Probabilistic Calibration of Personalised Heart Models from Sparse and Noisy Measurements

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Outline

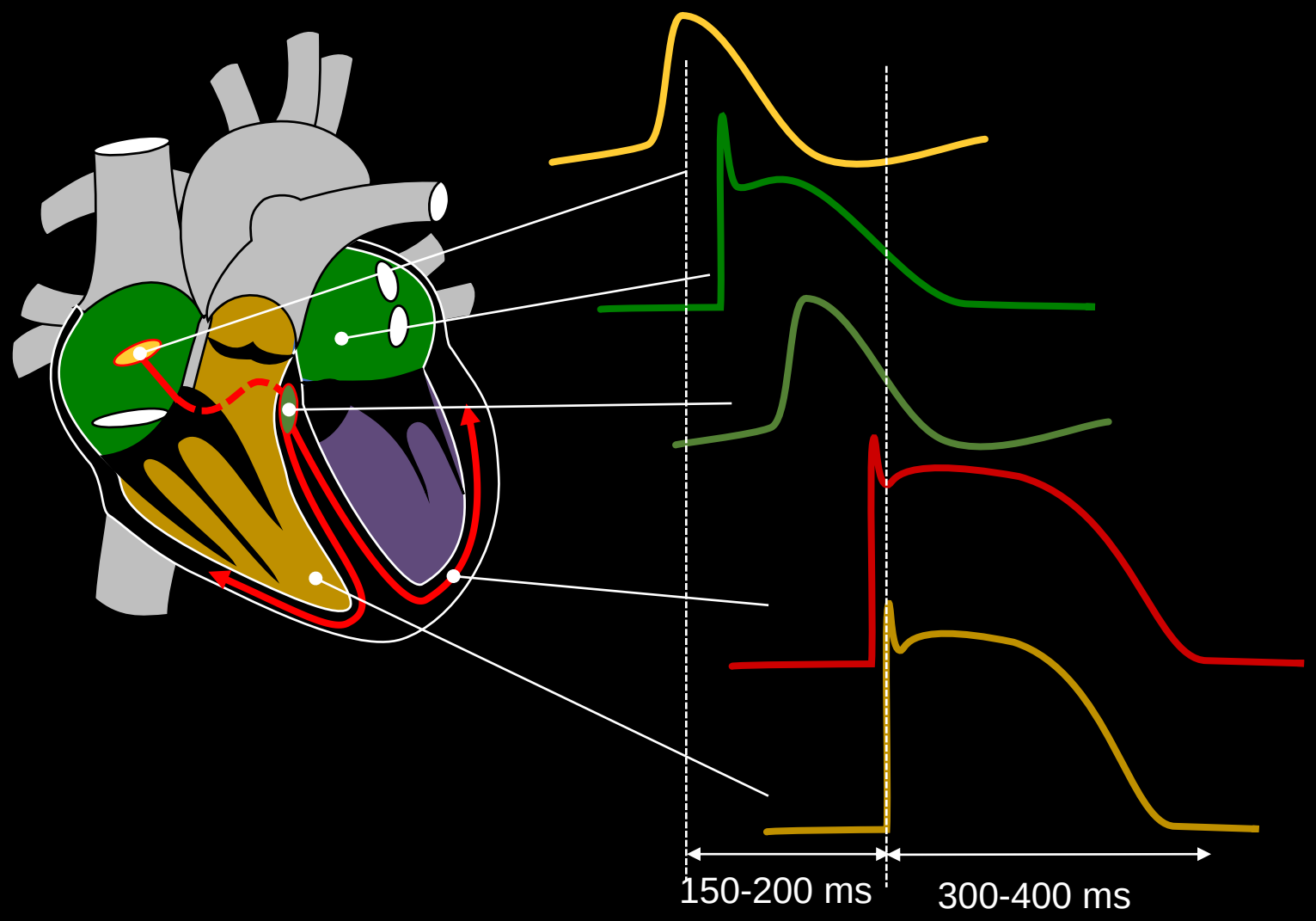
Overall aim – personalized calibration of a spatially extended model, from sparse and noisy measurements.

- Some background, and why the application is important.
- Interpolation of uncertain measurements over a manifold.
- (Calibration of model based on measurements.)
- (Interpolation of model parameters over the manifold.)
- Next steps

(Validation and verification are topics for another day!)

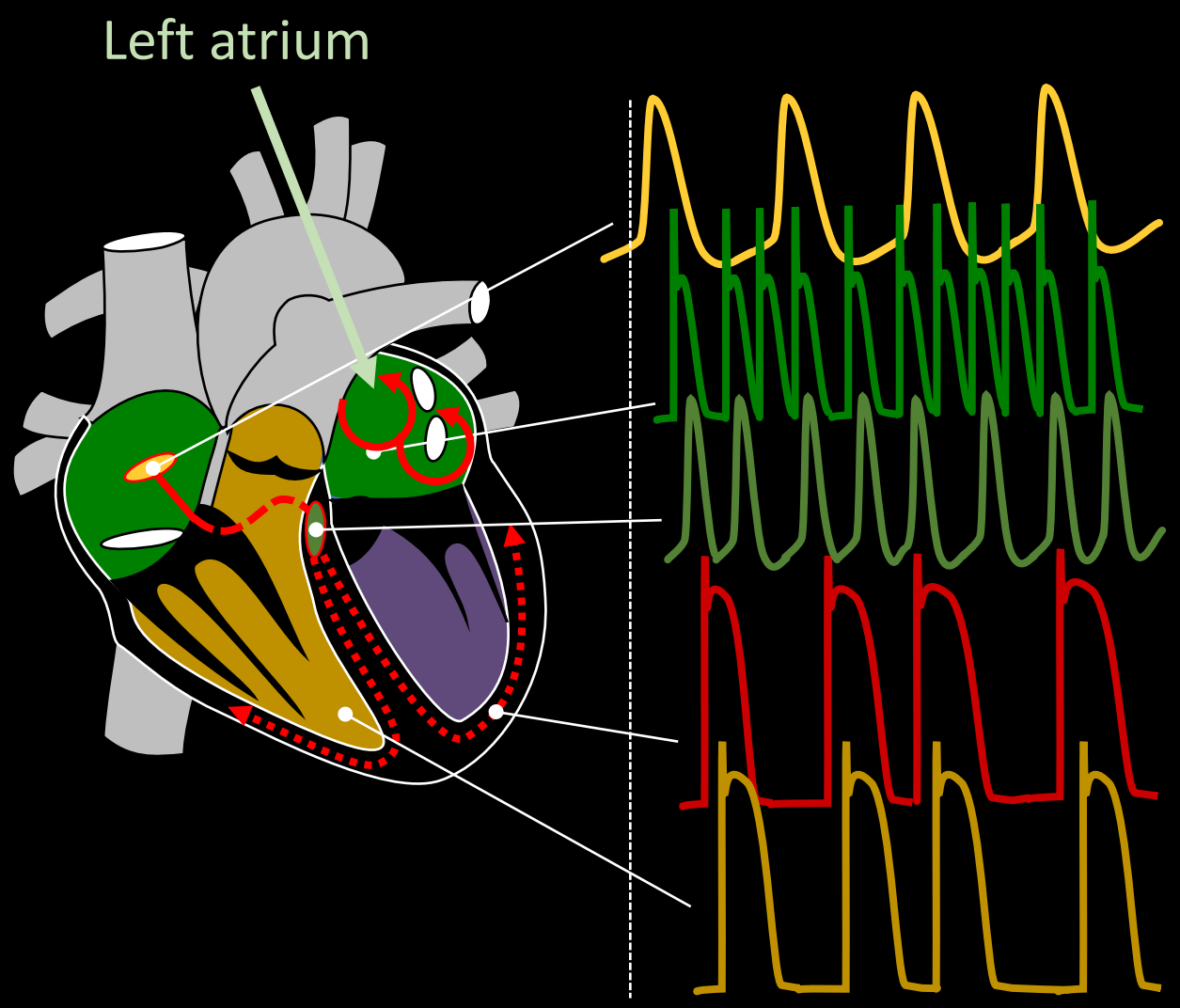
Background

- Heart is an electromechanical pump
- Abnormal formation or propagation of electrical activity is an ***arrhythmia***.



