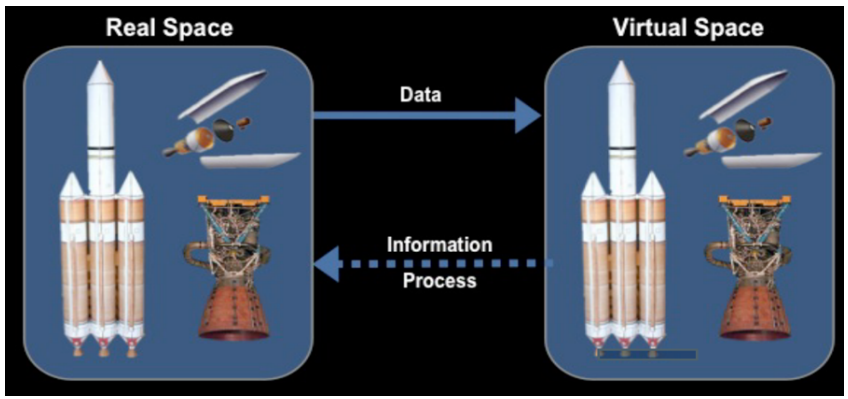
Statistical Challenges of Digital Twins

Richard Wilkinson

University of Nottingham

Digital twins

A set of virtual information constructs that mimics the structure, context and behaviour of an individual or unique physical asset, that is dynamically updated with data from its physical twin throughout its life-cycle that informs decisions that realise value.



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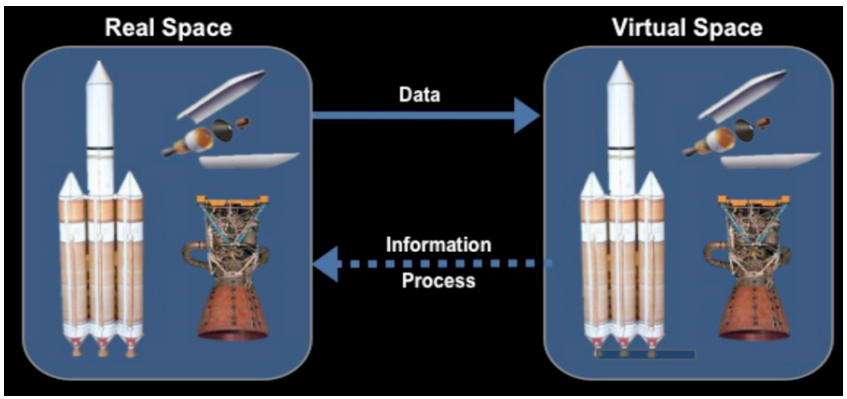


A model of an individual, informed by data, that influences decisions.

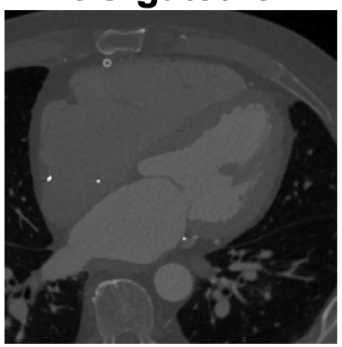
Motivating example: Cardiac physiology

With Steve Niederer, Richard Clayton, Sam Coveney, Cesare Corrardo, Chris Lanyon, Marina Strocchi, ...

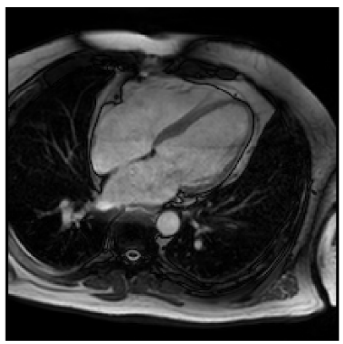
Aim: move from treatment based on guidelines derived from heterogeneous patient groups, to treatment tailored to individual patients based on their data.

