Uncertainty Quantification in Prospective and Predictive Patient Specific Cardiac Models

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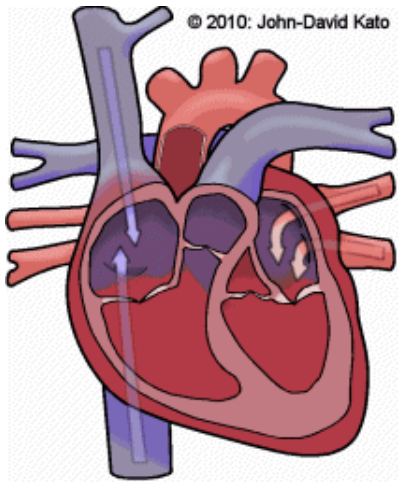
The heart

The heart is an electrical-mechanical pump, which contracts under electrical potential.
Focusing on the left atrium

- left atrium receives oxygenated blood from the lungs
- left atrium pumps this blood to the left ventricle
- left ventricle pumps this oxygenated blood to the body



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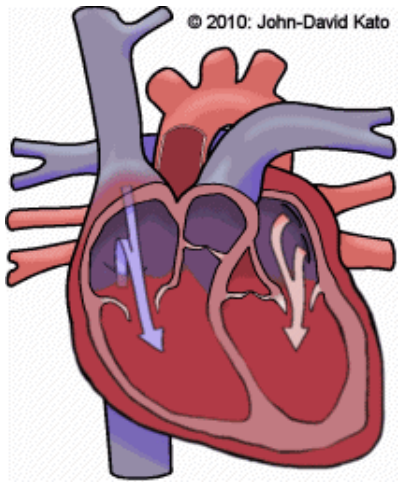

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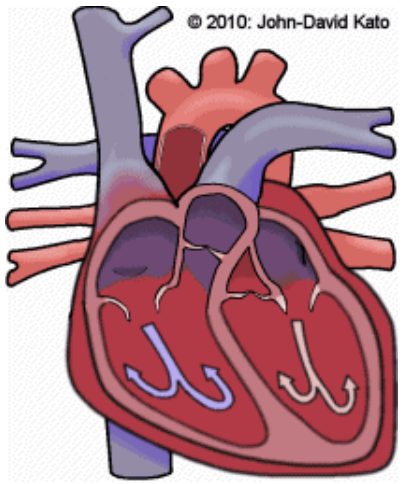

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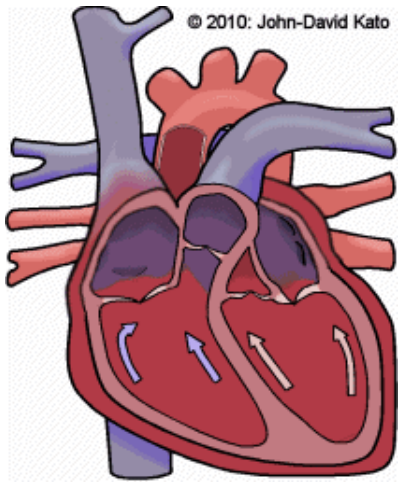

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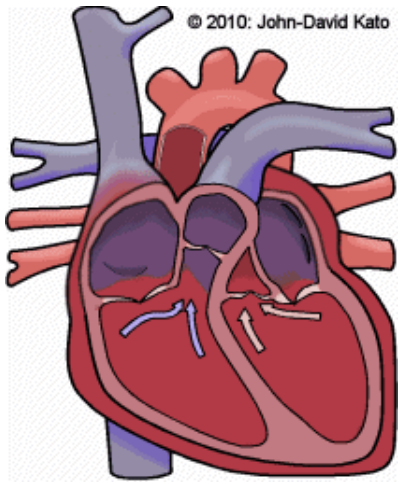

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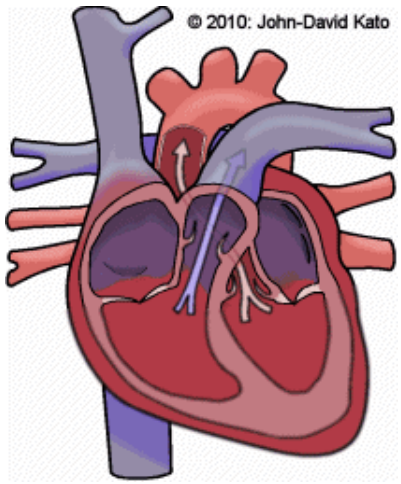

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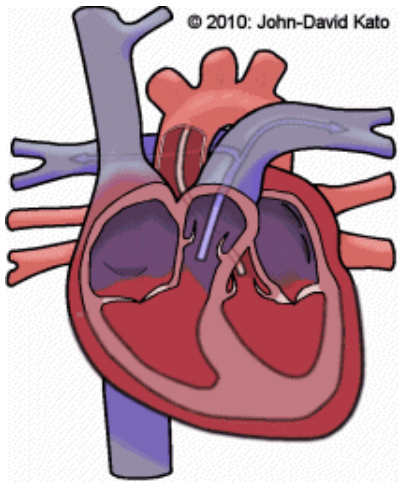

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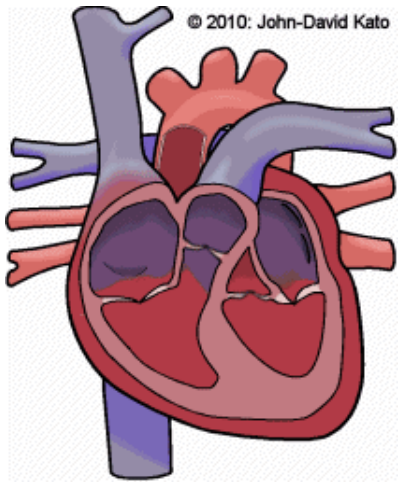
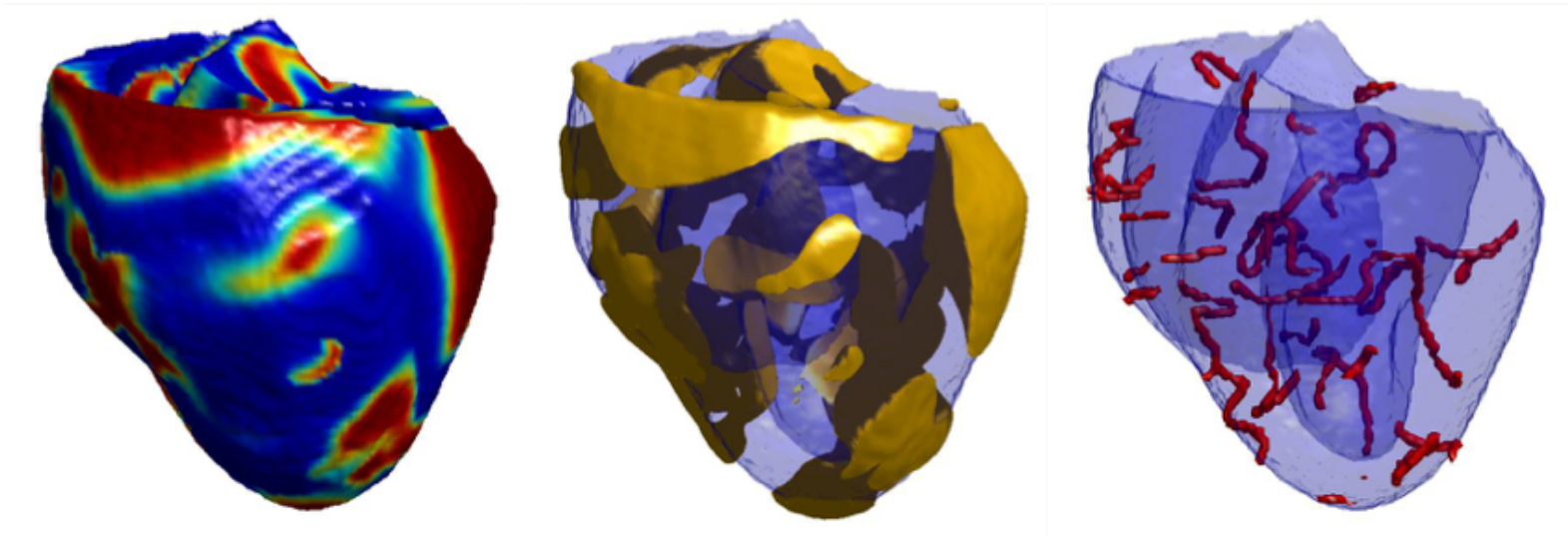


Project overview

Atrial fibrillation



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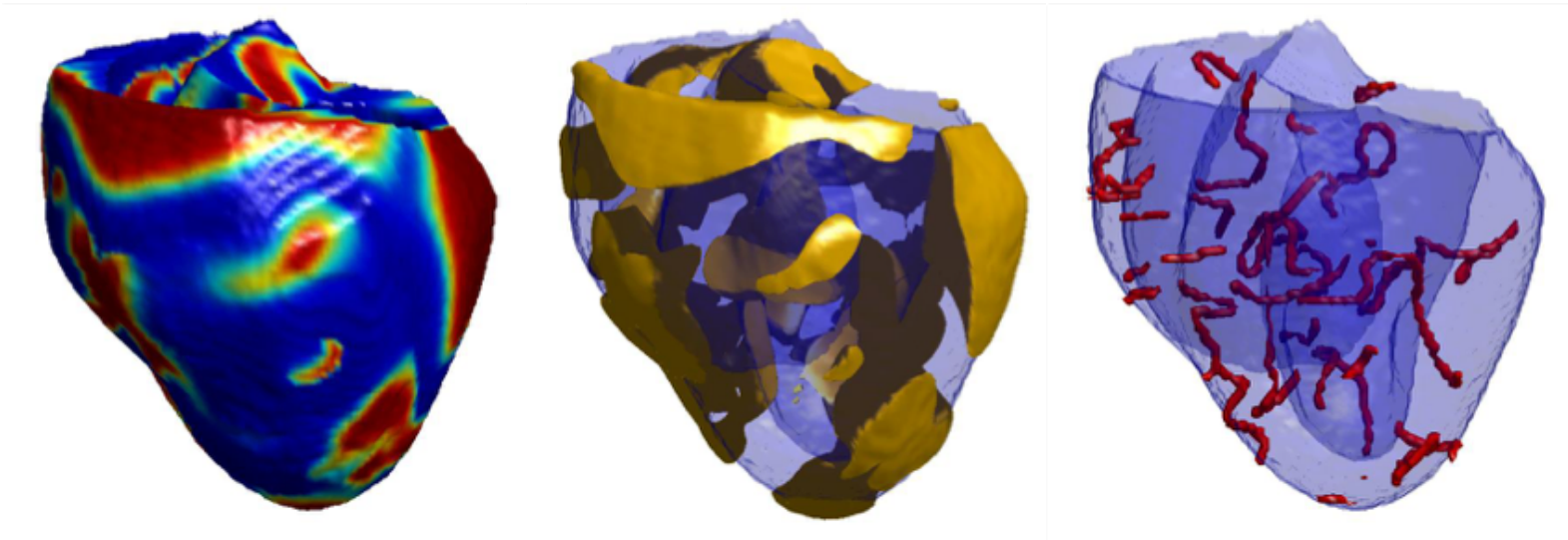

Atrial fibrillation (AF) - rapid and uncoordinated electrical activation (arrhythmia) leading to poor mechanical function.

- Affects around 1,000,000 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.

- Each intervention: 6% risk of major complication; cost $\sim$£8000.

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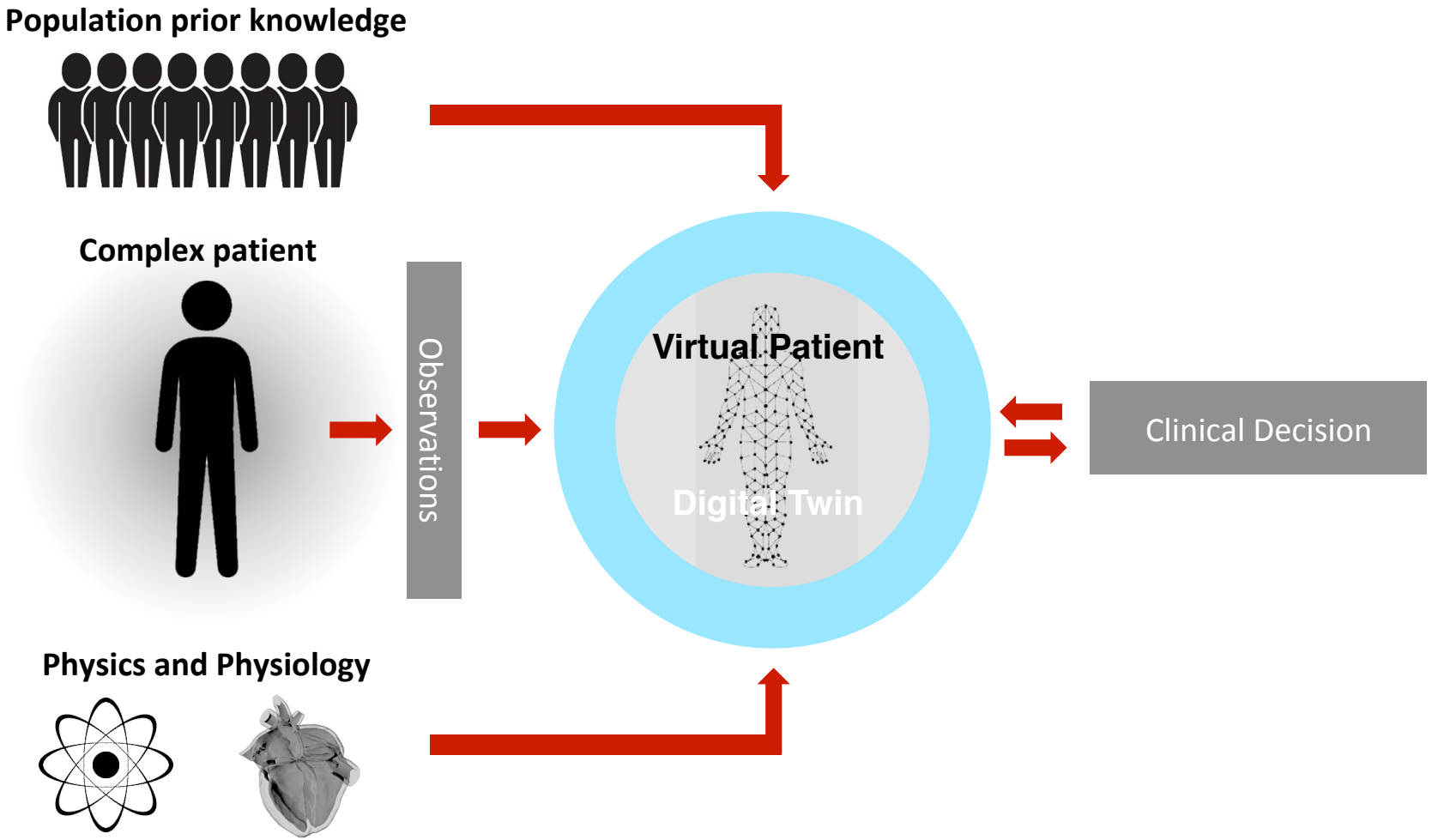
Personalised biophysical models have the ability to predict patient response to treatment

- models are deterministic - simulate a single outcome - but clinical diagnosis is rarely definitive
  - we need to account for uncertainties
- aim to consider costs and benefits across all potential outcomes weighted by their probability.
  e.g. if patient has 30% chance of complication - this should influence decision making.