Background

- Heart is an electromechanical pump
- Abnormal formation or propagation of electrical activity is an ***arrhythmia***.
- Atrial fibrillation (AF) is the most prevalent arrhythmia.
- Persistent AF can be treated by **radiofrequency ablation**.



Atrial fibrillation

- Atrial fibrillation in patients is frequently sustained by activity in the left atrium.
- RF ablation in the LA can suppress AF.
- ***Aim to predict success from personalised model of left atrial electrophysiology.***

- Calibration (personalisation):
  - Pace at different locations, with different S1 and S1S2 intervals.
  - Sparse measurements of local activation time (LAT) and effective refractory period (ERP).
  - Interpolation of measurements over LA mesh.
  - Identification of parameter fields.

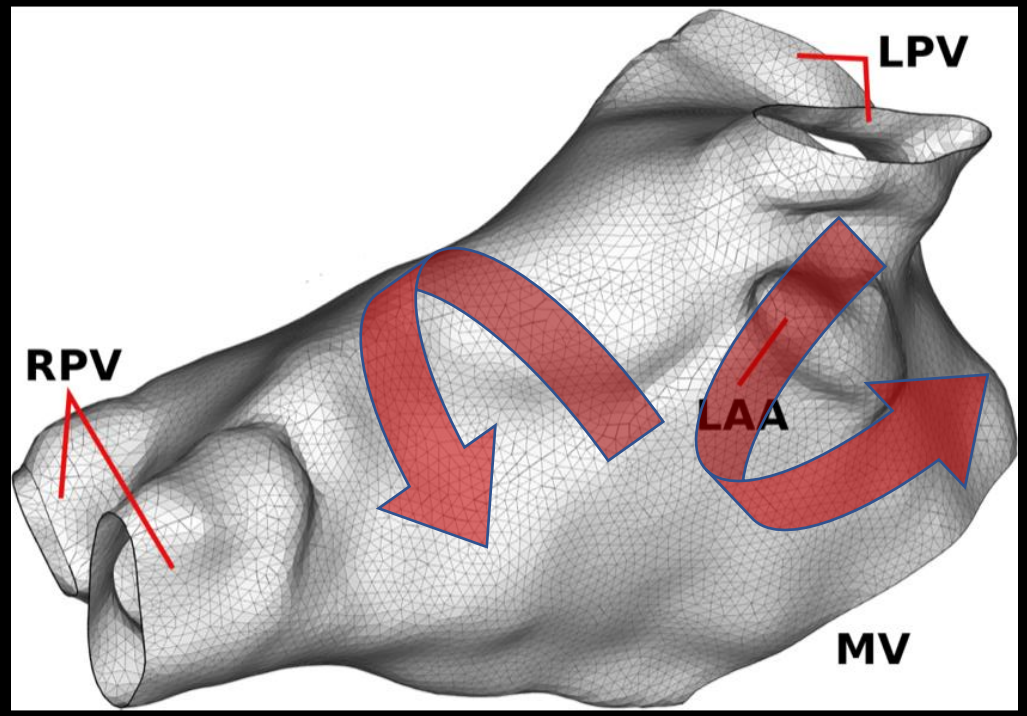


Image from Coveney et al *IEEE Trans Biomed Eng* 2019 10.1109/TBME.2019.2908486

Model of electrical activation

- Very simple phenomenological model of human atrial electrophysiology– Corrado, *Math Biosci* 2016 https://doi.org/10.1016/j.mbs.2016.08.010

$$\frac{\partial V_m}{\partial t} = D\nabla^2 V_m + h\frac{V_m(V_m - V_{gate})(1 - V_m)}{\tau_{in}} - (1-h)\frac{V_m}{\tau_{out}} + J_{stim}$$

$$\frac{\partial h}{\partial t} = \begin{cases} (1-h)/\tau_{open} & \text{if } V_m \leq V_{gate} \\ -h/\tau_{close} & \text{otherwise} \end{cases}$$

- **2 states:** V_m and h.
- **5 parameters:** D, tau_{in}, tau_{out}, tau_{open}, tau_{close} (V_{gate} fixed, J_{stim} stimulus).
- In the clinical setting, we can't measure either V_m or h, but we can indirectly estimate conduction velocity (CV) and action potential duration (APD).
- ***Need to characterise CV and APD at different pacing rates – restitution***.

Key ideas

- Electrical activity spreads over a manifold, modelled by reaction-diffusion PDE.
- We can generate (stationary) mesh from medical images.
- Cardiologist can make limited measurements of local activation times (LAT) and action potential duration (APD); these are uncertain.
- We wish to use these measurements to infer model parameters.
- Then sample these parameters to run simulations that can be used to predict treatment outcomes.

Uncertainties and challenges

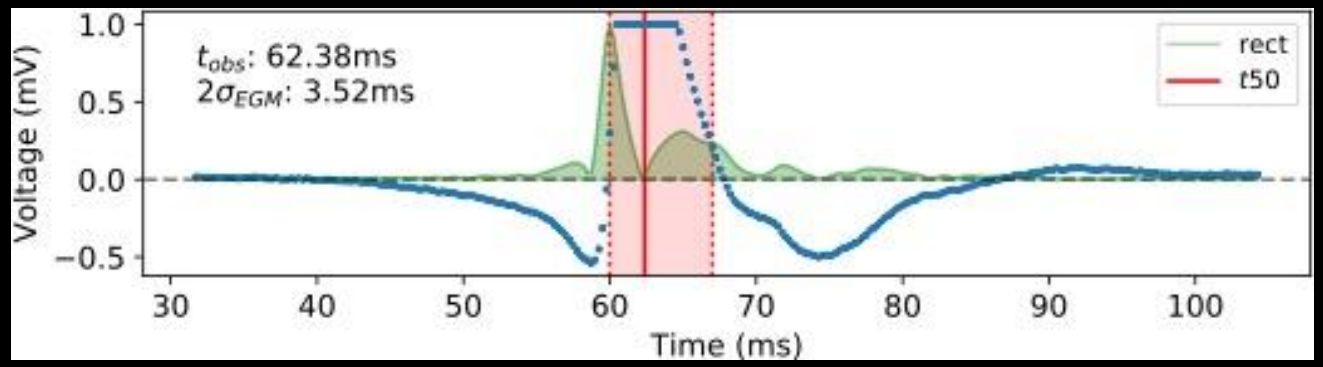
Sources of uncertainty in the calibration process include:

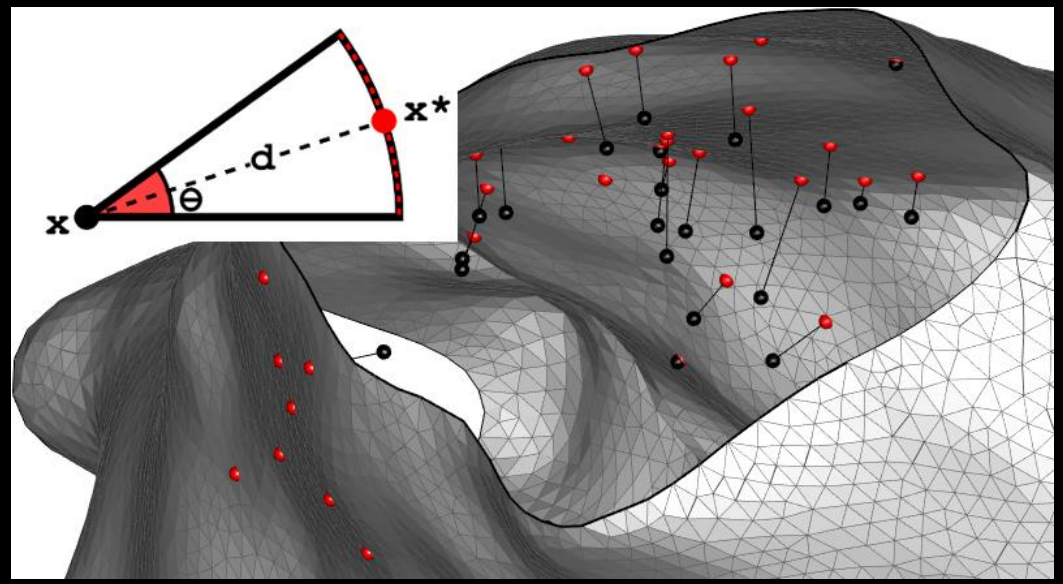
- ***Anatomical mesh*** – the atria move, and imaging is associated with uncertainty. See Corrado et al *Medical Image Analysis* 2020 https://doi.org/10.1016/j.media.2019.101626
- ***Registration*** of anatomical mesh (MRI) and location of recording catheters (mapping system).
- ***Noise*** in electrograms limits measurement of local activation time (LAT).
- ***Discrepancy*** between model and real system.

Challenges for models in the clinical setting :

- ***Interpolation*** over a complex manifold – can't use Euclidean or simple geodesic distances.
- ***Sampling*** posterior distributions when nonlinear operations are involved ($CV \propto 1/\nabla LAT$).
- ***Identifiability*** of model parameters given available measurements.

Uncertain conduction velocity (1/∇LAT)





- Blue dots – filtered bipolar electrogram.
- Green – differentiated, rectified, and smoothed signal.
- Red line is observed LAT t_{50}.
- Red dashed line shows t_{25} and t_{75}.

Error model for LAT observations

$$t_{obs} = LAT_{EGM} + \varepsilon_{EGM}\,, \quad \epsilon_{EGM} = \mathcal{N}(0, \sigma_{EGM}^2)$$

$$t_{obs} = t_{50}\,, \sigma_{EGM} = (t_{75} - t_{25})/4$$

Error model to account for misalignment of mesh and catheter location

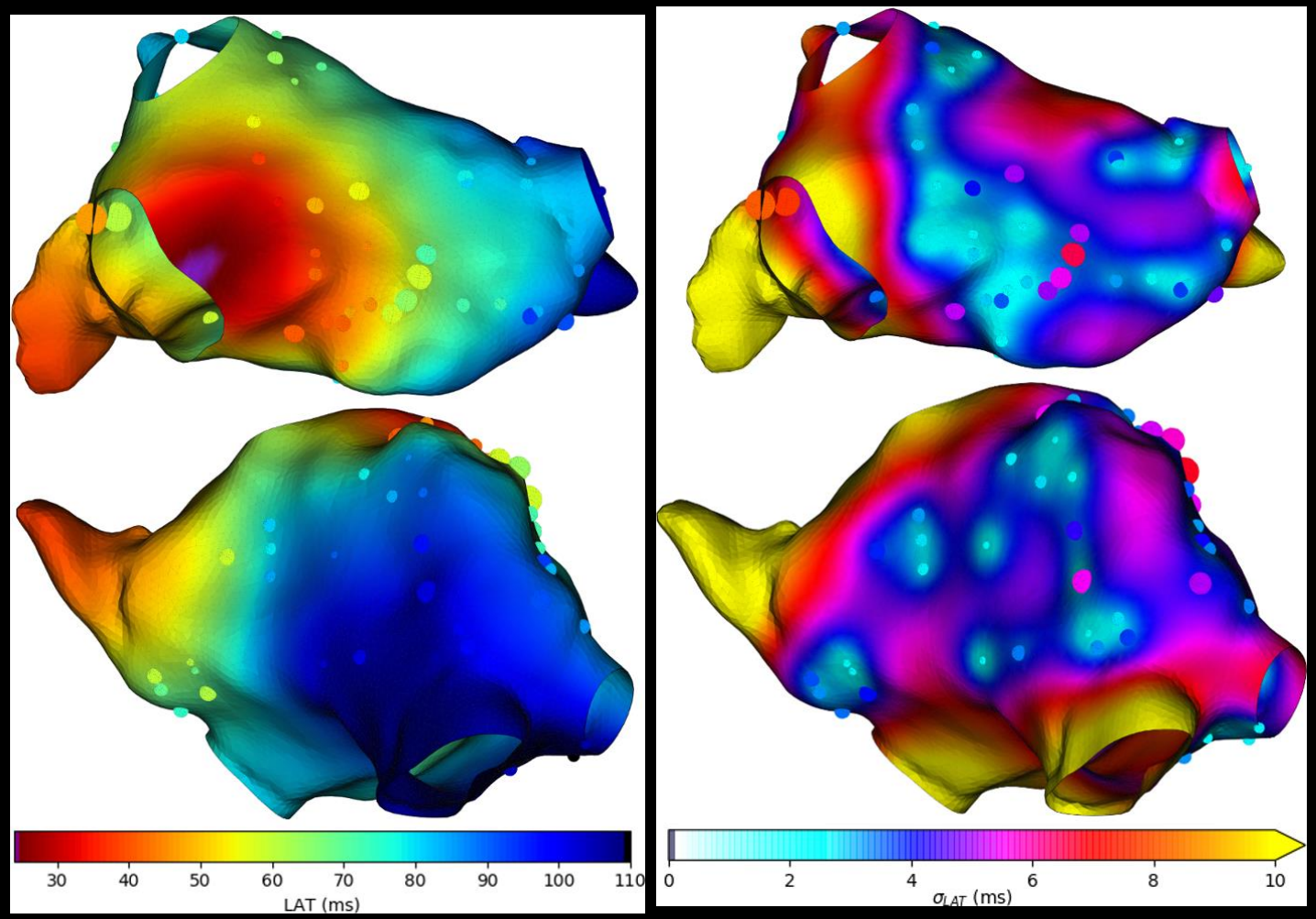
$$LAT_{EGM} = LAT_{mesh} + \varepsilon_{pos}\,, \quad \epsilon_{pos} = \mathcal{N}(0, \sigma_{pos}^2)$$

$$2\sigma_{pos} = \Delta t/2\,, \Delta t = \frac{d\theta}{CV} = \frac{d\,2\pi}{10 \cdot 0.35}$$

See Coveney et al *IEEE Trans Biomed Eng* 2019 10.1109/TBME.2019.2908486

LAT interpolation – 1

- Initial approach used a simple Gaussian process
  $$LAT(\boldsymbol{x}) \sim \mathcal{GP}(0, cov(\boldsymbol{x}, \boldsymbol{x}'))$$
- But Euclidian distances are not appropriate for covariance.
- Gaussian Markov Random Fields allow Gaussian field to be represented on the mesh probabilistically.
- Variance accrues from (i) uncertainty in LAT, and (ii) uncertainties in interpolation.
- Bigger variance in regions with lower recording density.