Imaging

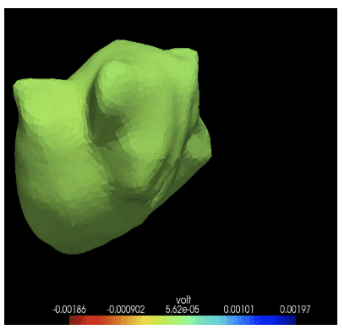
ECG-gated CT



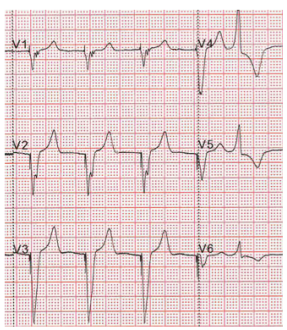
Cardiac MRI



Atrial voltage

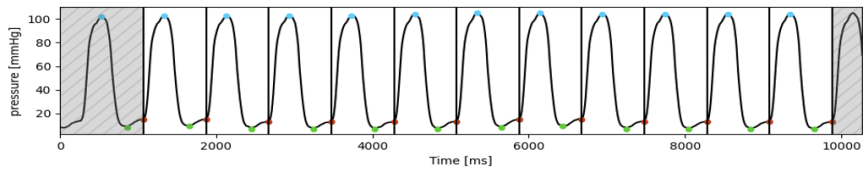


ECGs

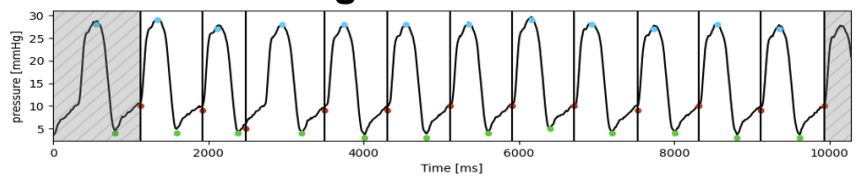


Pressure measurements

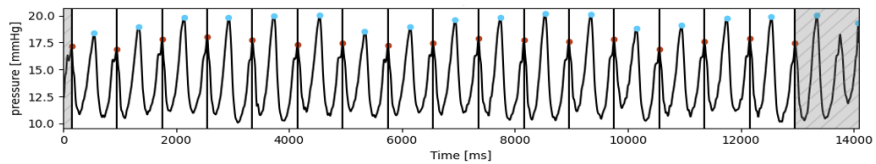
Left ventricle



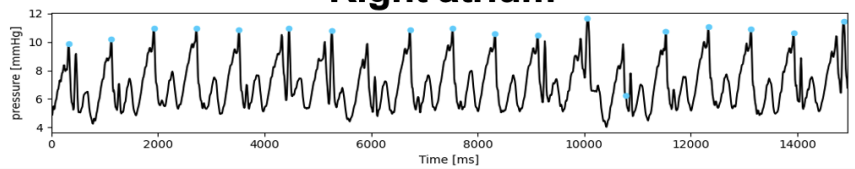
Right ventricle



Left atrium

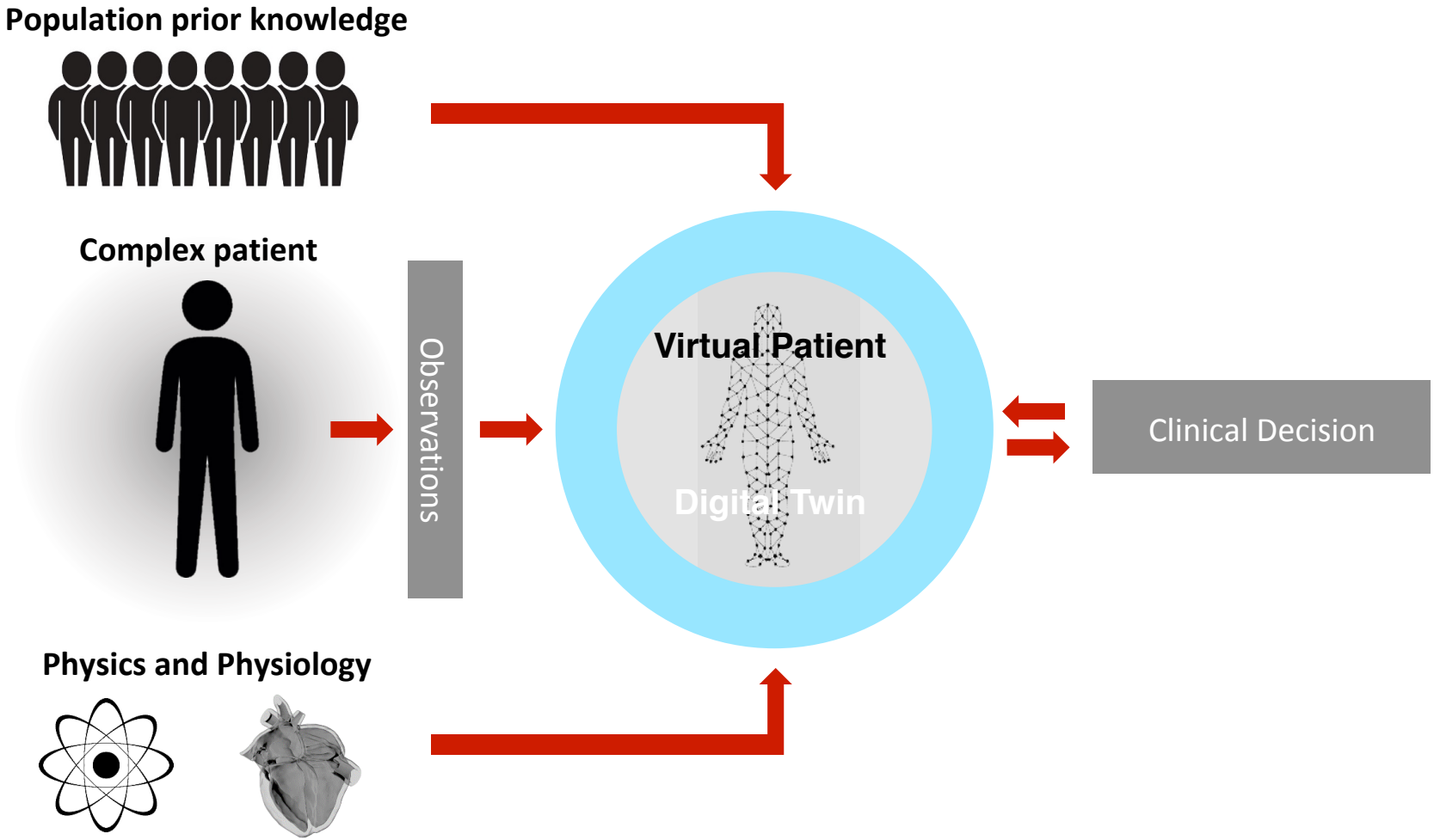


Right atrium



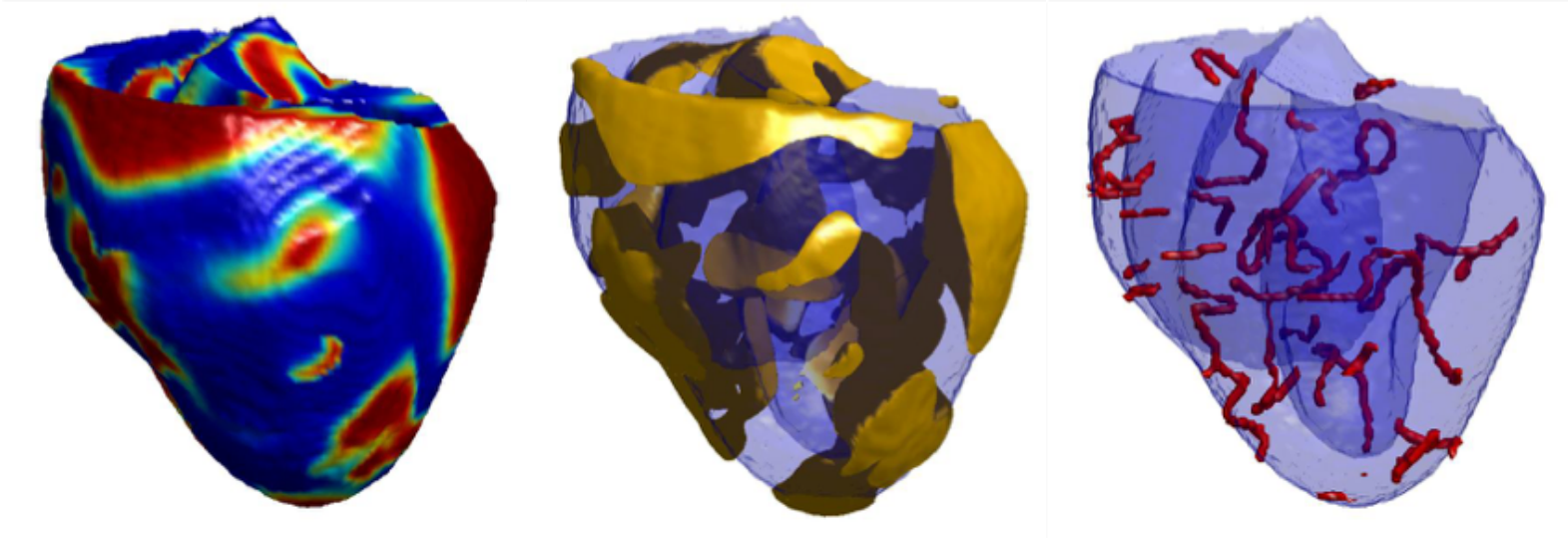
Cardiac digital twin