Cardiac digital twin



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 atrial tachycardia 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: build patient specific left atrium mesh, identify fibrosis.
- Electrophysiology study: learn electrical activation map
- Interpolate to entire atrium: estimate conduction velocity and restitution curves
- Estimate spatially resolved tissue parameters
- Predict atrial tachycardia pathways; make clinical recommendations

Requires us to track and account for uncertainty through all stages

Uncertainty quantification

Aim to characterize and combine uncertainties to make decisions that take lack of knowledge into account.

- Noisy data D, recorded at a small number of uncertain locations on an uncertain atrial manifold x
- Large number of unknown parameters θ, f
- Complex simulator (limited computational resource)
- Misspecification/discrepancy

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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 partially done in real time
- and the physics/simulator $\pi(D|\theta, x, f)$

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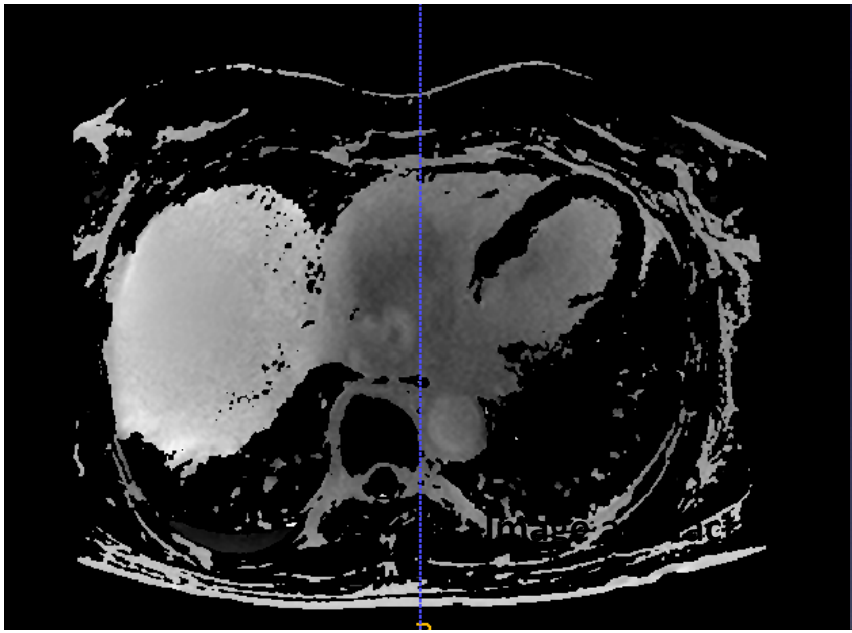
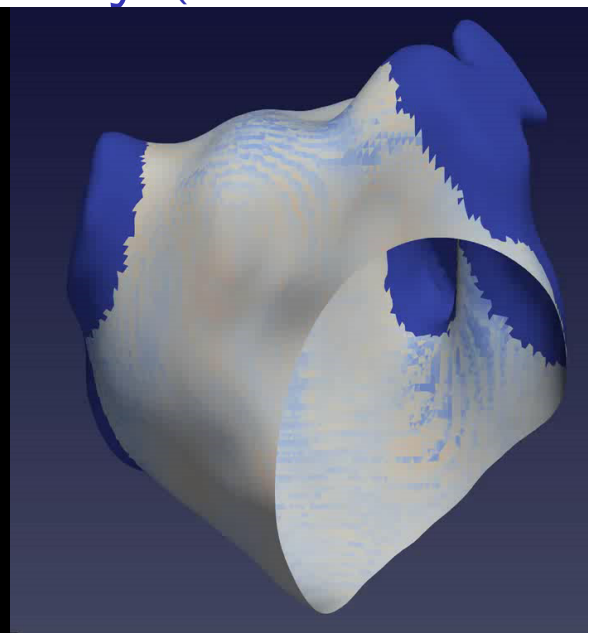
Pragmatic approach necessary.

Problem 1: Uncertain anatomy (Corrado *et al. MedIA* 2019)





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?

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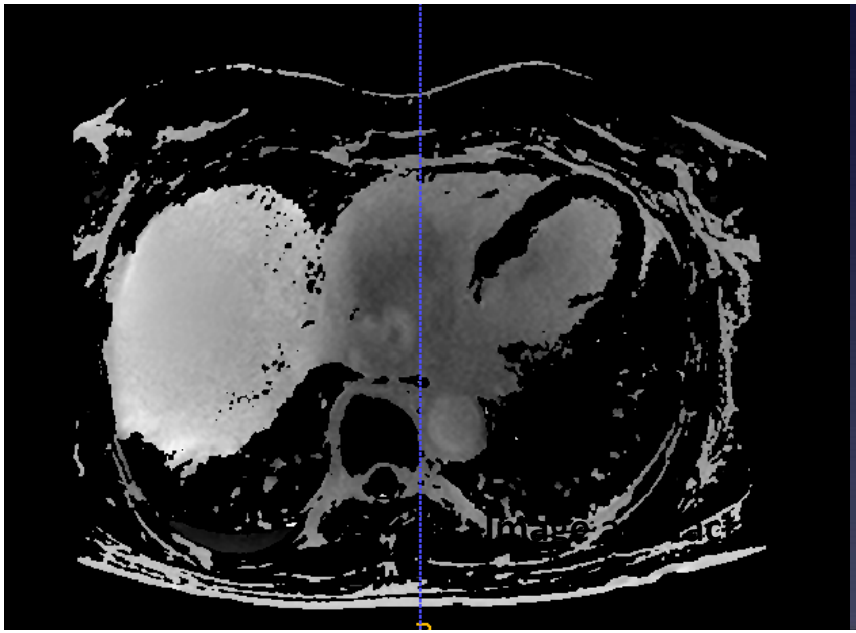

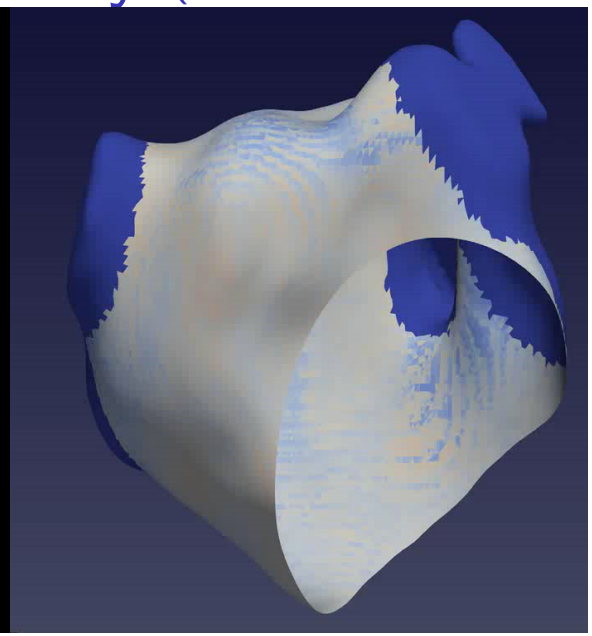

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Aim: change to a basis allowing variation to be described in low dimension

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

where $\lambda = (\lambda_1, \ldots, \lambda_d)^\top$ is the new coordinate describing variation for basis $\{u_1, \ldots, u_d\}$.

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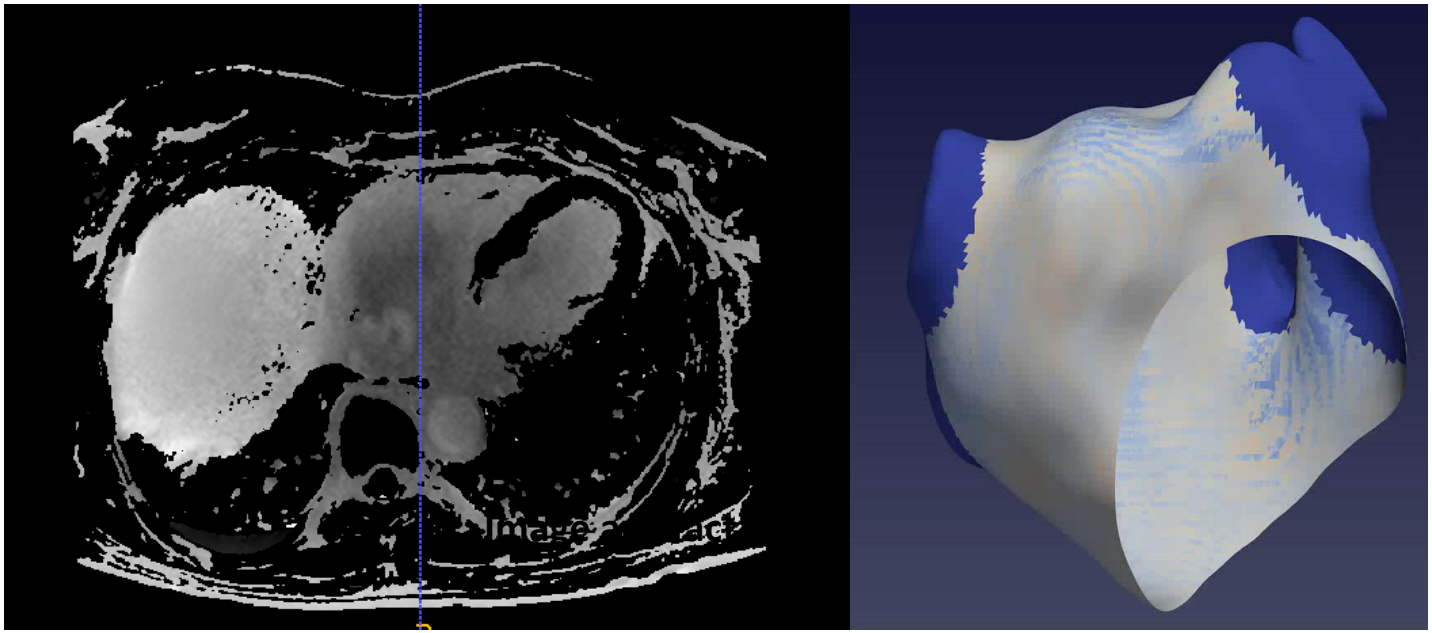

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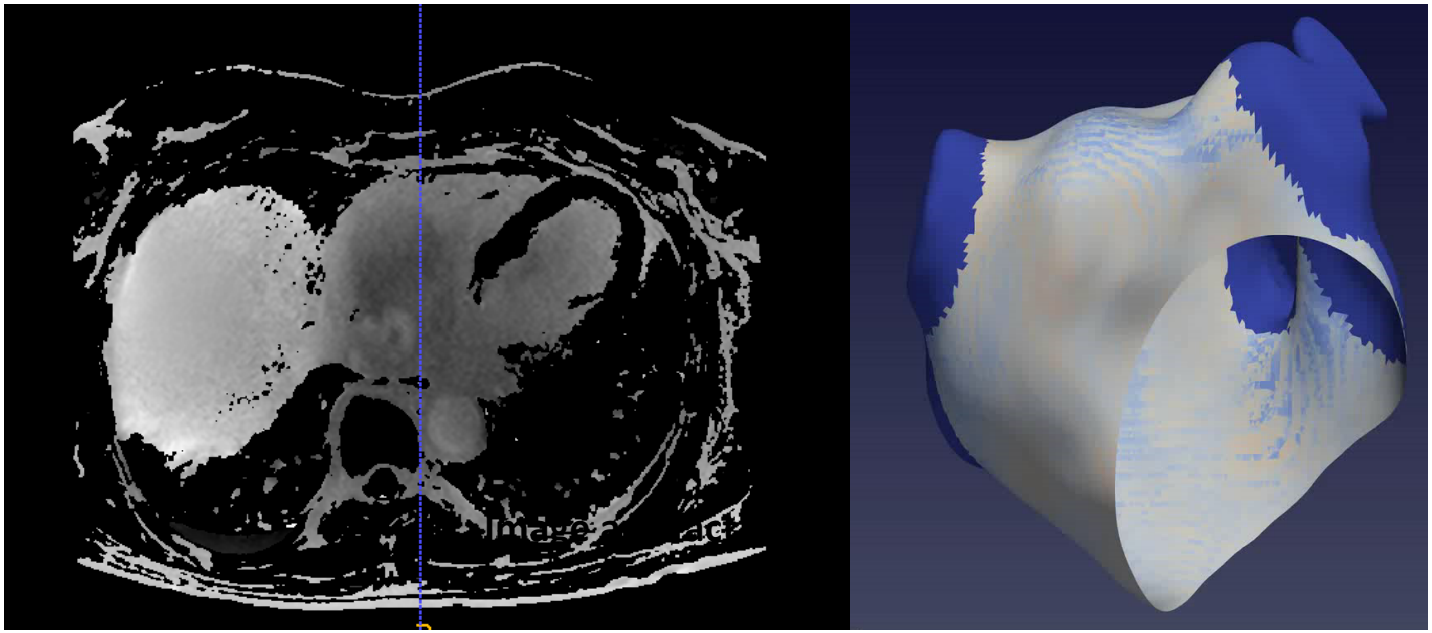

Determine the reduced basis, error variance Σ and prior $\lambda \sim N(0, \Sigma_\lambda)$ from the population.

