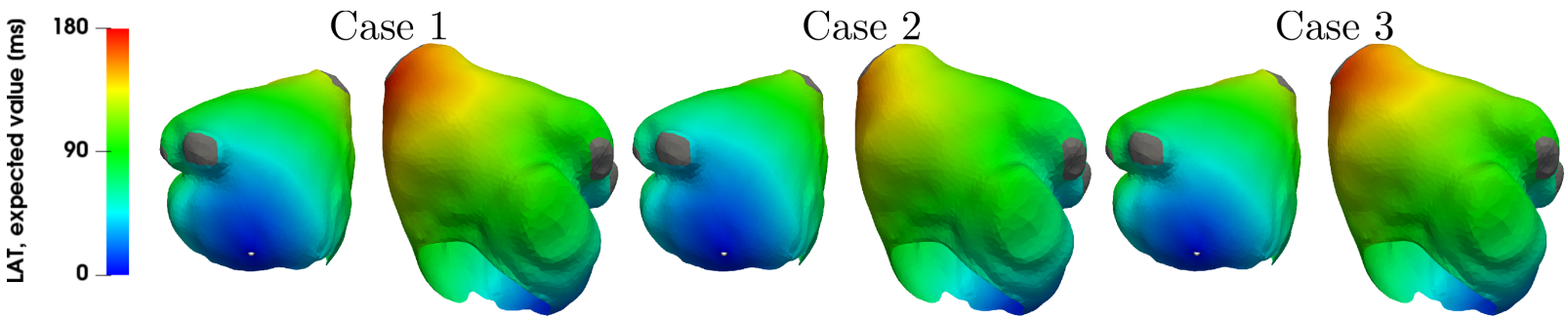




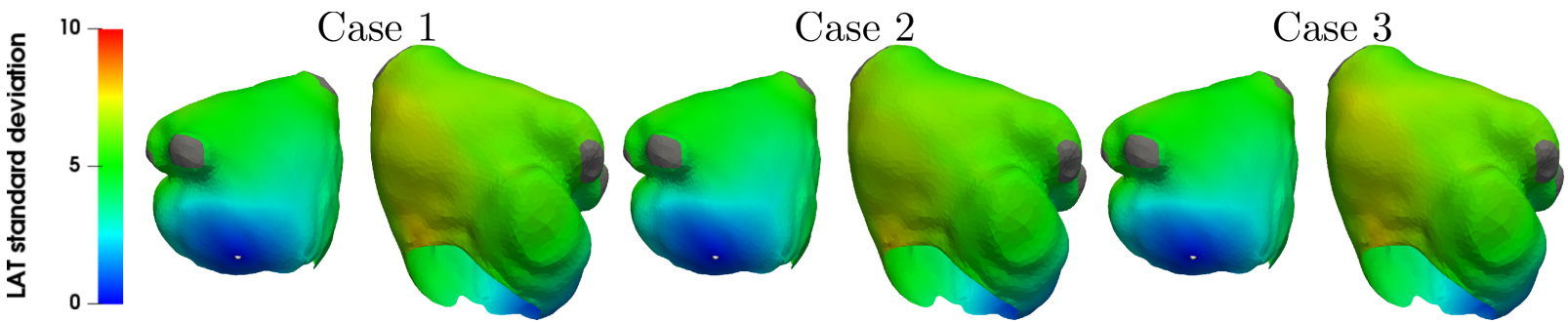
Population Mean and shape (λ) Priors

New Measure

Update Shape (λ) Posterior Distribution



Expected value



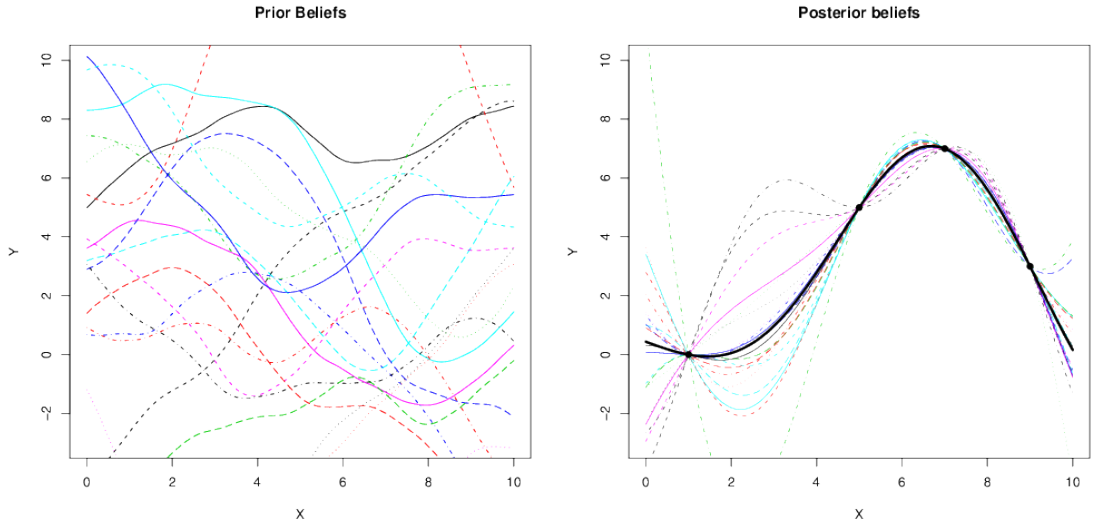
Standard deviation

Problem 2: Interpolation of LAT - Sam Coveney

Aside: Gaussian processes (GP)

Regression: given data $\{x_i, y_i = f(x_i)\}_{i=1}^n$ learn f.

- x is location on the atrium, $f(x)$ is activation time
- x is a simulator parameter, $f(x)$ a complex simulator prediction.



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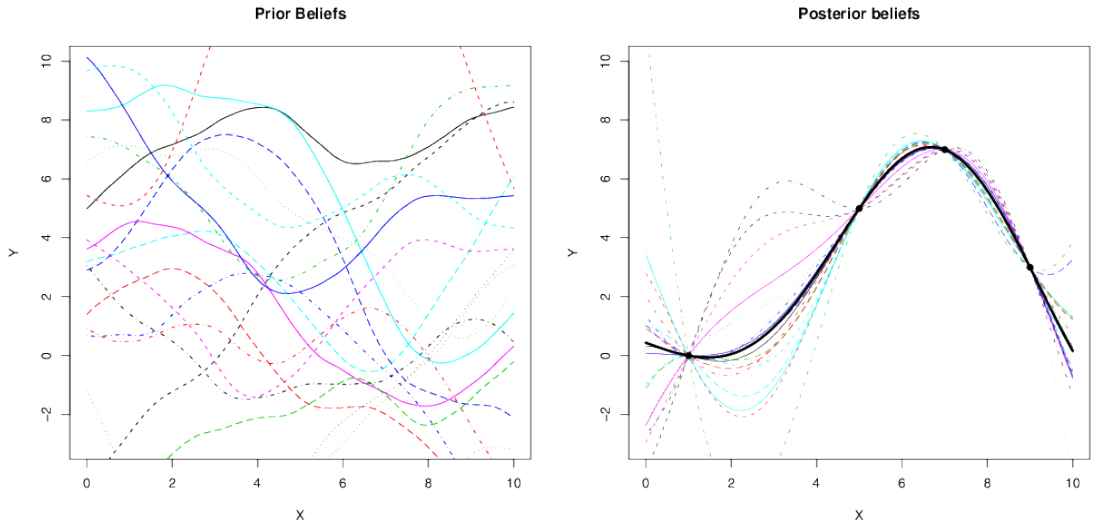

GPs can be thought of as probabilistic models of functions.

A GP is a random process indexed by $x \in \mathcal{X}$ say, such that for every finite set of indices, $x_1, \ldots, x_n$,

$$\mathbf{f} = (f(x_1), \ldots, f(x_n))$$

has a multivariate Gaussian distribution.