Slides by Marina Strocchi, Steve Niederer, Richard Clayton



But how confident are we in our prediction

Example: Atrial fibrillation



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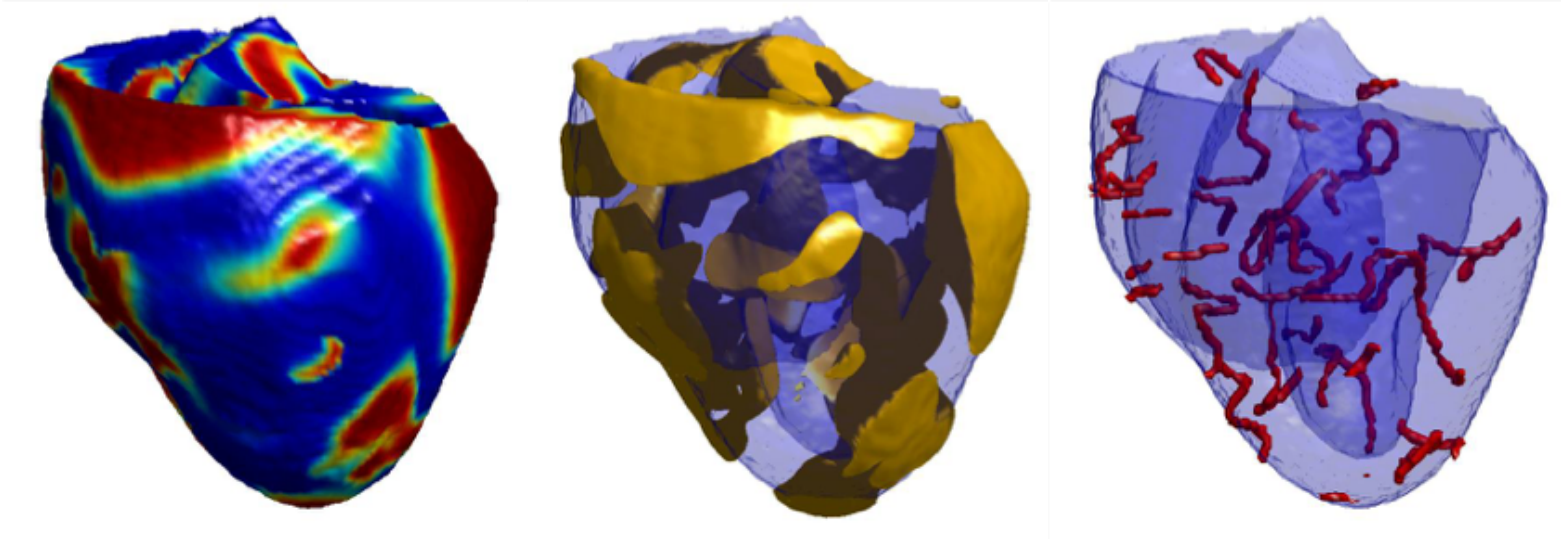

Atrial fibrillation (AF) - rapid and uncoordinated electrical activation (arrhythmia) leading to poor mechanical function.

- 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).

Patient Specific Cardiac Models

Aim: predict whether ablation will successfully treat an AF, by infering reentry pathways, and guiding the surgical ablation to treat for both AF and AT in a single procedure.

- Each intervention: 6% risk of major complication; cost $\sim$£10k.

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Cardiac models at forefront of personalised modelling

- Models are deterministic but clinical diagnosis is rarely definitive
  - uncertainty quantification/statistics challenge
- aim to consider costs and benefits across all potential outcomes weighted by their probability.