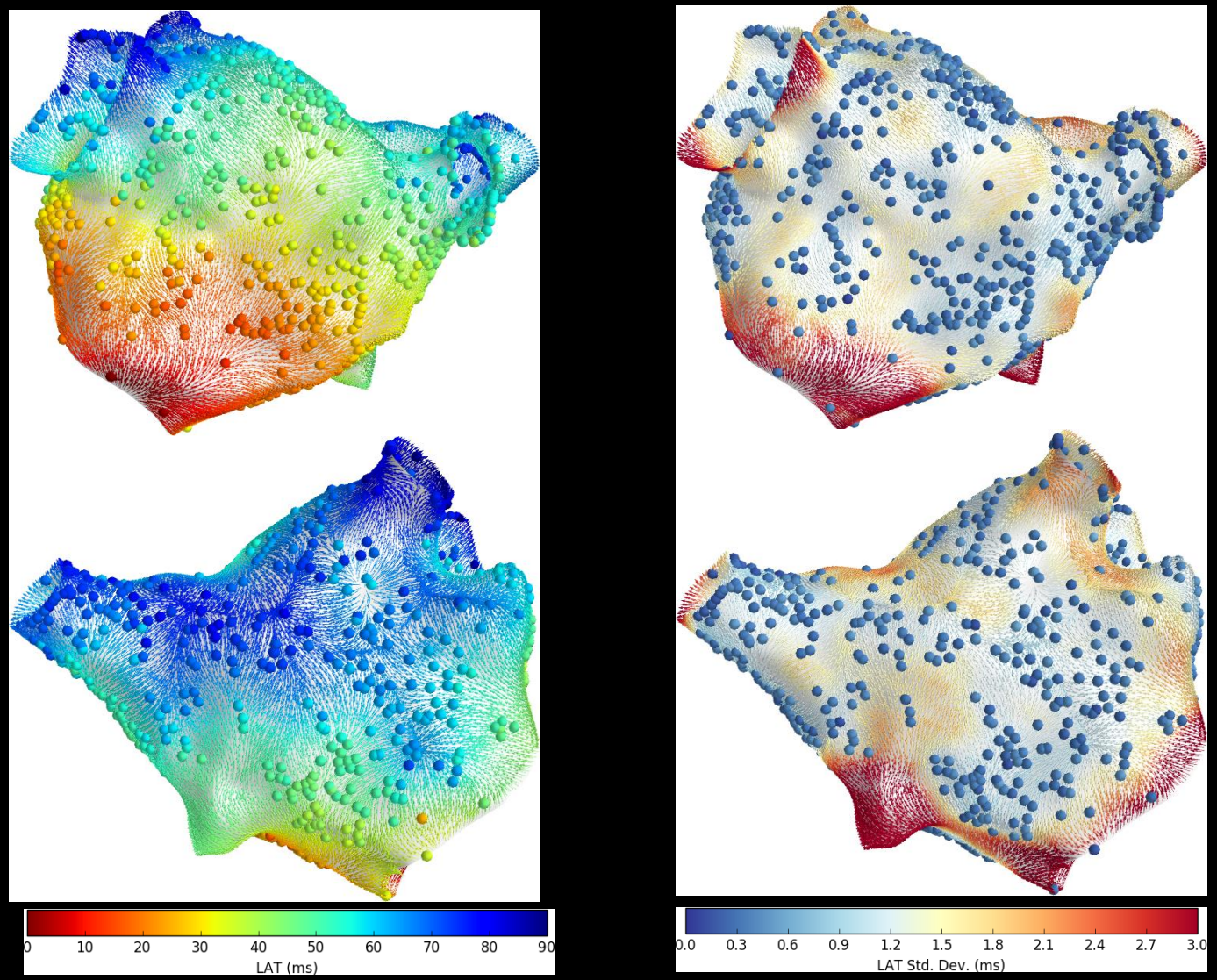


Example LAT map showing posterior mean and variance based on ***patient data***. Spheres show LAT observations. Sphere sizes increase with observation variance.

Coveney et al *IEEE Trans Biomed Eng* 2019 10.1109/TBME.2019.2908486

LAT interpolation – 2

- Refined approach with kernel spectral density and eigenvectors/values of Laplacian on atrial manifold.
- LAT is a GP
- Precompute first 16 eigenvectors/values of the Laplacian.
- Learnwights from uncertain observations of LAT.
- GPMI – Gaussian process manifold interpolation.