Key choice is the covariance/kernel function $k(x, x') = \mathbb{C}\text{ov}(f(x), f(x'))$

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- Closed under any linear operation. If $\mathcal{L}$ is a linear operator, then

$$\mathcal{L}f \sim GP(\mathcal{L}m, \mathcal{L}k\mathcal{L}^\top)$$

e.g. $\frac{df}{dx}$, $\int f(x)dx$, Af are all GPs. Can also analytically condition on $\mathcal{L}f = 0$, e.g. incompressible flow $\nabla \cdot \nabla f = 0$

Why use GPs? Answer 2: non-parametric/kernel regression

- Linear regression $y = x^\top \beta + \epsilon$ can be written solely in terms of inner products $x^\top x$.

$$\begin{aligned}
\hat{\beta} &= \arg\min ||y - X\beta||_2^2 + \sigma^2 ||\beta||_2^2 \\
&= (X^\top X + \sigma^2 I) X^\top y \\
&= X^\top (XX^\top + \sigma^2 I)^{-1} y \quad \text{(the dual form)}
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where $k : \mathcal{X} \times \mathcal{X} \to \mathbb{R}$ is a semi-positive definite function.
Kernel trick: lift x into infinite dimensional feature space by replacing inner products $x^\top x'$ by $k(x, x')$.
Never evaluate the features, only the $n \times n$ kernel matrix.

$$\hat{y}' = m(x') = \sum_{i=1}^{n} \alpha_i k(x, x_i)$$

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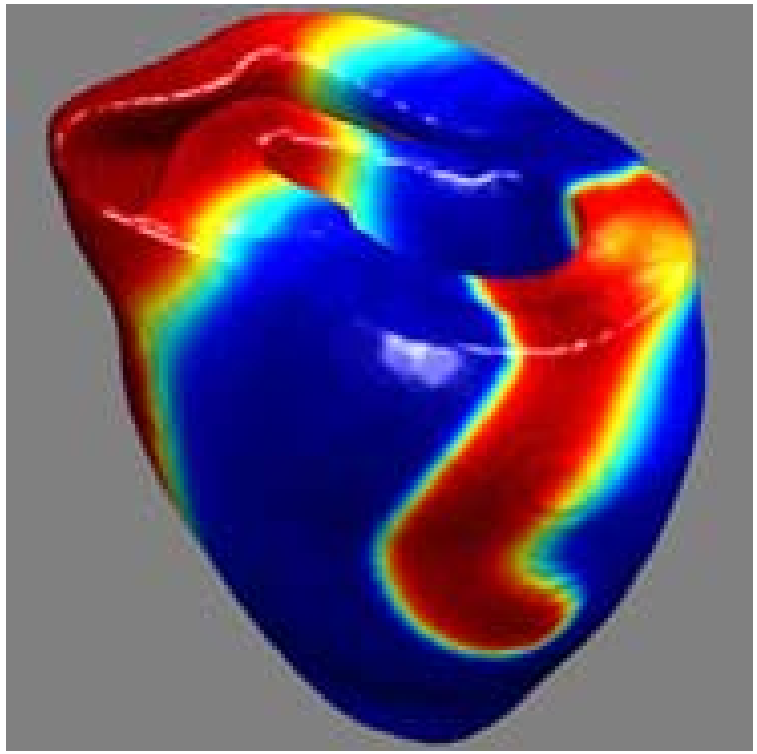
Although our simulator may not lie in the RKHS defined by k, this space is much richer than any parametric regression model (possibly dense in some set of continuous functions)

- more likely to contain an element close to the simulator than any finite class of models

Local activation time

Red: 'active' cardiac tissue Blue: 'inactive' cardiac tissue



We want to know the time of arrival of the 'electrical wave front' - the Local Activation Time (LAT).

- An electrophysiology (EP) study performed by inserting catheters and electrodes on left atrium surface, to measure electrical activity.

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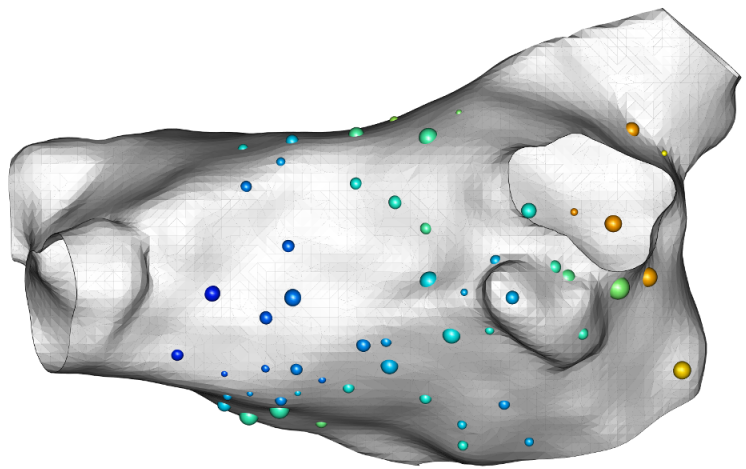

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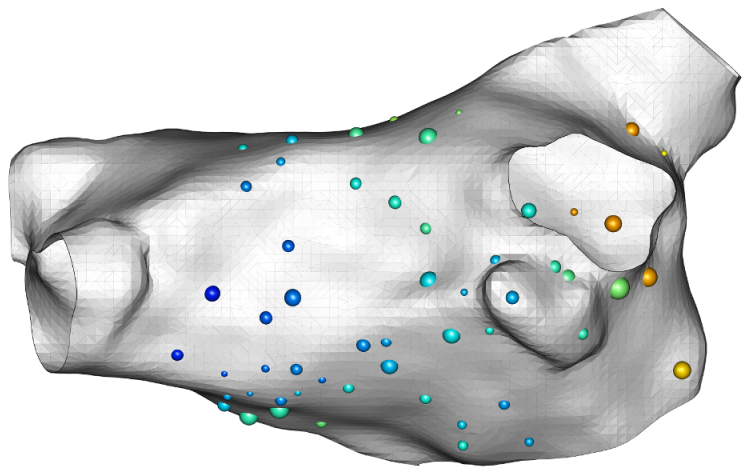

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How can we interpolate to other locations?

$$LAT_{obs}(x) = \mathrm{LAT}_{true}(x) + \epsilon_{EGM} + \epsilon_{position}$$

GP interpolation

We want to model

$$LAT(x) \sim GP(m(x), k(x, x'))$$

but standard approaches won't work on complex atrial manifolds

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We want the interpolation to take into account distance on the manifold travelled by electrical wave.

- Defining a valid positive definite covariance function on the manifold is hard!

INLA-SPDE approach: Lindgren, Rue, Lindstrom (2011)

Coveney *et al.* 2019

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$$(\kappa^2 - \Delta)^{\alpha/2} LAT(x) = W(x)$$

