Mathematical models to create cardiac digital twins for precision healthcare

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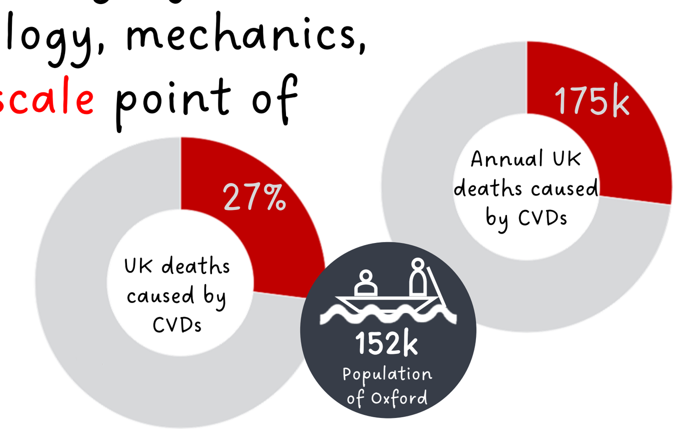
THE PROBLEM

- There are around 7.6 million people living with cardiovascular diseases (CVDs) in the UK
- CVDs cause 27% of all deaths in the UK – one every 3 minutes
- The specific causes require studying the heart from a multiphysics (electrophysiology, mechanics, fluid dynamics) and multiscale point of view (from molecules to whole-organ dynamics)



HOW CAN CARDIAC DIGITAL TWINS HELP?

- A cardiac digital twin (DT) is a virtual representation of the heart of a person
- This representation includes patient-specific data and the known biology and physics of the heart
- DTs allow us to run simulations of a patient's condition and test multiple treatments
- Create a DT of patient can take months because of the complexity of the process and the number of parameters involved in the biophysics equations

Electrophysiology

$$\|\nabla t(\boldsymbol{x})\|_V = \sqrt{\nabla t(\boldsymbol{x})^T \boldsymbol{V} \nabla t(\boldsymbol{x})} = 1 \qquad \forall x \in \Omega$$

$$\boldsymbol{V}(\boldsymbol{x}) \stackrel{\text{def}}{=} CV_f^2\,(\boldsymbol{f}(\boldsymbol{x}) \otimes \boldsymbol{f}(\boldsymbol{x})) + CV_s^2\,(\boldsymbol{s}(\boldsymbol{x}) \otimes \boldsymbol{s}(\boldsymbol{x}))$$

Mechanics

$$\boldsymbol{\Psi}(\boldsymbol{C}) = \frac{\kappa}{2}(\ln J)^2 + \frac{a}{2}(e^Q - 1)$$

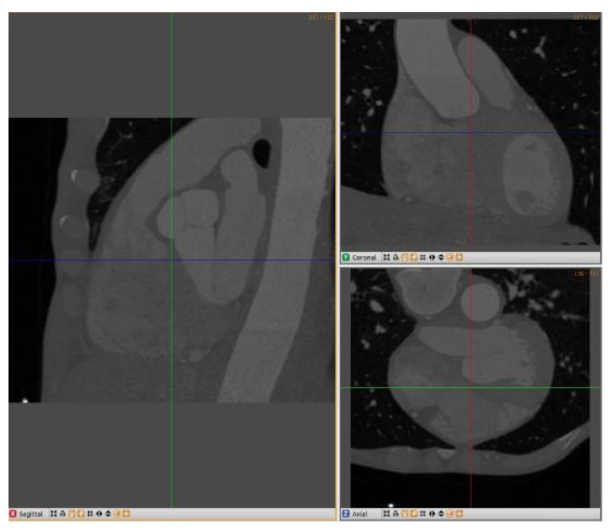
$$Q = b_f E_{ff}^2 + b_t(E_{ss}^2 + E_{nn}^2 + 2E_{sn}^2) + 2b_{fs}(E_{fs}^2 + E_{fn}^2)$$