Statistical challenges

For a given patient, we want to select a model from our class of models $f(\theta, \omega)$ where

- ω are directly observable parameters specific to the patient such as geometry (ie for the computational mesh)
- θ are patient specific model parameters, eg diffusion parameters, which may be spatially varying ($\theta(x)$ for $x \in \omega$).

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to estimate

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Many of the statistical challenges familiar from UQ, but (cardiac) DTs also present new challenges.

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In practice we need to be pragmatic

- Complex simulator and limited computational resource
- Large number of unknowns θ, ω, f
- Sparse noisy data
- Misspecification/discrepancy

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We need to characterize variability at the

- population level $\pi(\theta), \pi(\omega)$ etc
- individual level $\pi(\theta, \omega, f, ...|D)$ – may need to be partially done in real time
- and the physics/simulator $\pi(D|\theta, \omega, f)$

Surrogate models

Cf Victoria's talk

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which are trained on a small ensemble of simulator evaluations $C = \{\theta_i, f(\theta_i, \omega)\}_{i=1}^{n}$

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Note that this adds an additional uncertainty

$$\pi(f|C)$$

Other methods: NNs (e.g. PINNs), polynomial chaos, ROM, POD etc.

Compact representation

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- Global sensitivity analysis: select a subset of the most important parameters (re contribution to variance).
- Basis expansions

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Given the cost of forward evaluation, how should we choose A so that θ is identifiable?

- Trade-off with dimension: accuracy, emulation, and identifiability.

Non-identifiability

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How can we identify non-identifiabilities?

- Difference between training and prediction tasks. We use data D

$$D = h_1 f(\theta, \omega) + e$$

to estimate $A\theta$.
But suppose our prediction task is then

$$h_2 f(\theta, \omega)$$

How should we choose projection A?

Fast and/or cheap inference

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Distinguish between

- Case-based inference: for each new dataset D, run a separate optimization to approximate $\pi(\theta|D)$.
- Amortized inference: global upfront training (before data collected) using simulations, so that inference at test time is rapid. (Cf Micheal's automated history matching)

Case based inference

For each new dataset, D, solve the inference problem (e.g. via MCMC).

- Kalman sampling methods:
  - Small ensemble of particles $\{\theta_i^t\}_{i=1,\ldots,n}$. At each iteration $(t = 1, \ldots, T)$, forward simulate, then adjust using a Kalman update.
  - Compute mean and variance for a Gaussian approximation of $p(\theta|D)$.

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  - Solve

$$\arg\min_\phi KL(q_\phi(\theta)||p(\theta|D)) = \arg\min \mathbb{E}_{q(\theta)} p(D, \theta) - \mathbb{E}_{q(\theta)} \log q(\theta)$$

  - Can be minimized using stochastic gradient descent within a variational auto-encoder (VAE) framework

Amortied inference

Train a model that predicts $p(\theta|D)$ for any D:
Large upfront cost, rapid test time inference.

- Conditional VAE. Assume

$$q_\phi(\theta|D) = N(m_\phi(D), s_\phi^2(D))$$

where m_ϕ and s_ϕ^2 are pre-trained neural networks.

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- Neural posteriors. Eg use a normalizing flow:
  - Find invertible f such that

$$\theta \sim p(\theta|D) \iff f(\theta; D) \sim N(0, I)$$

    then $f^{-1}(z; D) \sim p(\theta|D)$ when $z \sim N(0, I)$.
  - Model f as an invertible NN with easily computable Jacobian.
  - Can include an additional summary network $S : D \mapsto \mathbb{R}^p$ to learn optimal summary $p(\theta|S(D))$

Scalable DTs

At the moment, we create a new surrogate model for each new patient, e.g. estimating ω from imaging data

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How can we reduce this cost?

- Learn a statistical shape model $\omega = \sum_{i=1}^{M} z_i \phi_i$ for small M, e.g. via PCA and include z in the inputs to the surrogate.
- Learn the discrepancy from a set of reference heart simulations to the new heart
$$f(\cdot, \omega') = f(\cdot, \omega^r) + \delta(\cdot)$$
- Learn diffeomorphism: hearts are topologically equivalent. If $\omega' = T\omega^r$, can we learn a T' from T such that $f(\cdot, \omega') = T' f(\cdot, \omega^r)$?

Not clear *a priori* which approach, if any, will work best.

Networked Digital Twins

CDT-Net 2024-2029

Suppose we have DTs of 1000s of patients.

- How we we learn informative priors?
- How do we transfer knowledge through the network?
- How do we cheaply initialize new twins?