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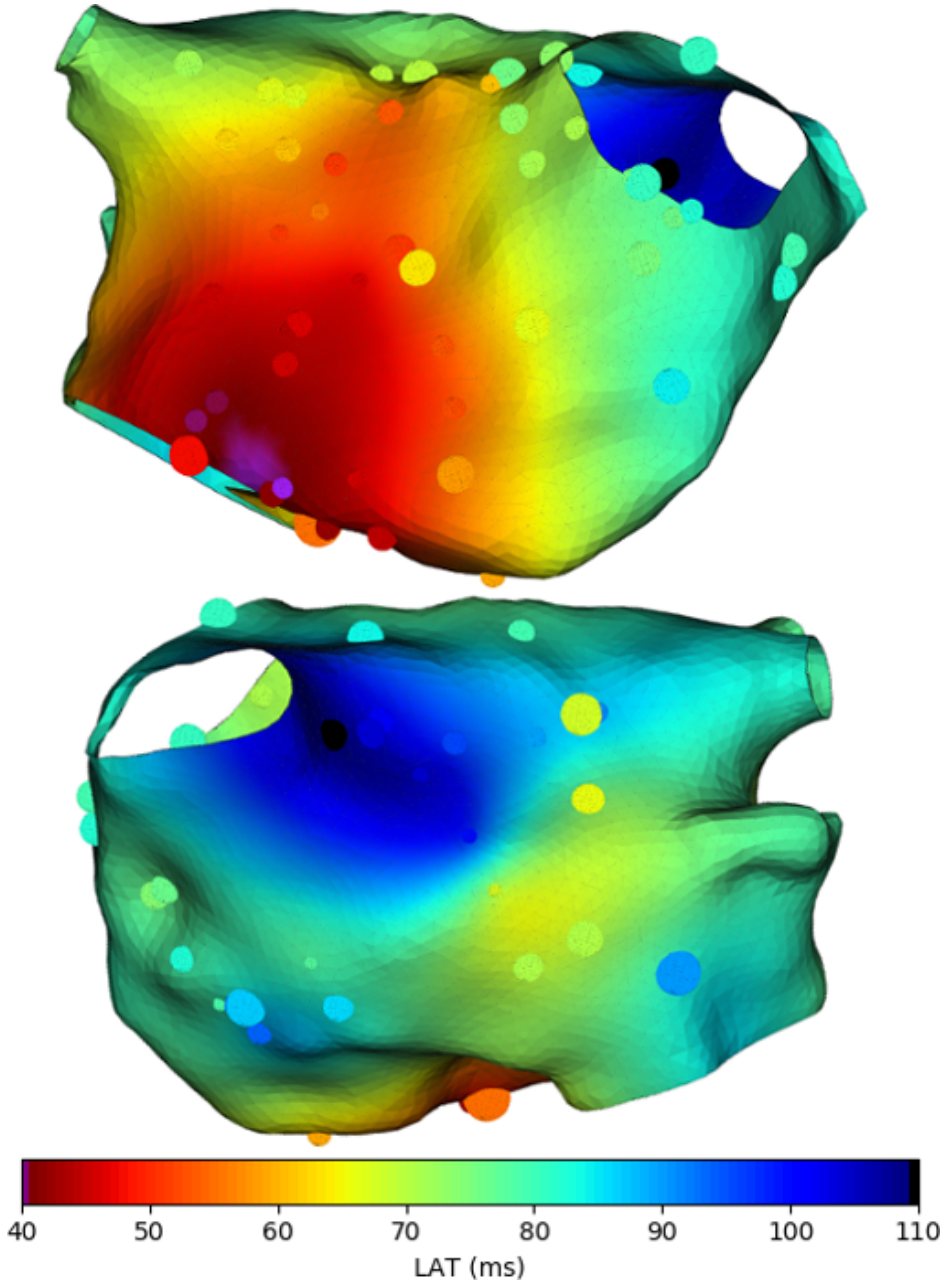
$$LAT(x) = \sum_{k=1}^{n} w_k \psi_k(x)$$

with $w_k \sim N(0, \tilde{Q}^{-1})$ where $\tilde{Q}$ is sparse. Note

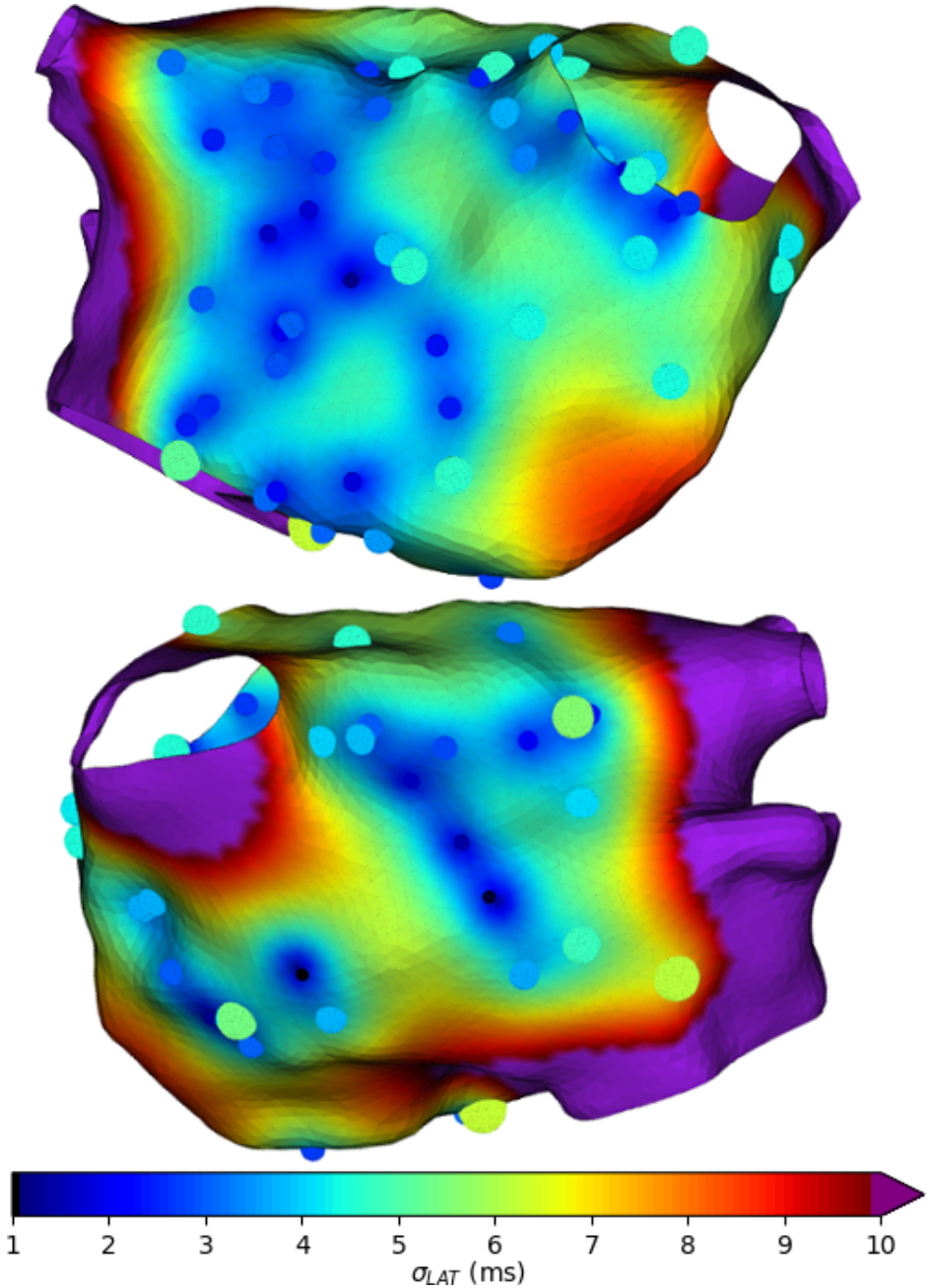
$$LAT(\cdot) \sim GP(0, Q^{-1})$$

for some Q

Results - mean



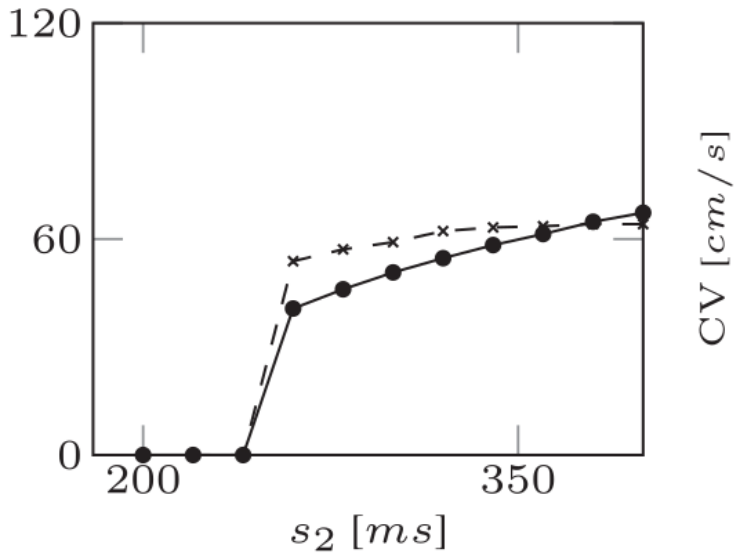
Results - standard deviation



S1-S2 interpolation

The **electrical restitution curve** describes the recovery of action potential duration as a function of the interbeat interval.