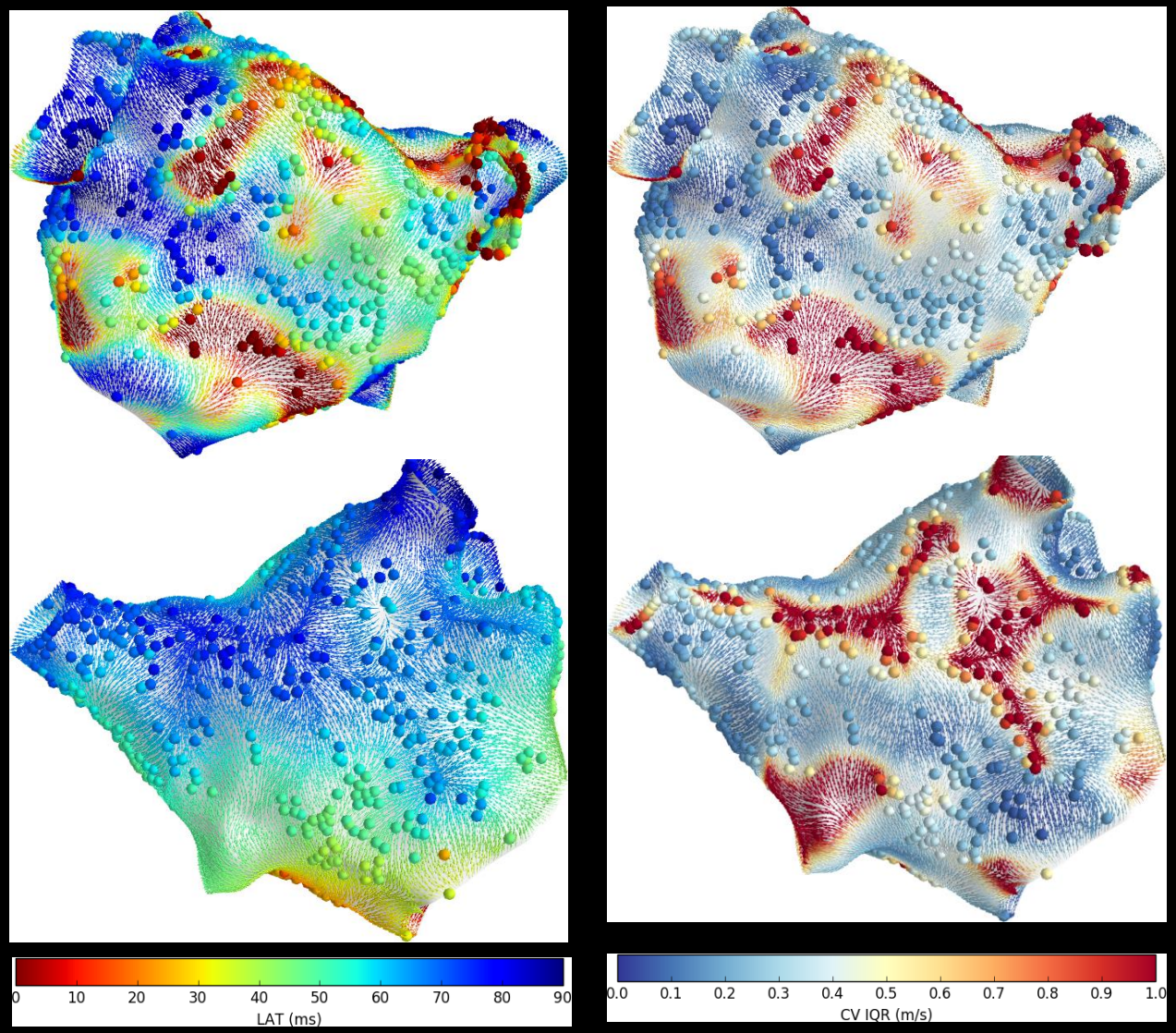


Example LAT map showing posterior mean and variance of LAT recovered from ***simulation***. Spheres show recording locations. Arrows indicate gradients of LAT

Coveney et al *Phil Trans Royal Soc A* 2020 https://doi.org/10.1098/rsta.2019.0345

Uncertain CV

- Not straightforward because of nonlinearity: $CV \propto 1/\nabla LAT$
- Regions where ∇LAT is small (e.g. wave collisions) produce large CV that can tend to ∞.
- Posterior mean of $1/\nabla LAT$ can be used to generate mean CV at centre of each mesh triangle.
- Sampling (2000 samples) can be used to obtain percentiles of ∇LAT, which can be inverted to determine uncertainty in CV.



Example CV map showing posterior mean and IQR of CV recovered from simulation.

Coveney et al *Phil Trans Royal Soc A* 2020 https://doi.org/10.1098/rsta.2019.0345

Model of electrical activation

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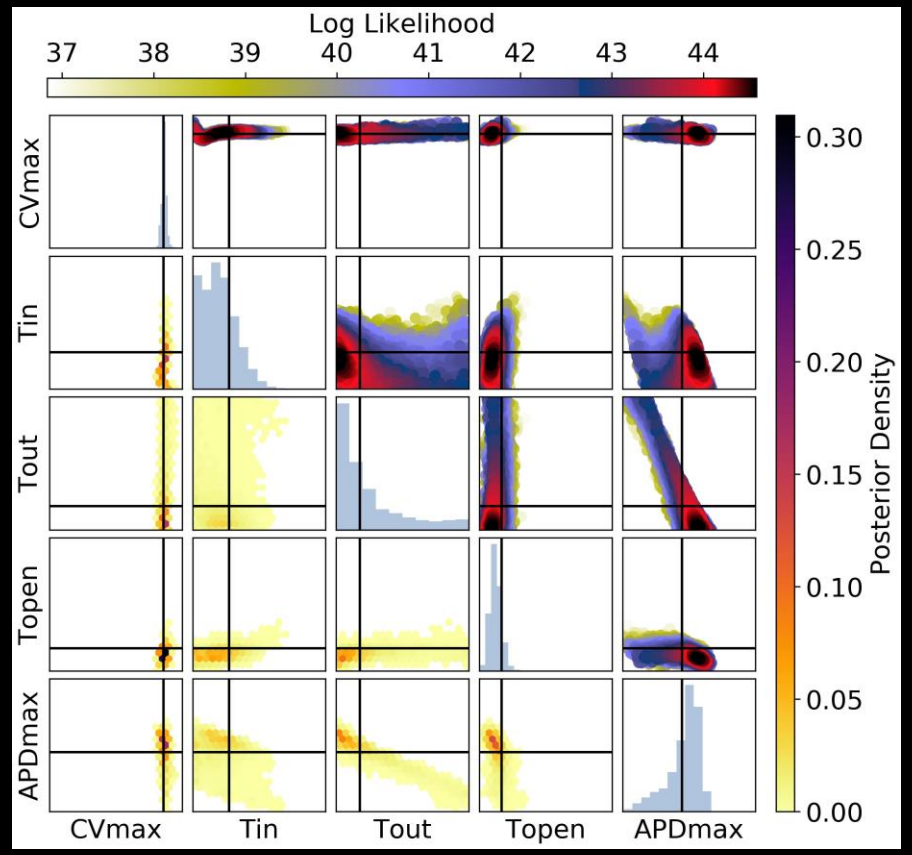
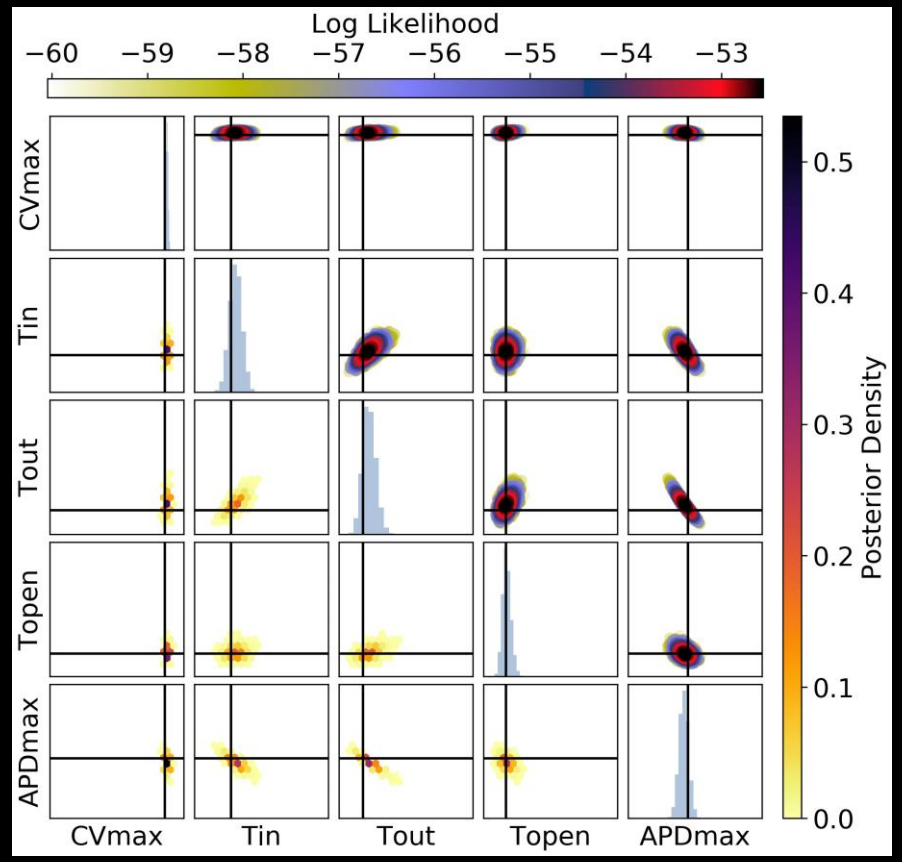
Model calibration