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Jobs available at Imperial, Sheffield, Nottingham and Turing starting 1 Oct.

Physics-informed models

Building knowledge into data-models

How can we incorporate relatively simple physics into data-models?

$$\frac{\partial u}{\partial t} = \nabla.(p_1 u) + \nabla.(p_2 \nabla u) - p_3 u + g$$

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Suppose we want to infer forcing function g in the linear system

$$\mathcal{L}u = g \text{ given observations } d_i = \langle h_i, u \rangle + e \qquad i = 1, \ldots, n$$

for example by solving constrained optimization problem

$$\min_g (D - Hu)^\top (D - Hu) \text{ subject to } \mathcal{L}u = g$$

or finding the Bayesian posterior

$$\pi(g|D)$$

where $g(x) \sim GP(m(x), k(x, x'))$.

Adjoint aided inference

$\mathcal{L}u = g$. Observations $d_i = \langle h_i, u \rangle + e_i$

Introduce n adjoint systems $\mathcal{L}^* v_i = h_i$

where $\mathcal{L}^*$ is the adjoint operator of $\mathcal{L}$ (automatable).

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$$D = \Phi z + e$$

i.e., an unconstrained linear model in z. Thus exact inference for g possible at zero additional cost.

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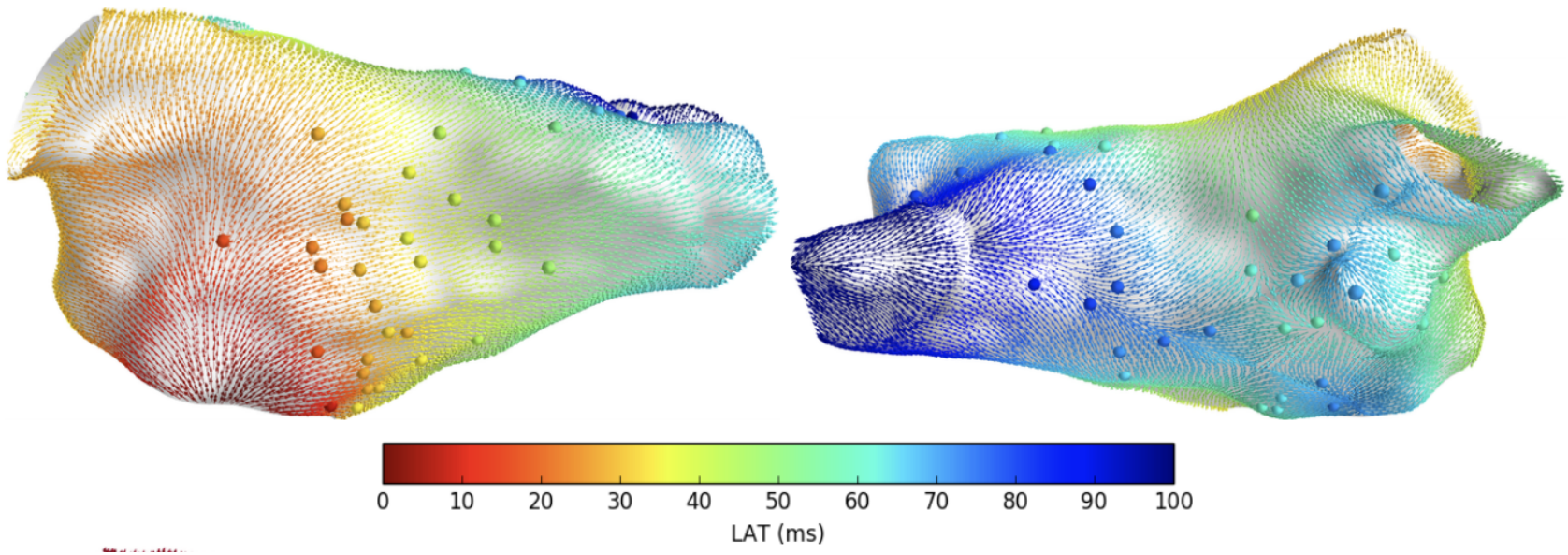
- Many possible basis expansions of GPs, e.g. Mercer, random Fourier features, Laplace etc.
- Computational cost is n (#data points) adjoint solves.
- Method is sequential: each additional data point just requires one additional adjoint sovle.