- During an EP study the heart is 'paced' at a regular S1 interval.
- Premature interbeats introduced at interval S2
- As the S2 interval shortens the heart tissue will eventually cease to recover in time to activate for both beats



S1-S2 interpolation

The EP study measures activation time at $\sim$30 locations and $\sim$ 10 S2 intervals. We use INLA-SPDE approach to interpolate LAT at the locations for a given S2 value.

- allows us to borrow strength from different S2 intervals to improve the interpolation?

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- allows us to borrow strength from different S2 intervals to improve the interpolation?

Simplest way is to add S2 as an input, and assume an AR(1) relationship between $LAT(x, S2_{i+1})$ and $LAT(x, S2_i)$

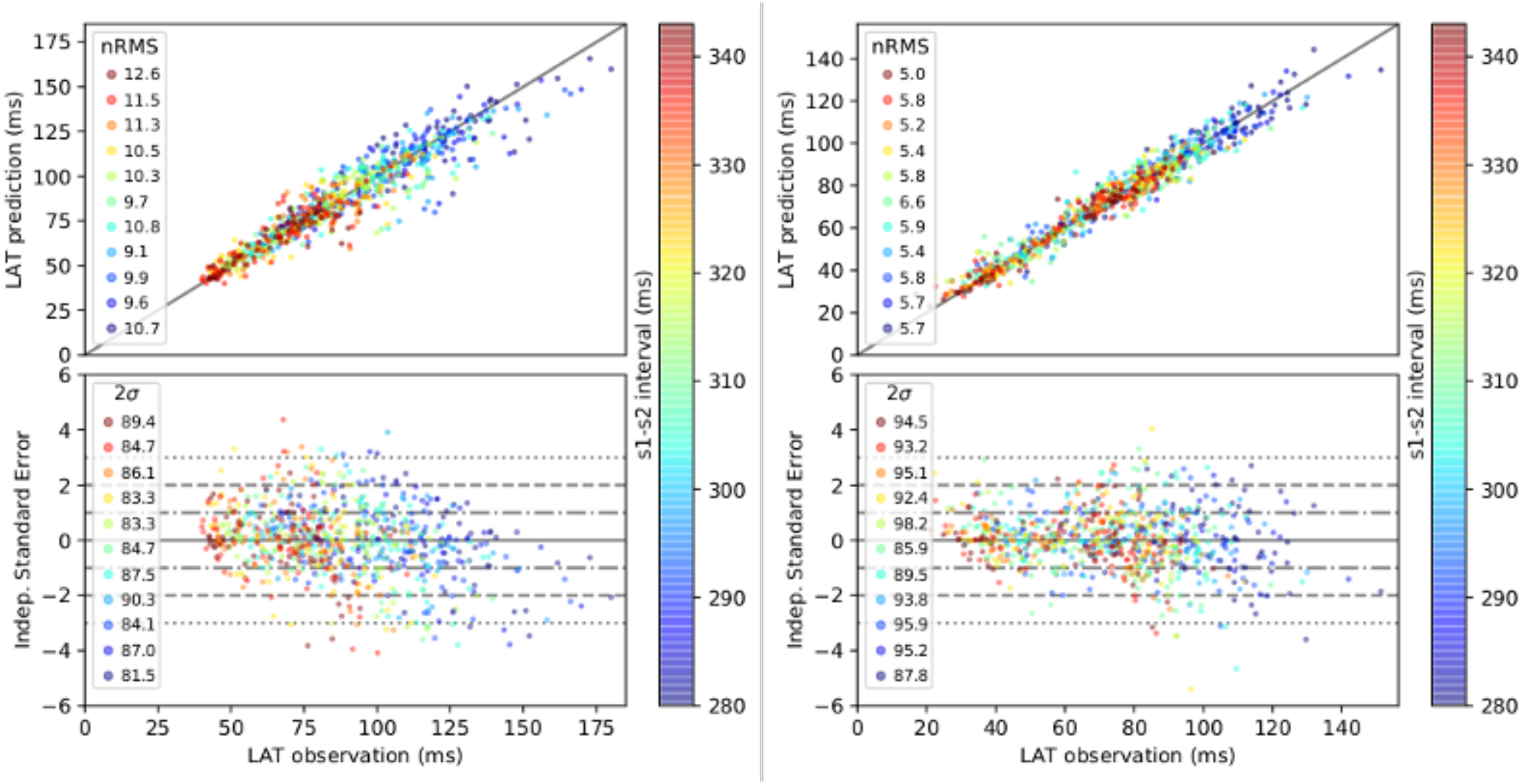
$$LAT(x, S2_{i+1}) \sim N(\rho LAT(x, S2_i), (1 - \rho^2)Q^{-1})$$

or more precisely

$$LAT(x, S2) \sim GP(0, Q_{S2}^{-1} \otimes Q^{-1})$$

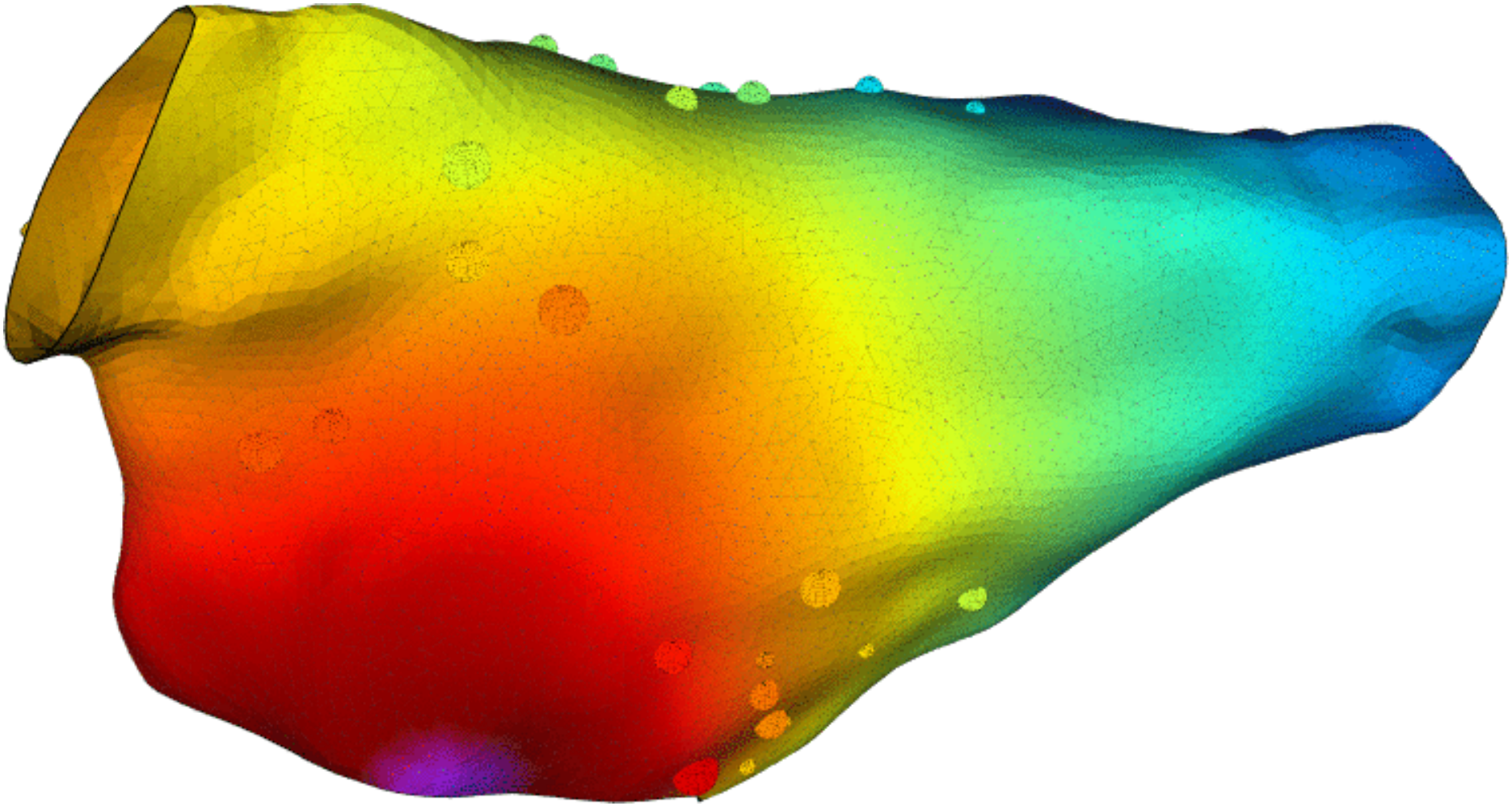
Cf Dirk Husmeier's talk with multi-output GPs.