- Getting from measurements of LAT to CV on a manifold ***with uncertainty*** was hard – ***nonlinearity***.
- In general, calibration was not easy because model parameters do not map to uniquely observable quantities – ***model identifiability***.
- There also limits on what measurements can be made.
- How we solved this problem – Coveney et al, *Front Physiol* 2021 https://doi.org/10.3389/fphys.2021.693015
  - Re-parameterise model so that observables become parameters.
  - PCA of APD and CV restitution, sensitivity of each component to model parameters.
  - Build ***emulators*** of APD and CV restitution.
  - Use MCMC on emulators to estimate model (re-)parameters.

Example calibration

- Aim to recover model parameters used to simulate measurements, with added noise.
- Black lines are true values.
- Two different (simulated) protocols.





Coveney et al, *Front Physiol* 2021
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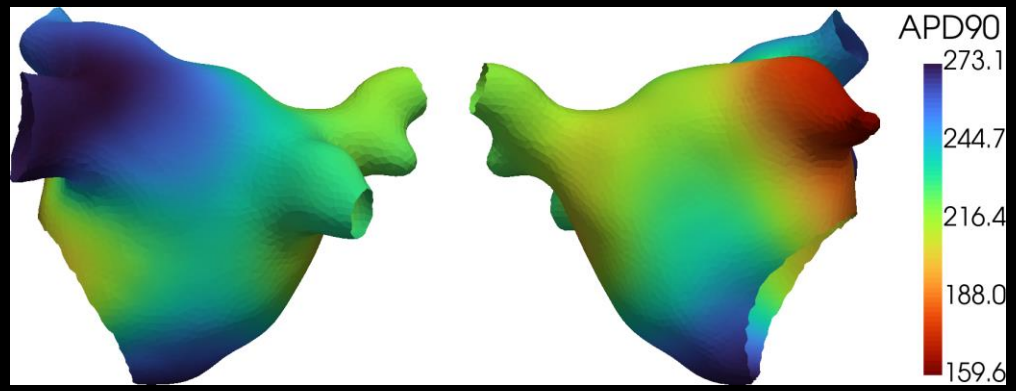
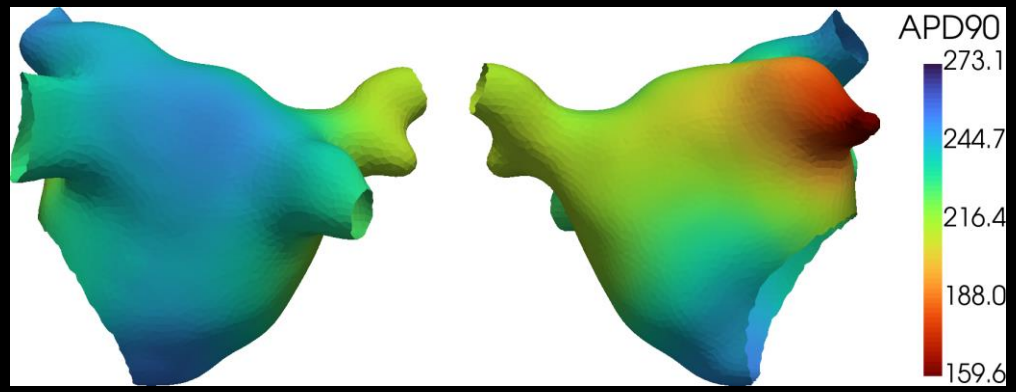
Conclusions and lessons learned

- Calibration of cardiac electrophysiology models from sparse and uncertain clinical data is challenging.
- Identifiability of parameters from observations is a significant obstacle.
- But probabilistic approaches and emulation are powerful tools.
- Enable design of optimal pacing protocols.
- And preliminary results show that parameters from simulations can be recovered.

APD90 from initial simulation



APD90 from simulation with inferred model parameters



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Cardiac modelling and data analysis – Cesare Corrado, Caroline Roney, Steve Niederer (KCL)

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Model reparameterisation

- ***Reparameterise*** model so APD_{max} and CV_{max} are parameters.
- ***Model evaluations*** sampling parameter space to give restitution curves.
- ***Dimensionality reduction*** of restitution curves with PCA.
- ***Restitution curve emulators*** GPs to predict restitution from parameters, based on PCs.
- ***Sensitivity analysis*** using RCEs

$$CV_{max} = 0.5(1 - 2V_{gate})\sqrt{2D/\tau_{in}}$$

$$APD_{max} = \tau_{close}\log(1 + \tau_{out}(1 - V_{gate})^2/4\tau_{in})$$

Restitution

- ***Reparameterise*** model so APD_{max} and CV_{max} are parameters.
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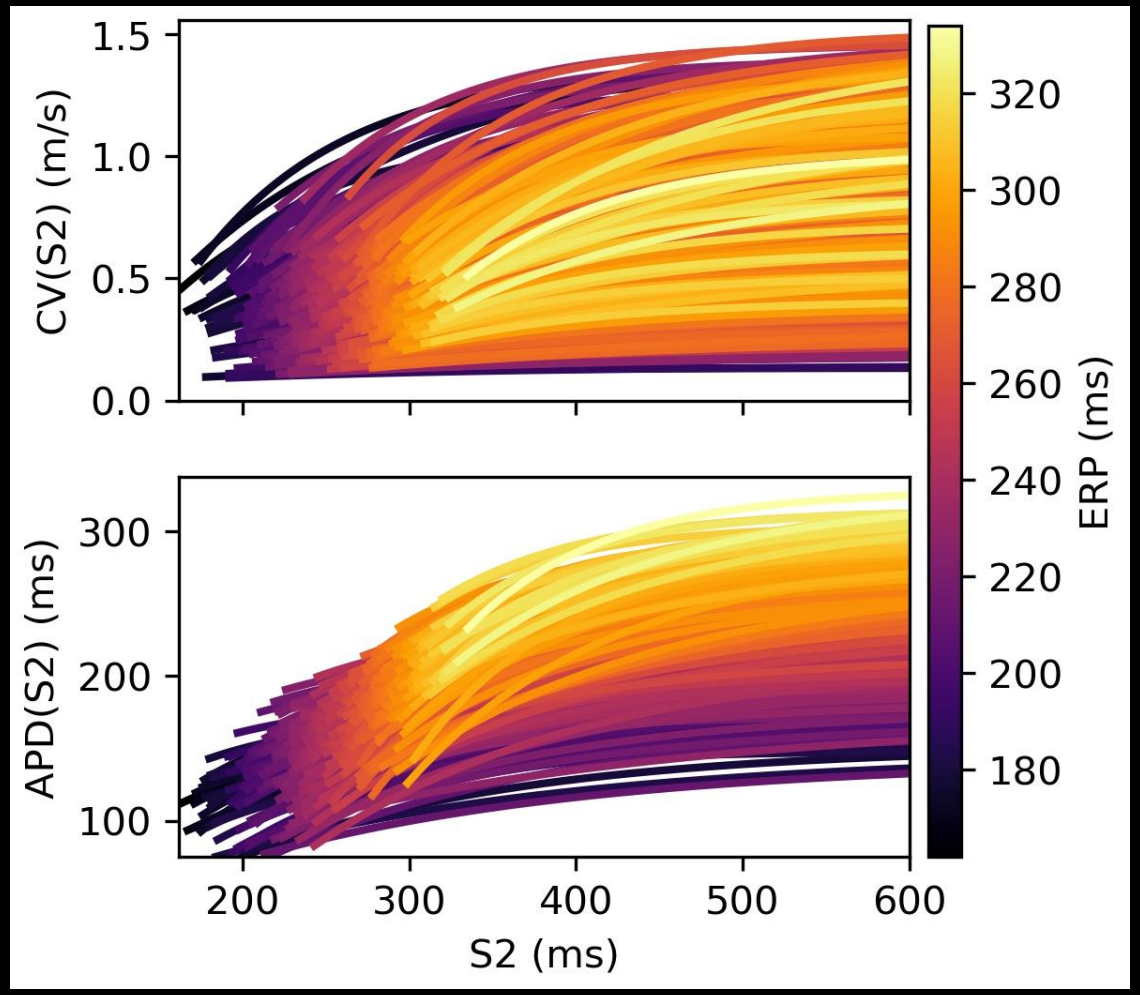