Manifold valued data

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

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



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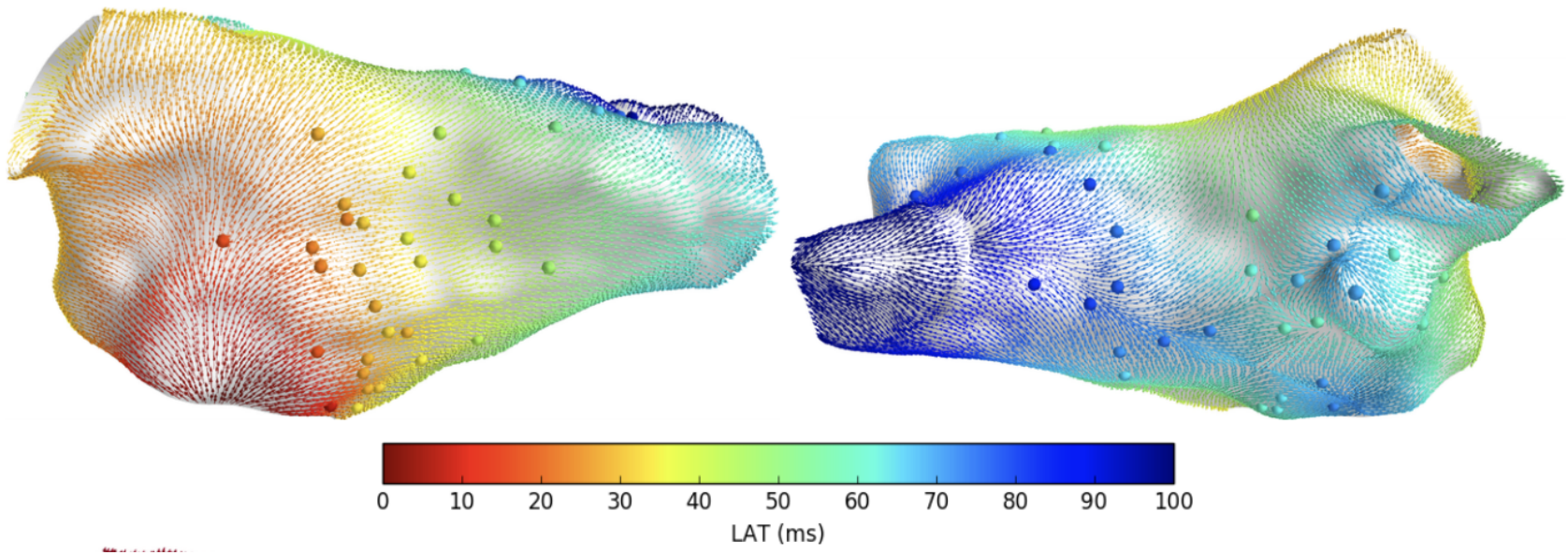

How can we interpolate to other locations $x \in \omega$?

GP interpolation

We want to model

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

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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!

Laplacian basis functions

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

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

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

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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

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

is a GP with spectral density S.

This allows us to

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and that unlike many other expansions (e.g., Mercer, RFF), the basis functions 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