Results: Cross validation



Opens interesting design questions around data collection protocols

Random samples



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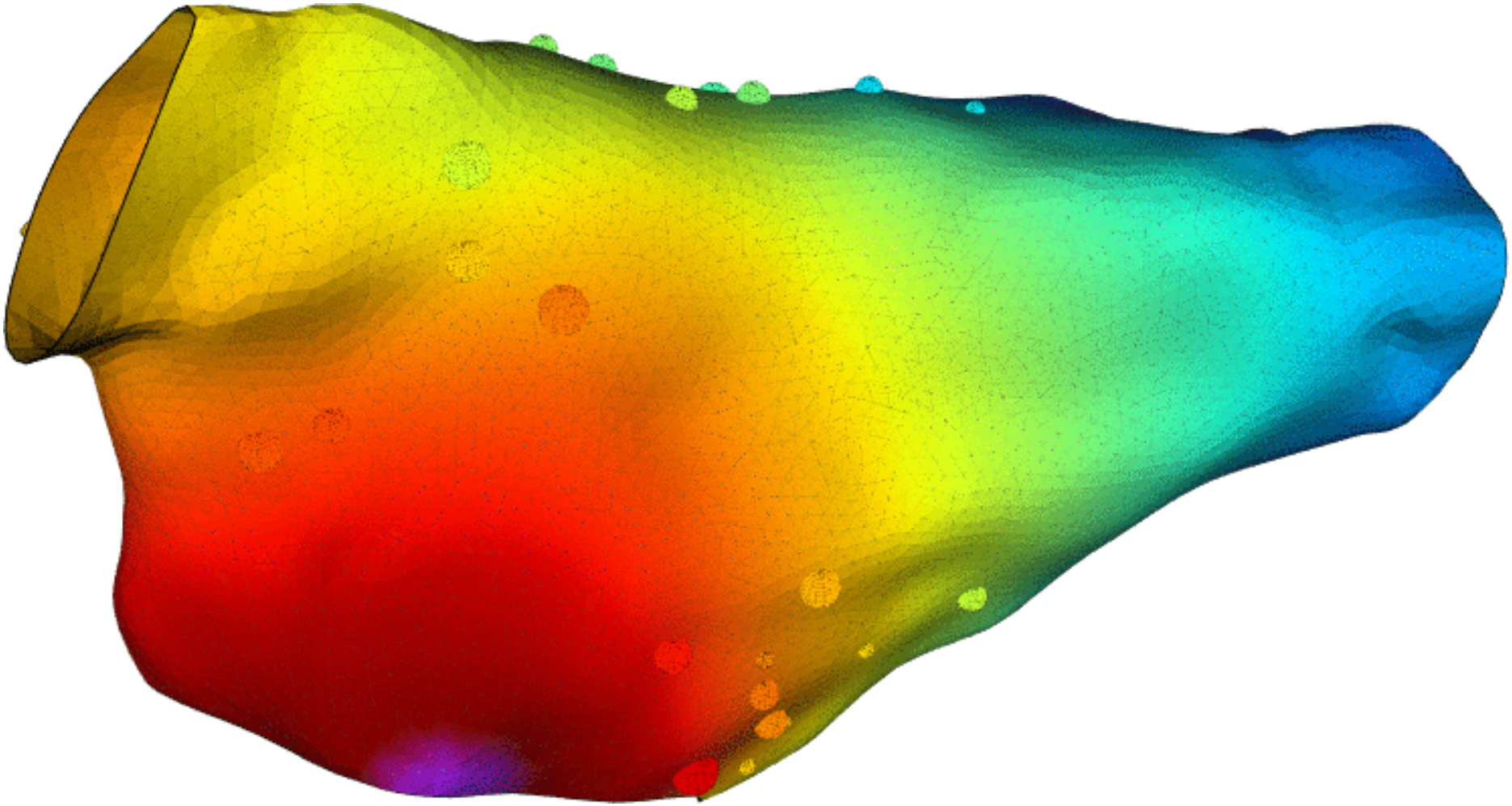

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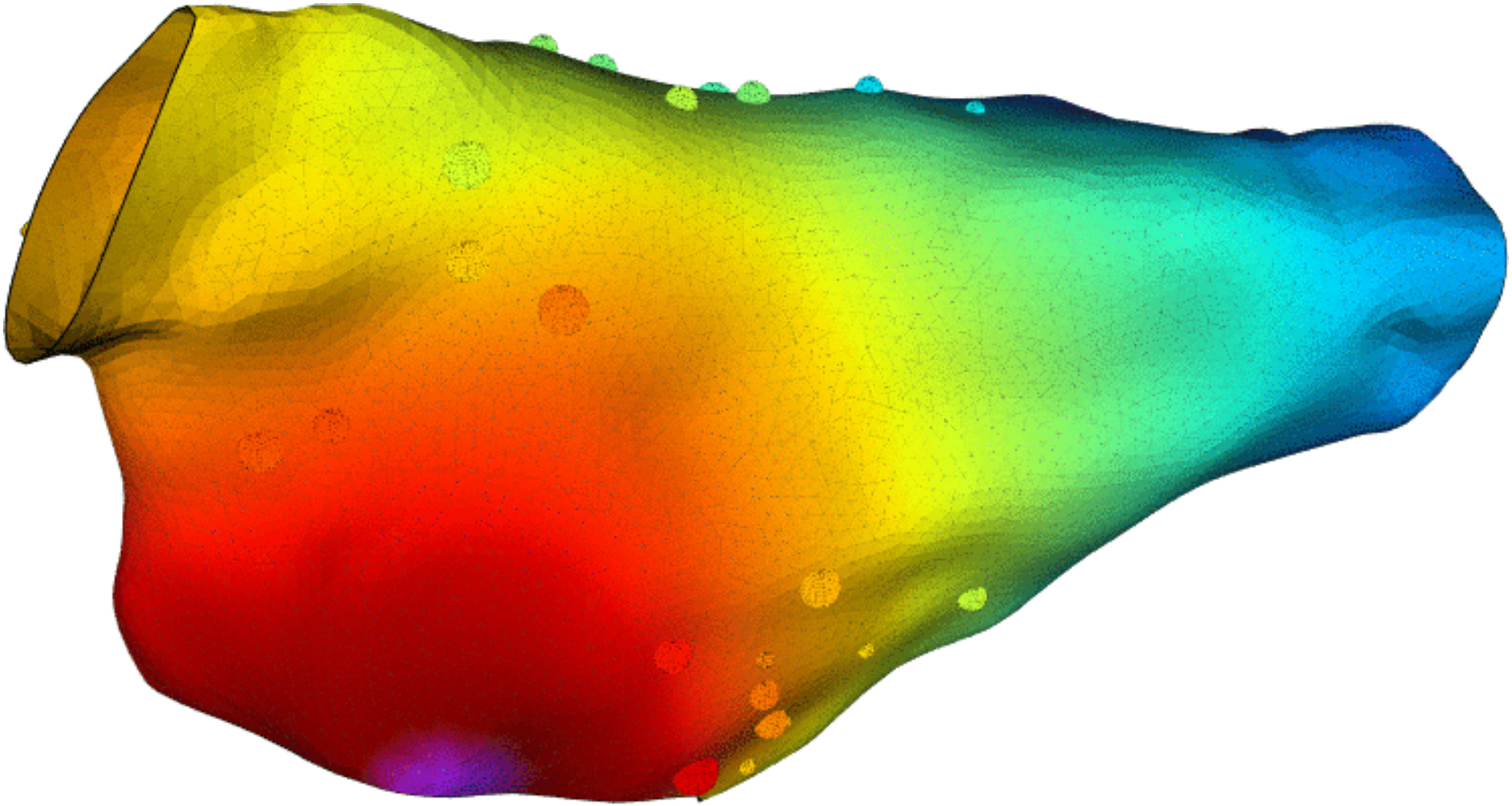