Restitution curves generated from 500 samples of 5D parameter space, model evaluated using this tissue strip paced from one end.

Coveney et al, *Front Physiol* 2021
https://doi.org/10.3389/fphys.2021.69301

Decomposition

- ***Reparameterise*** model so APD_{max} and CV_{max} are parameters.
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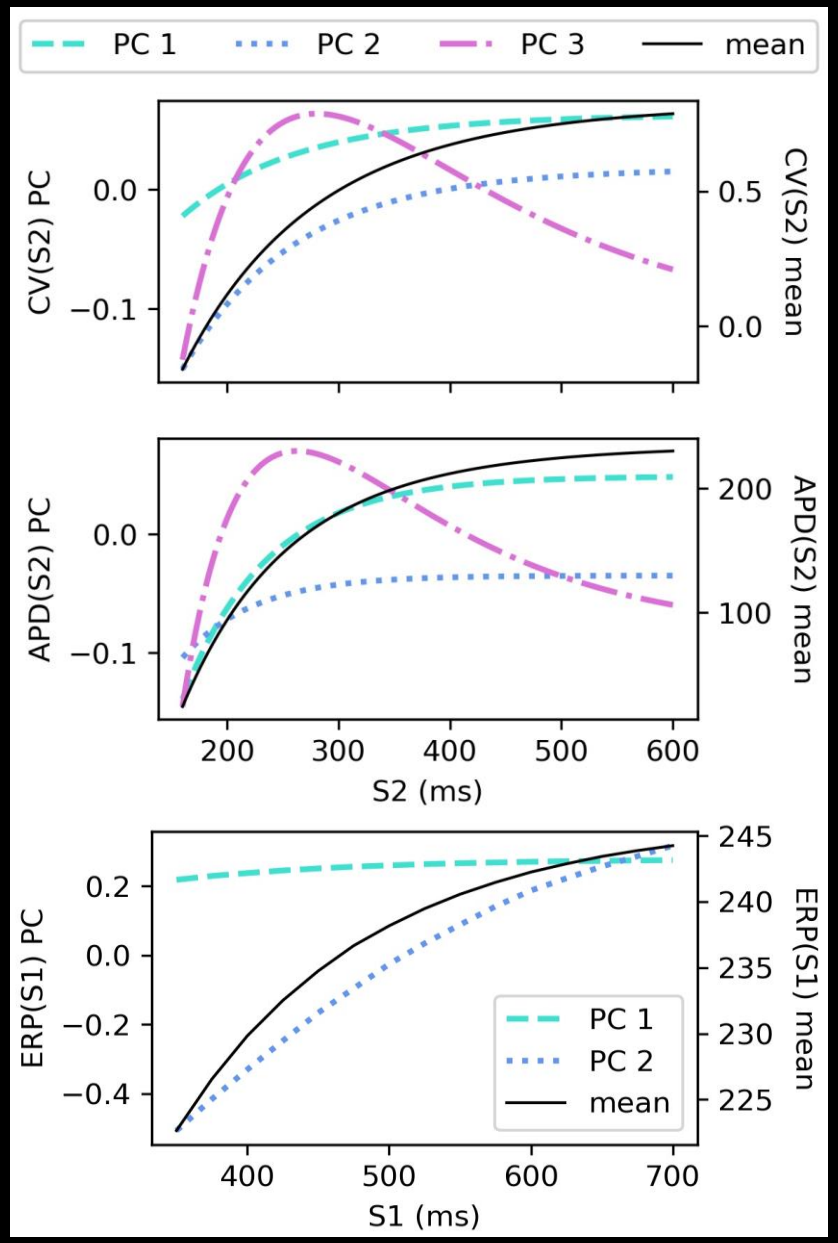

Coveney et al, *Front Physiol* 2021
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Restitution curve emulators

- ***Reparameterise*** model so APD_{max} and CV_{max} are parameters.
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PCA provides expansion of restitution curves:

$$F(S2) \approx \Phi_0(S2) + \sum_c f_c \cdot \Phi_c(S2),$$

RCEs can emulate restitution curves for new parameters **x***

$$\mathcal{F}(\mathbf{x}^*, S2) \sim \mathcal{GP}\left(\mathcal{M}(\mathbf{x}^*, S2), \mathcal{V}(\mathbf{x}^*, S2)\right)$$

$$\mathcal{M}(\mathbf{x}^*, S2) = \Phi_0(S2) + \sum \mathcal{M}_c(\mathbf{x}^*) \cdot \Phi_c(S2)$$

$$\mathcal{V}(\mathbf{x}^*, S2) = \sum \mathcal{V}_c(\mathbf{x}^*) \cdot \Phi_c(S2)^2$$

