

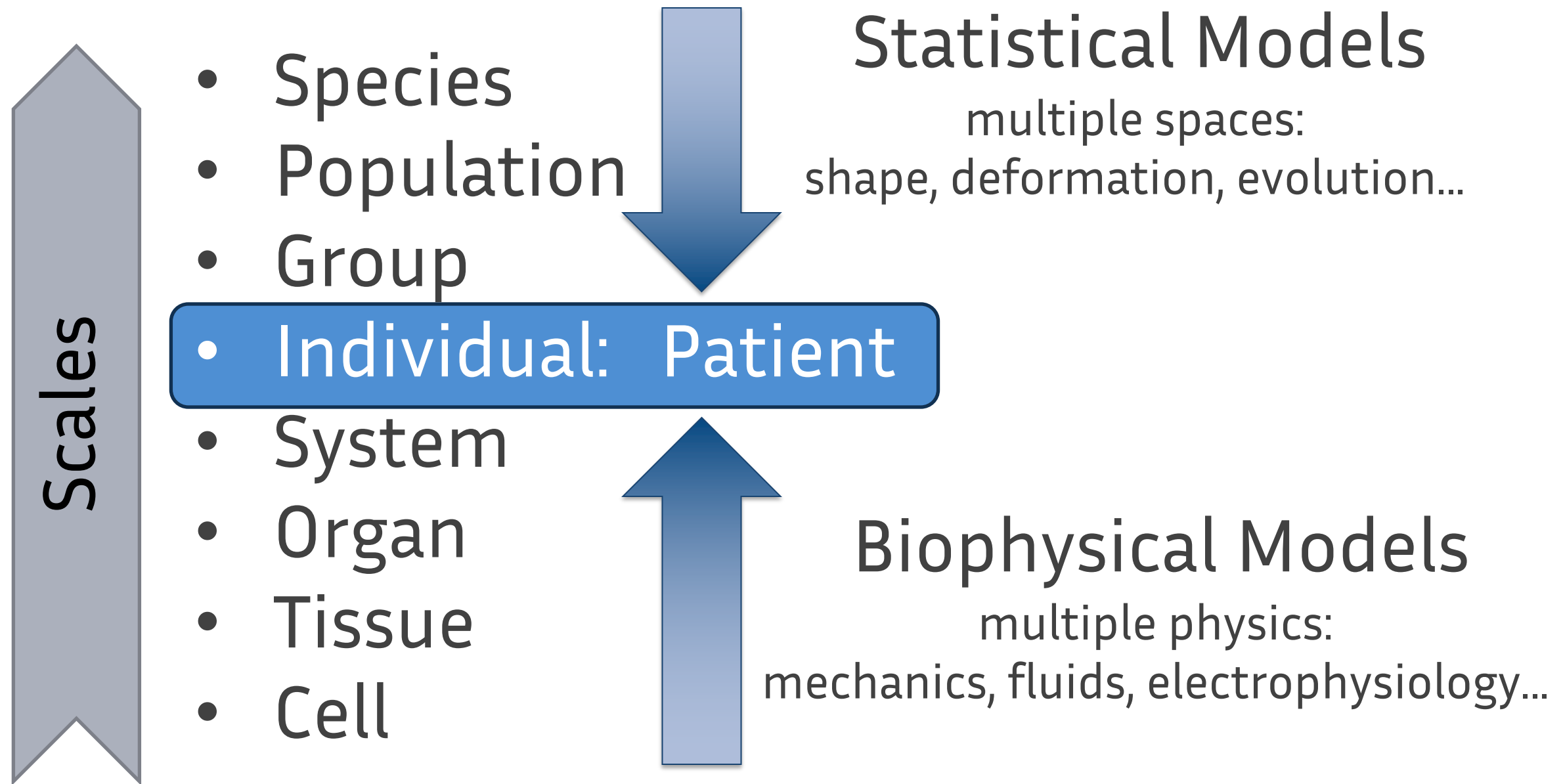


Cardiac Modelling & Machine Learning:

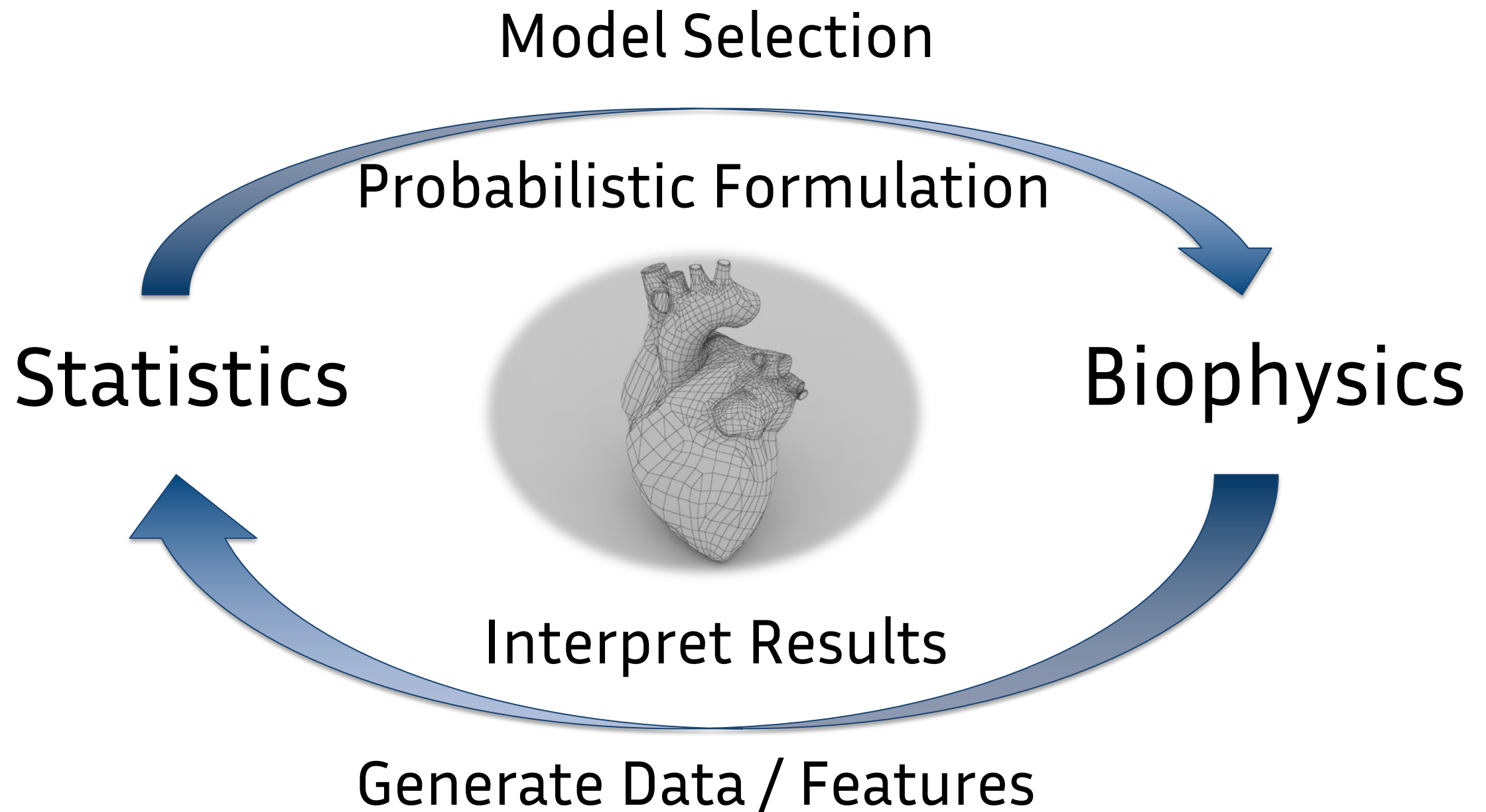
Physiology-based Constraints for Data-driven Methods in Healthcare

Maxime Sermesant
Inria, Epione team
Sophia Antipolis, France

Personalised Cardiac Models

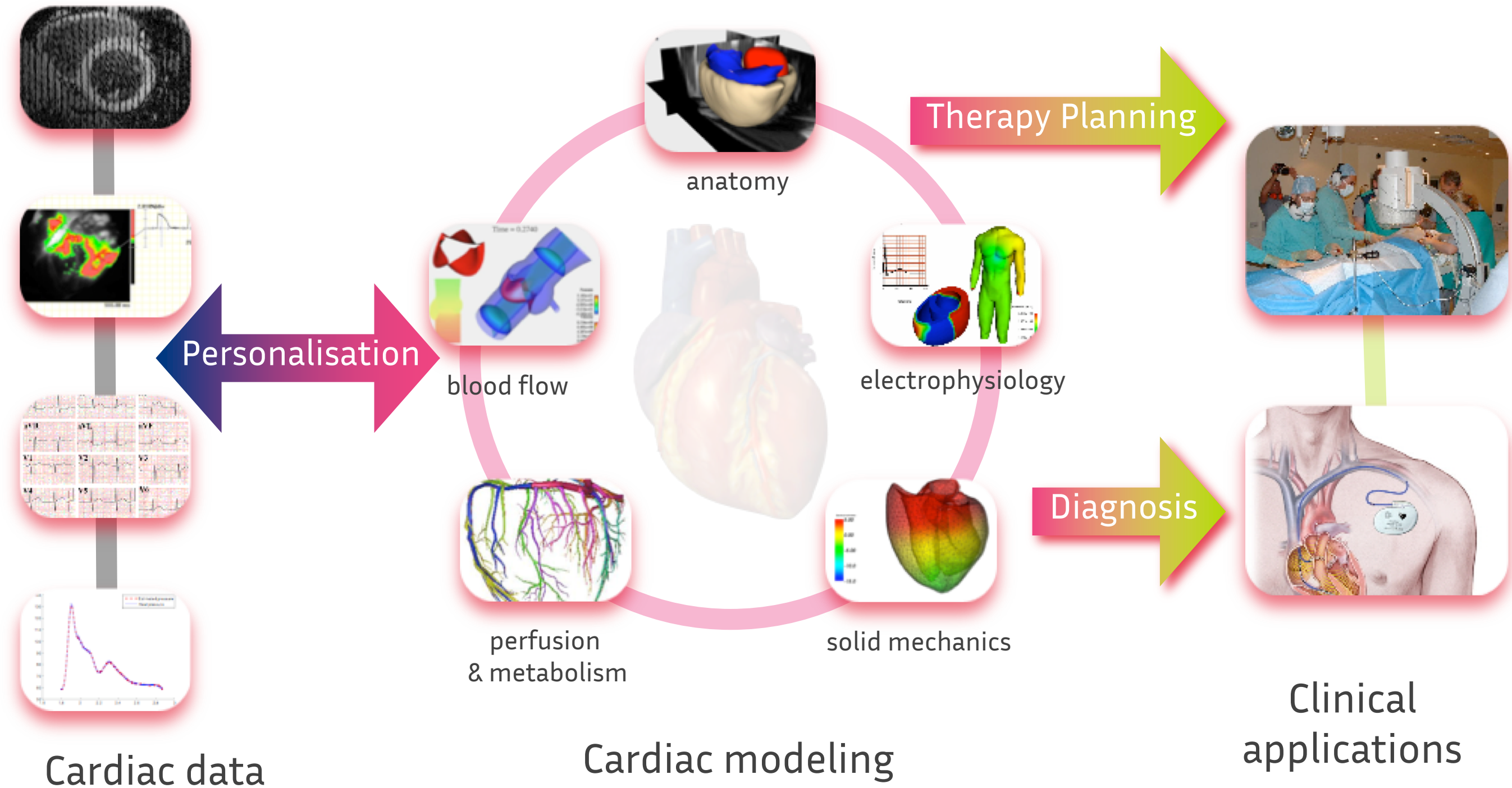


Complementary Methodologies



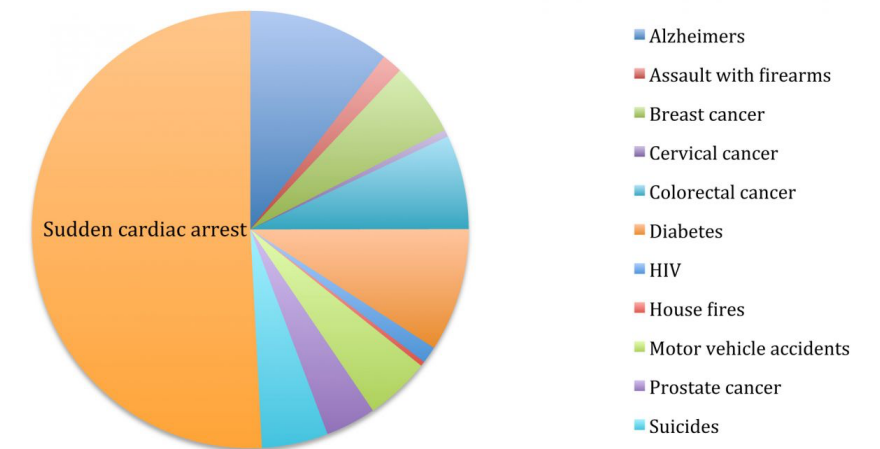
- Biophysical Model = integrative representation for large heterogeneous databases
- Uncertainty Quantification in modelling and machine learning: confidence in predictions, data / model uncertainty, group-wise statistics

Computer Models of the Human Heart



Ventricular Tachycardia / Fibrillation

- 3 000 000 persons experience SCA (Sudden Cardiac Arrest) worldwide annually, including 400 000 in Europe.
- Only 10% survive.
- Most common mode of death.
- 80–90% due to ventricular tachycardia (VT).



Causes of death (Sudden Cardiac Arrest Foundation)

Cardiac RadioFrequency Ablation (RFA) is an effective treatment for VT patients but:



No consensus in optimal ablation strategy

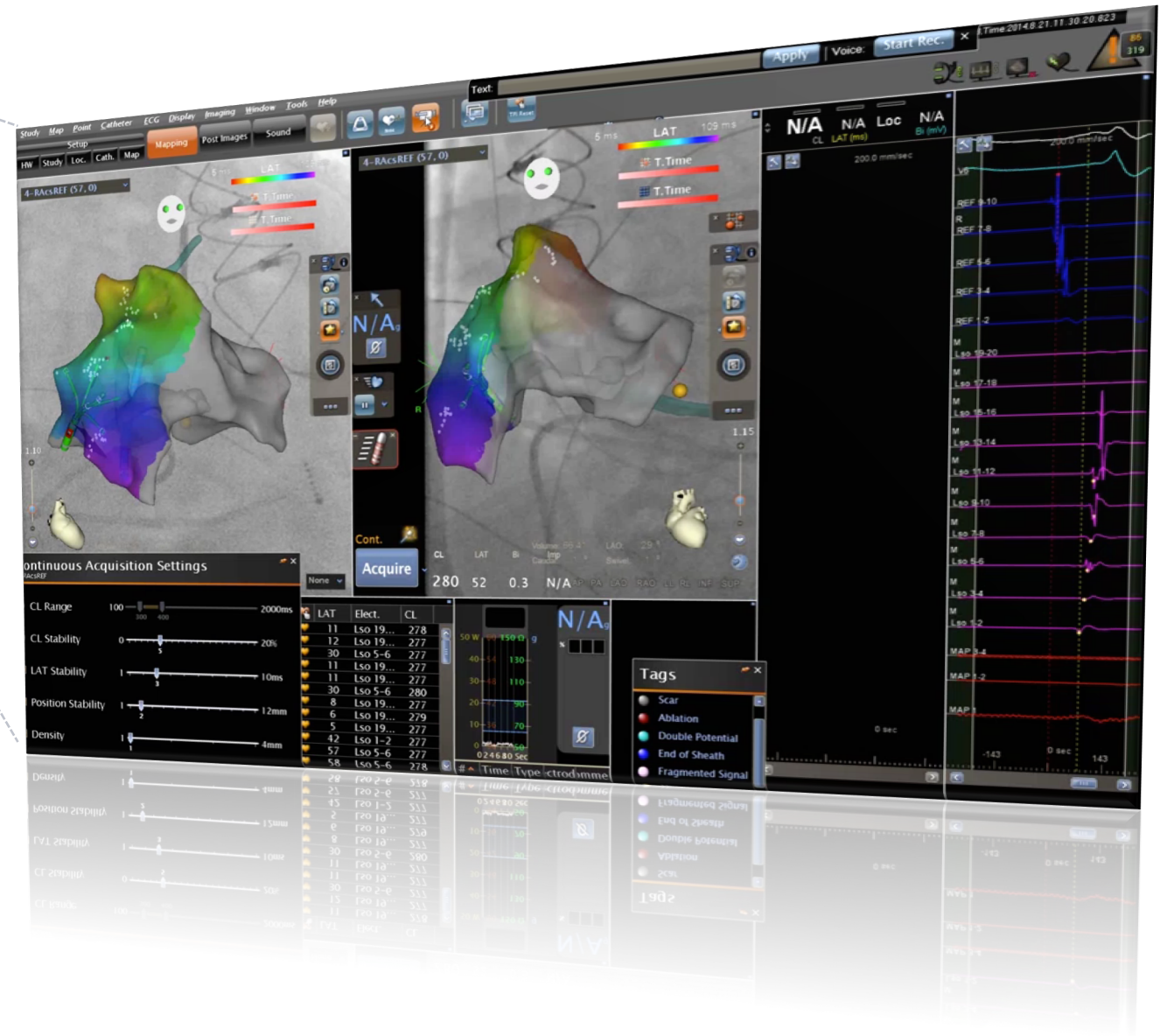
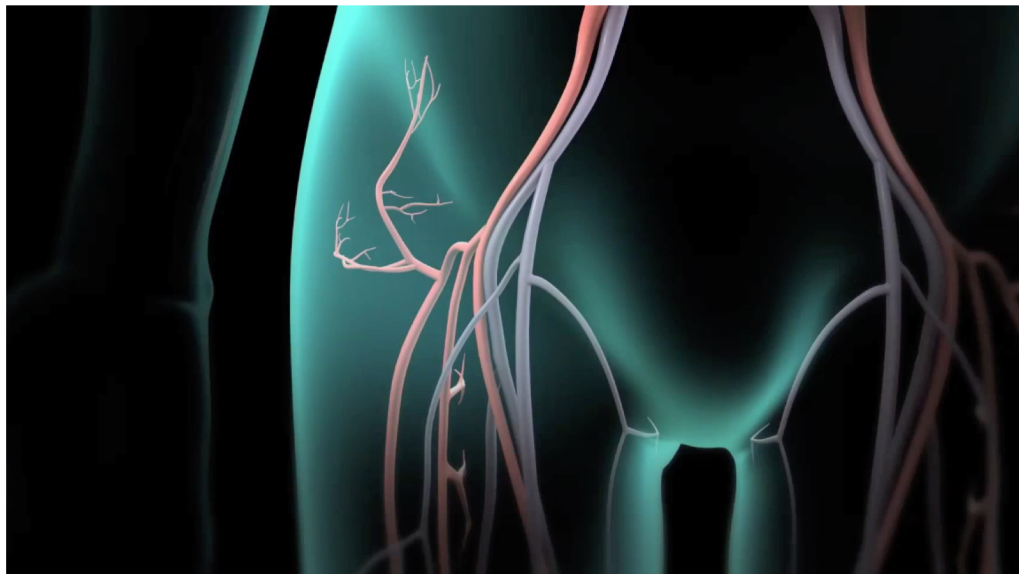