Use Bayesian approach to characterize uncertainty about individual anatomy via

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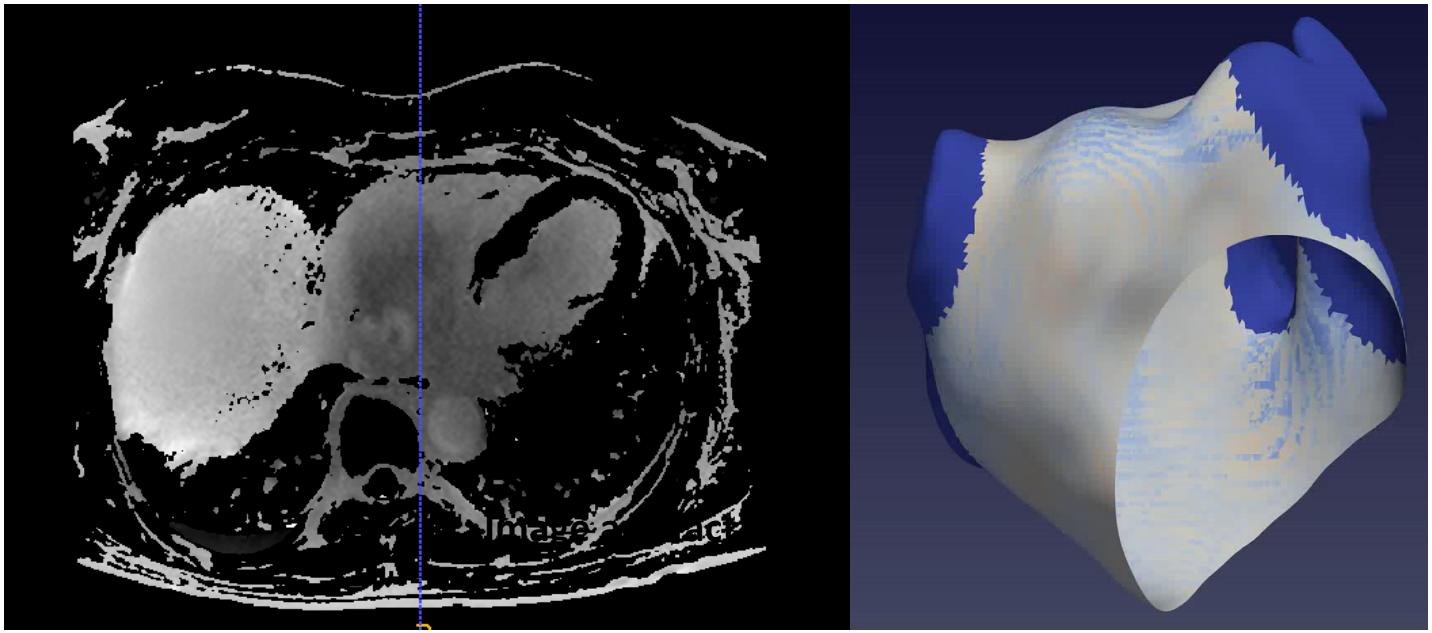

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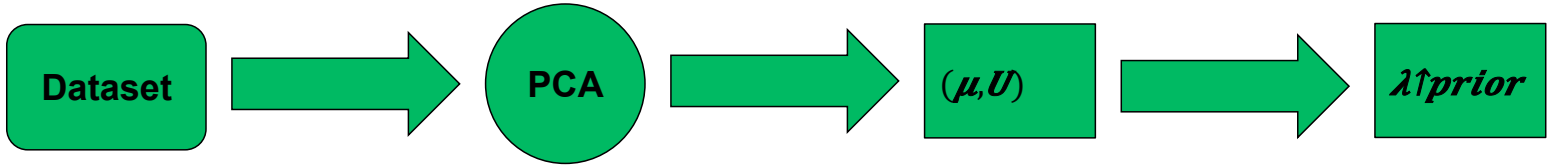
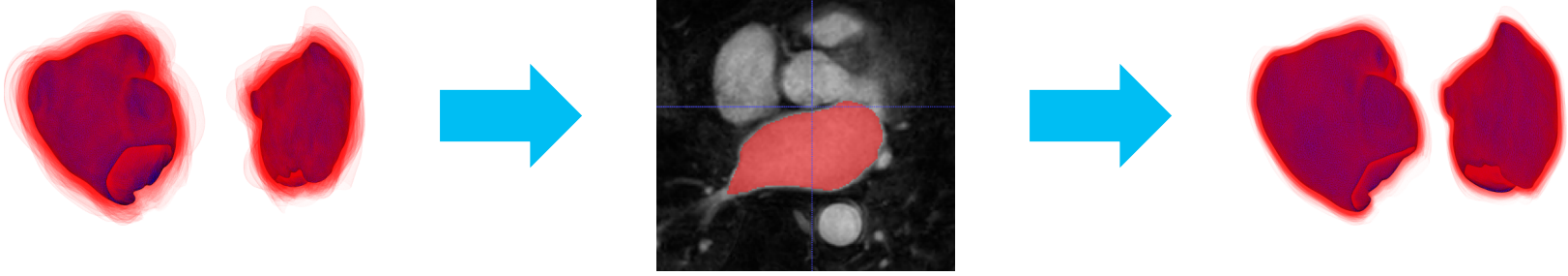
- PCA basis is optimal

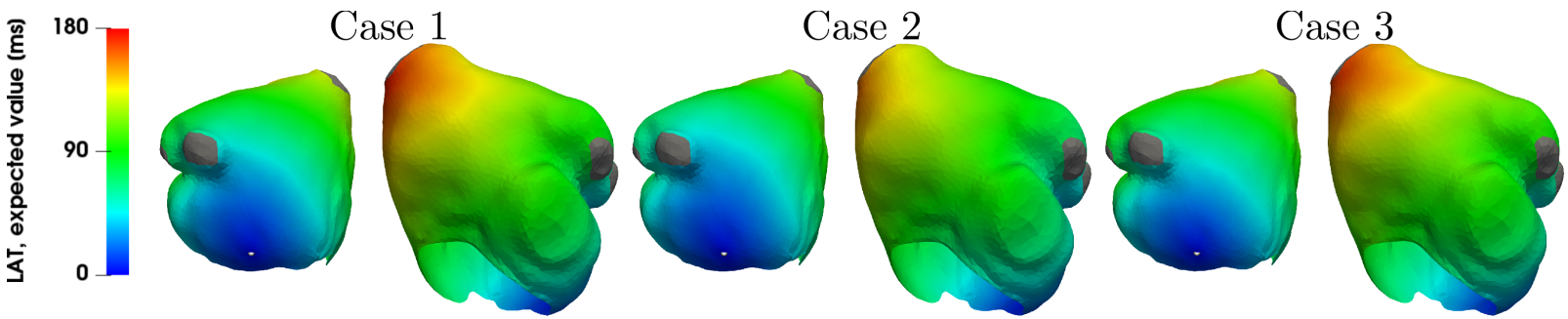




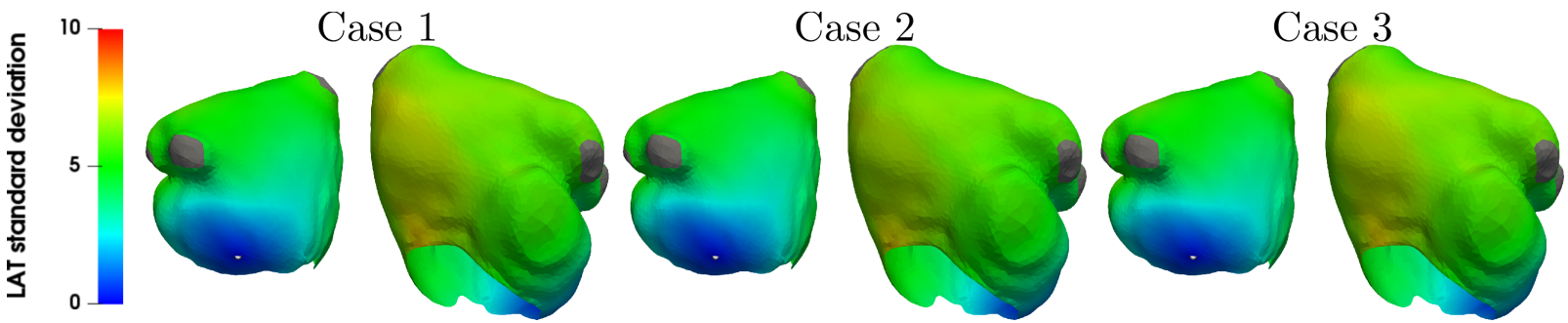
Population Mean and shape (λ) Priors

New Measure

Update Shape (λ) Posterior Distribution



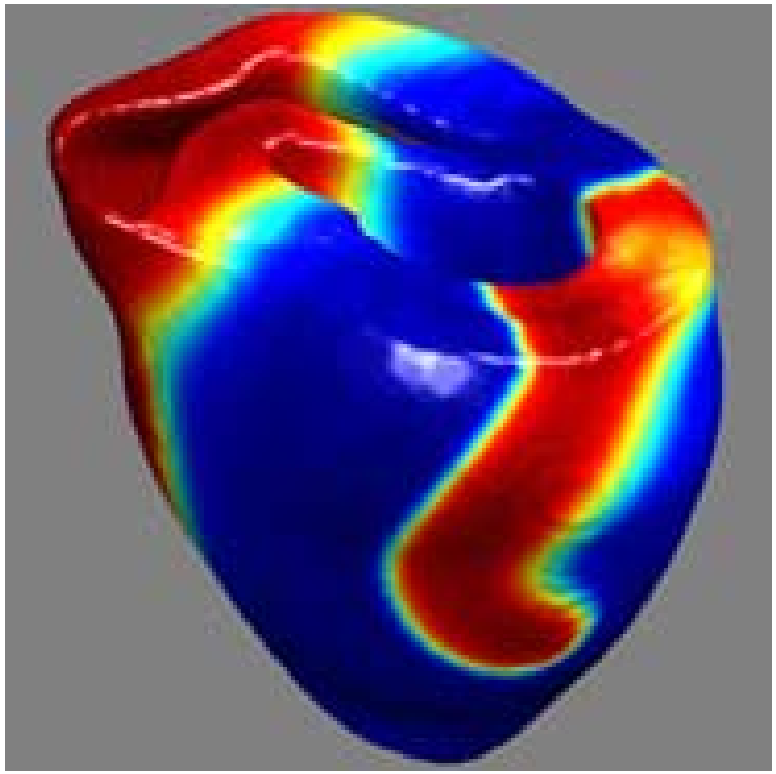
Expected value



Standard deviation

Problem 2: Interpolation of local activation time (LAT)

Coveney *et al.* *IEEE TBME* 2019



Think of electrical activation as a wave spreading over the atria

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

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

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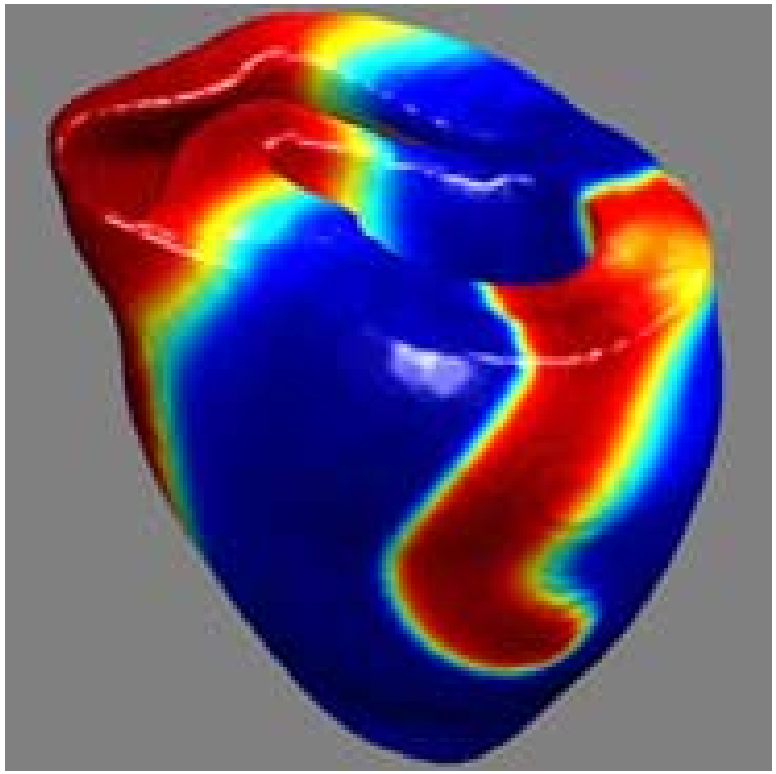

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Electrophysiology (EP) study: electrodes placed on the surface of the atrium and electrical pacing applied at various frequencies. We measure electrical activity across the atria.

Estimating local activation times from electrograms

Coveney *et al.* *IEEE TBME* 2019

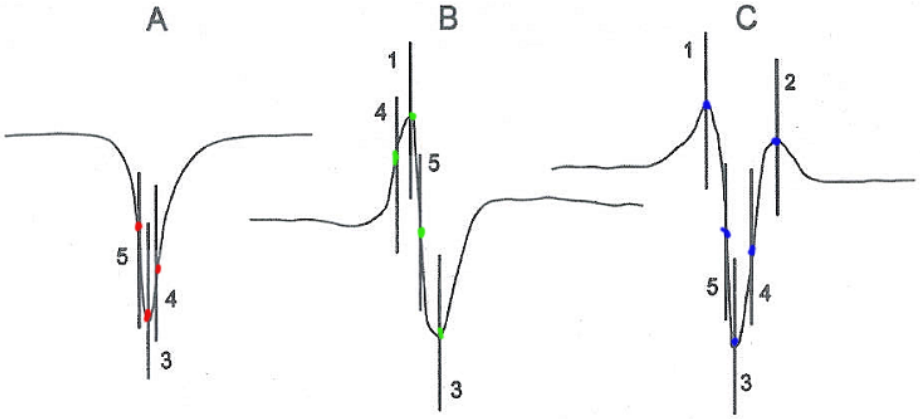
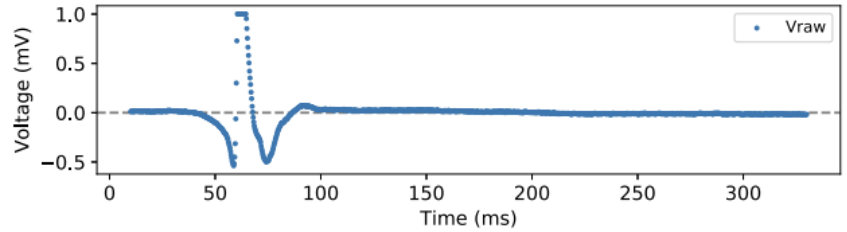


Figure 4. *Example of bipolar electrogram configurations and associated landmarks used for activation time analysis. A: uniphasic; B: biphasic; C: triphasic. 1: peak positive voltage; 2: secondary peak positive voltage; 3: peak negative voltage; 4: maximum positive derivative; 5: maximum negative derivative. See text for details.*

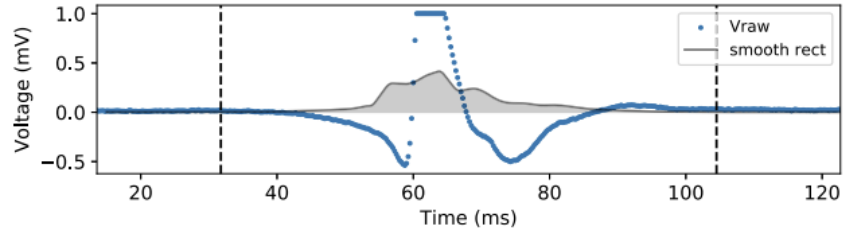
How should local activation times (LAT) be inferred from a bipolar electrogram?

- Some methods more robust than others (esp. for AF patients), and few include uncertainty.