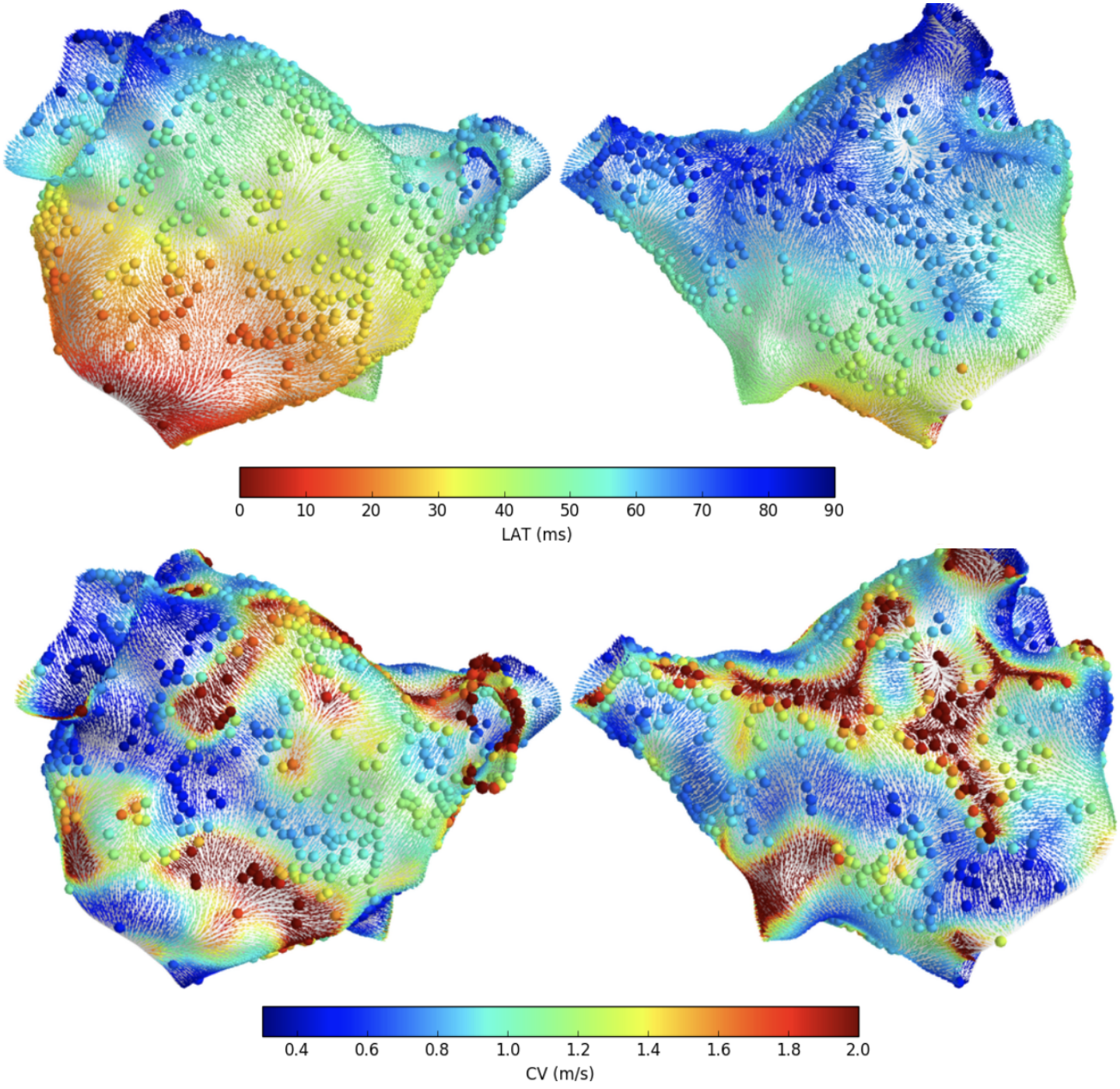
$$\mathbb{E}\left[\frac{\partial f(\mathbf{x}^*)}{\partial \mathbf{x}^*} \mid \mathcal{D}\right] = \frac{\partial \mathbf{k}_*^{\mathbf{T}}}{\partial \mathbf{x}^*}(\mathbf{K}+\boldsymbol{\Sigma})^{-1}\mathbf{y}$$

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

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...


0
10
20
30
40
50
60
70
80
90
LAT (ms)
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
CV (m/s)

Other topics

- Geometric uncertainty
  - Heart is never still, segmentation of MRI/CT image imperfect, images are obtained in unnatural situations.
  - Data are collected from an uncertain geometric location.
  - Need manifold valued models etc.
- Design
  - What data should we collect from the patient?
  - What simulations should we perform with expensive simulators?
- Model discrepancy
  - How can we use the network of DTs to learn the model error?
- Multi-fidelity/multi-level methods
  - If we have models $f_1, f_2, \ldots$, of varying costs and accuracies, how do we make the most accurate predictions we can within some given computational budget?
- Modular models
  - Can we calibrate model components independently before coupling?

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  - We can currently build DTs for a single patient, but at great expense
  - Need to scale and speed up this process
- The huge number of uncertain parameters and cost of the simulations will mean we need to compromise:
  - find regularities in the problem to allow us to reduce dimension sufficiently in order to make inference possible
  - learn strong population structured prior distributions
  - develop fast method to approximately infer parameters.

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- Jobs at Imperial, Nottingham, Sheffield from 1 Oct
- INI Newton Institute programme on *Representing, Calibrating and Leveraging Uncertainty* May-August 2025 with 3 workshops.

Thank you for listening!

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