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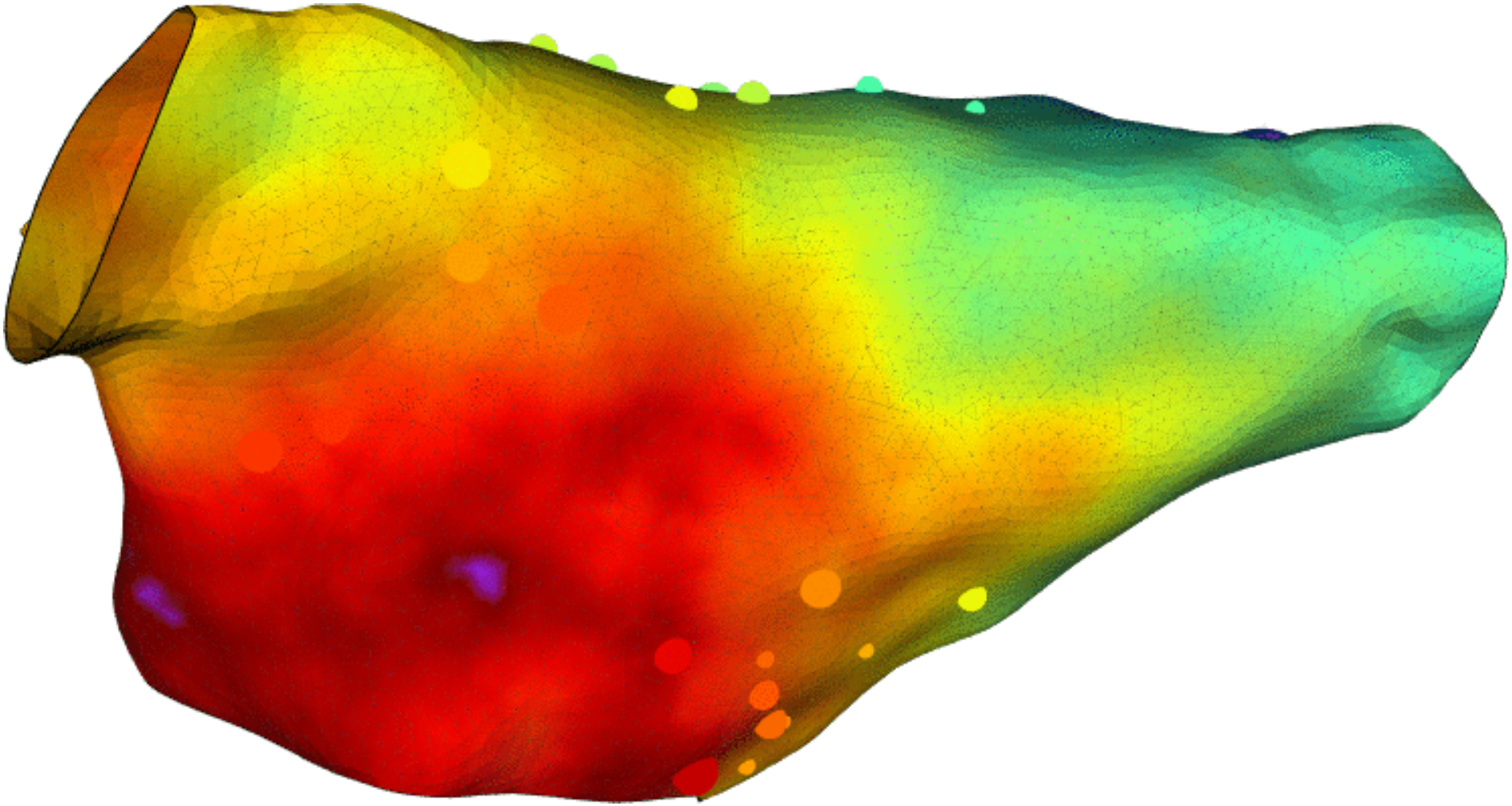

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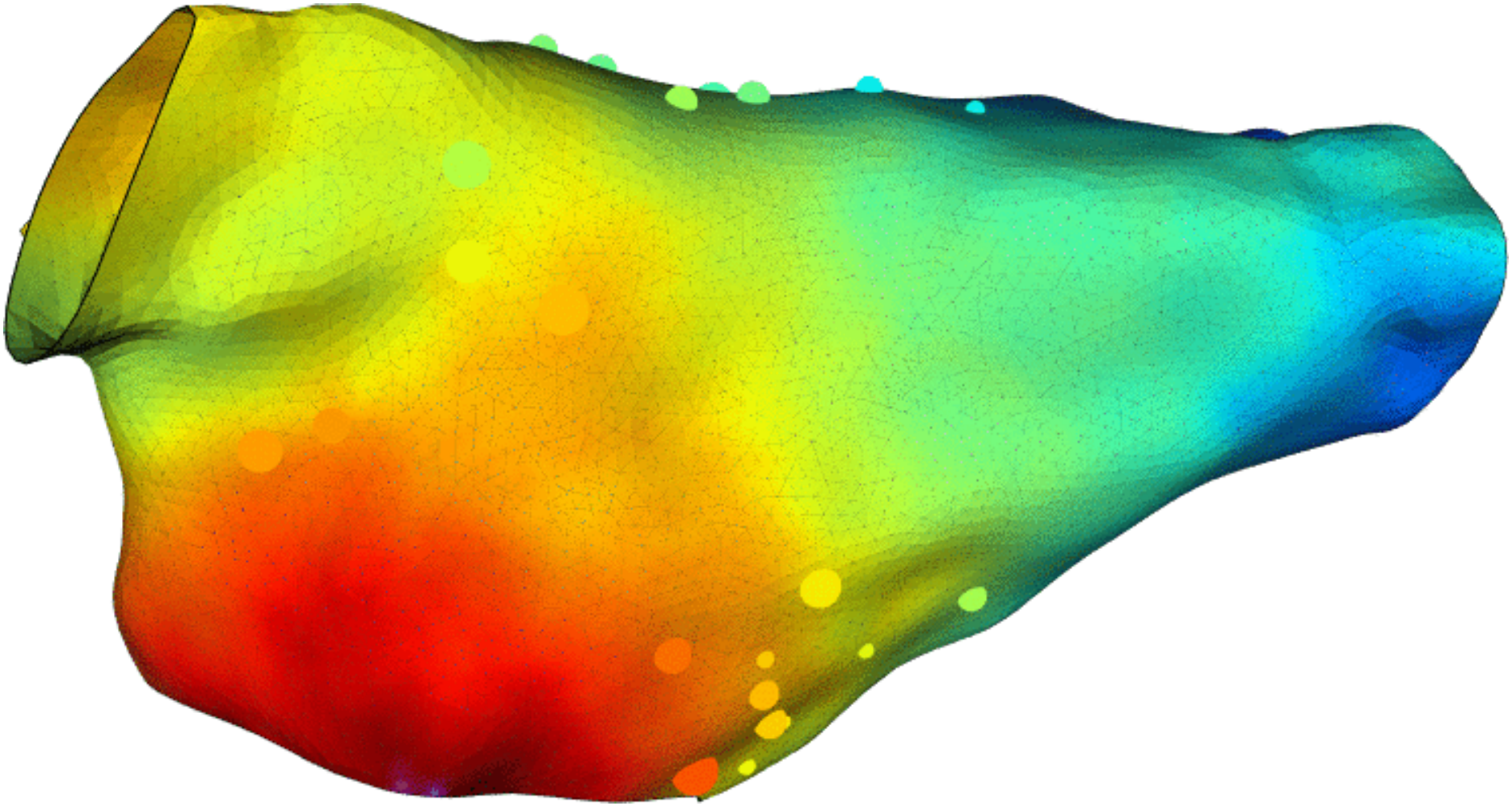