Recurrence rate: 20 – 40 %



Long procedure times (> 6h)

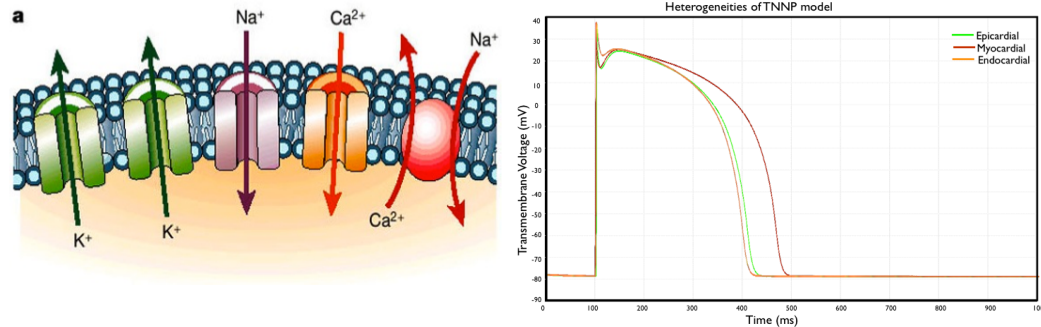
Cardiac catheter ablation



Tedious and Complex

→ Build patient-specific model from electrophysiology mapping and images
to Predict ablation targets in-silico before the procedure

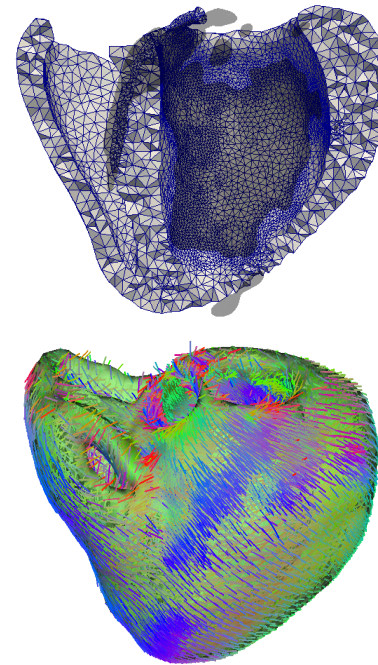
Cardiac Model Ingredients



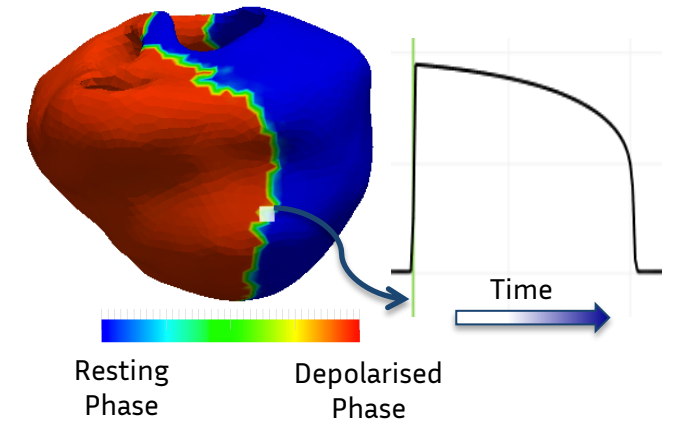
Ionic current computation

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{Ca,L} + I_{NaCa} + I_{NaK} + I_{p,Ca} + I_{p,K} + I_{b,Ca} + I_{b,Na}.$$

Ionic currents and transmembrane potential equations



3D anatomy and fibre orientation

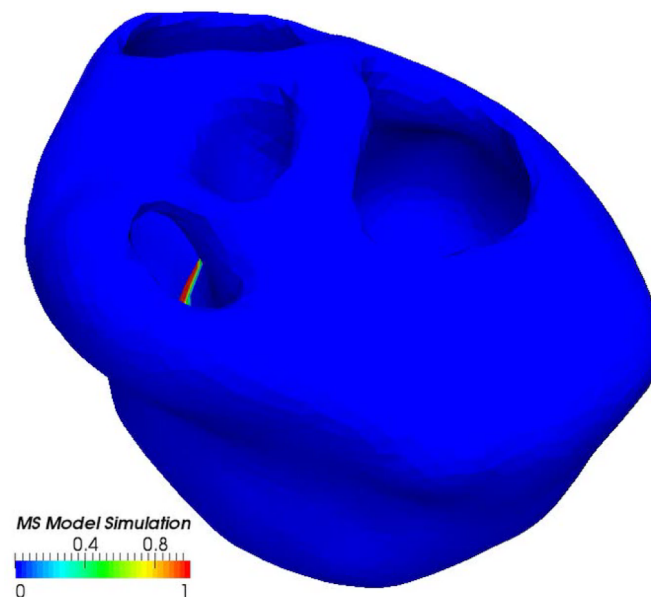


Spatial integration

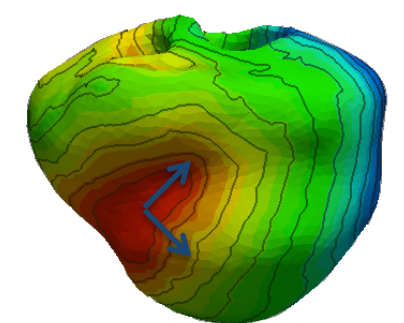
$$\partial_t V_m = \text{div}(D \nabla V_m) - I_{ion}/C_m$$

Equation solver on 3D domain

3D Simulation

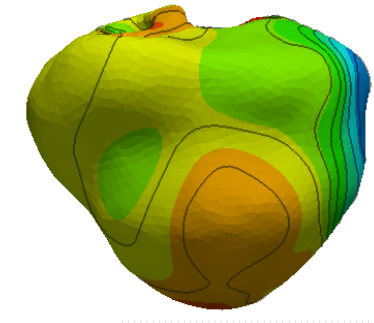


Activation Maps



Early Activation Late Activation

APD Maps



Low APD High APD

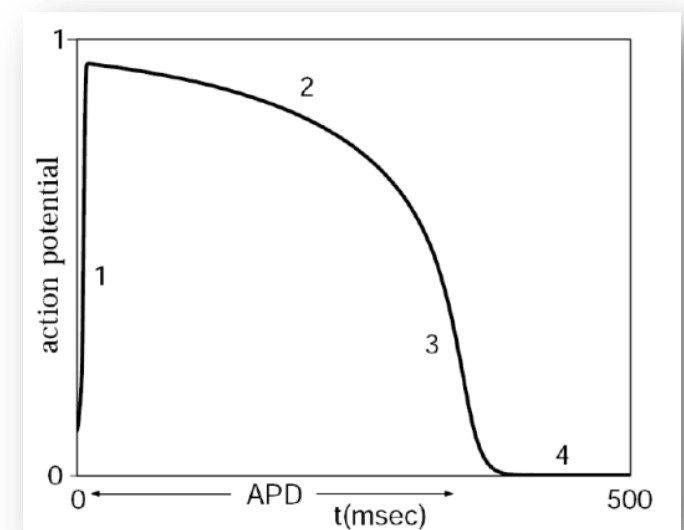
Mitchell-Schaeffer Model

Model features

- Phenomenological model (simplified biophysical model)
- Small number of parameters, related to global behaviour
- Targeting simulation at organ scale

Reaction-Diffusion Equations:

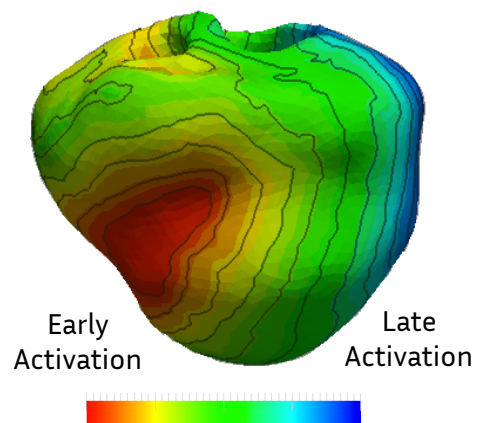
$$\begin{cases} \partial_t u = \text{div}(D \nabla u) + \frac{zu^2(1-u)}{\tau_{in}} - \frac{u}{\tau_{out}} \\ \partial_t z = \begin{cases} \frac{(1-z)}{\tau_{open}} & \text{if } u < u_{gate} \\ \frac{-z}{\tau_{close}} & \text{if } u > u_{gate} \end{cases} \end{cases}$$



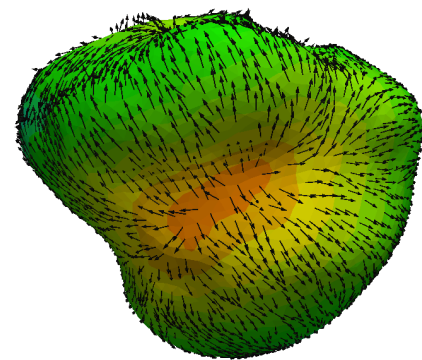
Building Personalised Electrophysiology Models

Simulation

Isochrones

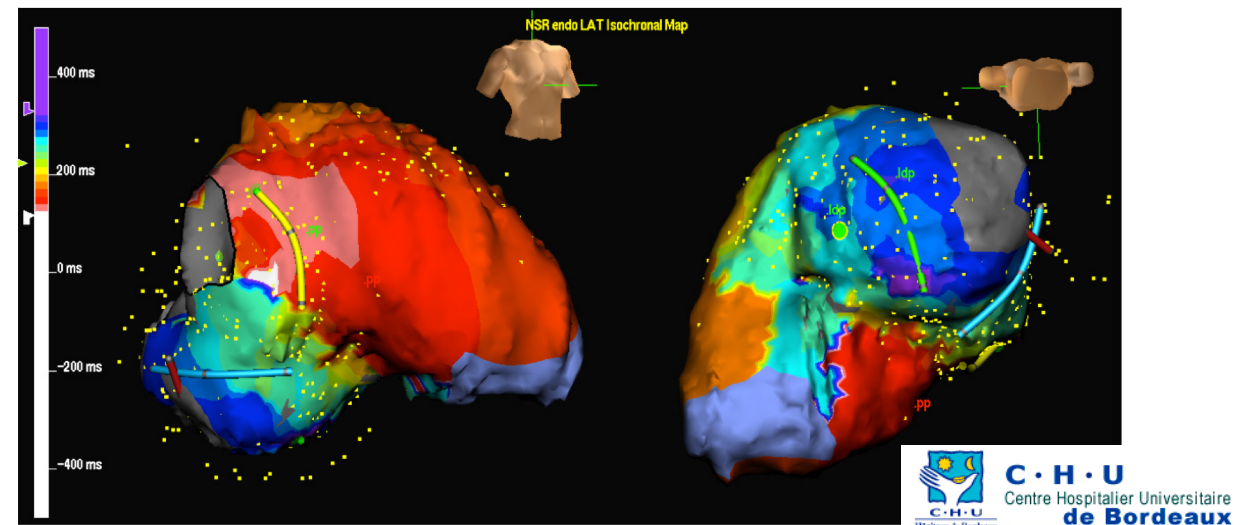


Conduction Velocity

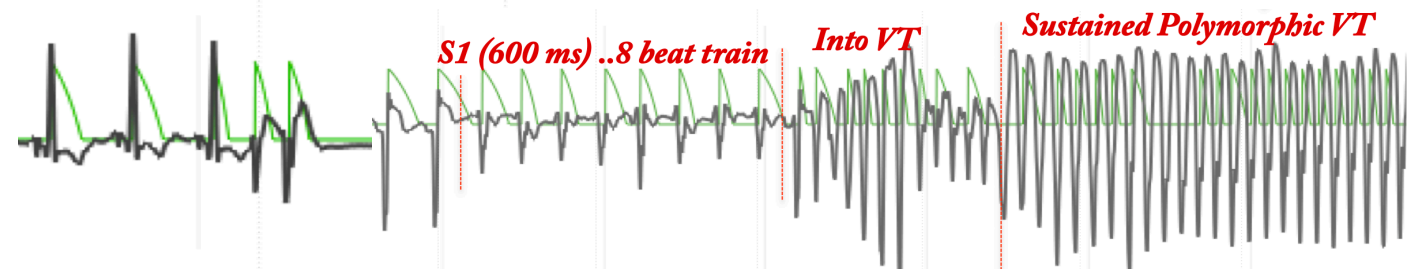
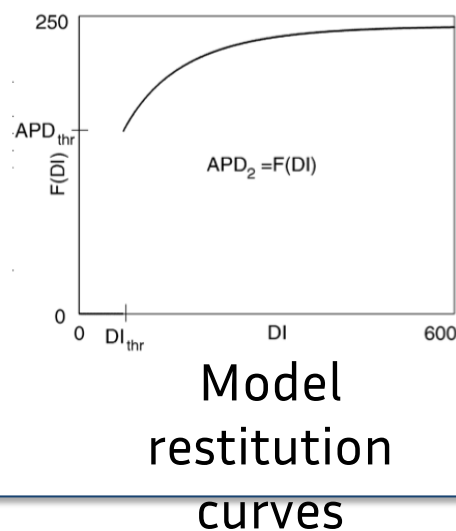
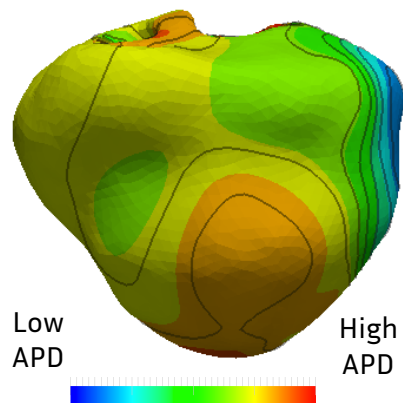


Spatial orientation

Clinical observations



APD Map



→ Algorithms for patient-specific Tissue Conductivity & Restitution

Validation of Model Prediction for VT

Ischemic VT patient selection & Clinical data (2011)

■ Patients history

- Male patient, 72 yrs old, with **ischemic heart disease (IHD)**, myocardial infarction (MI) in the infero-lateral wall, **LV EF < 35%**, **QRS < 120 ms**, with NSVT on 24 hr tape.
- Male patient, 58 yrs old, with **IHD**, MI in the infero-lateral wall, **LV EF < 25%**, **QRS < 120 ms**, NSVT on 24 hr tape.