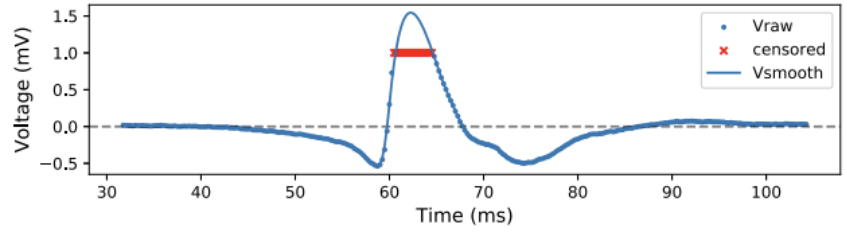
Method allows crude estimation of LAT with uncertainty



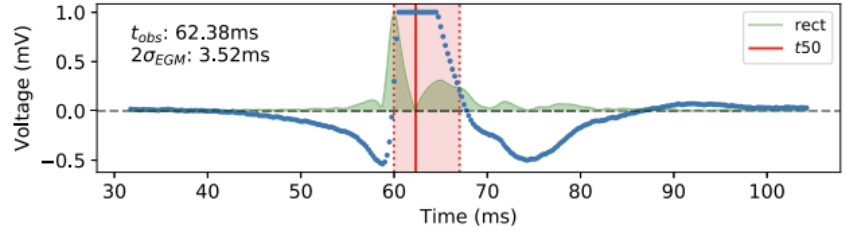
(a) **Regularize signal**. Blue points show $V_{raw}(t)$, the signal minus the mean with normalized amplitude. Recording has clipped the peak.



(b) **Bracket activation complex**. EGM is smoothed, rectified, and smoothed again (black line/area). Vertical dashed lines are brackets.



(c) **Smooth the signal**. Gaussian Process fit to $V_{raw}(t)$, ignoring censored data (red points), giving $V_{smooth}(t)$ (smoothed and *reconstructed*).

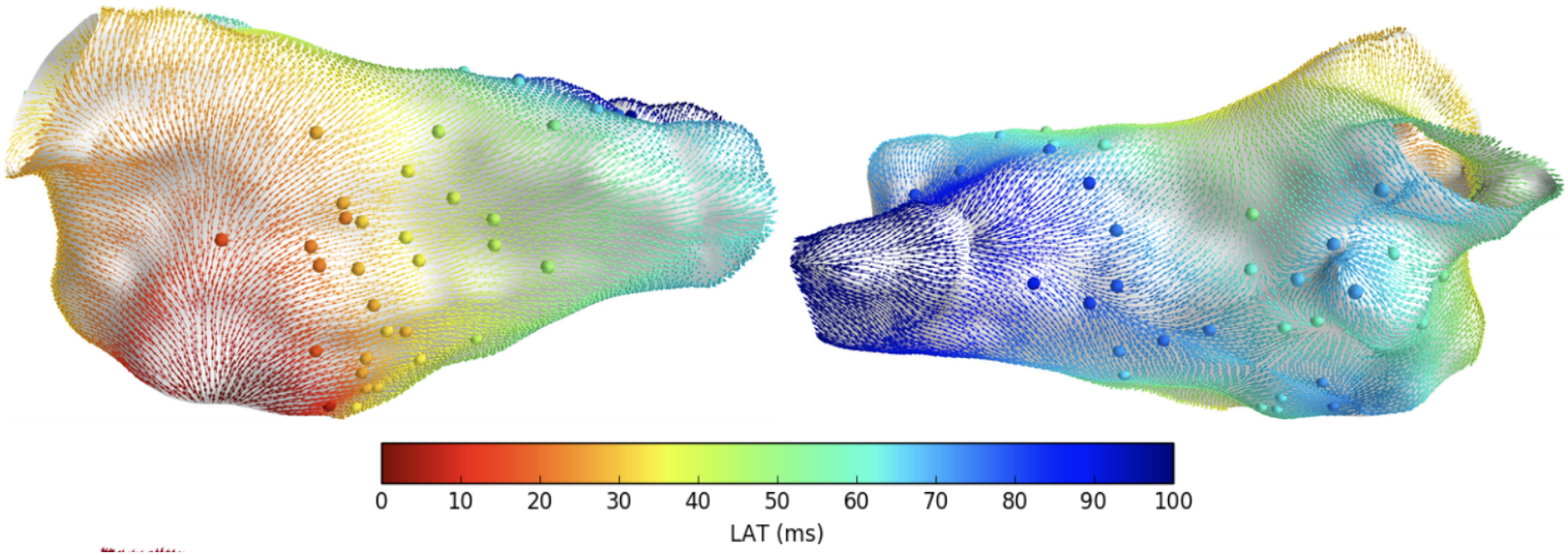


(d) **Assign uncertain LAT**. Rectified smoothed signal (green area). The solid red line is t_{50}, shaded area edges are t_{25} and t_{75}.

Interpolation

We want to estimate activation times at all locations on the atria (the *LAT map*)

- Typically, only able to measure LAT a small number (∼10s) of locations on the atrium.



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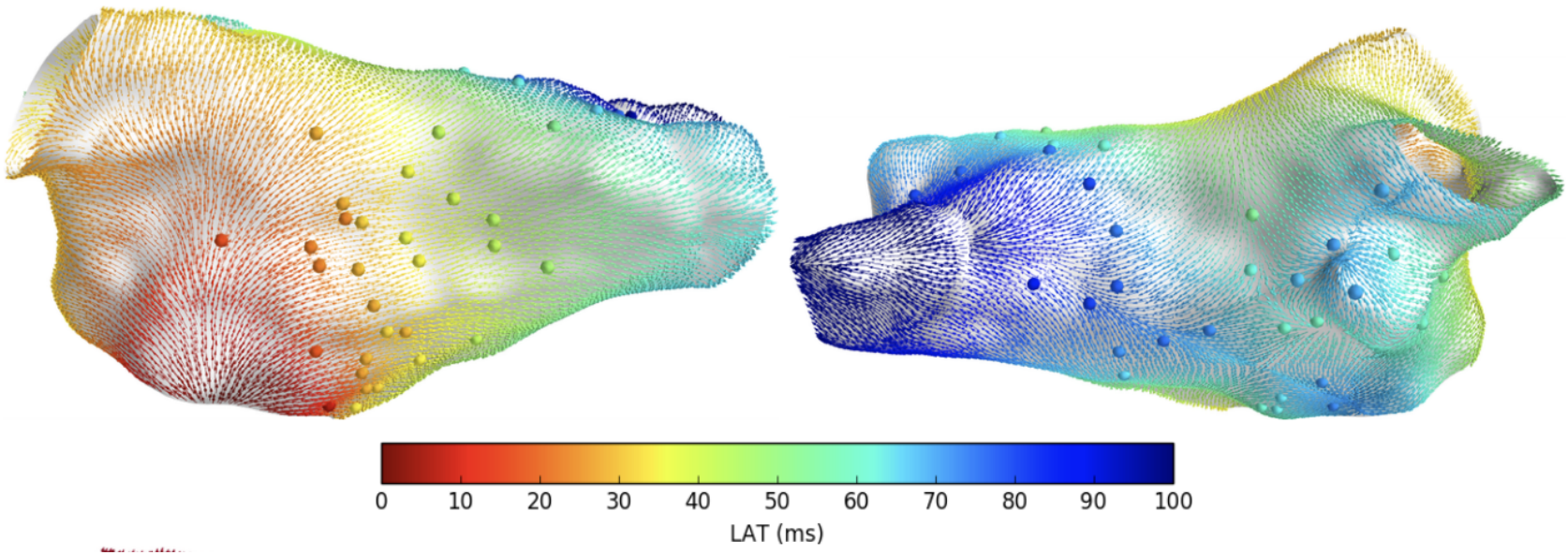


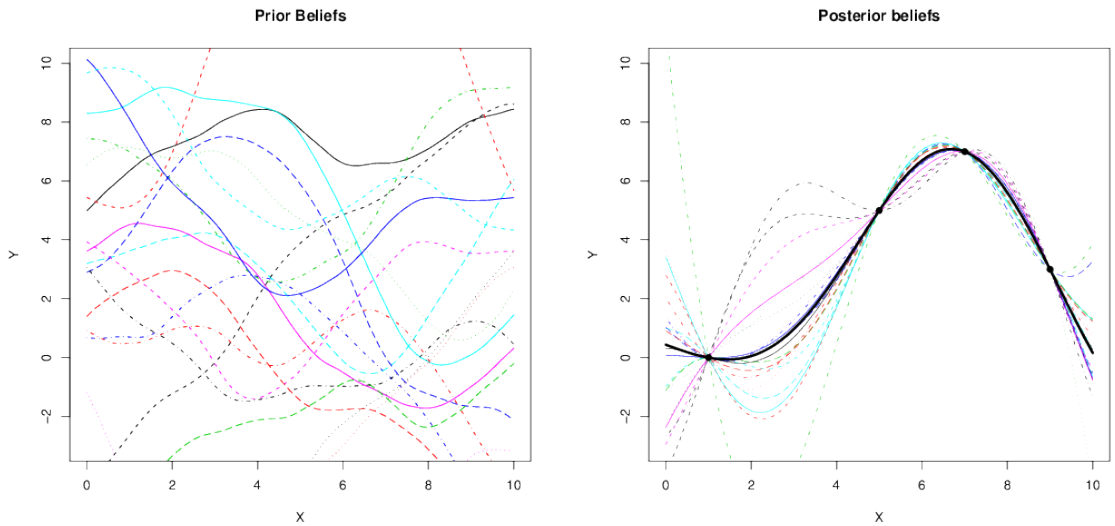
How can we interpolate to other locations?

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

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



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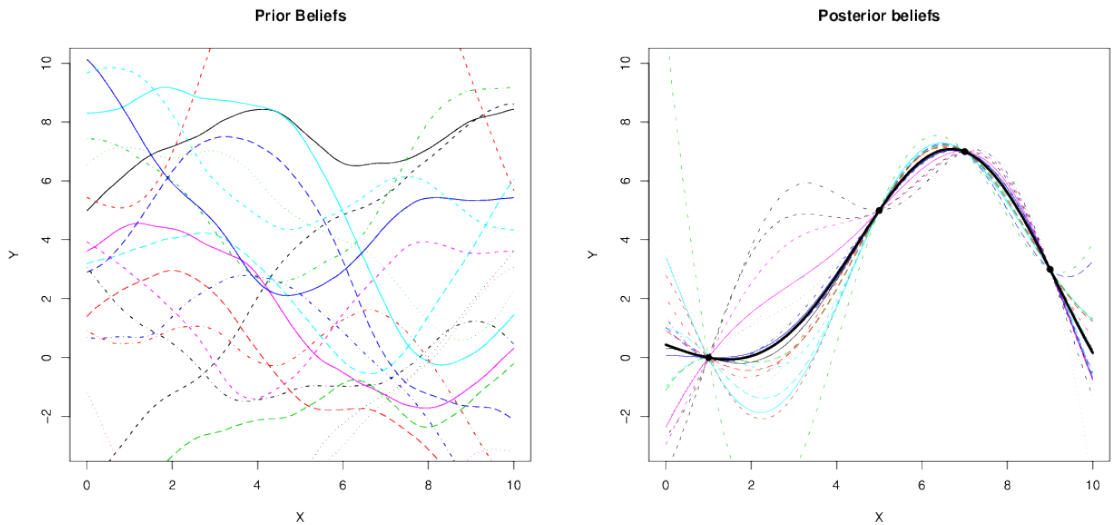

GPs can be thought of as probabilistic models of functions.

- a random process indexed by $x \in \mathcal{X}$, such that for $x_1, \ldots, x_n$,

$$\mathbf{f} = (f(x_1), \ldots, f(x_n)) \sim N_m(\mathbf{m}, \mathbf{K})$$

where $K_{ij} = k(x_i, x_j)$

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 $\nabla \cdot \nabla f = 0$

GP interpolation

We want to model

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

but standard approaches won't work when the domain is an atrial manifold

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GP interpolation

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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!

GP basis expansions

We can consider basis expansions of GPs

$$f(x) = \sum_{i=1}^{\infty} w_i \phi_i(x)$$

where $\phi(x)$ are basis functions, and w_i random coefficients.

If $w_i \sim N(0, \lambda_i)$, then $f(x)$ is a zero-mean GP with covariance function

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We want to avoid specifying $k(x, x')$ explicitly, as it is difficult to do so on the atrium.

Approach 1: INLA-SPDE approach: Lindgren *et al.* 2011

Coveney *et al.* 2019

For Matern covariance functions, there is a link between GPs and stochastic partial differential equations (SPDE, Whittle) :

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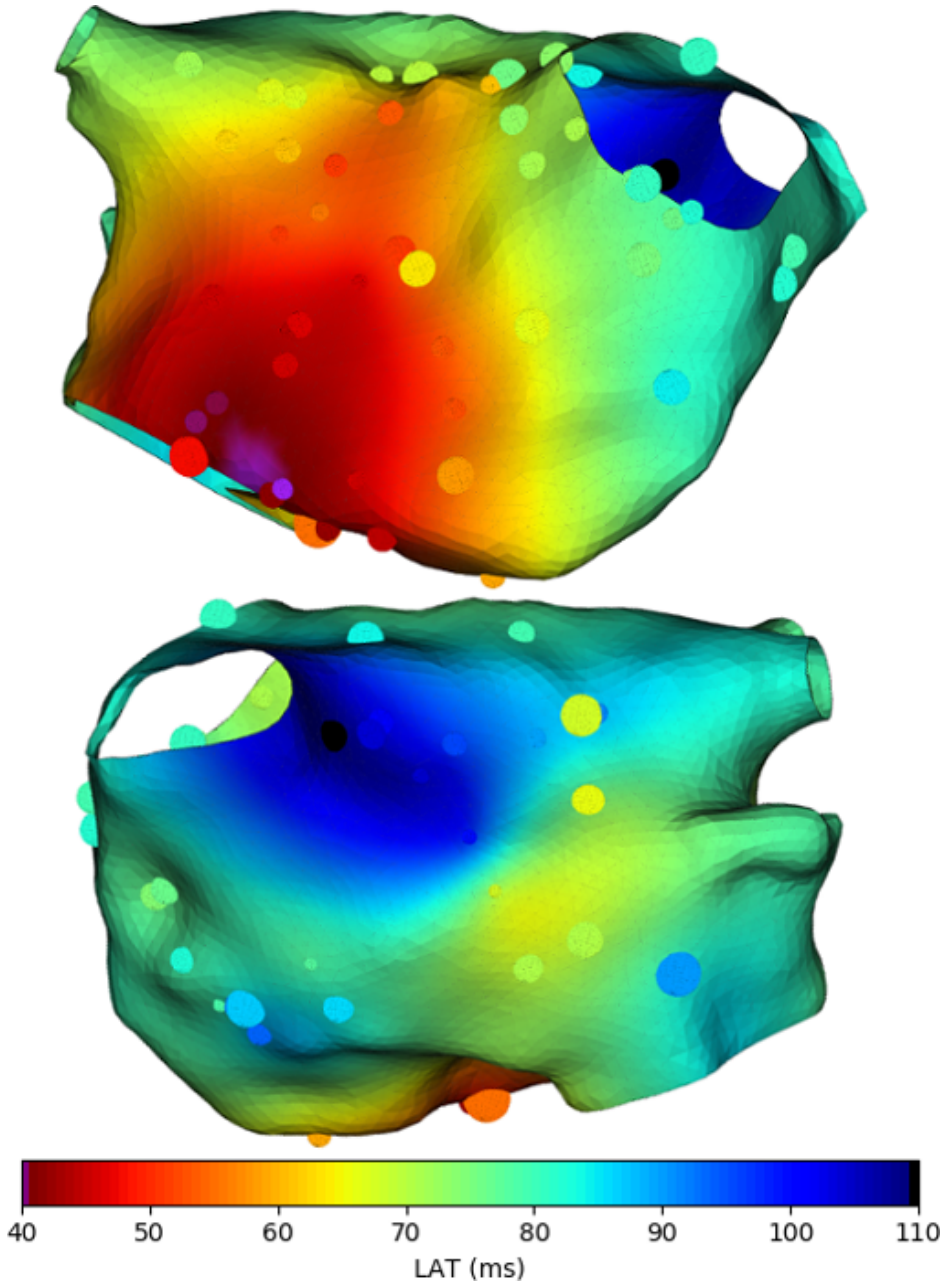
$$LAT(x) = \sum_{k=1}^{n} w_k \phi_k(x)$$