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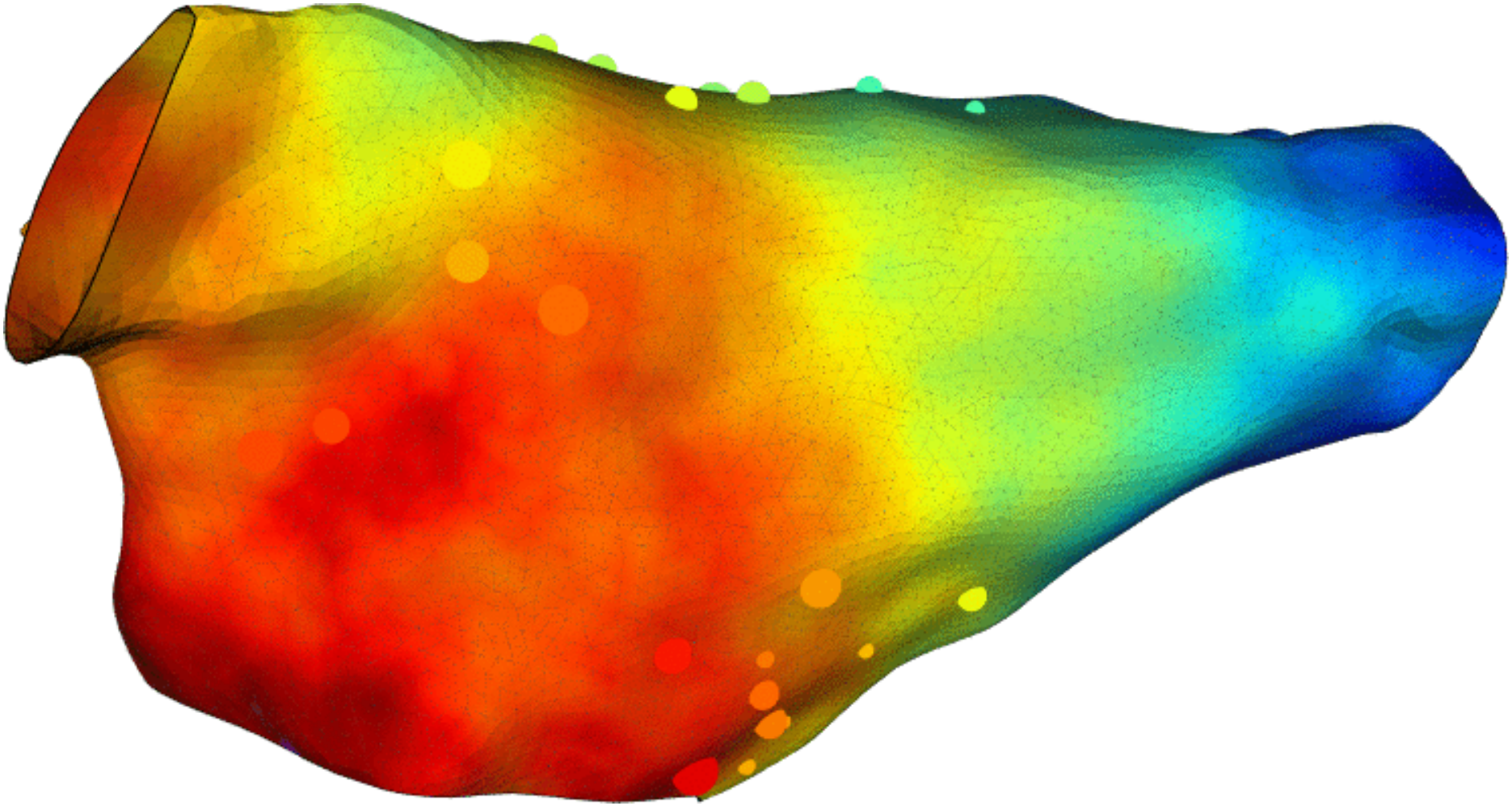

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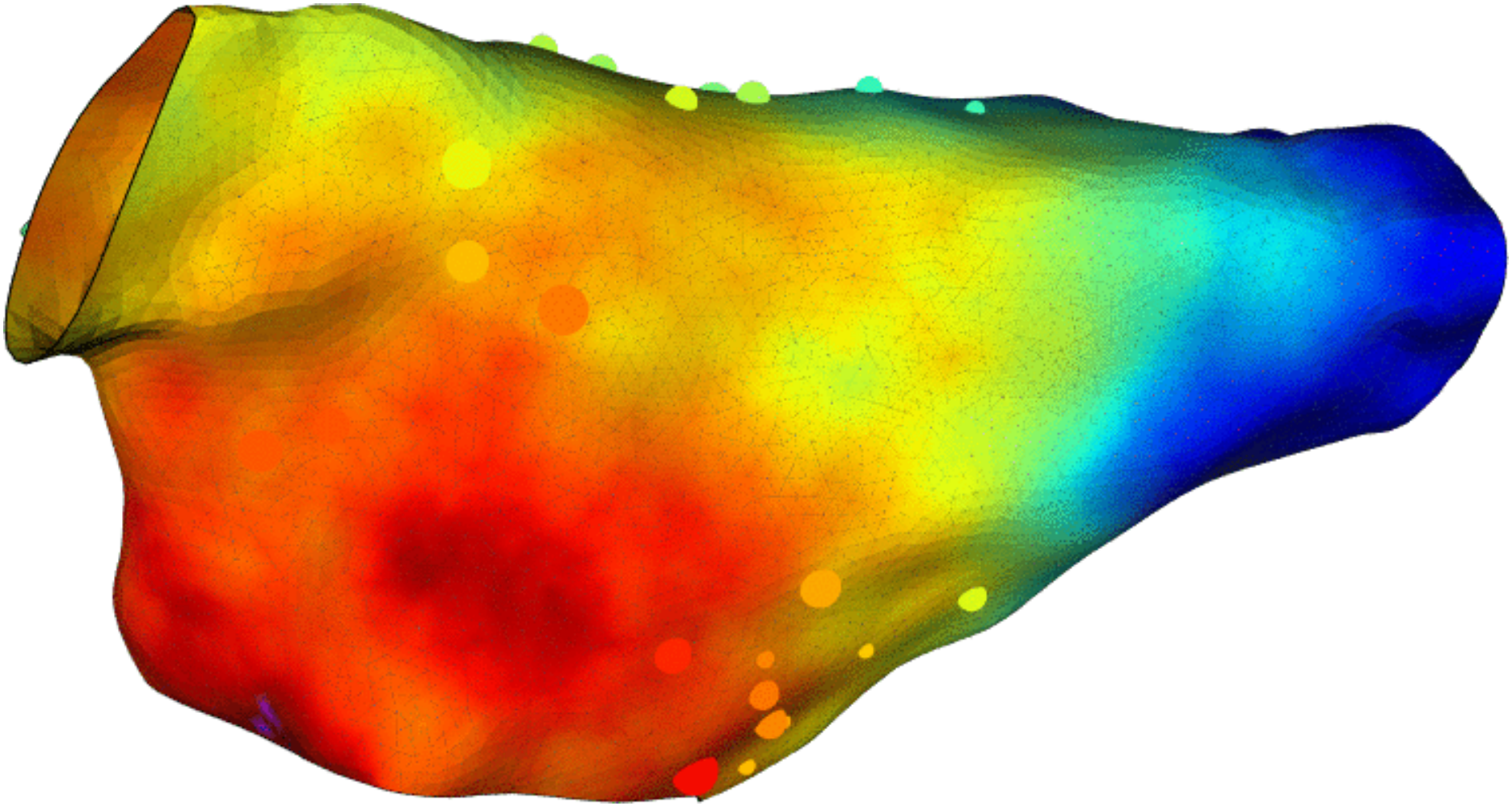