■ Anatomical imaging

- 3D SSFP MR
- LE MR
- Cine MR

■ Electrophysiology mapping

- **Non-contact** electro-anatomical mapping (EnSite) (St. Jude Medical) & **contact** mapping in only few local areas
- **BSPM** (IBT Karlsruhe, Germany)

■ VT induction

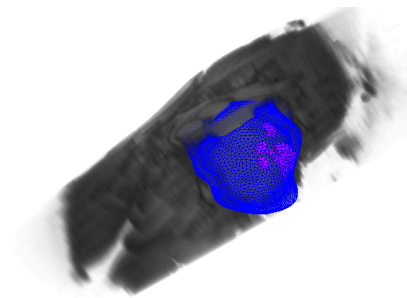
- **Standard Wellen's protocol** for VT-Stim
- pacing from **RV apex**



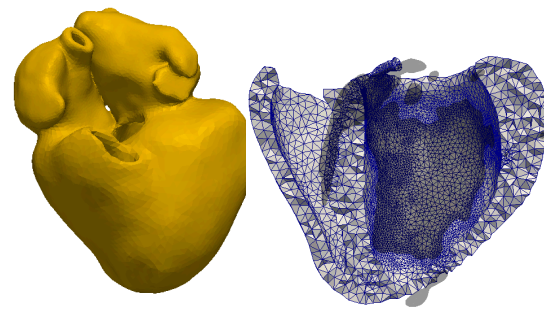
European Commission
Information Society and Media



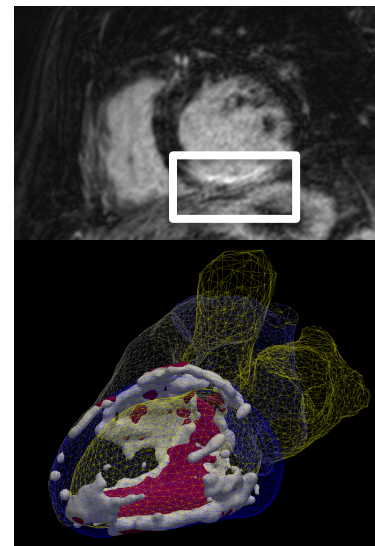
Anatomy– MRI



3D SSFP, Cine-MR
and Gad-MR

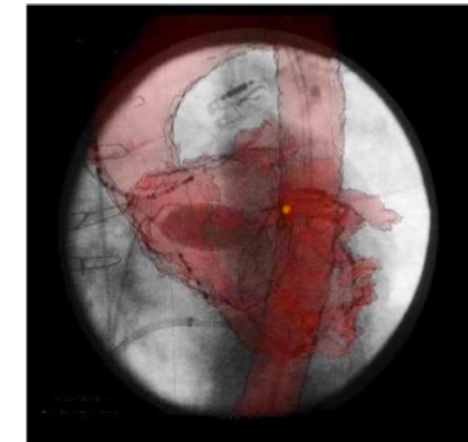


Whole Heart &
Ventricular Model



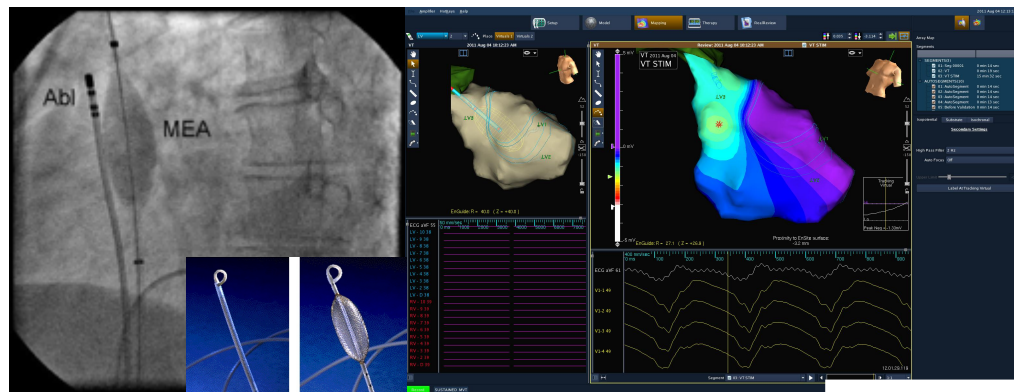
Scar & Gray Zone

MR & EP fusion

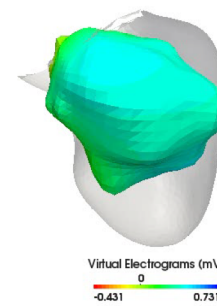


XMR registration

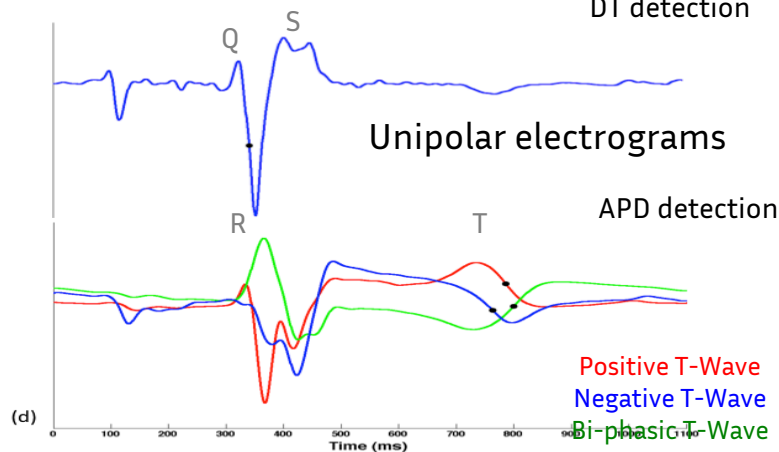
Electrophysiology mapping – EnSite & BSPM



DT detection



Virtual Electograms (mV)
-0.431 0 0.731

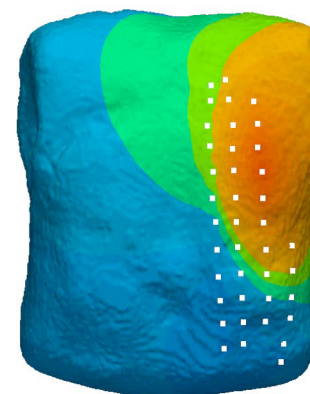


Unipolar electrograms

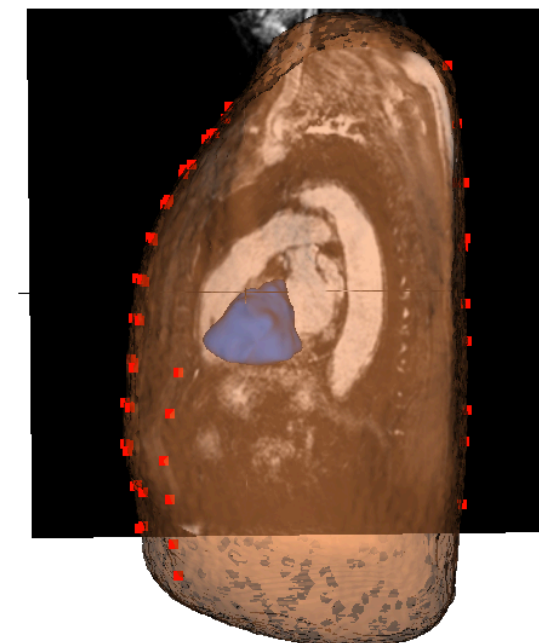
APD detection

Positive T-Wave
Negative T-Wave
Bi-phasic T-Wave

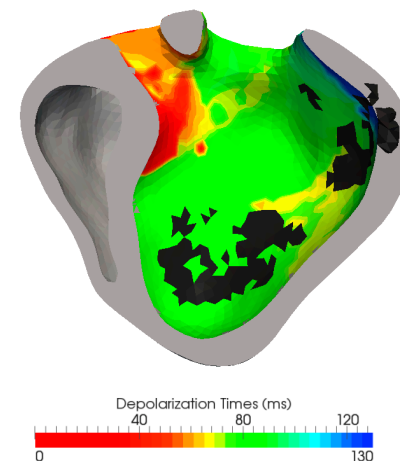
Time: 0.0 ms



Body Surface Potential
Mapping (BSPM)



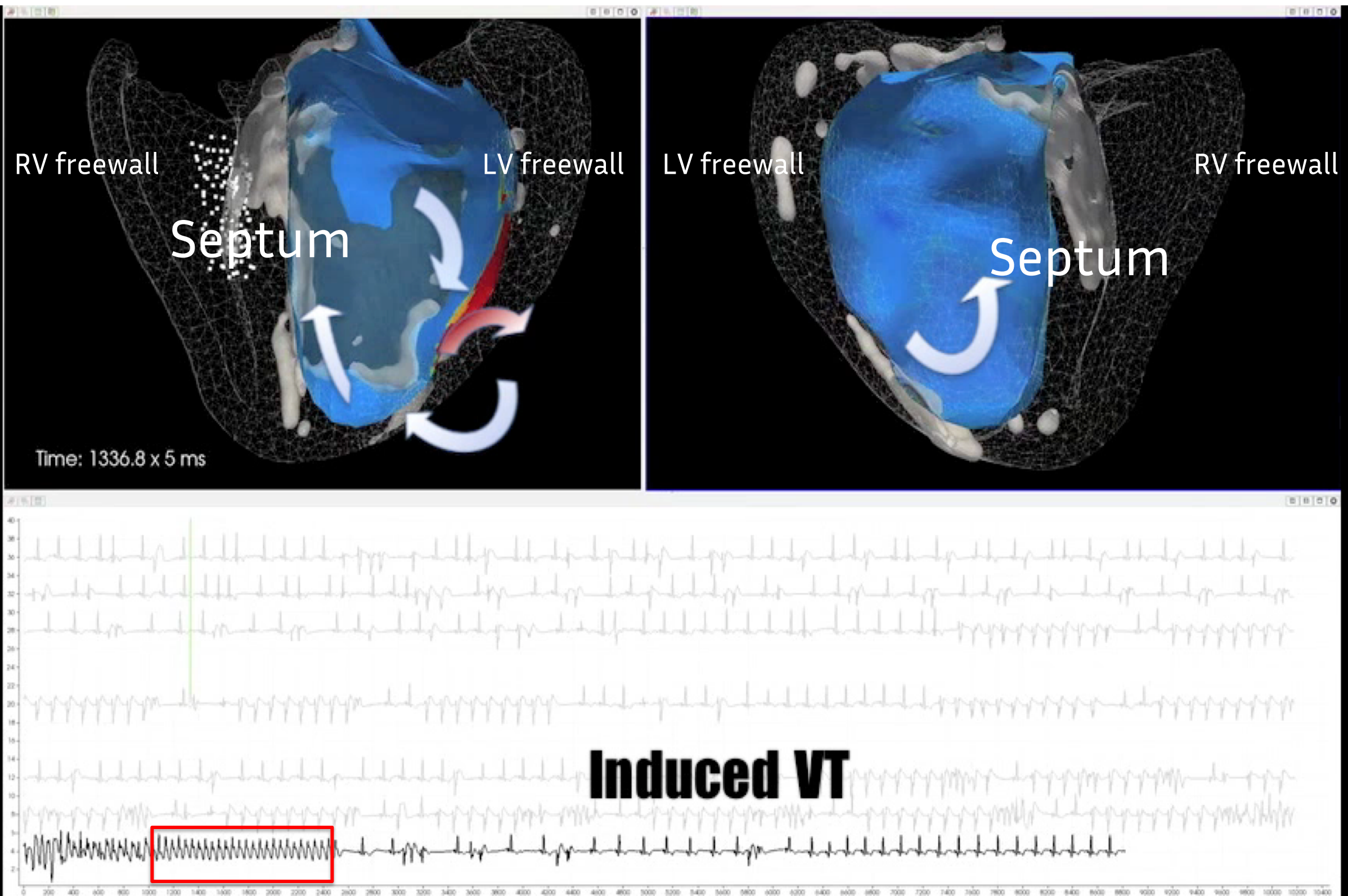
BSPM – MR – EnSite integration



DT Map

DT: Depolarisation Time
LAT: Local Activation Time
EP: Electrophysiology

EP Model Prediction – Induced VT

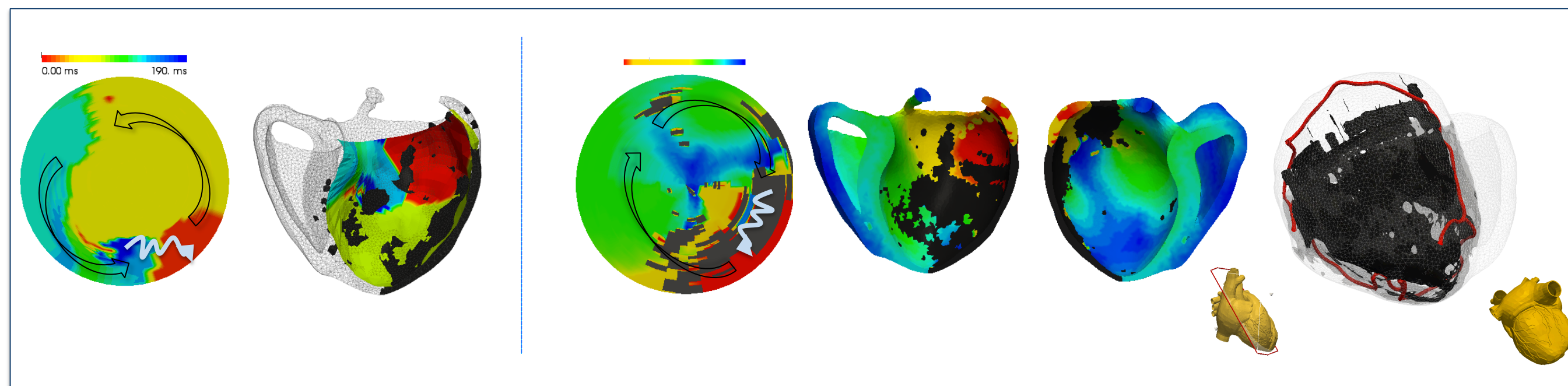
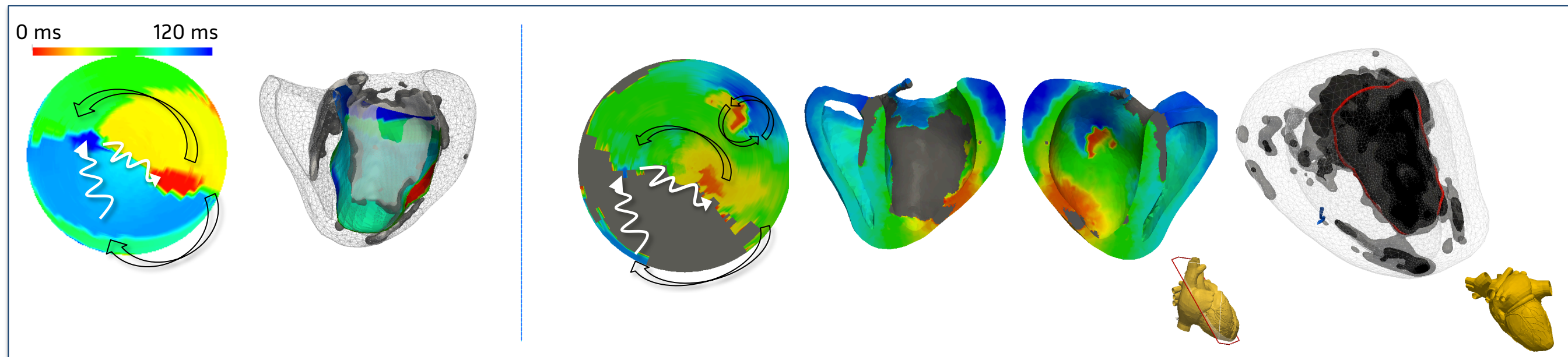


Personalised Models – Induced VT Circuits

- Comparison of activation isochrones for **model predicted induced VT in silico** with **clinically observed induced VT**

DATA

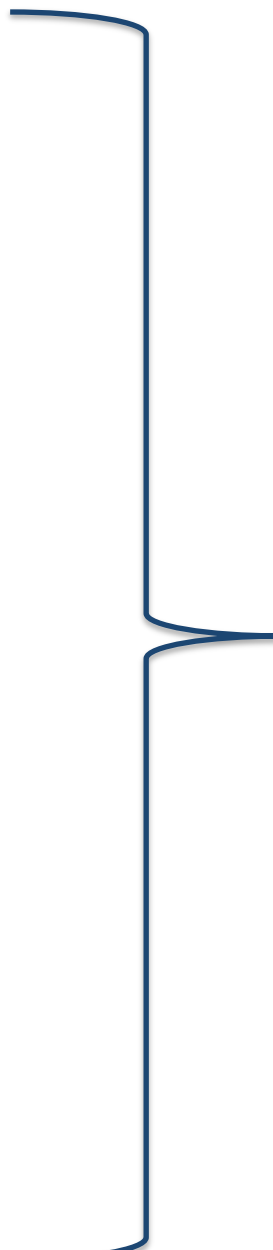
MODEL PREDICTION



Nice Results on Few Cases: What is missing for wider application?