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

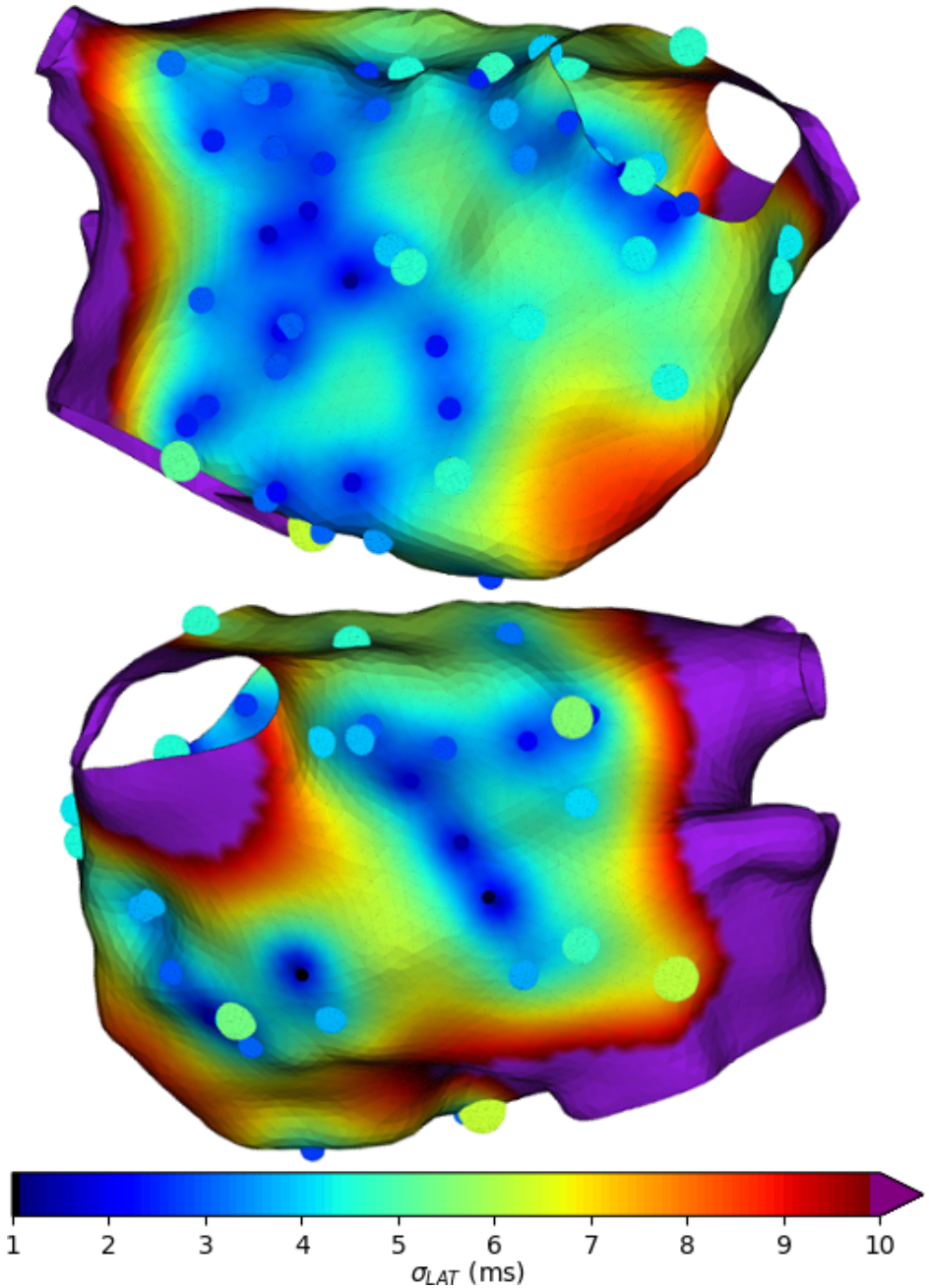
$$f(\cdot) \sim GP(0, Q^{-1})$$

for some Q

Results - mean



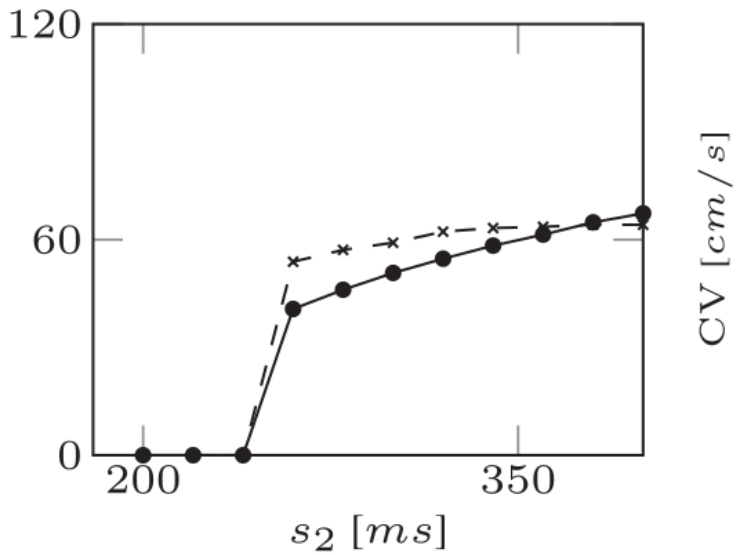
Results - standard deviation



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?

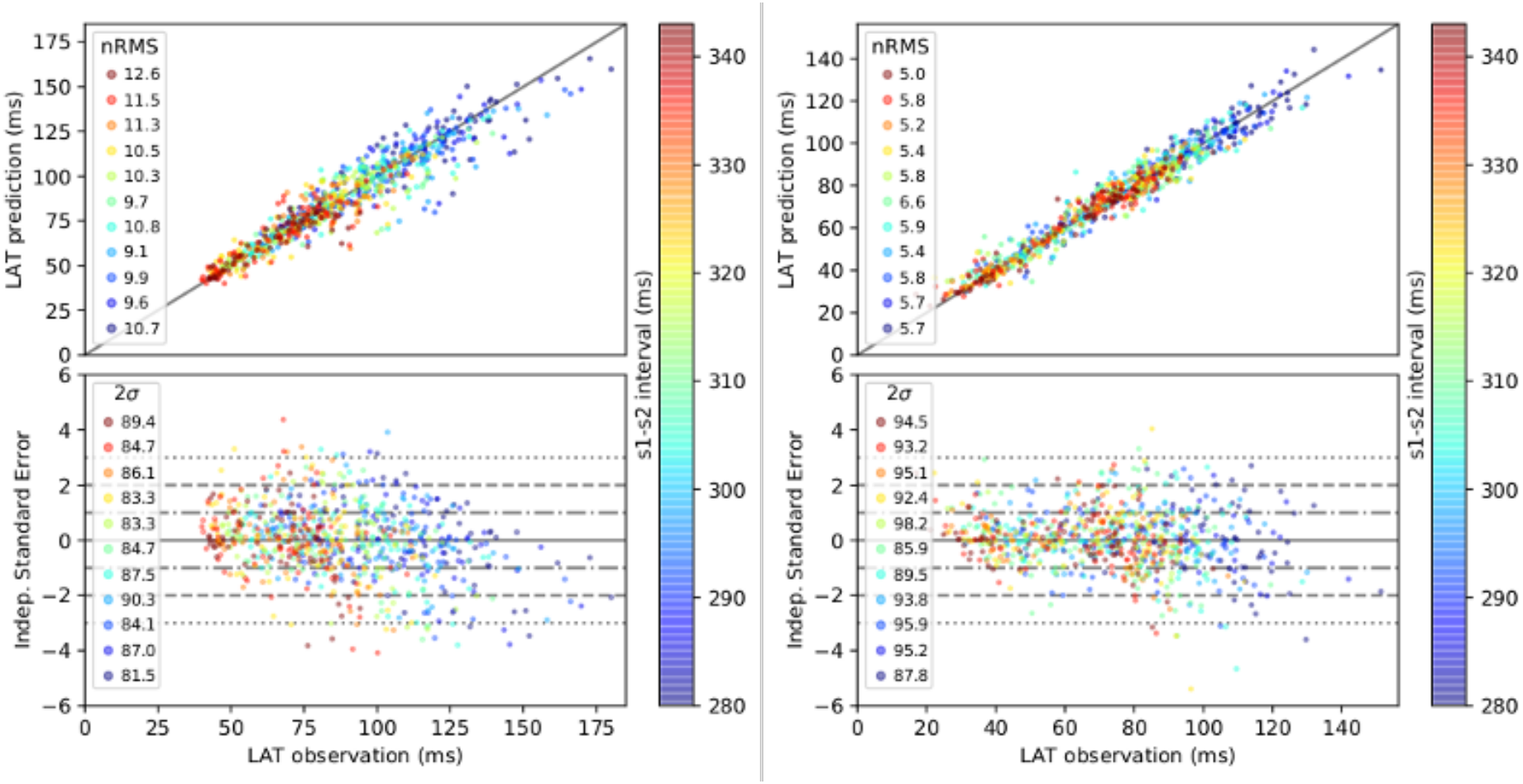
Simplest way is to add S2 as an input, and assume an AR(1) relationship between $LAT(x, S2_{i+1})$ and $LAT(x, S2_i)$

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

or more precisely

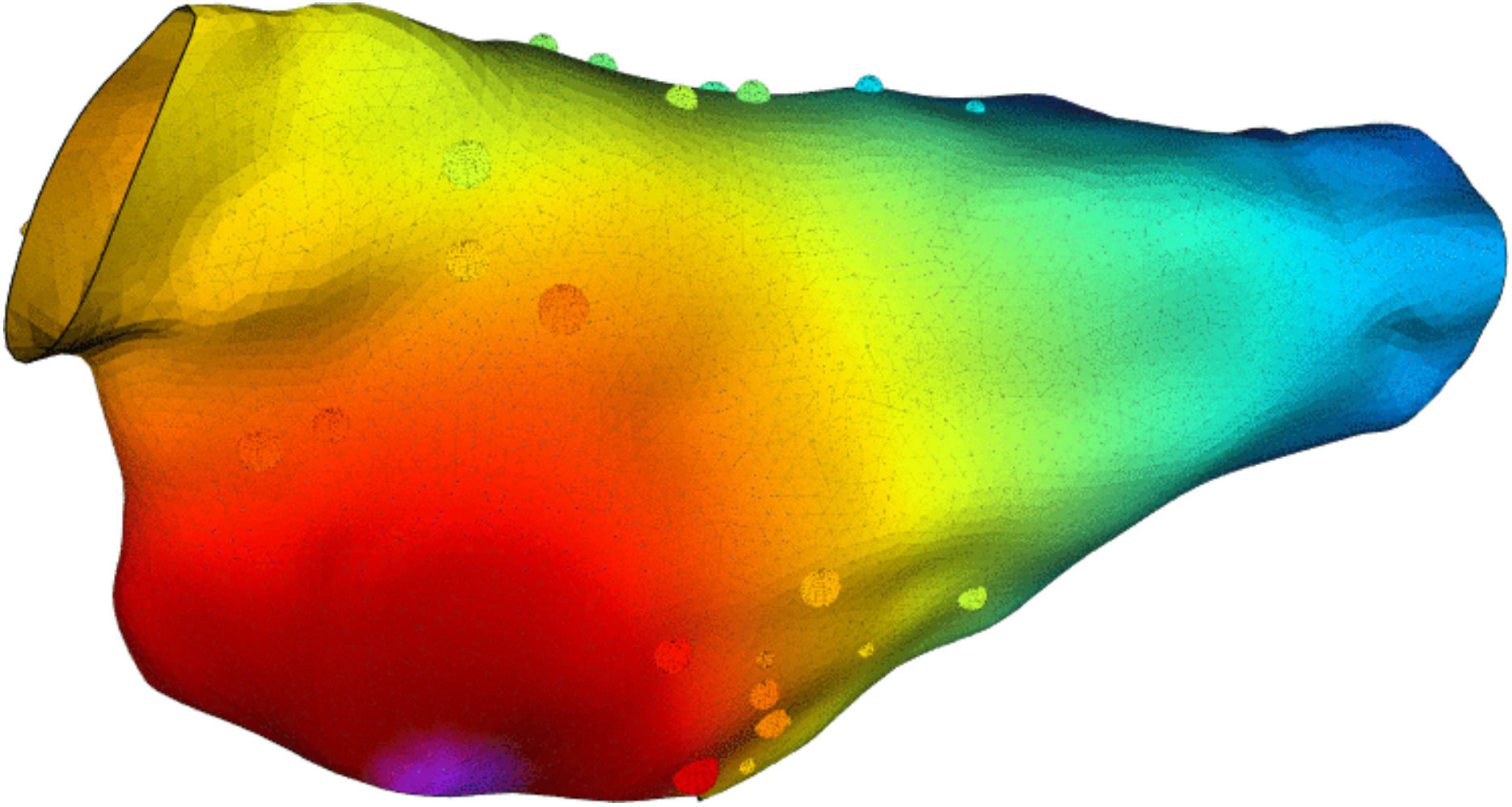
$$LAT(x, S2) \sim GP(0, Q_{S2}^{-1} \otimes Q^{-1})$$