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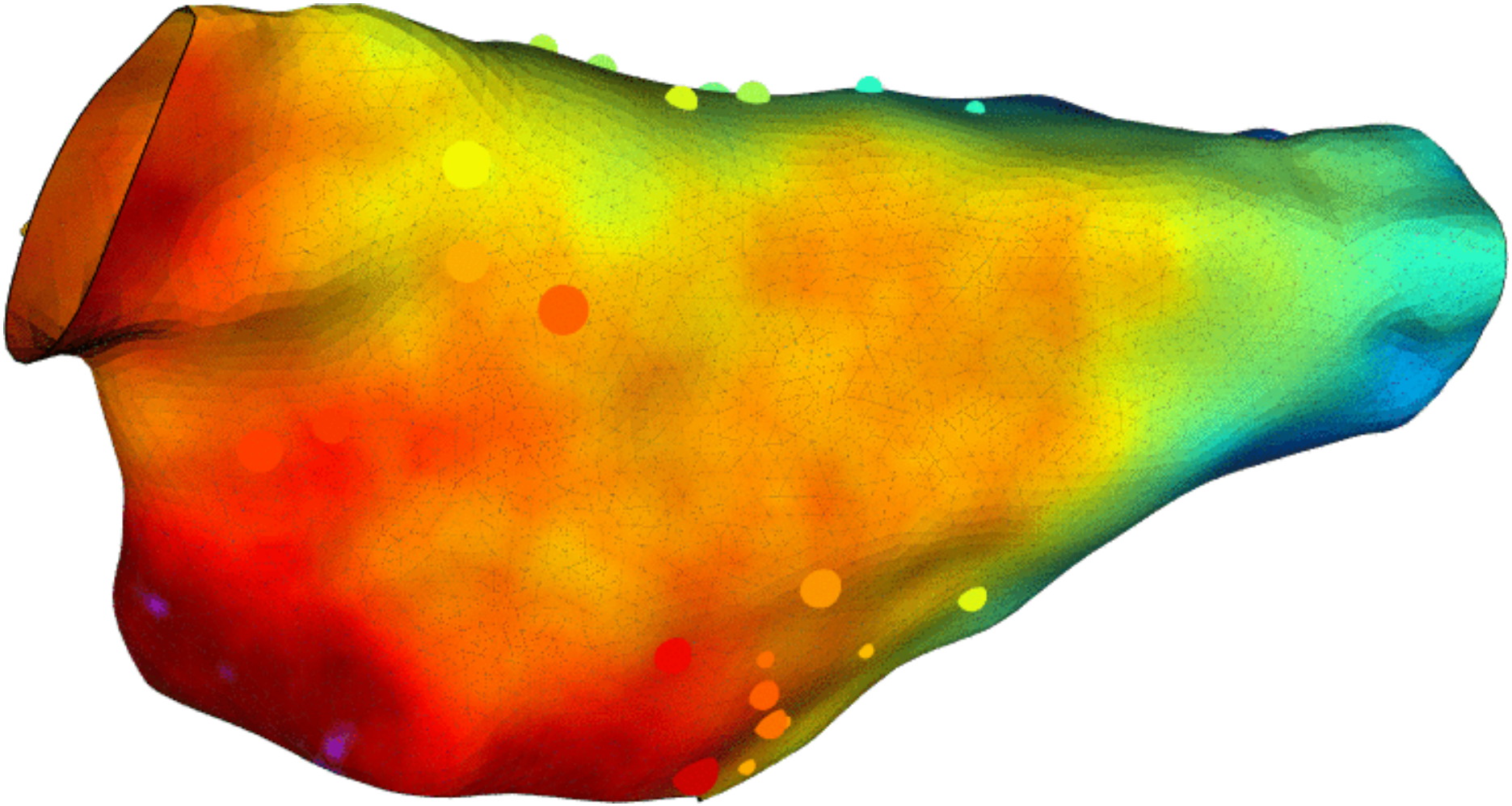

Unfortunately random samples produce unphysical (non-monotonic) patterns...
Not a surprise - the GP isn't a scientific model - it doesn't 'know' it is modelling a wave.....

Problem 3: Learning tissue parameters from complex simulators - ongoing

Incorporating physics

Model cellular electrophysiology using the Mitchell-Schaeffer (MS) ionic model that captures conduction velocity and refractory restitution properties.

- 5 parameters

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The electrophysiology of the left atrium is simulated $S(\cdot)$ using a monodomain equation in a shell anatomy with local activation given by the MS model, isotropic tissue conductivity, and infarcted, dense fibrotic and ablation regions modelled as non-conducting tissue

- ie 5 parameters at every location $\theta(x)$
- Think of the simulator as a black box $S(\theta)$ where $\theta \in \mathbb{R}^{5N_{cell}}$

Emulation in high dimension

S is expensive to evaluate so we wish to resort to emulation.

- given a training set $\{\theta_i, y_i = S(\theta_i)\}_{i=1}^n$ we want to learn a statistical representation of the mapping $S : \theta \to y$.

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- hard/impossible to learn a non-linear function in high dim space (all points are far apart)

We need to find a representation λ of θ that allows us to build emulator $\tilde{S} : \lambda \to y$ st

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Conflicting pressures... The representation needs to be

- sufficiently detailed to allow us to answer the question about reentry waves (so can't be too low dim)
- low enough dimension to allow GP emulation to be done.

Options

- Given a prior distribution $p(\theta)$ we could repeat the PCA trick and use a truncated Karhunen-Loeve expansion

$$\theta(x) \approx \sum_{j=1}^{d} \lambda_j \phi_j(x)$$

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We then seek to solve the inverse problem for λ and thus θ.

Technical aside: PCA with two datasets

with Howard Elman

We want to solve the following optimization problem:

$$\max_x x^\top Ax \text{ subject to } x^\top x = 1 \text{ and } B^\top x = 0$$

where A is an $n \times n$ positive definite matrix. B here is a set of orthonormal basis vectors (an incomplete basis) for $\mathbb{R}^n$, i.e. B is $n \times p$. This is a non-convex problem with quadratic constraint.

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Solution:

The condition $B^\top x = 0$ is equivalent to $x \in \text{null}(B^\top) := Z$ i.e., x lies in the null space of B. We then have that

$$\mathbb{R}^n = Z \oplus Z^\perp = Z \oplus B$$

Thus $x = Zw$ for some w, and so the problem becomes

$$\max_w w^\top Z^\top A Z w \text{ subject to } w^\top Z^\top Z w = w^\top w = 1$$

This is the original eigenvalue problem $\rightarrow$ solve with the SVD!

I.e., if $A = X^\top X$, then we do the SVD of XZ.

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- Regression problem
- Inverse problem

Currently looking into sufficient dimension reduction: find B so that

$$y \perp\!\!\!\perp \theta | B\theta$$

$\exists$ kernel sufficient dimension reduction, kernel CCA, kernel PCA, eg instead of $\theta = \sum \langle \theta, u_i \rangle u_i$ use

$$\theta = \sum \langle \phi(\theta), v_i \rangle_F v_i$$

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  - Can some uncertainties be ignored?
  - Do some uncertainties need more degrees of freedom to be described than others?
- Simulator discrepancy - can we model our way out of trouble?

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Thank you for listening!