Main Limitations:

- Model Realism
- Patient Selection
- Invasive Measurements
- Processing Timeframe
- Robustness to Variability
- Uncertainty Quantification



Leverage
Machine
Learning

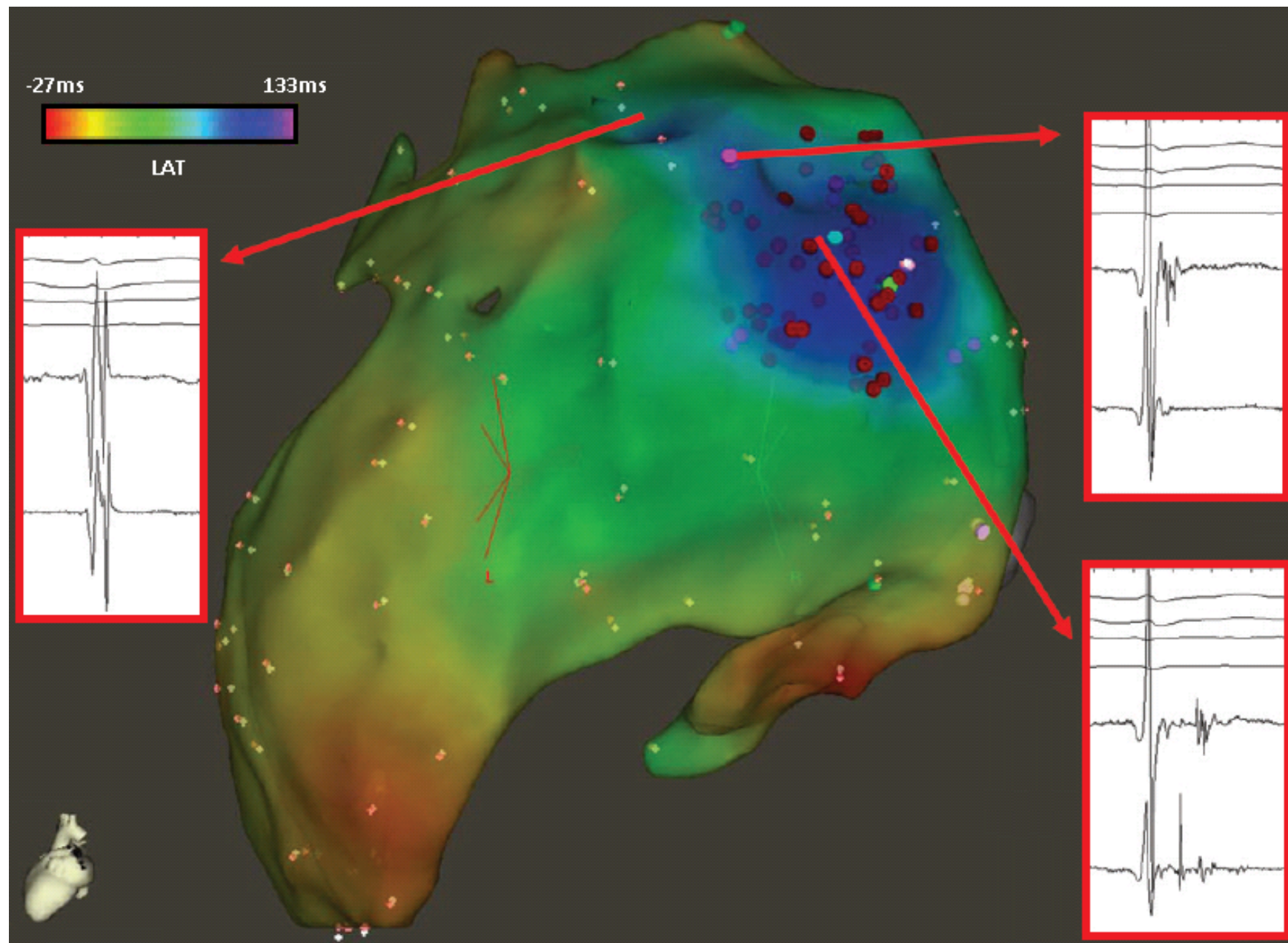
Overview

- Cardiac Modelling & Machine Learning
 - Feature Augmentation
 - Data Augmentation
 - Transfer Learning

Overview

- Cardiac Modelling & Machine Learning
 - Feature Augmentation
 - Data Augmentation
 - Transfer Learning

Local Abnormal Ventricular Activities



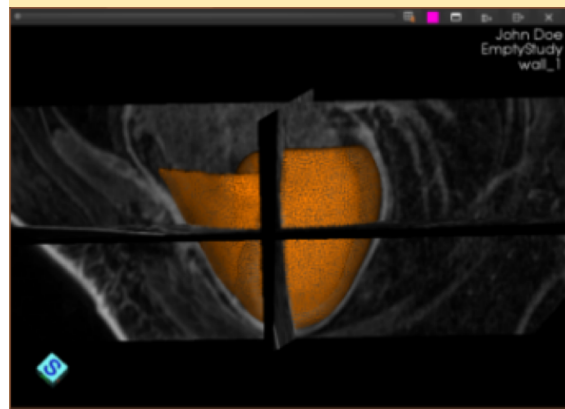
Sharp high-frequency potentials, possibly of low amplitude, distinct from the far-field electrogram

LAVA elimination by RFA is
feasible, safe and
associated with superior VT
free survival

Epicardial map and potentials with LAVA

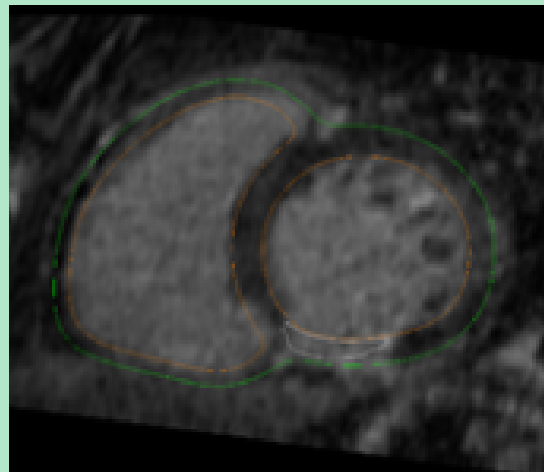
Prediction of RFA Targets from non-invasive Imaging data: Using Models to Augment the Features for Machine Learning

Clinical Data



Imaging Study

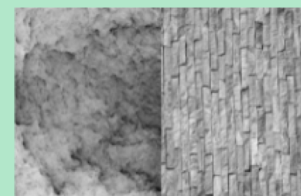
Image Processing



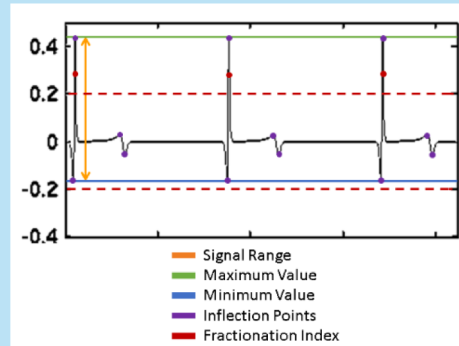
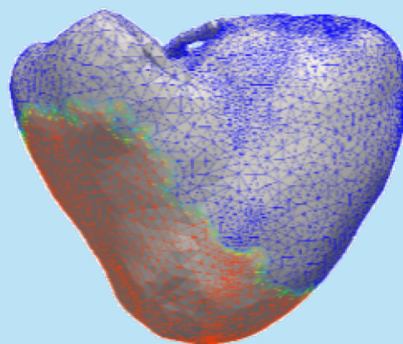
Intensity



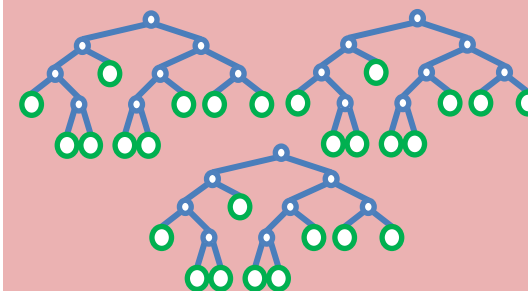
Texture



Biophysical Modeling



Machine Learning



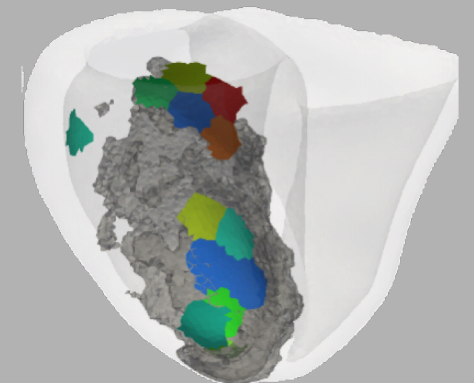
Predictions



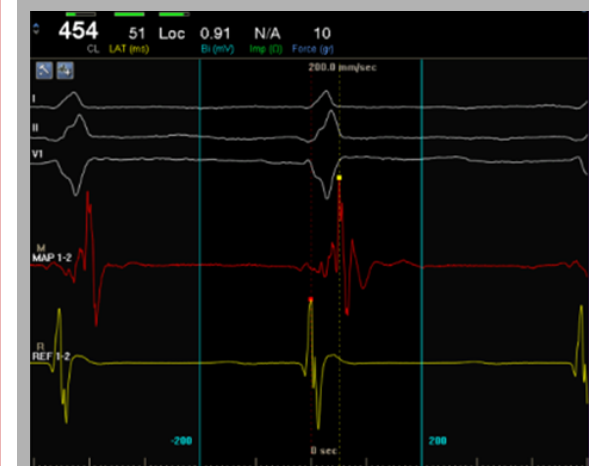
Confidence



Results

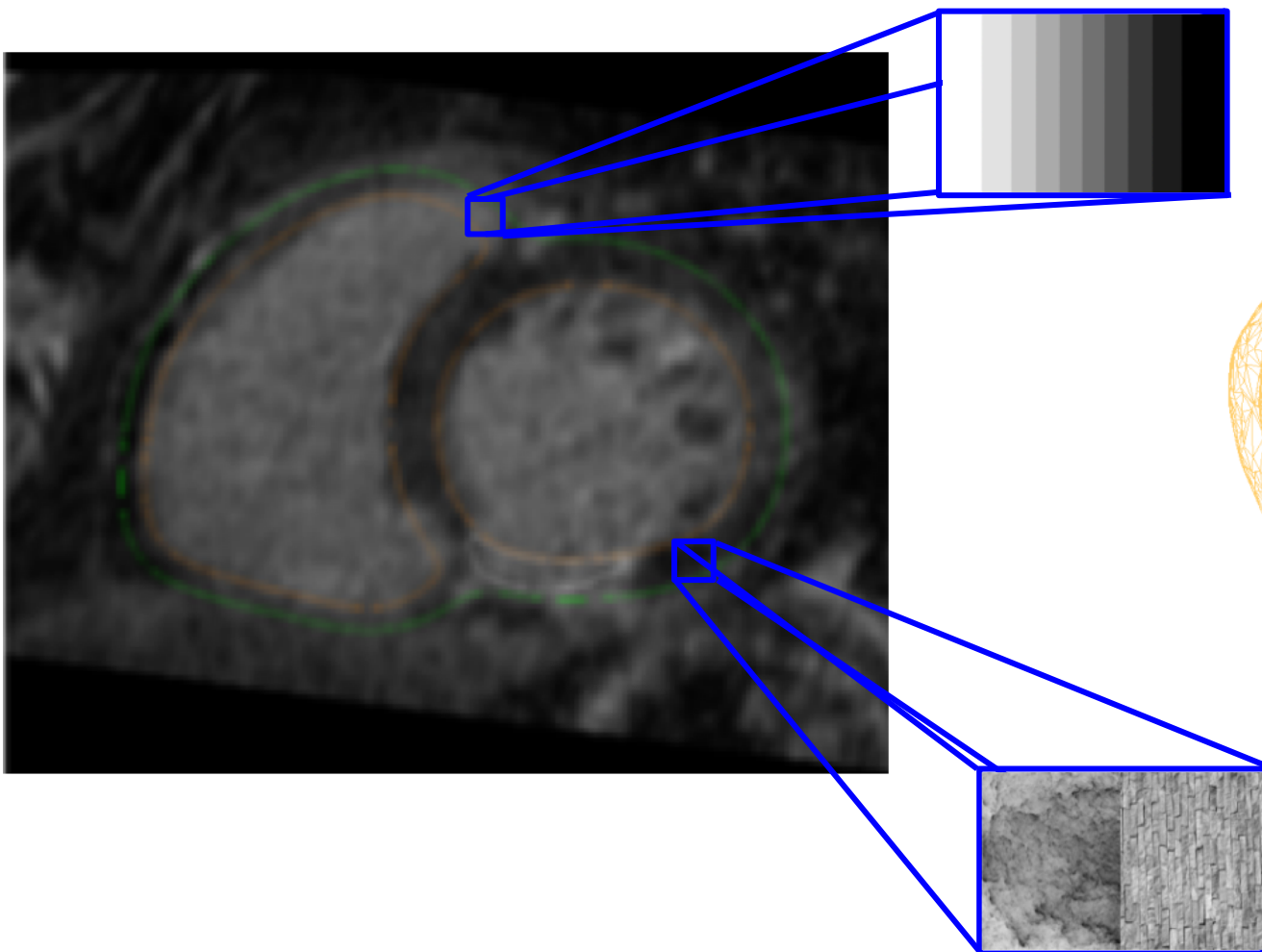


Ablation Guidance Maps



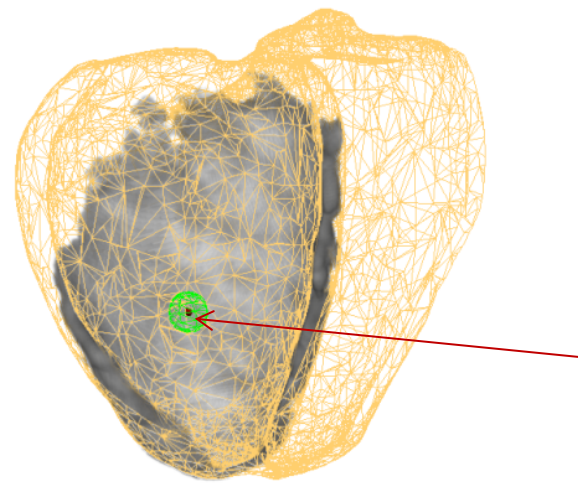
Electrophysiology Study for validation

Image Processing



Intensity Features

min	max	μ	σ	$\frac{\sigma}{\mu}$	Myocardium Thickness	Scar Transmurality
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- Voxels within the catheter's sensing range at the position of a given electro-anatomical point

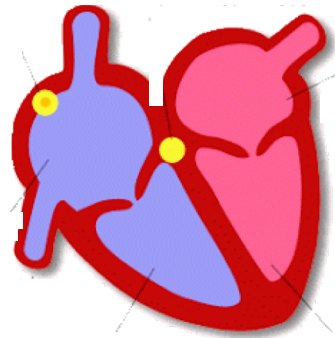
Texture Features

Energy	Entropy	Correlation	Contrast	...
--------	---------	-------------	----------	-----

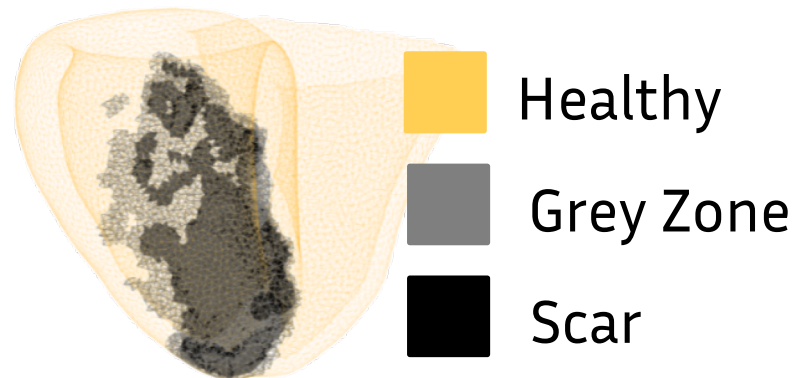
- Gray Level Co-Occurrence Matrix
- 3 distances x 13 directions
- 12 Haralick Features
- Statistics that emphasize specific texture properties

Biophysical Modeling

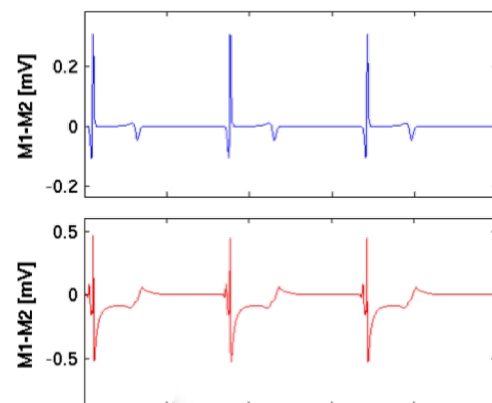
Cardiac Source Model



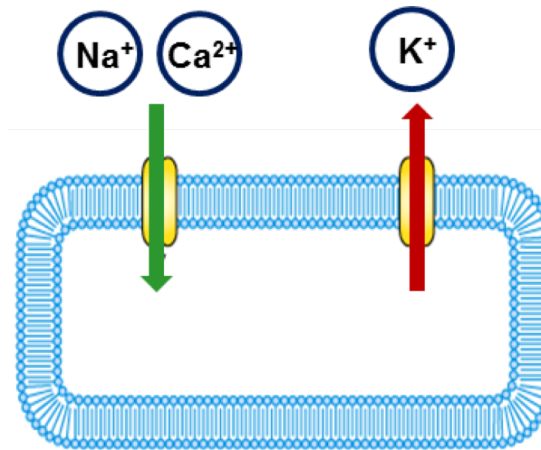
Tissue Model



EGM Recordings Model



Mitchell-Schaeffer Electrophysiology Model



$$\partial_t u = \frac{zu^2(1-u)}{\tau_{in}} - \frac{u}{\tau_{out}} + \text{div}(D\nabla u)$$

Reaction Diffusion

Conductivity [$10^{-3} \frac{m^2}{s}$]

AP Amplitude

τ_{in} [ms]