Sensitivity analysis

- ***Reparameterise*** model so APD_{max} and CV_{max} are parameters.
- ***Model evaluations*** sampling parameter space to give restitution curves.
- ***Dimensionality reduction*** of restitution curves with PCA.
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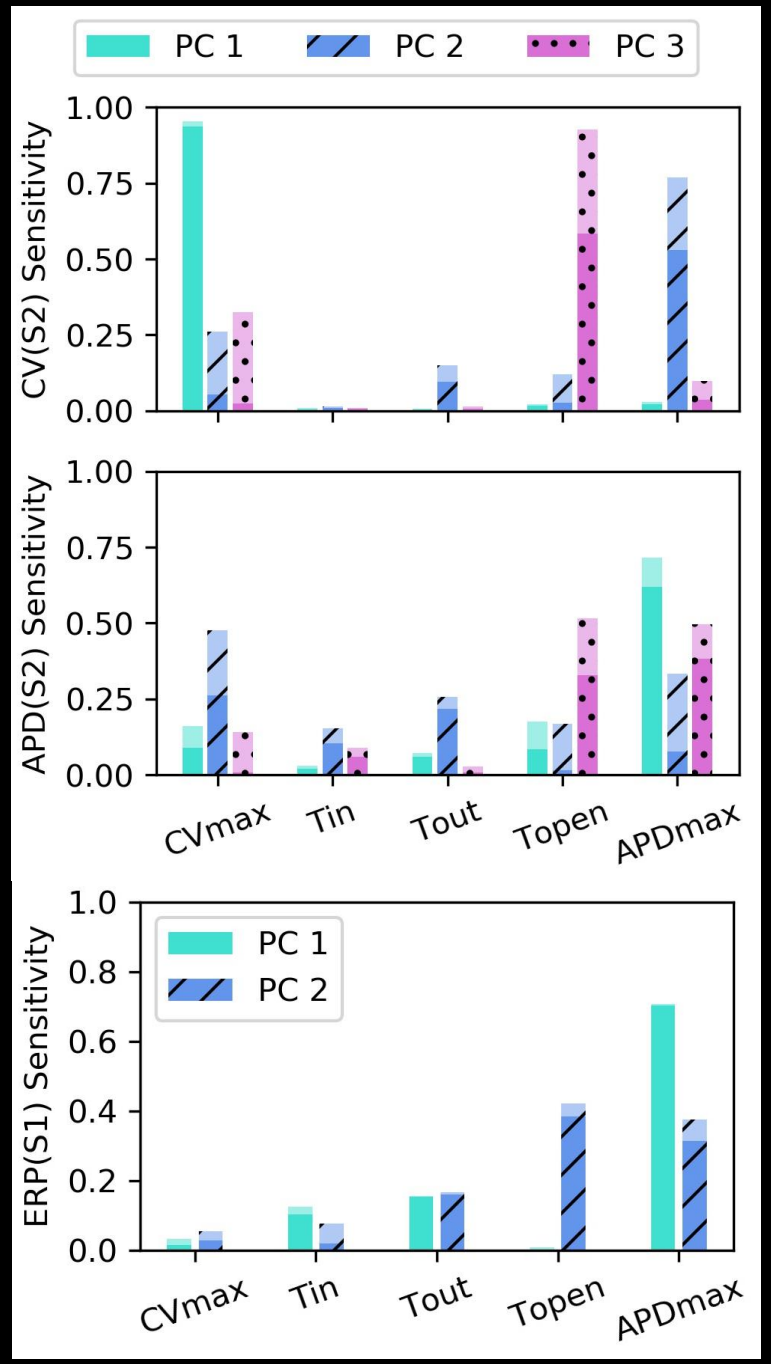
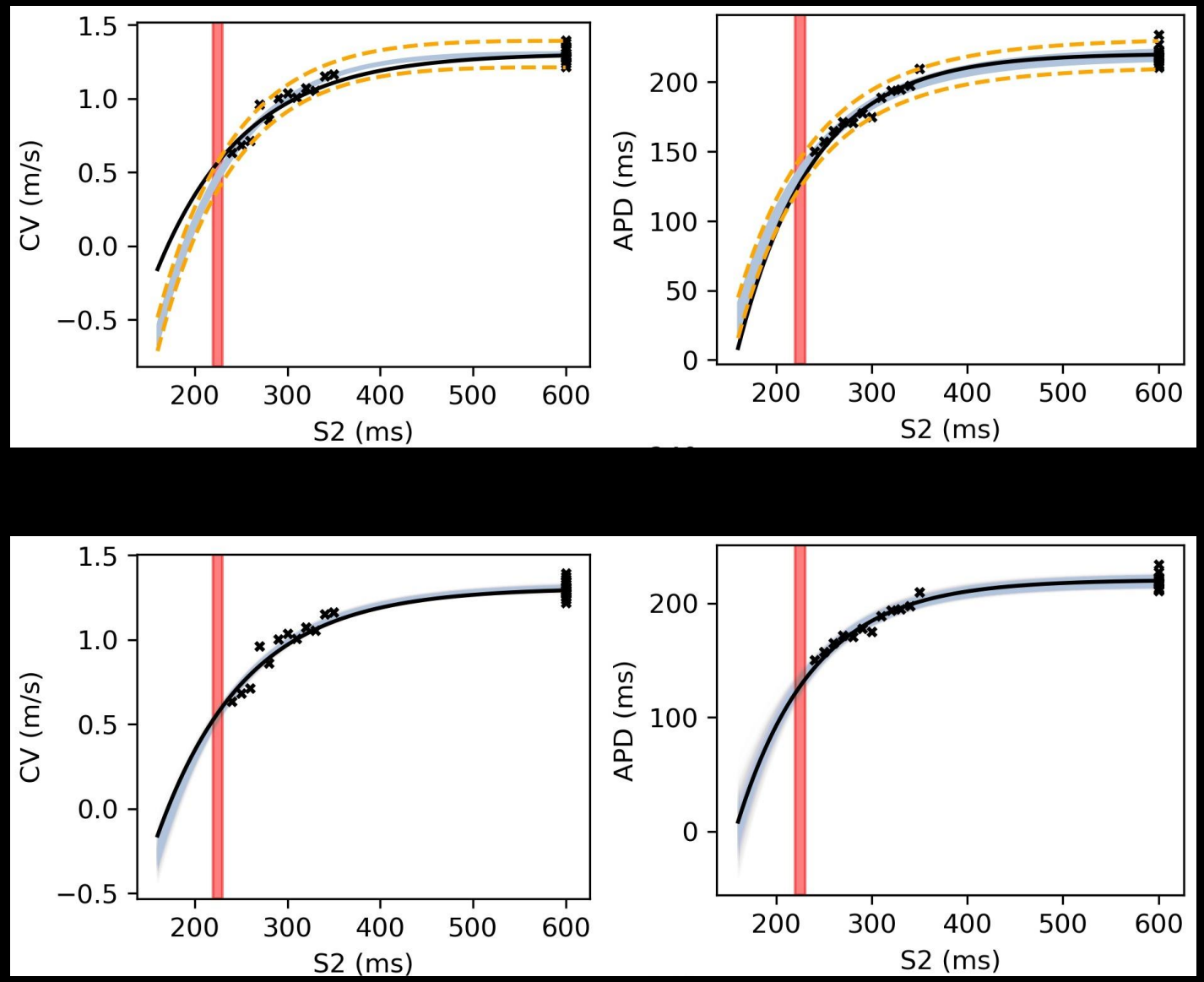


1st order and total effect sensitivity indices for each principal component and each input.

Coveney et al, *Front Physiol* 2021
https://doi.org/10.3389/fphys.2021.693015

Calibration – 1

- Maximum a posteriori (MAP) estimation of parameters (**x**) and observation noise.
- Black lines (upper plots) are true restitution curves, black points are noisy data ***from simulations***.
- Grey shaded region is 95% confidence interval, orange lines are 95% CI plus estimated noise.
- Red regions denote ERP(S1).
- Obtain samples of posterior with MCMC (lower plots)



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