Results: Cross validation

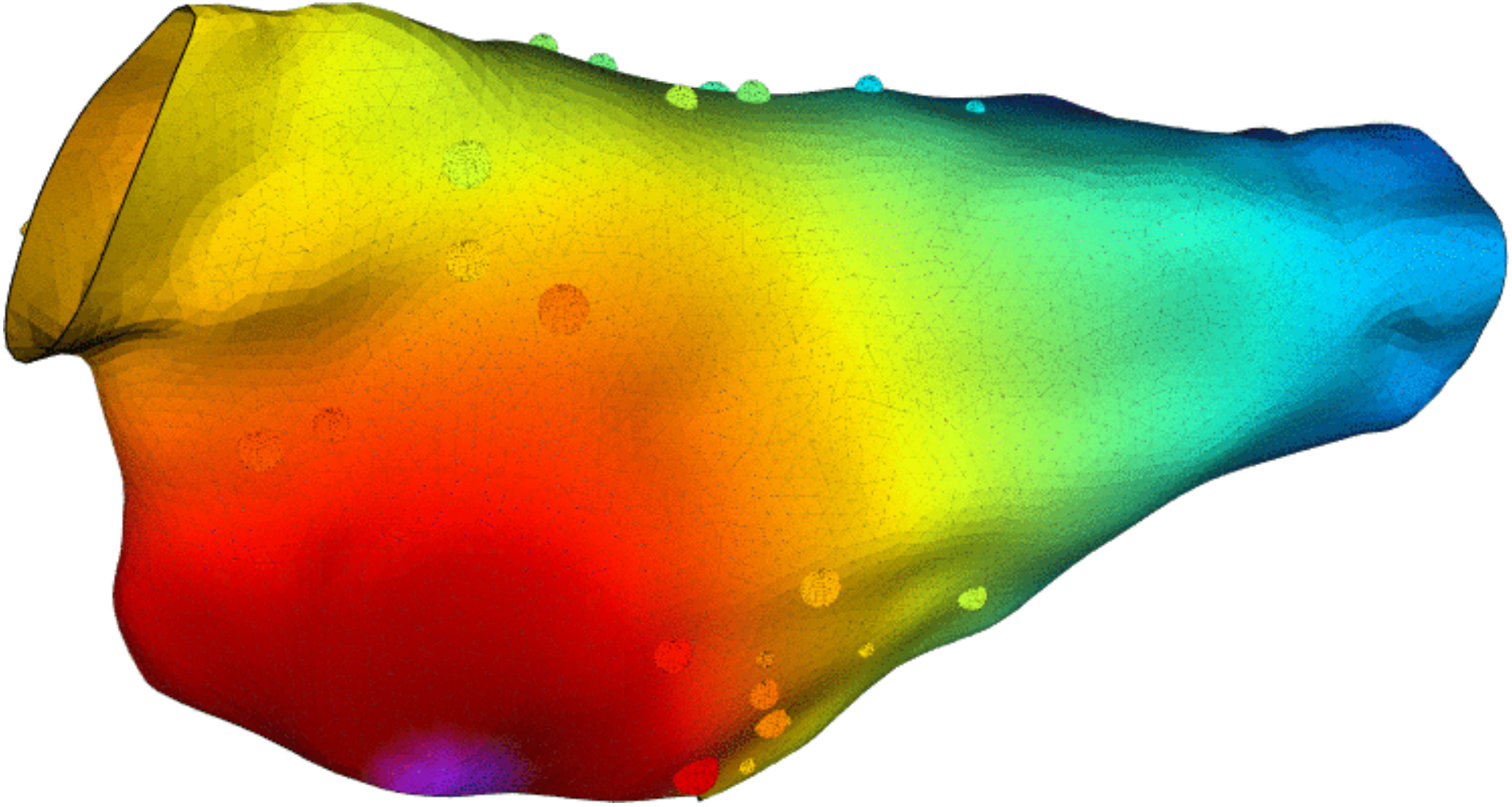


Opens interesting design questions around data collection protocols

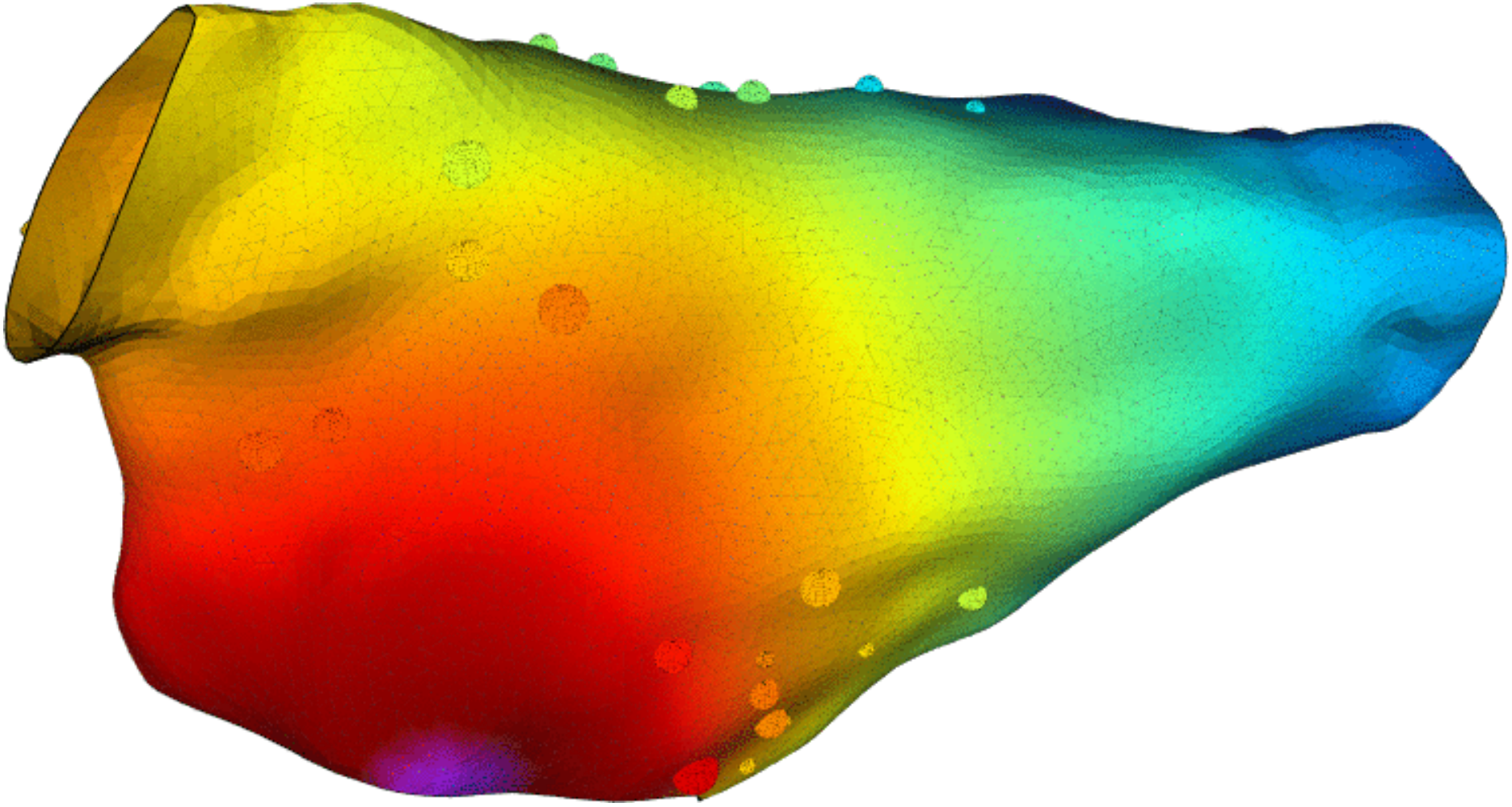
Random samples



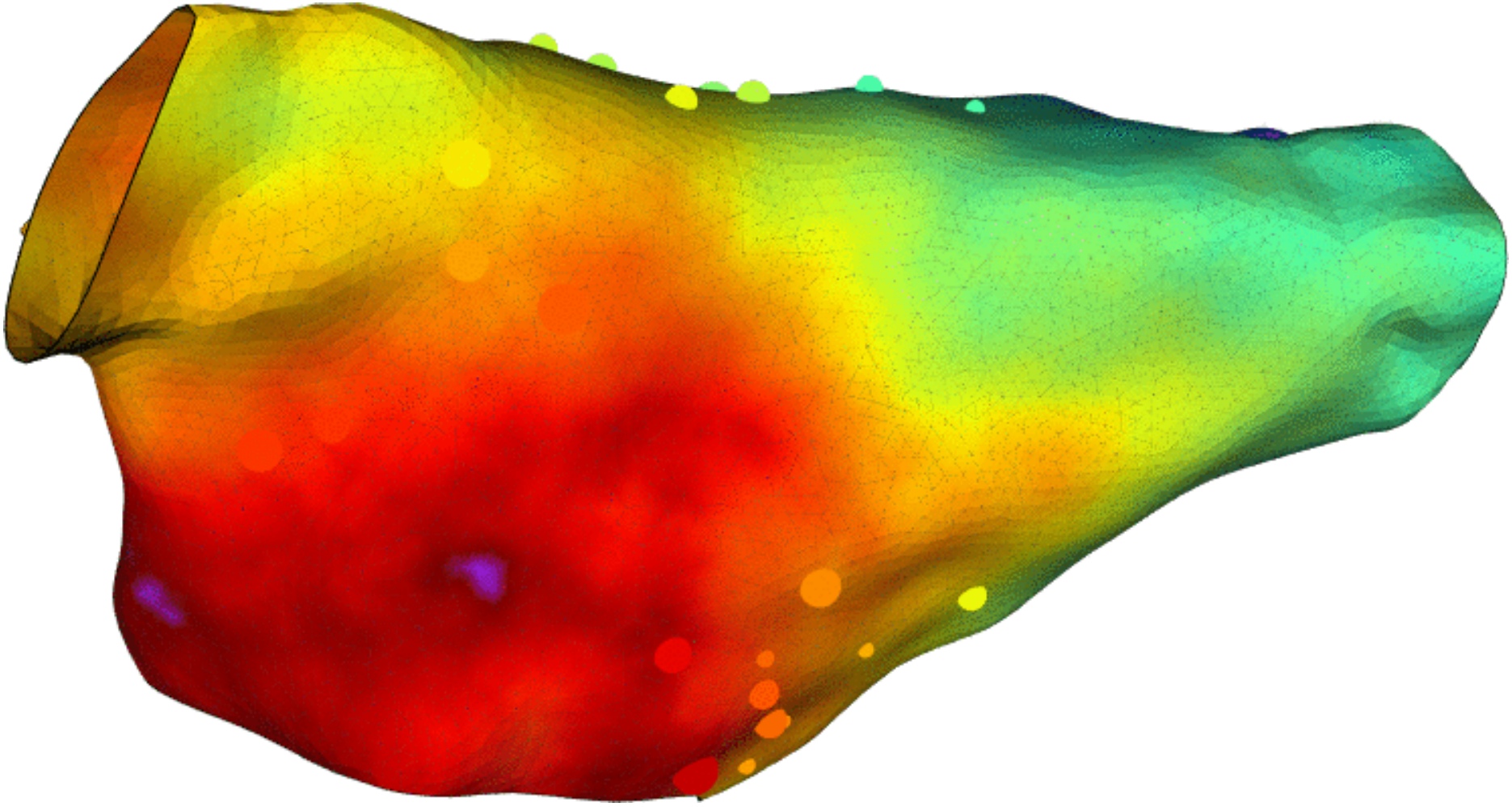
Random samples



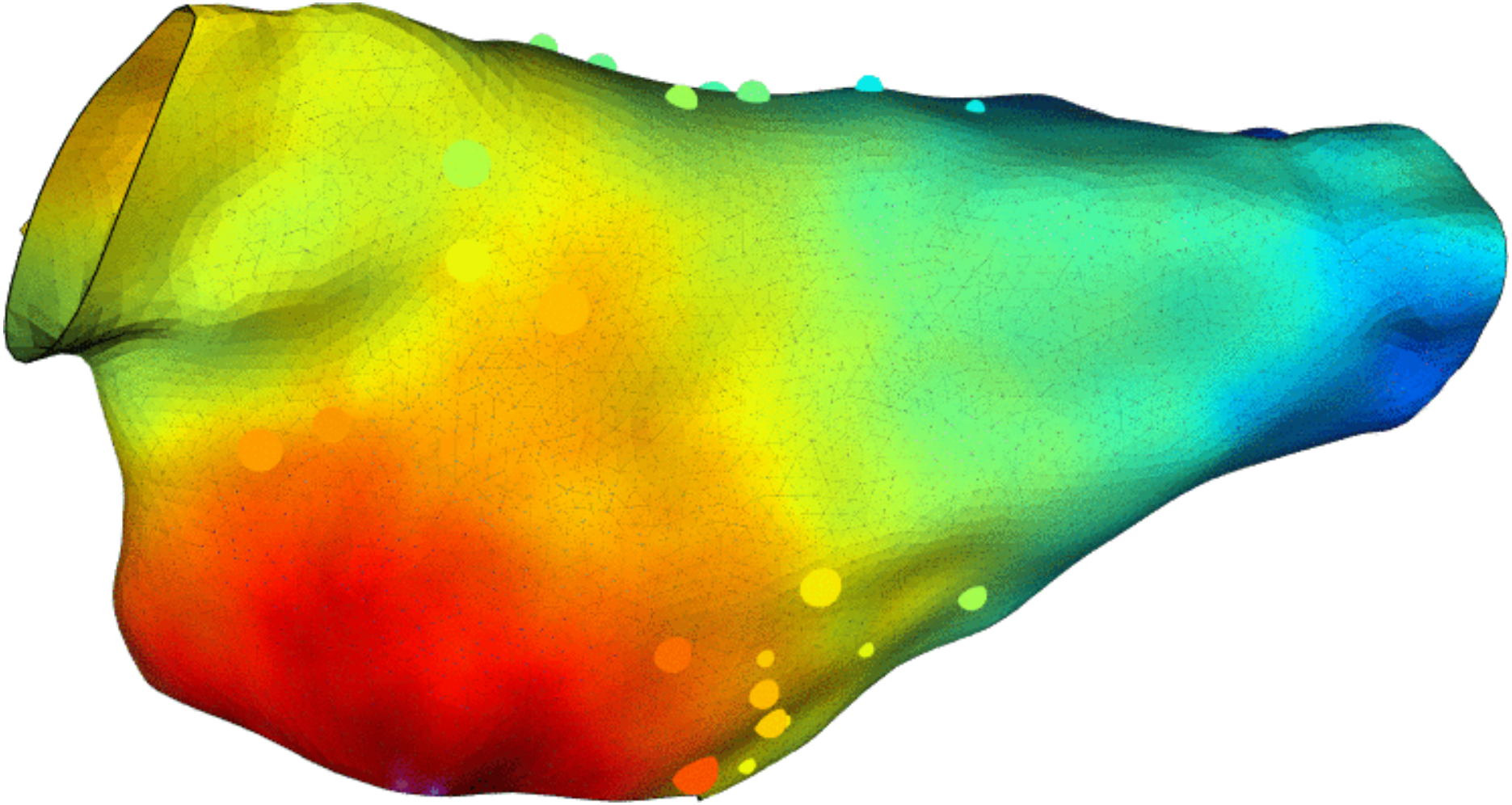
Random samples



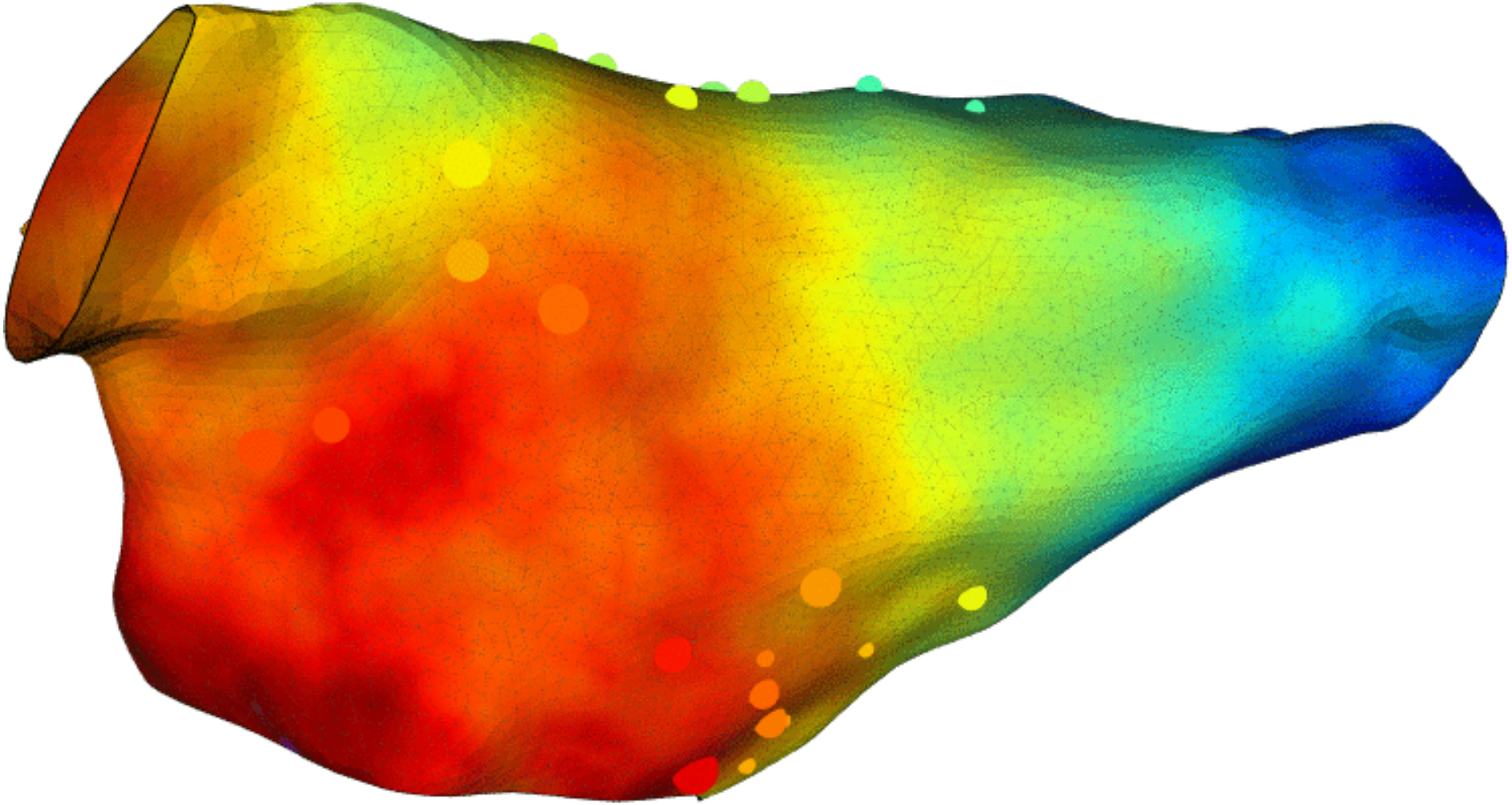
Random samples



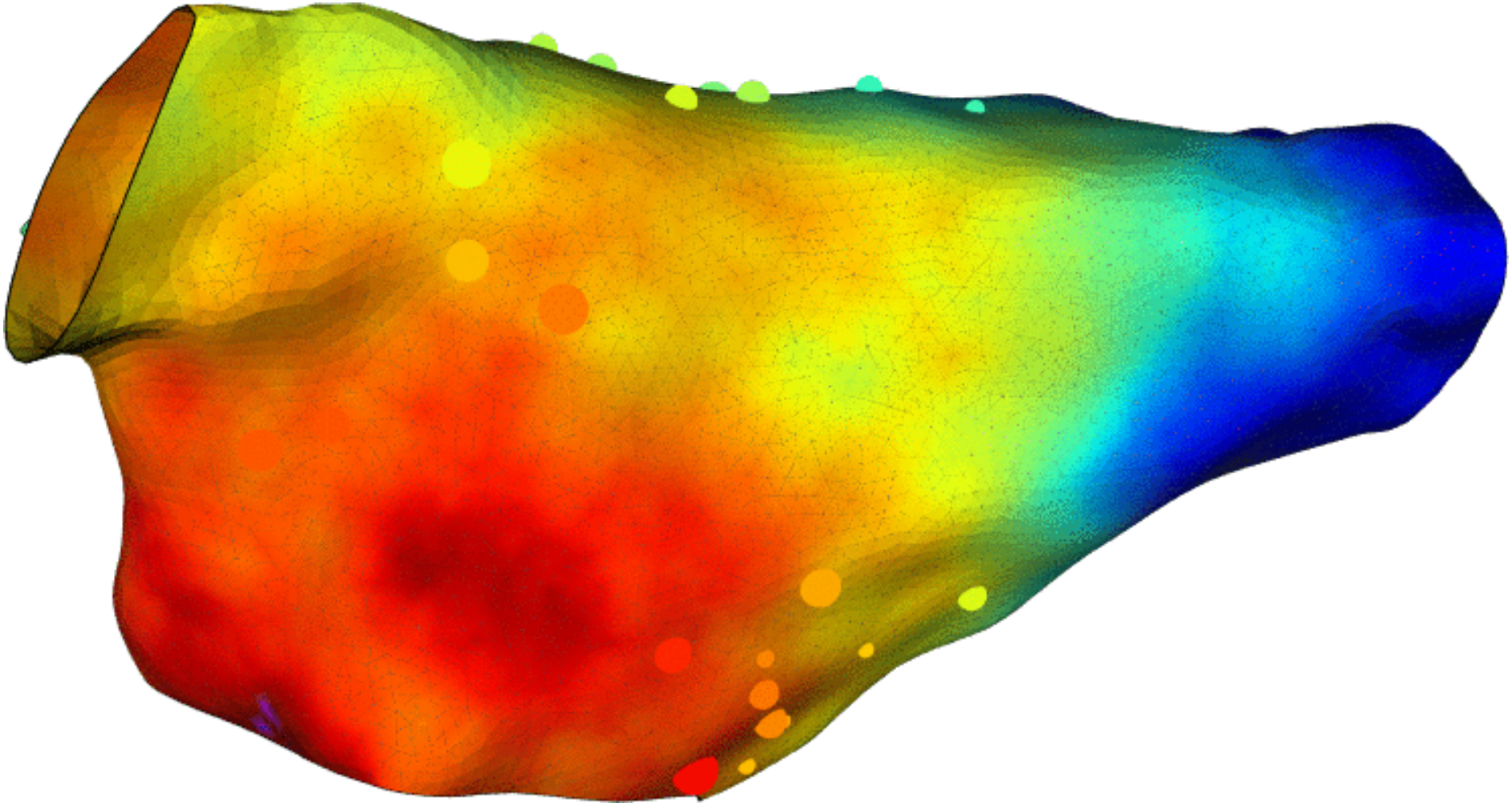
Random samples



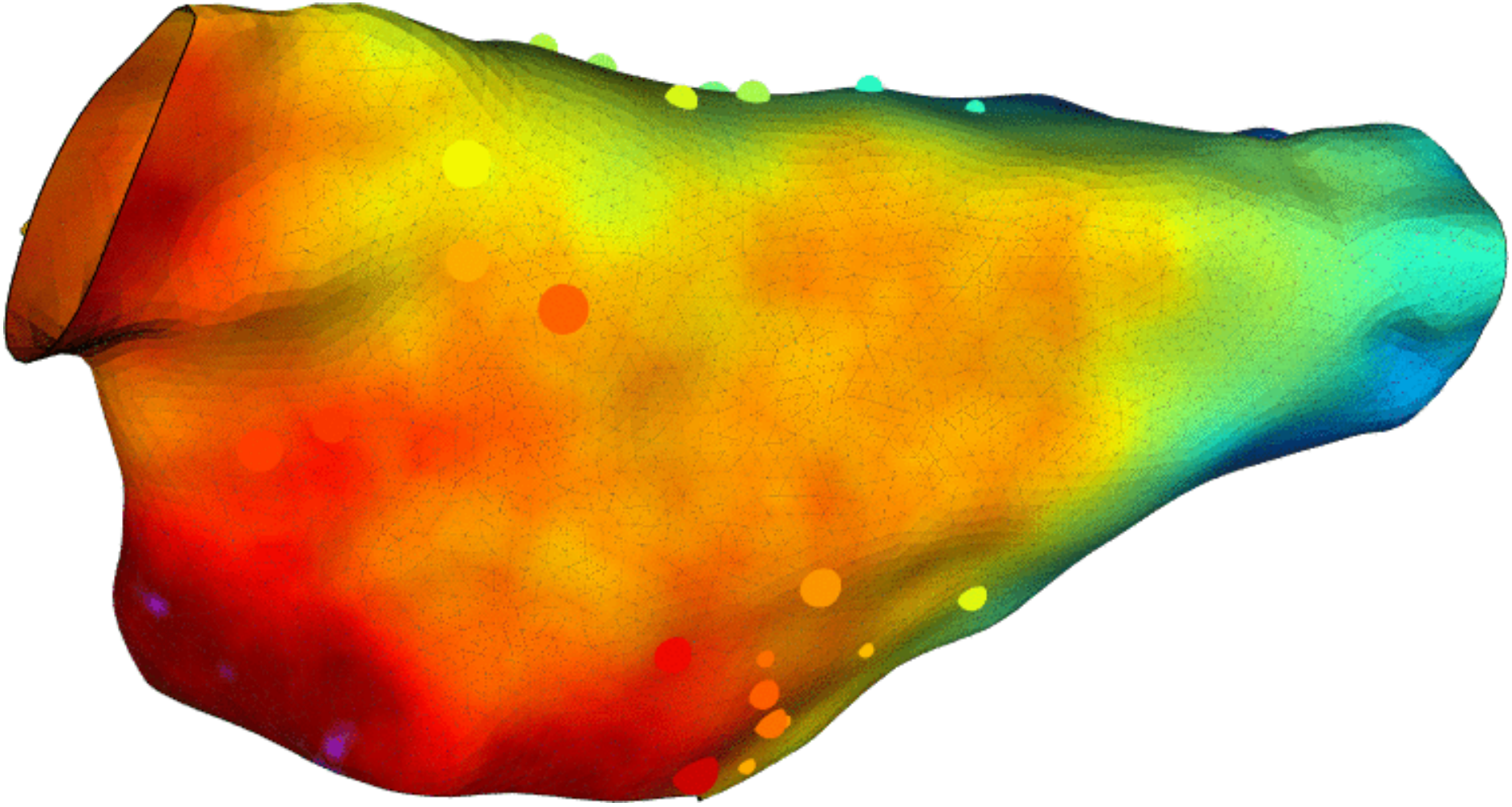
Random samples



Random samples



Random samples



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

We can improve the situation by using a smoother covariance function

Laplacian basis functions

Coveney *et al.* Phil. Trans. Roy. Soc. 2020

There is a duality between stationary covariance functions, and spectral densities (Wiener-Khinchin):

$$S(\omega) = \int k(r) \mathrm{e}^{-i\omega r} \mathrm{d}r$$

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$$S(\omega) = \int k(r) \mathrm{e}^{-i\omega r} \mathrm{d}r$$

Solin and Sarkka (2019) showed that if we use the Laplacian eigenbasis