Blood flow

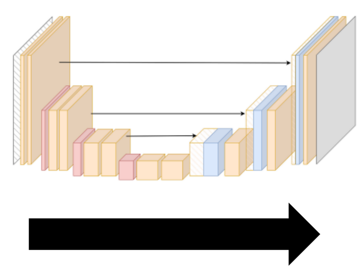
$$\frac{d^2V(t)}{dt} = A_1 \cdot V(t) + A_2 \frac{dP(t)}{dt} + A_3\,P(t)$$

$$A_1 = \frac{1}{Z \cdot C} + \frac{1}{R \cdot C}, \qquad A_2 = -\frac{1}{Z}, \qquad A_3 = -\frac{1}{Z \cdot R \cdot C}$$

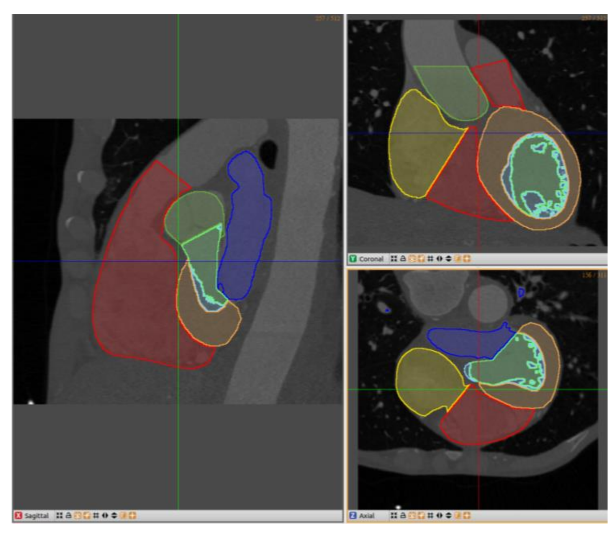
FROM MEDICAL IMAGES TO DIGITAL TWINS



Cardiac computerised tomography (CT)