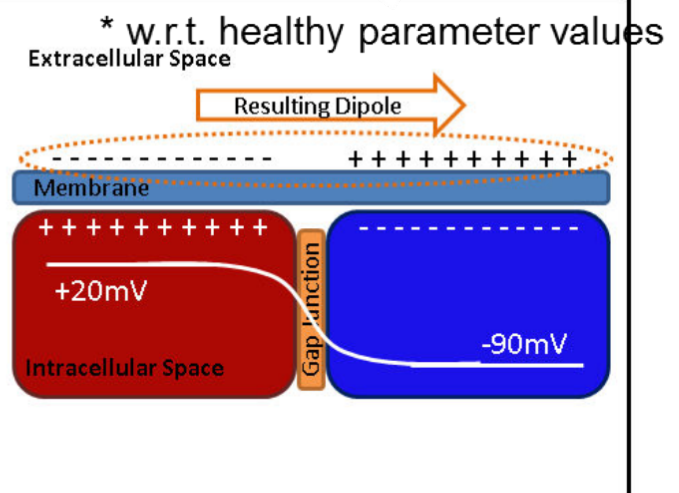
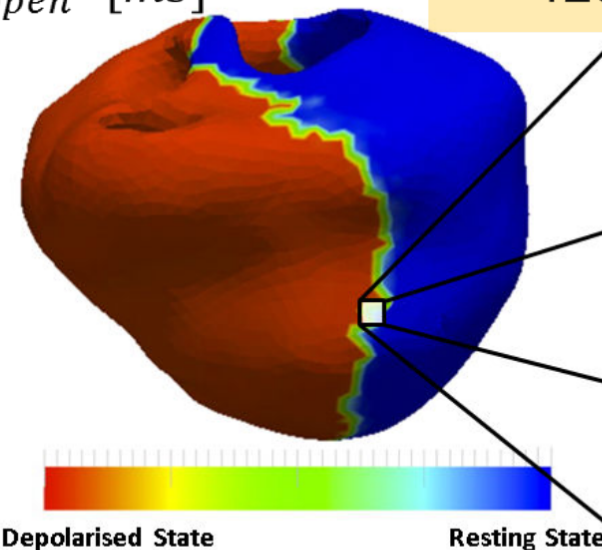
τ_{close} [ms]

τ_{out} [ms]

τ_{open} [ms]

healthy	grey zone	scar
$\partial_t z = \begin{cases} 1-z \\ -z \end{cases}$		
4.0	90% *	90% *
1.0	30% *	
0.3	31% *	
150	25% *	
6	31% *	
120	=	

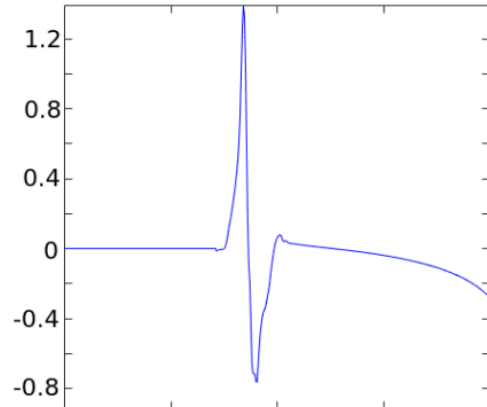
Dipole formulation



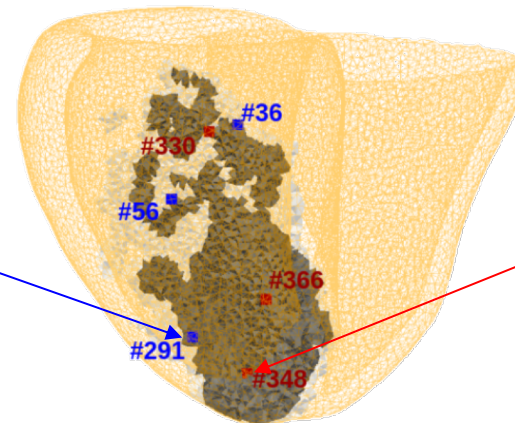
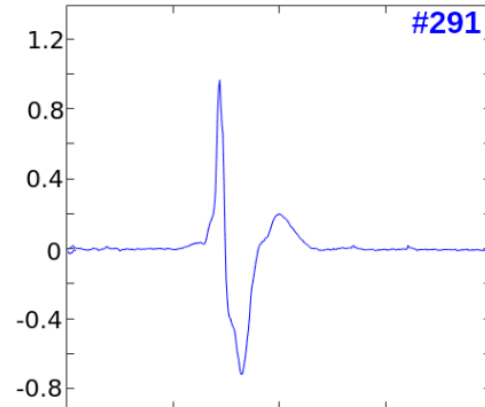
Biophysical Modeling: Qualitative Results

normal EGMs

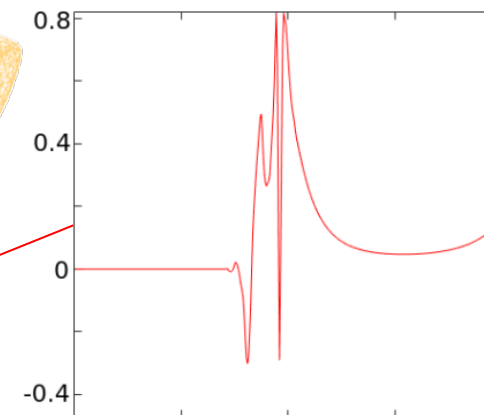
Simulated Signals



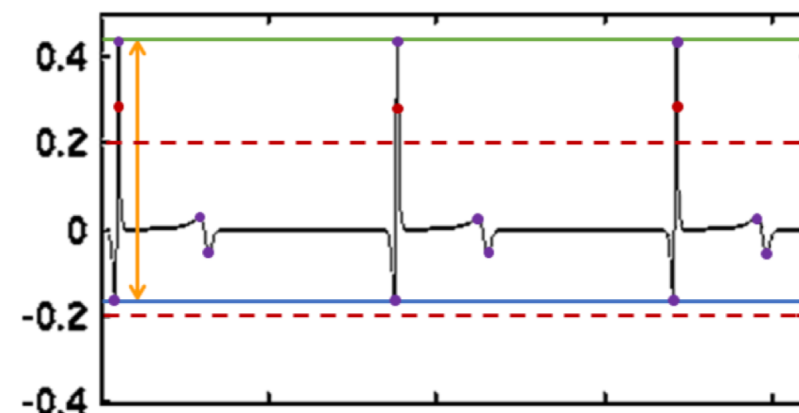
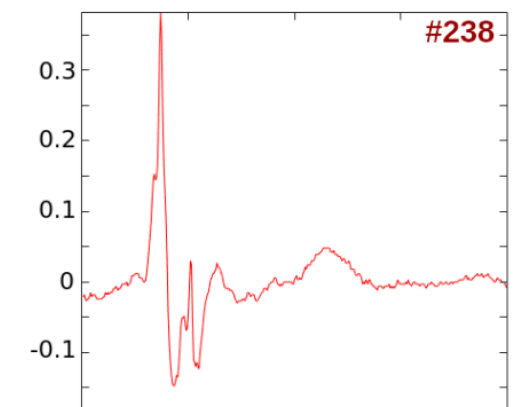
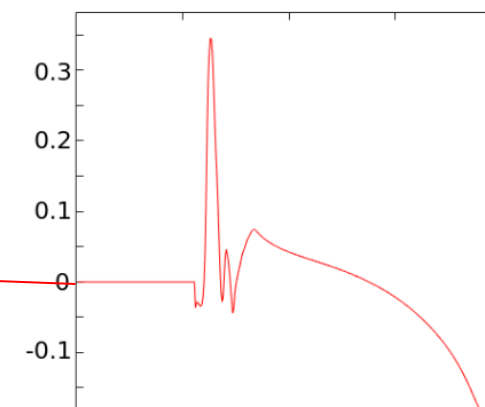
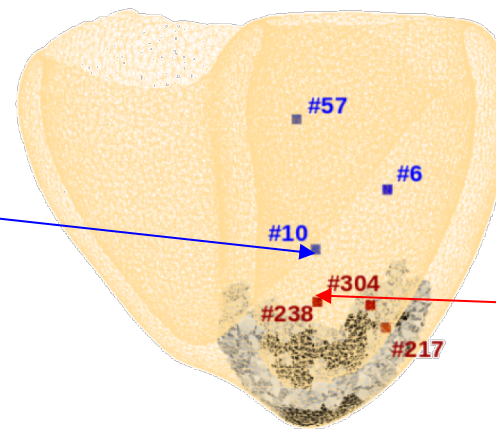
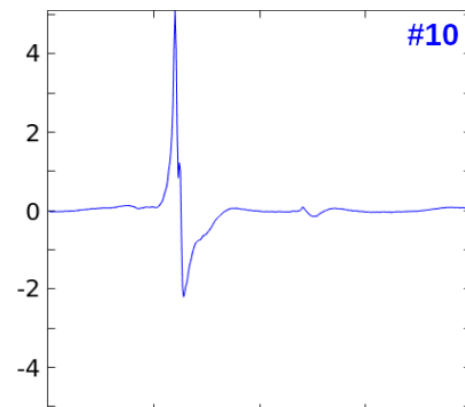
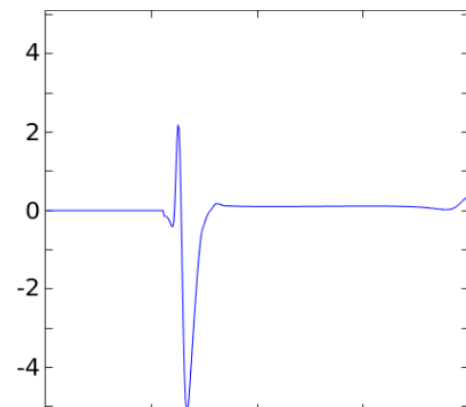
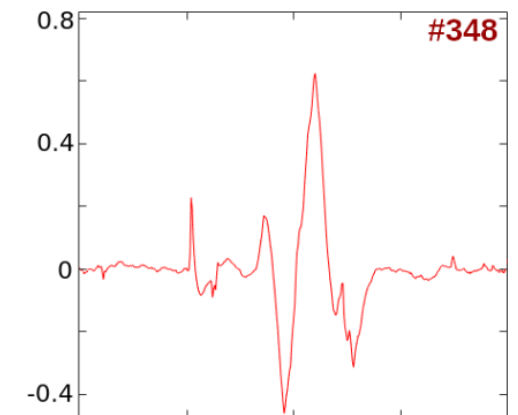
Clinical Signals



Simulated Signals



Clinical Signals

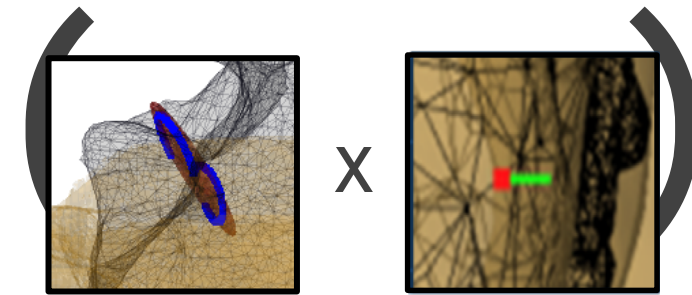


- Signal Range
- Maximum Value
- Minimum Value
- Inflection Points
- Fractionation Index

Uncertainty Quantification

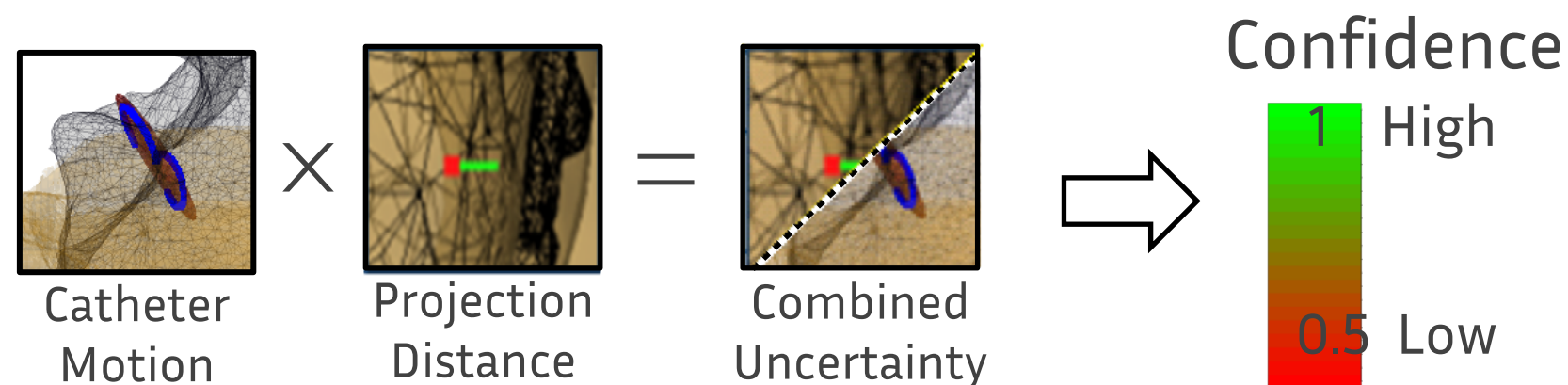
Combined Uncertainty: catheter motion + registration error

The product of both uncertainty sources



Intuitively, features from EAPs with smaller catheter motion and projection distance are more reliable

Confidence values per EAP are assigned by scaling weight parameters



Machine Learning with Uncertainty

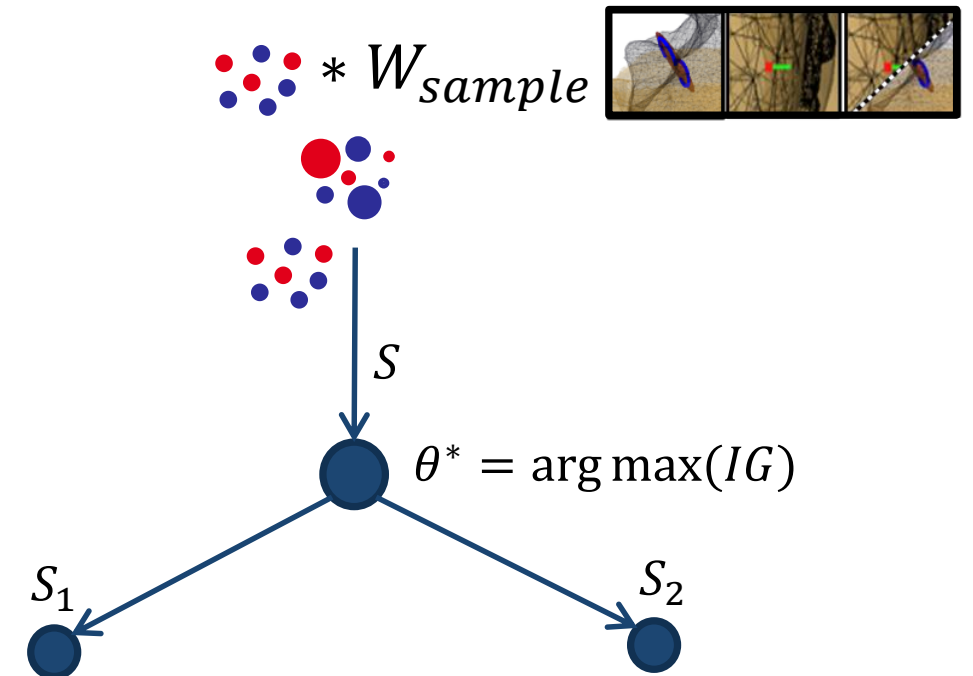
- Random forests define the node split criterion (information gain) as :

$$IG = H(S) - \sum_{i=1,2} \frac{|S^i|}{|S|} H(S^i)$$

samples after split @ child node
samples before split @ parent node

Shannon Entropy: $H(W) = -\sum_{c \in C} p_w(c) \log(p_w(c))$

Weighted instances redefine entropy



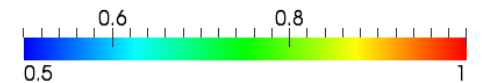
Sample weighted formulation of IG:

$$IG = H(W) - \sum_{i=1,2} \frac{\sum_s W^i}{\sum_s W} H(W^i)$$

Augmenting Features with Personalised Models

Five patients referred for RFA for post-infarction VT

Prediction Confidence

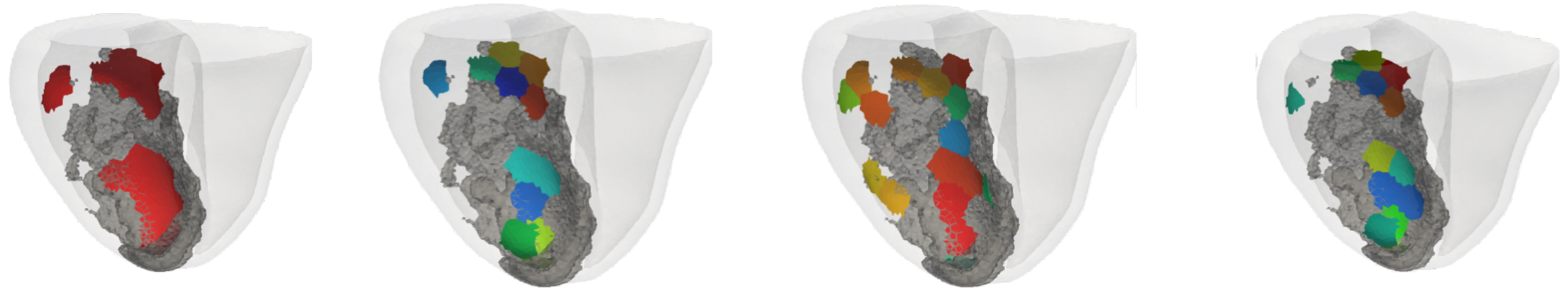


Ground Truth

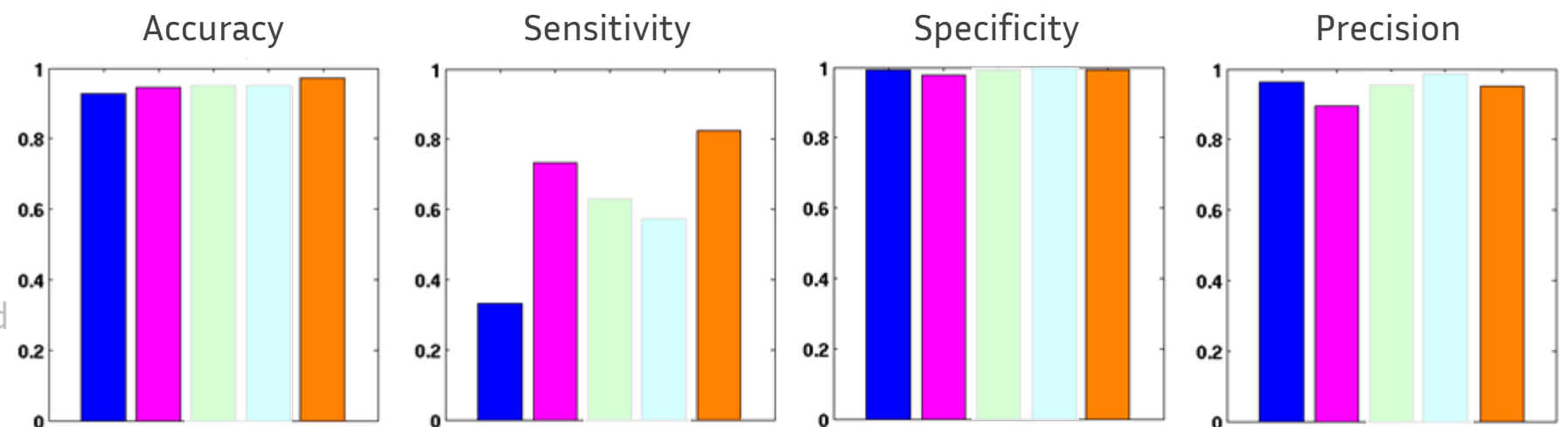
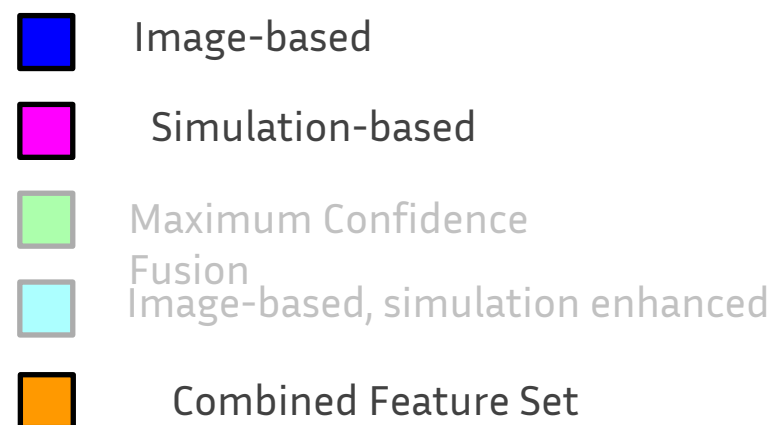
Image Features

Simulation Features

Image + Simulation



Average results across five patients

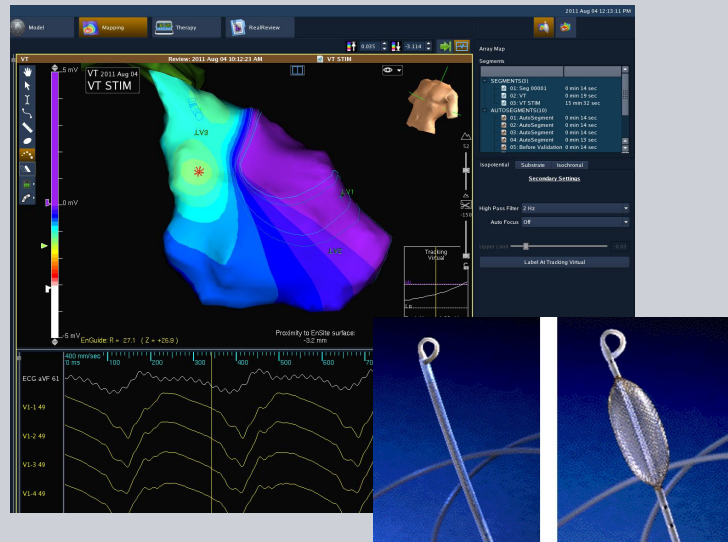


→ Simulated features improve machine learning results

Overview

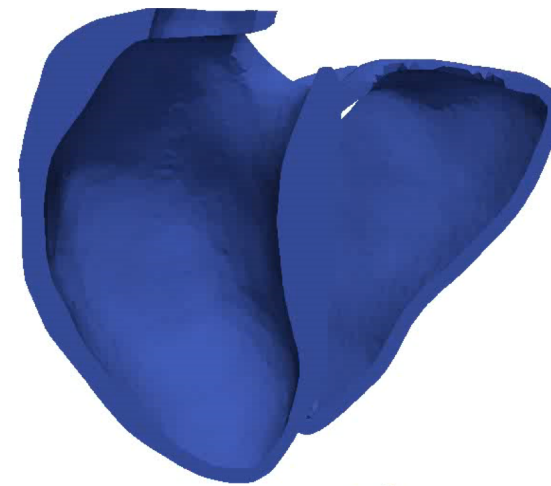
- Cardiac Modelling & Machine Learning
 - Feature Augmentation
 - Data Augmentation
 - Transfer Learning

Electrophysiological (EP) Personalisation



Invasive measurements

- + precise
- risk
- long procedure
- X-ray radiations



EP Cardiac Model

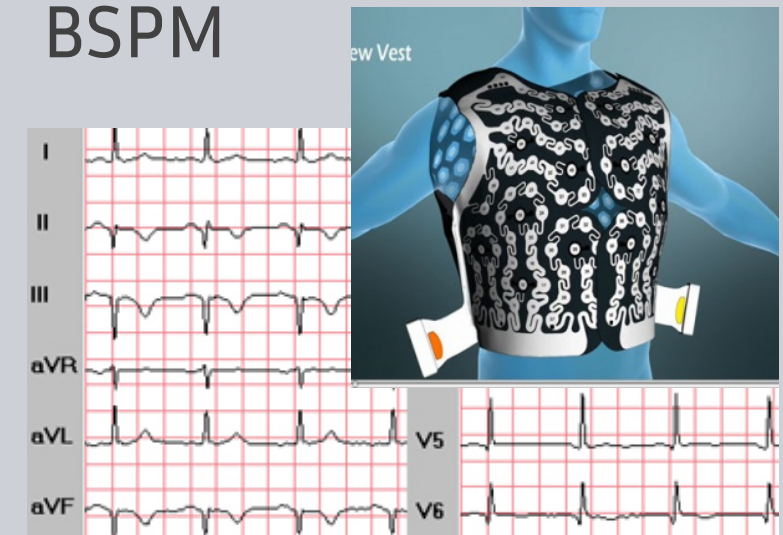


Personalise
parameters



Understand pathologies
and predict therapies

BSPM



Non-invasive measures

- low-risk +
- shorter procedure +
- Ill-posed problem -

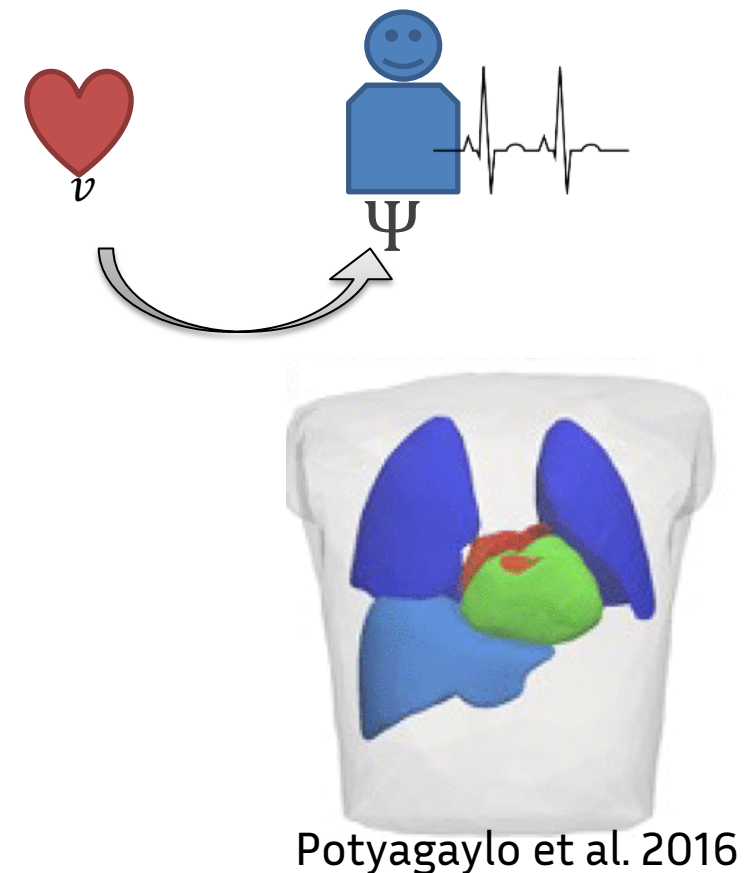
Forward Model in ECG imaging

- Classical numerical approaches BEM / FEM:
 - Null current across the body surface
 - Different properties of torso tissues
- Dipole formulation [1,2]:
 - simplified framework
 - homogeneous and infinite torso domain Φ_B

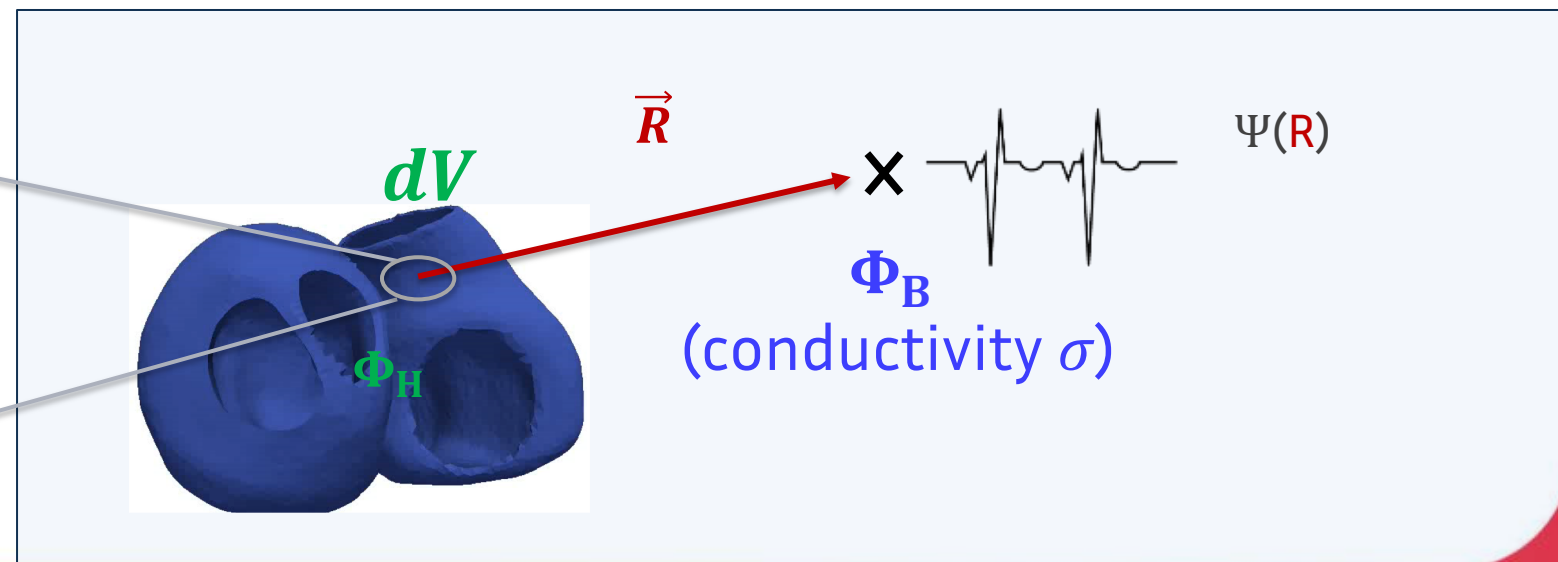
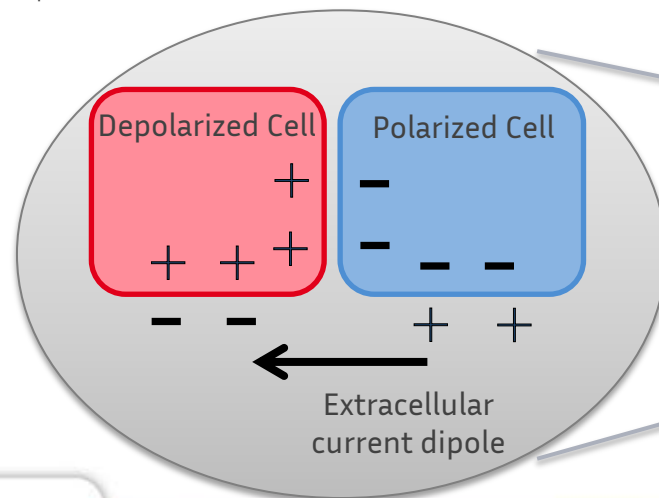
$$\text{Potential } \Psi(\mathbf{R}) = \frac{1}{4\pi\sigma} \int_{\Phi_H} \mathbf{j}_{eq} \cdot \nabla \left(\frac{1}{R} \right) dV$$

$\mathbf{j}_{eq}$ = eq. current density

Forward problem

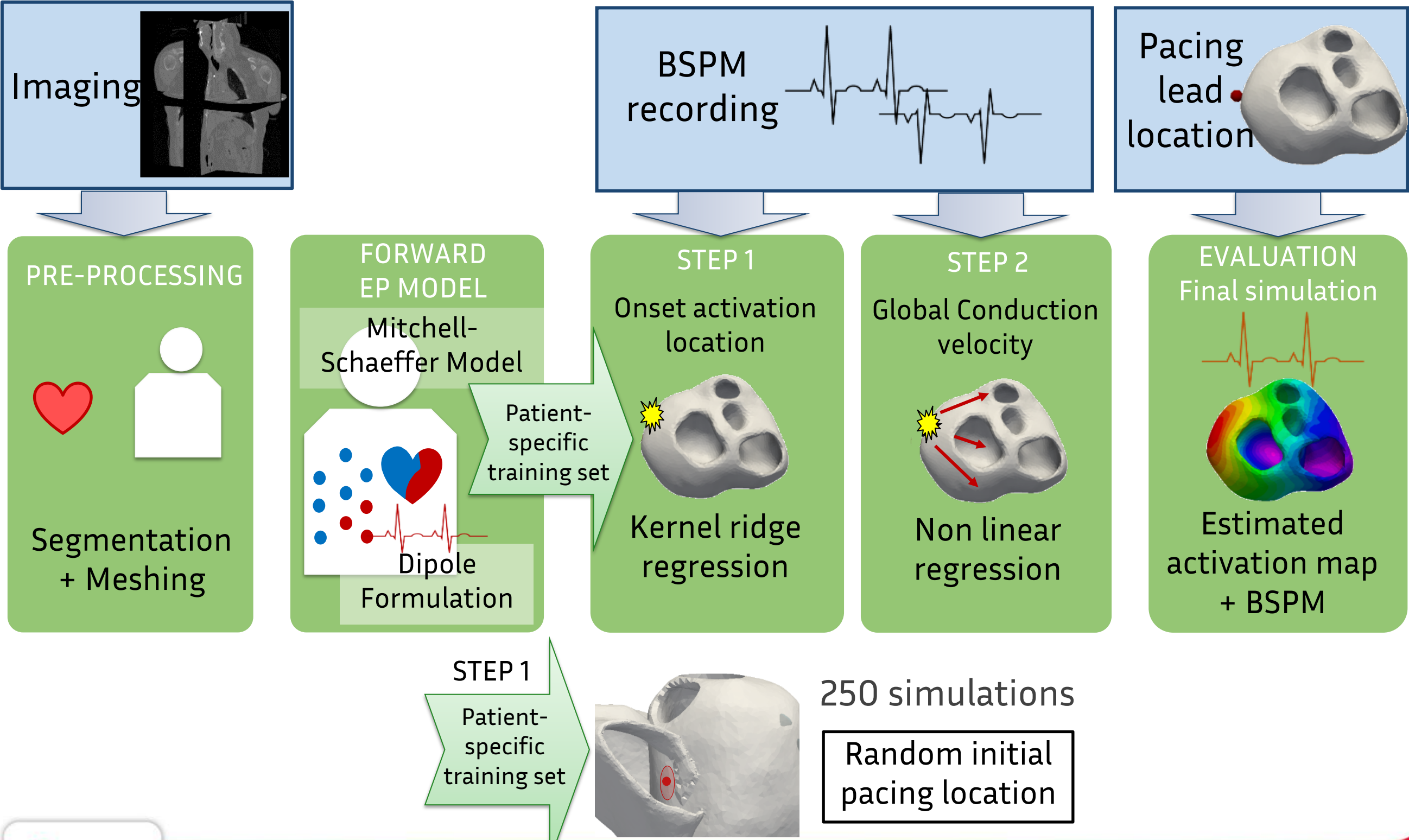


Potential of current dipoles



Personalisation Pipeline

For every patient



Kernel Ridge Regression

$$\begin{matrix} \text{Nb torso} \\ \text{electrodes} \times \\ 7 \end{matrix} \begin{bmatrix} x_{1,1} \\ x_{1,2} \\ \dots \\ x_{200,7} \end{bmatrix}$$