$$\begin{aligned} -\nabla^2 \phi_j(x) &= \lambda_j \phi_j(x) \qquad & x \in \Omega \\ \phi_j(x) &= 0 & x \in \partial\Omega \end{aligned}$$

then

$$f(x) = \sum w_k \phi_k(x) \qquad \text{with } w_k \sim N(0, S(\sqrt{\lambda_j}))$$

is a GP with spectral density S.

This allows us to

- specify a GP in terms of its spectral density, bypassing the need to explicitly define a covariance function
- work directly with processes on the atrial manifold

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Note that

$$k(x, x') = \sum S(\sqrt{\lambda_j})\phi_i(x)\phi_i(x')$$

and that unlike many other expansions (e.g., Karhunen-Loeve), the eigenfunctions don't change if the hyper-parameters of the GP change (so we only need compute them once).

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and that unlike many other expansions (e.g., Karhunen-Loeve), the eigenfunctions don't change if the hyper-parameters of the GP change (so we only need compute them once).
Truncating the sum gives us an approximate low rank GP

$$k(x, x') \approx \sum_{i=1}^{M} S(\sqrt{\lambda_j})\phi_i(x)\phi_i(x'), \quad f(x) \approx \sum_{i=1}^{M} w_k\phi_k(x)$$

for which inference can be done in $O(M^3)$ operations.