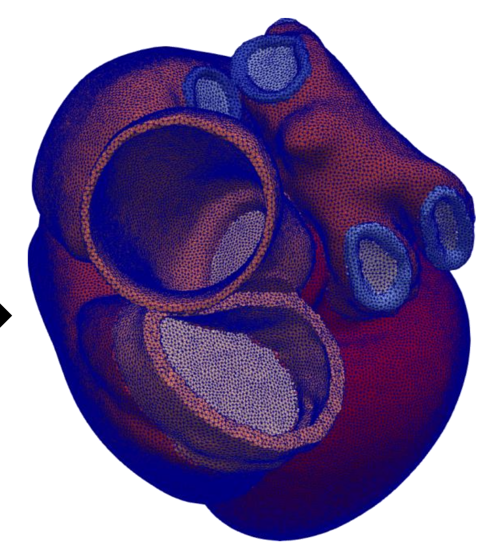


Neural network



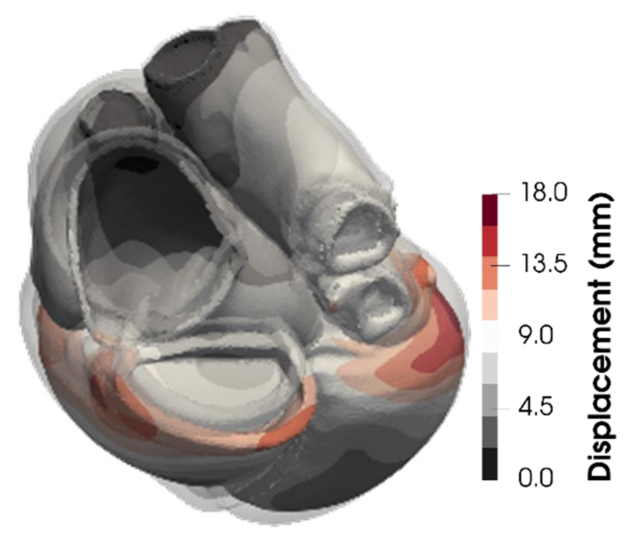
Segmentation

Semi-automated pipeline



Anatomical digital twin

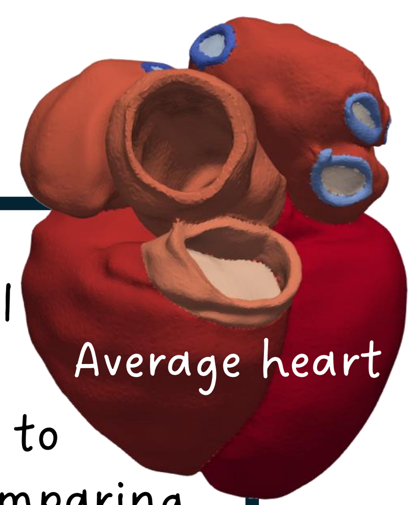
Biophysics simulations



Functional digital twin

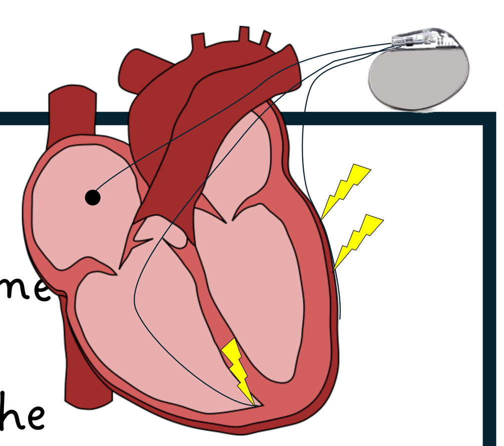
We applied this pipeline to 20 healthy subjects and made openly available the first cohort of healthy whole-heart models

TAKING SHAPE INTO ACCOUNT



- There is a poor understanding of how specific anatomical changes affect different cardiac outputs
- Statistical shape modelling is a mathematical technique to describe complex shapes with a limited set of numbers comparing them to a generated "average" shape
- We applied this technique to our cohort of healthy hearts and used those numbers to link localised changes in anatomy to changes in the simulation of the cardiac function
- We found how small changes in the shape can indicate early indications of hypertension
- We made open-source a synthetic cohort of more than 1000 heart models generated using this technique

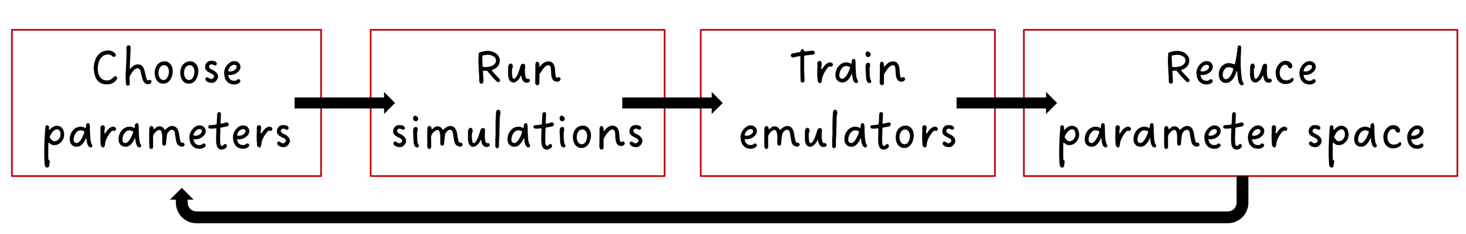
IN-SILICO TRIAL OF MEDICAL DEVICES



- Dissynchronous heart failure (HF) is a condition where the two sides of the hearts do not beat at the same time
- Cardiac resynchronization therapy (CRT) is one of the main treatments, where a pacemaker is inserted and the heart is shocked at several locations
- Where to install the CRT electrodes can change between patients and it is not clear if there is an optimal location
- We created DTs of 24 HF patients and 20 healthy ones representing recovered patients
- We tested more than 8000 pacemaker configurations, representing a virtual (or in-silico) trial
- We found that differences in anatomy was more relevant than differences in the electrodes' locations

ACCELERATING CLINICAL TRANSLATION

- One of the main bottlenecks with DTs is parameter fitting
- Parameter fitting consists of finding the set of parameters that describes best given clinical data
- We developed a pipeline based on Bayesian History Matching and Gaussian Process Emulators to find a reduced parameter space
- We can then reuse that information with new patients reducing drastically the computational load to create DTs



NOW WHAT?

- New modalities, like magnetic resonance imaging (MRI)
- New diseases, like hypertrophic cardiomyopathy (HCM)
- Scale up: can we do hundreds of DTs in a sensible timeframe?
- How can we update DTs with new visits to the hospital?
- Can we add the explicit effect of hormones?

THE PAPERS

Digital twins and simulations | Taking shape into account | In-silico trial | Bayesian History Matching

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