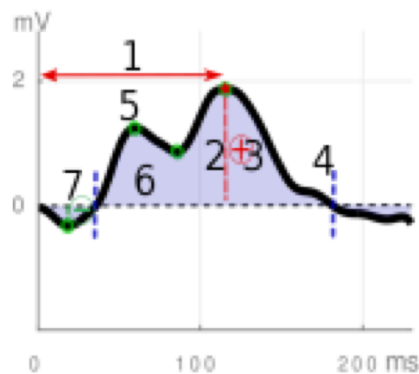
$\mathbf{x}$:
features



KERNEL RIDGE
REGRESSION

$$\begin{matrix} \text{Nb} \\ \text{vertices} \end{matrix} \begin{bmatrix} T_{d,1} \\ T_{d,2} \\ \dots \\ T_{d,k} \end{bmatrix}$$

$\mathbf{y}$:
targets



➤ Ridge regression : minimize $\|\mathbf{y} - \mathbf{X}\mathbf{w}\|^2 + \lambda\|\mathbf{w}\|^2$

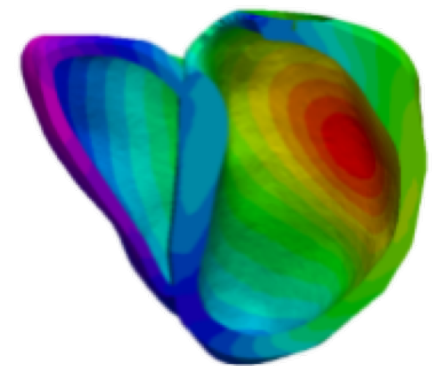
➤ Prediction $\mathbf{y}'$ of novel observation $\mathbf{x}'$:

$$\hat{\mathbf{y}}' = \mathbf{y}^T (\mathbf{K} + \lambda \mathbf{I})^{-1} \boldsymbol{\kappa}, \quad \kappa_i = \mathbf{K}(\mathbf{x}', \mathbf{x}_i)$$

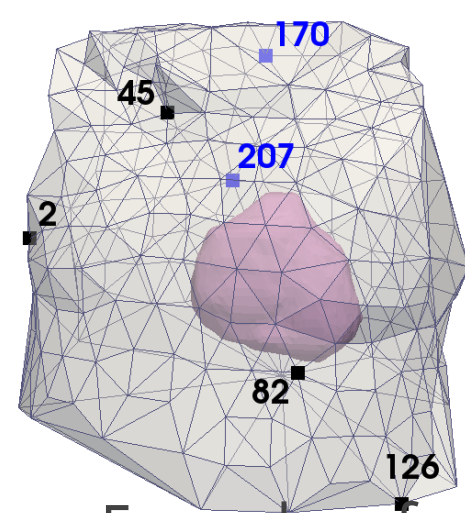
➤ Gaussian kernel: $\mathbf{K}(\mathbf{x}_i, \mathbf{x}_j) = \exp\left(-\frac{\|\mathbf{x}_i - \mathbf{x}_j\|^2}{2\sigma^2}\right)$

➤ 2 parameters: λ, σ

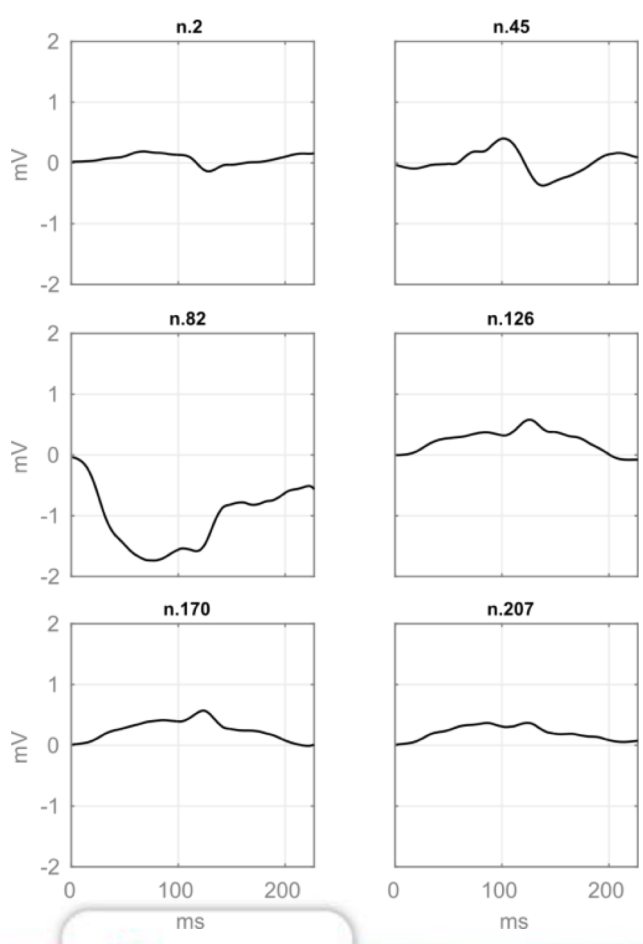
➤ from 10-fold cross-validation



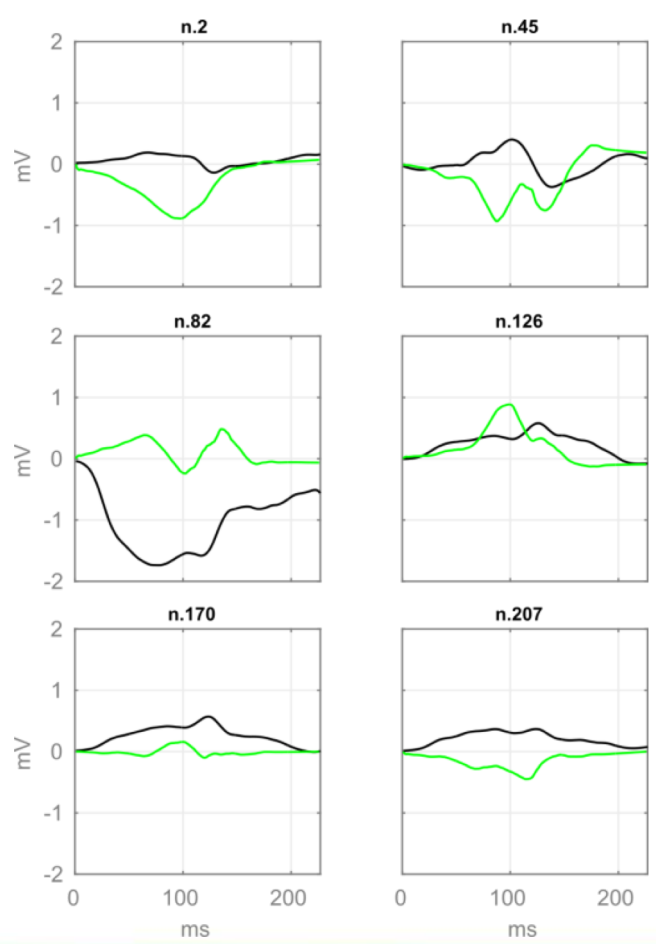
Non-invasive personalisation: pipeline



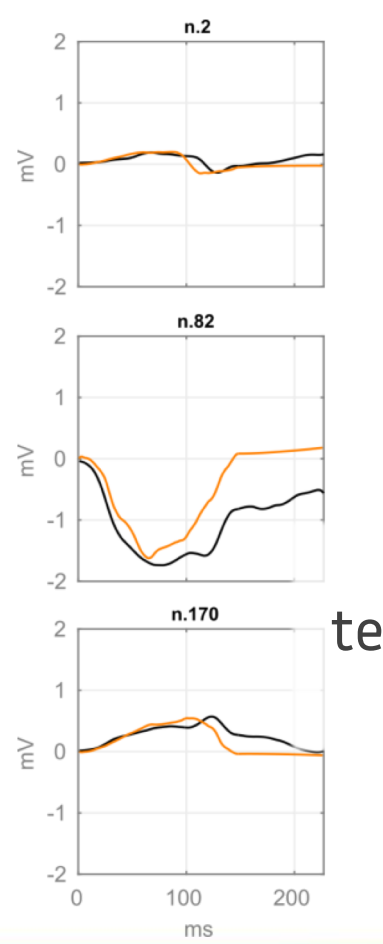
Examples of measured torso potentials



After pre-processing
 $\overline{CC} = -0.15$

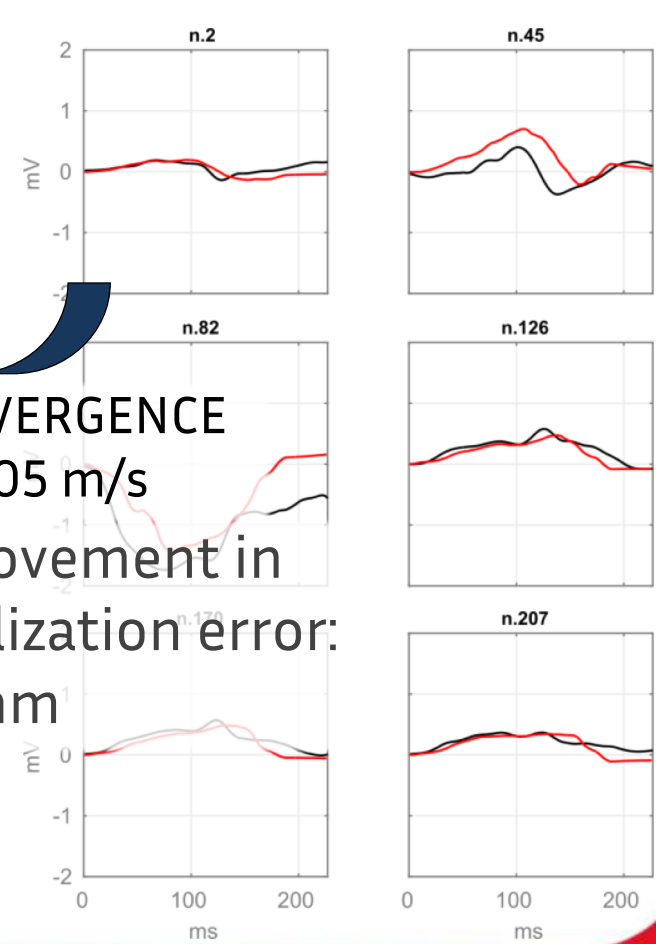


After step 1
(Activation onset)
 $\overline{CC} = 0.65$



After step 2
(Conduction velocity)
 $\overline{CC} = 0.83$

UNTIL CONVERGENCE
 $\Delta c < 0.05$ m/s
Mean improvement in terms of localization error: 2mm



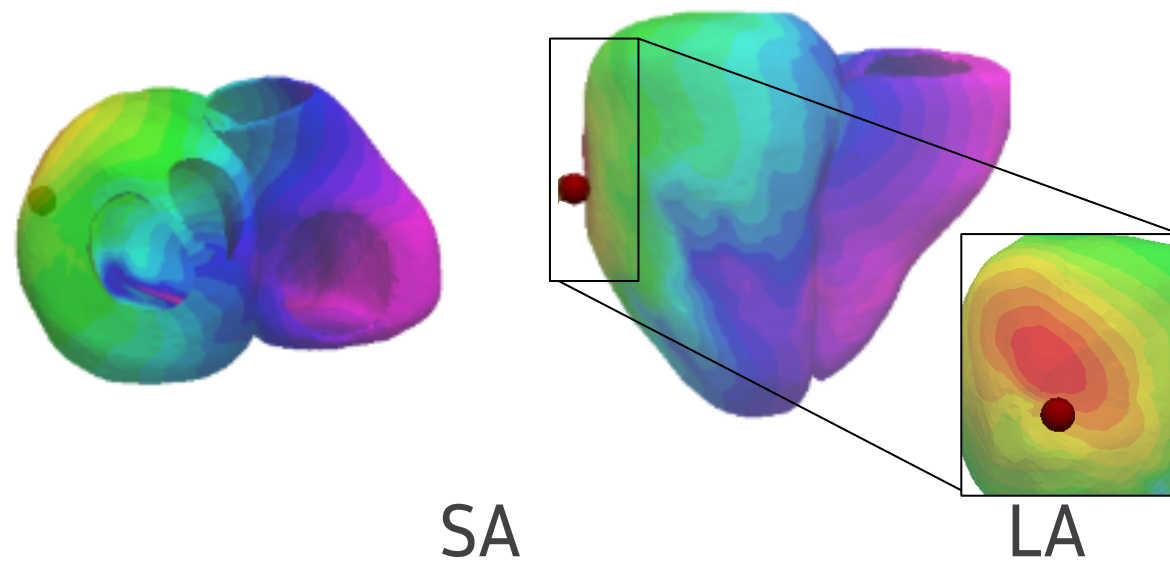
* $\overline{CC}$: averaged cross-correlation



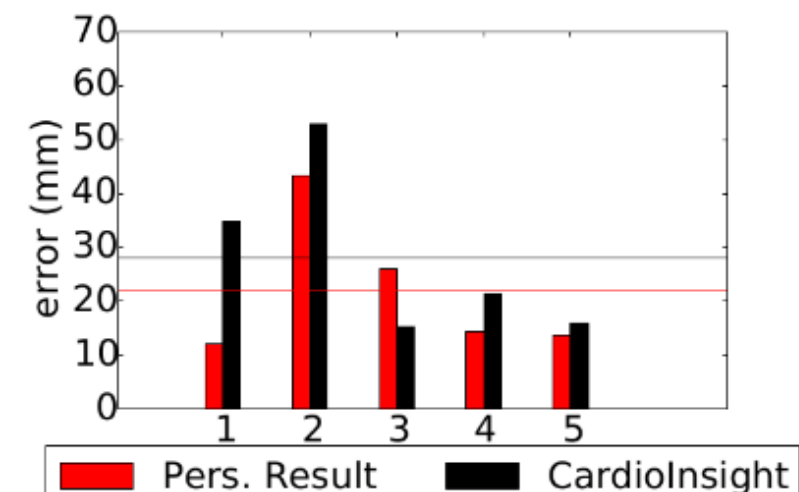
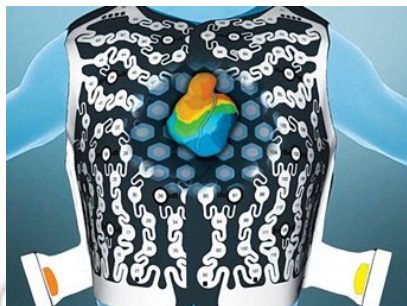
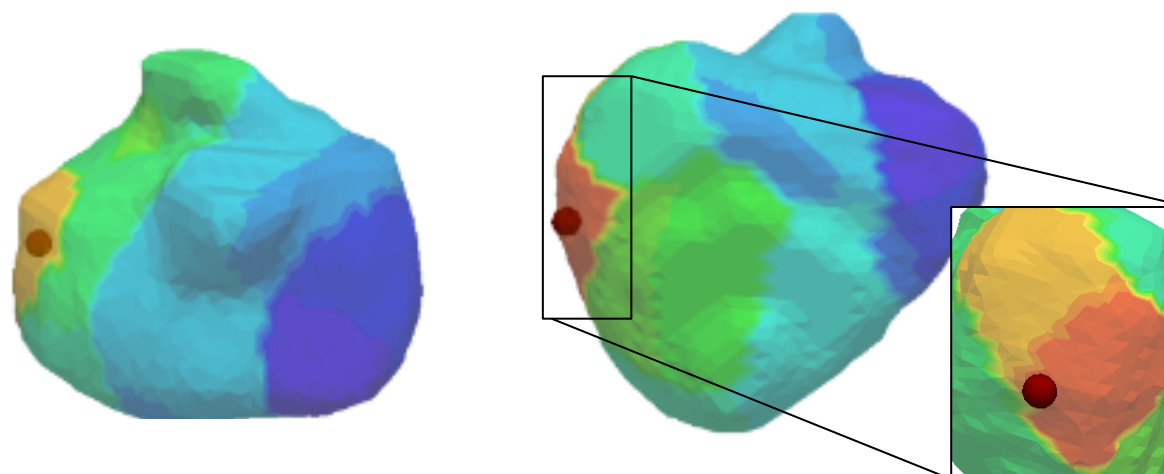
Non-invasive personalisation: evaluation

- Ex. Left ventricular (LV) pacing
- Comparison with CardioInsight inverse solution