Computing conduction velocities

Interest lies in conduction velocities, which are the inverse of the LAT gradient. The Laplacian eigen expansion allows us to compute these

$$\mathbb{E}\left[\frac{\partial f(\mathbf{x}^*)}{\partial \mathbf{x}^*} \mid \mathcal{D}\right] = \frac{\partial \mathbf{k}_*^{\mathbf{T}}}{\partial \mathbf{x}^*}(\mathbf{K}+\boldsymbol{\Sigma})^{-1}\mathbf{y}$$

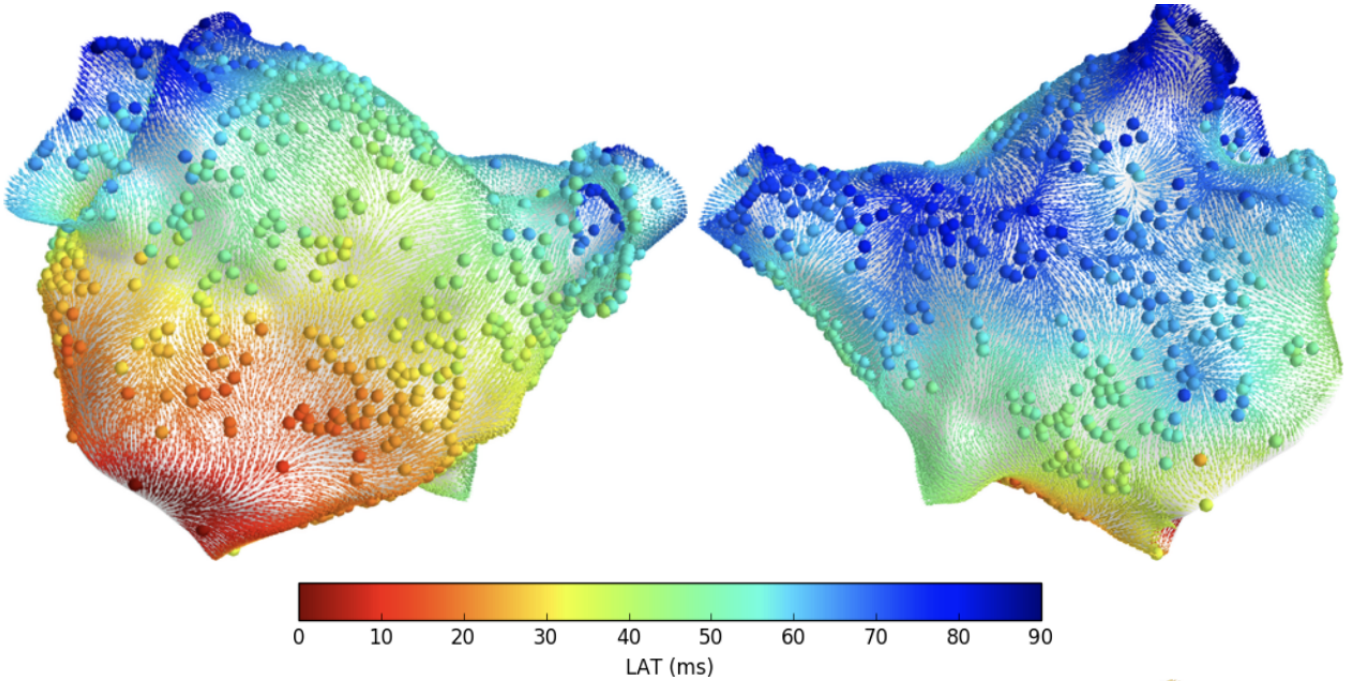
$$\mathbb{V}\left[\frac{\partial f(\mathbf{x}^*)}{\partial \mathbf{x}^*} \mid \mathcal{D}\right] = \tau^2 \left.\frac{\partial^2 k(\mathbf{x_a}, \mathbf{x_b})}{\partial \mathbf{x_a} \partial \mathbf{x_b}}\right|_{\mathbf{x_a}=\mathbf{x_b}=\mathbf{x}^*} - \frac{\partial \mathbf{k}_*^{\mathbf{T}}}{\partial \mathbf{x}^*}(\mathbf{K}+\boldsymbol{\Sigma})^{-1}\frac{\partial \mathbf{k}_*}{\partial \mathbf{x}^*}$$

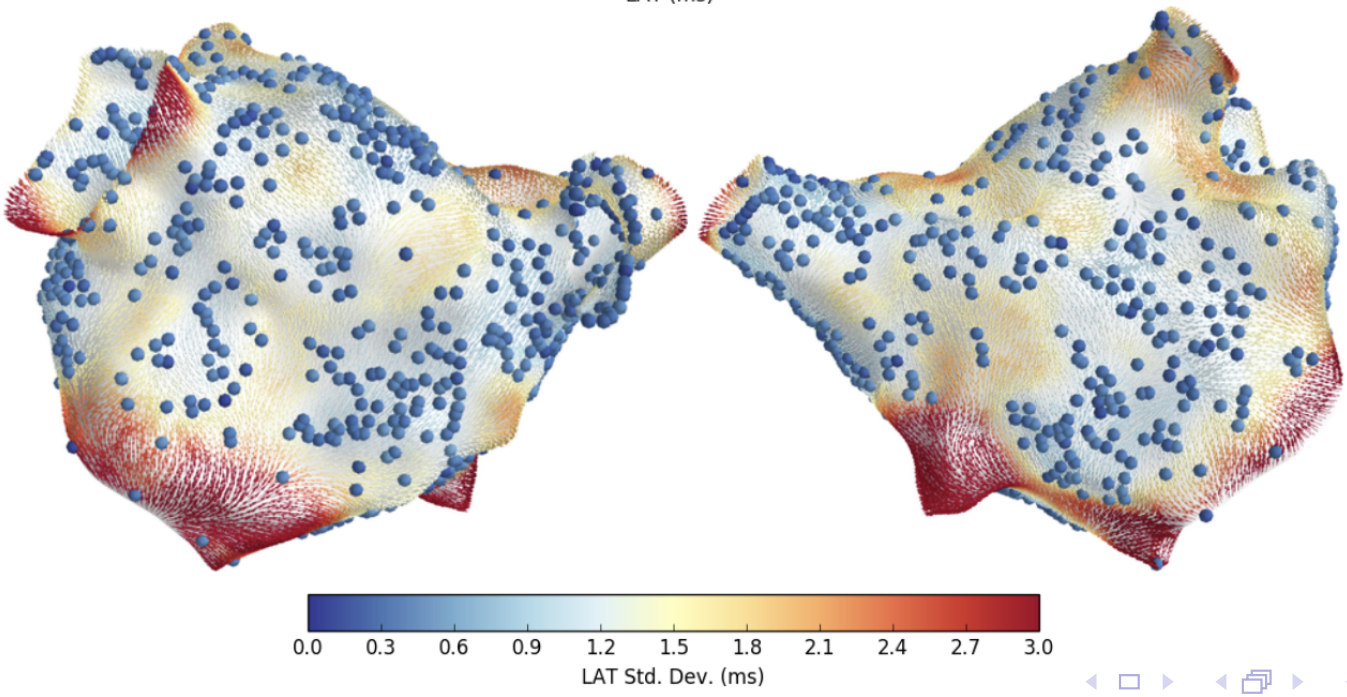
where

$$\frac{dk(x,x')}{dx} = \sum_{i=1}^{M} S(\sqrt{\lambda_j})\frac{d\phi_i}{dx}(x)\phi_i(x')$$

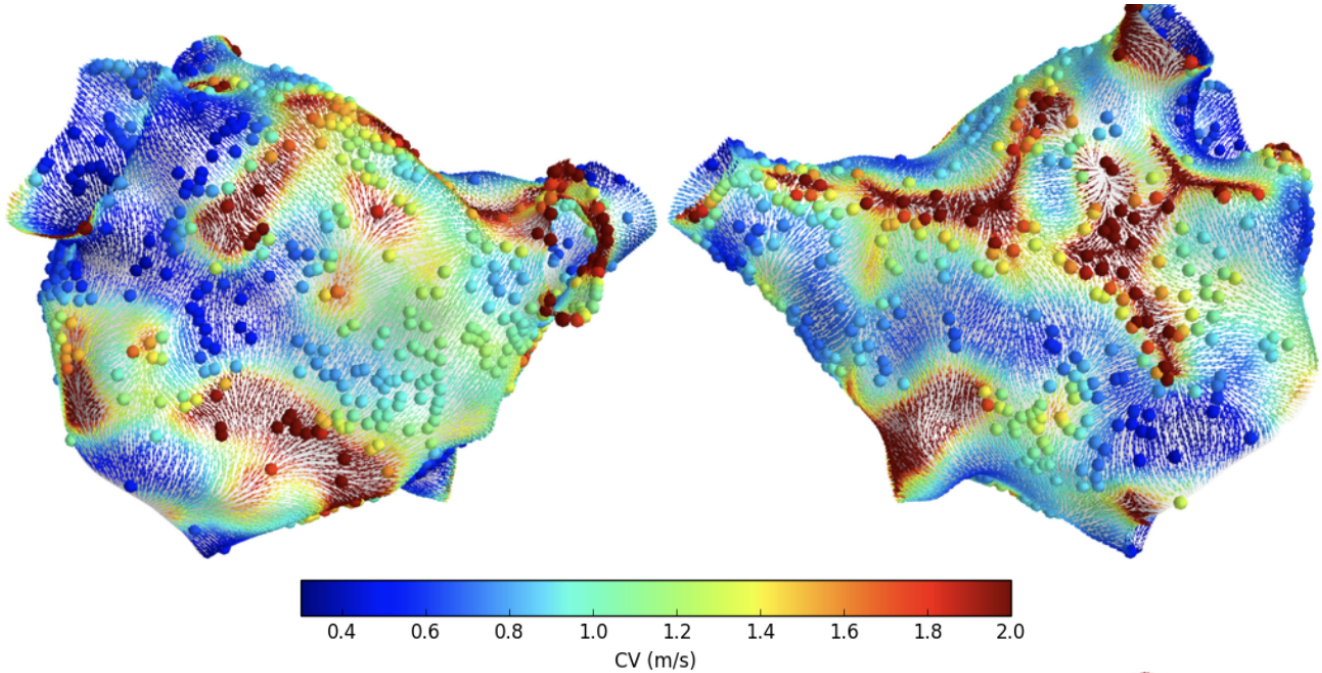
allowing us to compute variance estimates of the estimated conduction velocities...

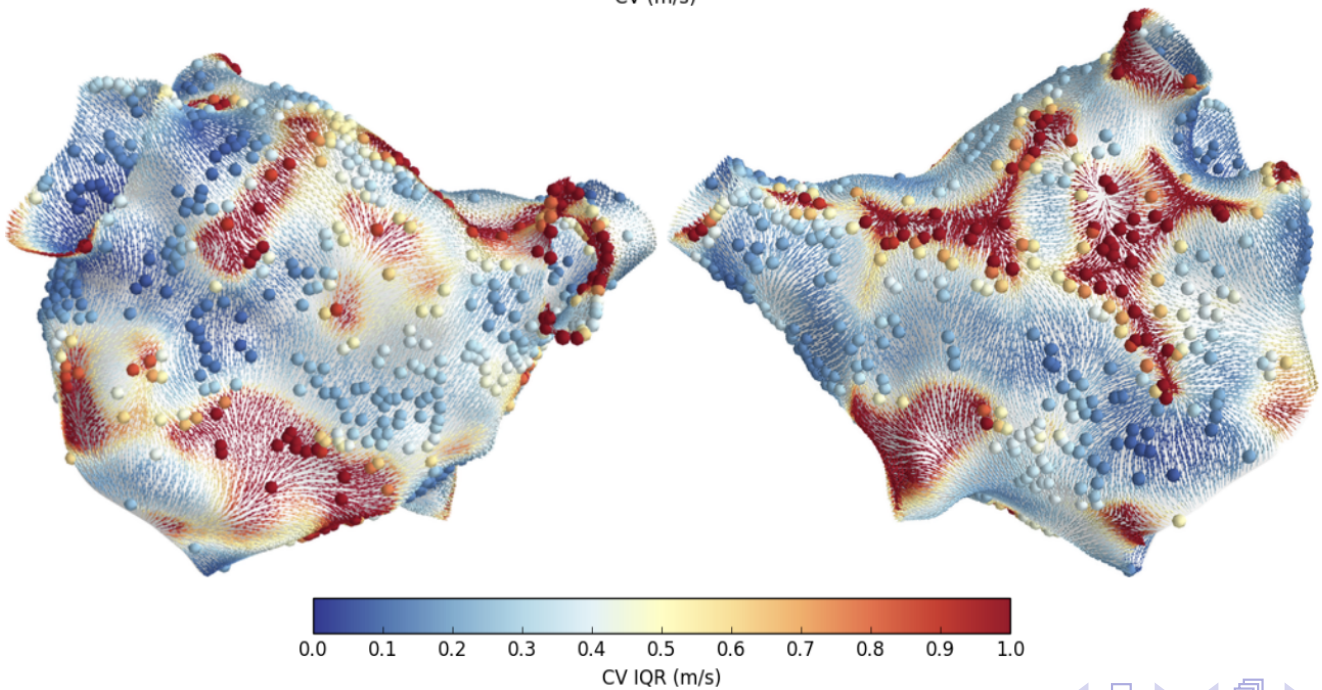
Results


0
10
20
30
40
50
60
70
80
90
LAT (ms)


0.0
0.3
0.6
0.9
1.2
1.5
1.8
2.1
2.4
2.7
3.0
LAT Std. Dev. (ms)

Results


0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
CV (m/s)


0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
CV IQR (m/s)

Problem 3: Learning tissue parameters from complex simulators - ongoing

Incorporating physics

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

- 5 parameters

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Electrical activation across the atrium is simulated using a monodomain equation 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 $\theta \in \mathbb{R}^{5N_{cell}}$, which predicts the local activation time map for a given pacing.

- We need to estimate the parameters from the EP data.

Parameter estimation

At present we have a working heuristic approach

- At each location x_i, infer $\theta(x_i)$ using ABC with a look-up table of simulations
- Interpolate $\theta(x)$ across the atrium.

In-procedure calibration

In future we need to train a digital twin during a procedure.

- MRI obtained pre-procedure to learn atrial geometry and fibrotic regions
- In-procedure, we record electrophysiology measurements D
- Update prior belief about tissue parameters, and predict the result of ablation therapy.

  $$\pi(\theta(\cdot)|D) \qquad \mathbb{P}(E|D)$$

  in a ~ 30 min window during the procedure

We can do as much computation as needed pre-procedure, but inference/training in-procedure needs to be fast.

In procedure calibration

Some options

- Approximate Bayesian computation: use a precomputed set of simulations $\{\theta_i, S(\theta_i)\}$ and accept θ_i if $|S(\theta_i) - D|$ is small
- History matching: train a GP emulator to predict $S(\theta)$ for any θ in advance of surgery, and then in-procedure use the emulator to find plausible values of θ.
- Amortized-VAE: seek a variational approximation to the posterior

$$q(\theta|D) = \mathcal{N}(\theta; m, \Sigma)$$

and train a neural net to predict this variational approximation for any given dataset D

$$m(D), \quad \Sigma(D)$$

All options will require effective dimension reduction of θ (e.g. using sensitivity analysis/active subspaces etc)

Conclusions

- At present, catheter ablation doesn't use computer simulation to guide therapy.
- By building a digital twin of a patient, we may be able to improve patient outcomes
  - predict tachycardia
  - for patients suffering from heart failure and arrhythmia infer index disease
- However, there are a huge number of uncertain parameters we need to estimate from limited noisy data.
  - need to find regularities in the problem to allow us to reduce dimension sufficiently in order to make inference possible
  - Unknown if we can constrain parameters sufficiently (either via better data or better population priors) to accurately predict.
- Will it be possible to do this in real time?

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Thank you for listening!