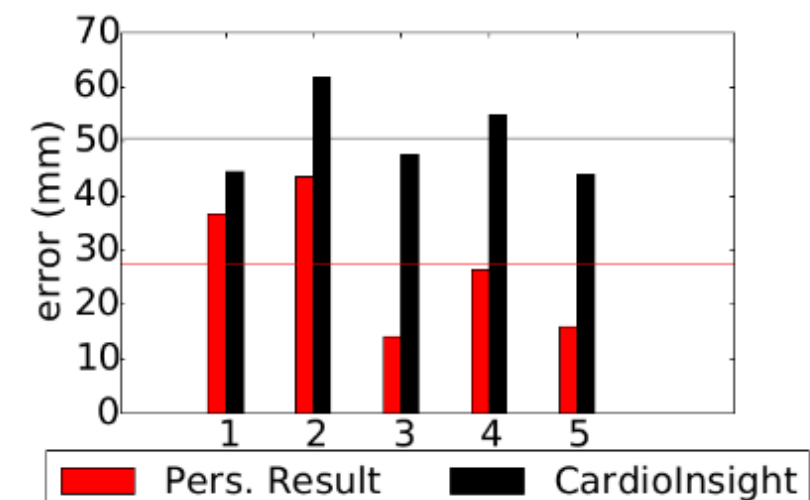
Personalisation
Result



CardioInsight
Result



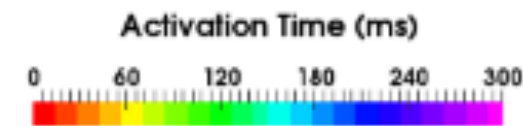
(b) LV pacing



(a) RV pacing

Non-invasive Predictions

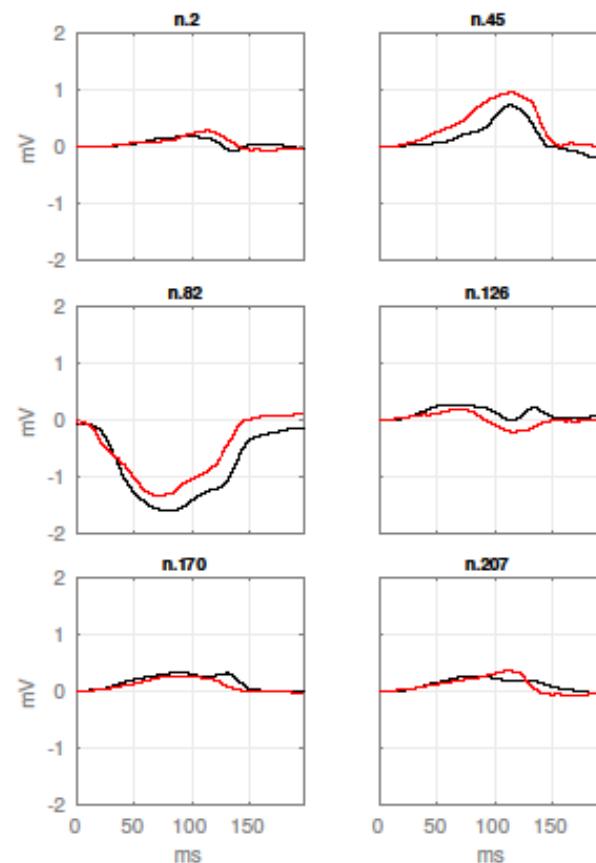
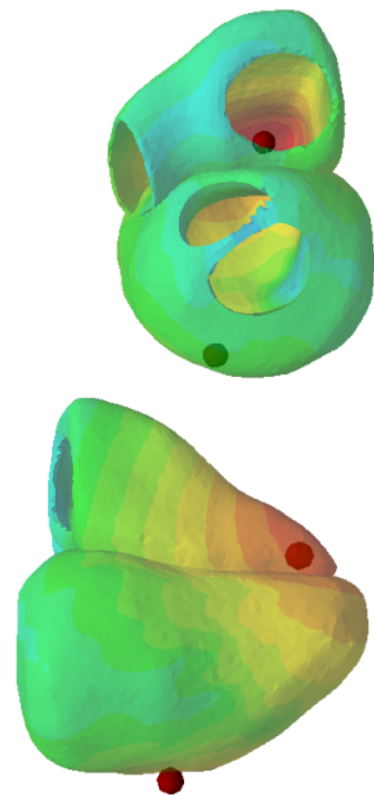
- 2 different patients



Measured BSPM

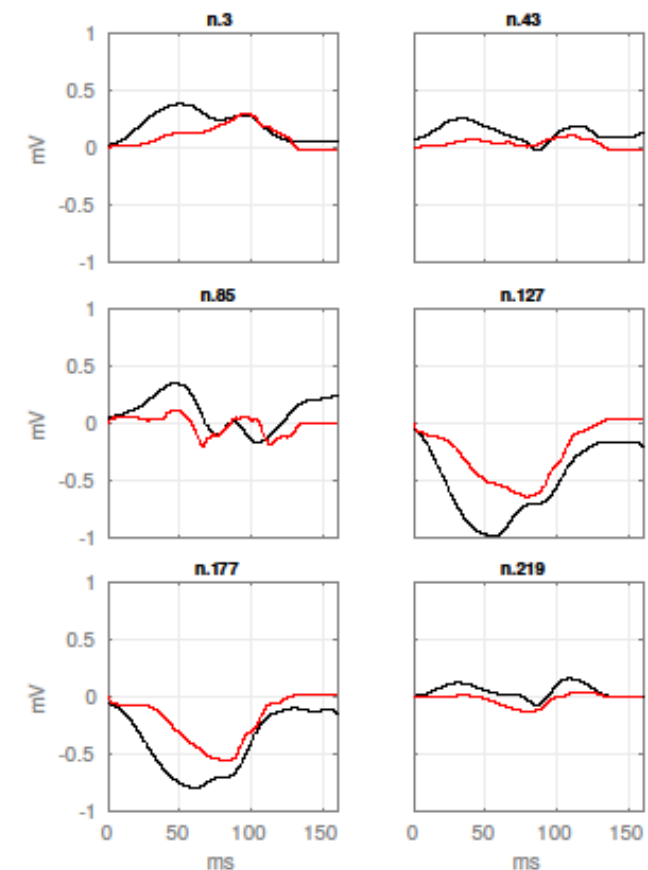
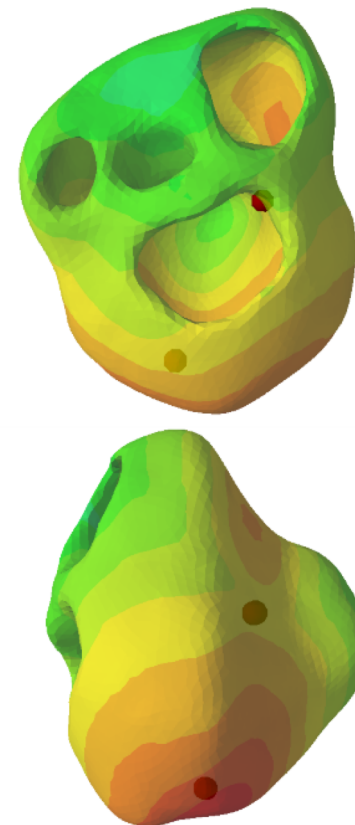
Predicted BSPM

Right pacing ahead by 40 ms on Left pacing



$$\overline{CC} = 0.61$$

Left pacing ahead by 40 ms on Right pacing



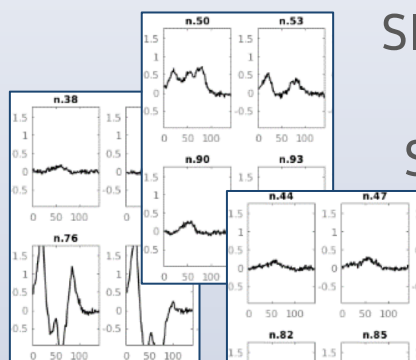
$$\overline{CC} = 0.70$$

$\overline{CC}$: averaged cross-correlation

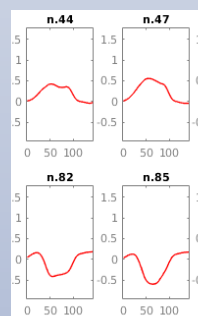
Regression for onset localisations

ECG signals

SIMULATED
TRAINING
SET (1000)

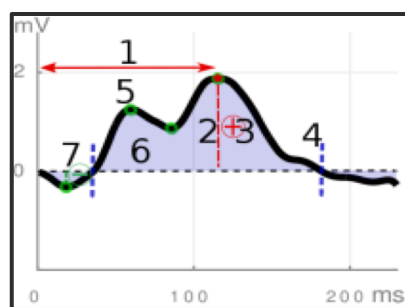


205 electrodes
QRS window

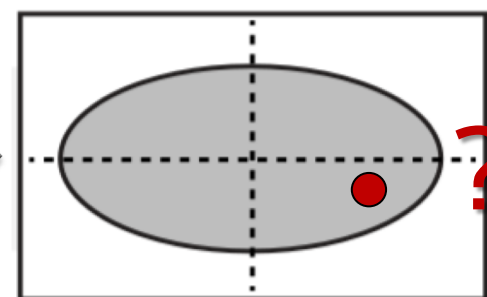


NEW SAMPLE
(REAL)

Feature space



Reduced shape space



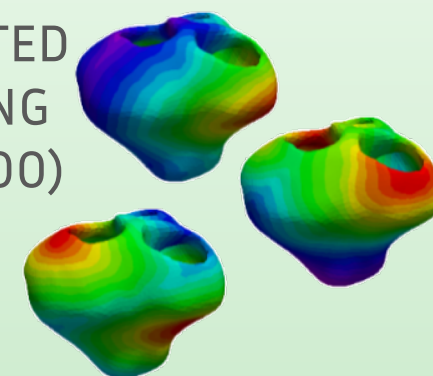
REGRESSION

RVR:

Relevance Vector
Regression
single-valued approach

Activation maps

SIMULATED
TRAINING
SET (1000)

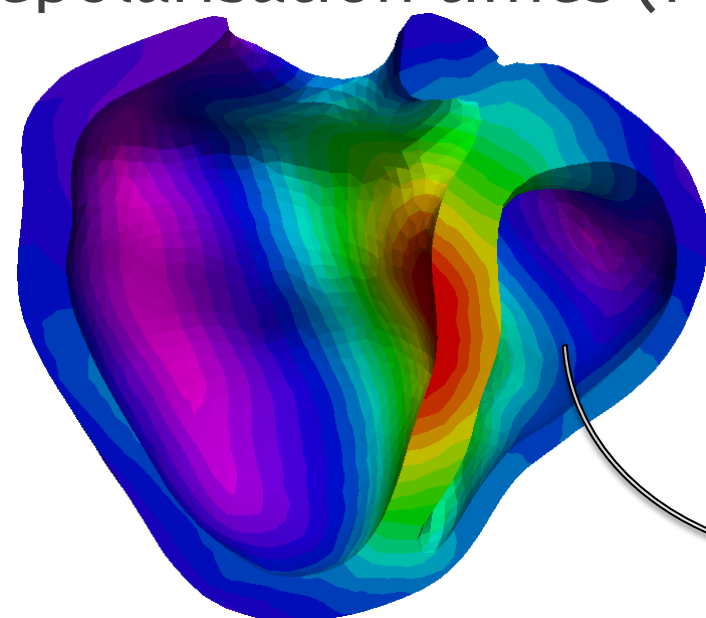
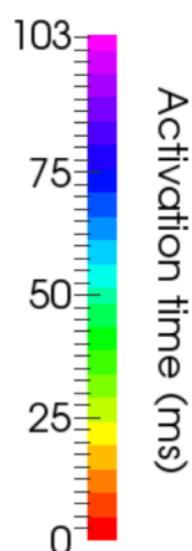


NEW SAMPLE
(ESTIMATION)

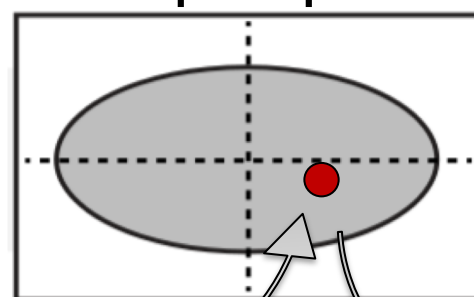


Dimensionality reduction of the cardiac shape

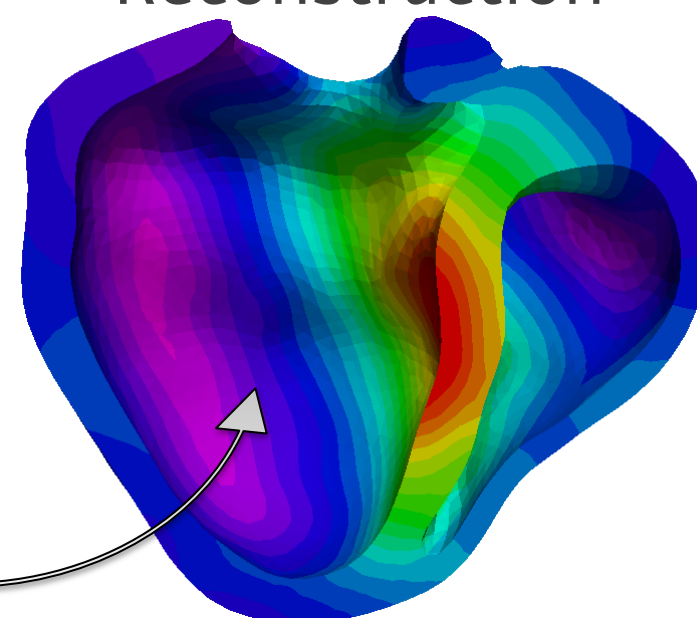
Y = Original
depolarisation times (14 K



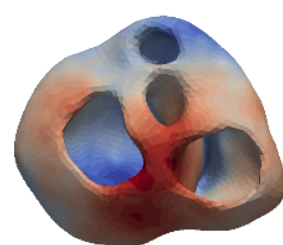
Reduced
shape space



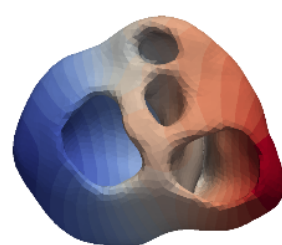
Y_{rec} =
Reconstruction



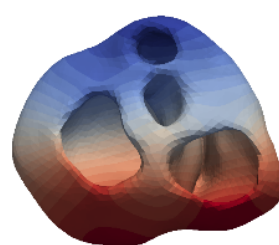
- Hierarchical decomposition of the mesh
- Eigen-decomposition of the stiffness matrix associated with the Laplacian operator
- Linked to the modes of vibration of the shape



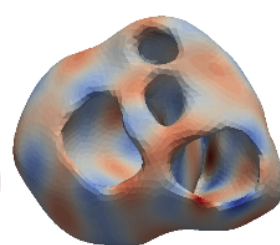
Mode 1



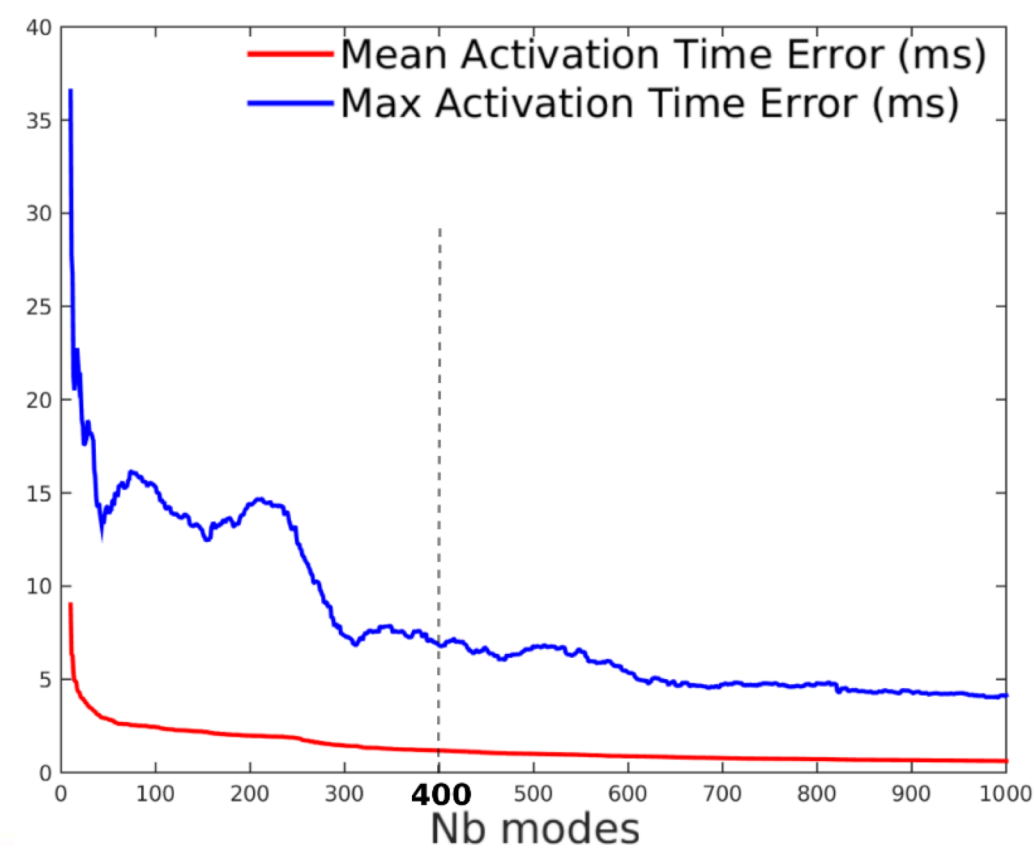
Mode 2



Mode 3



Mode 100



Example of result: bipacing data

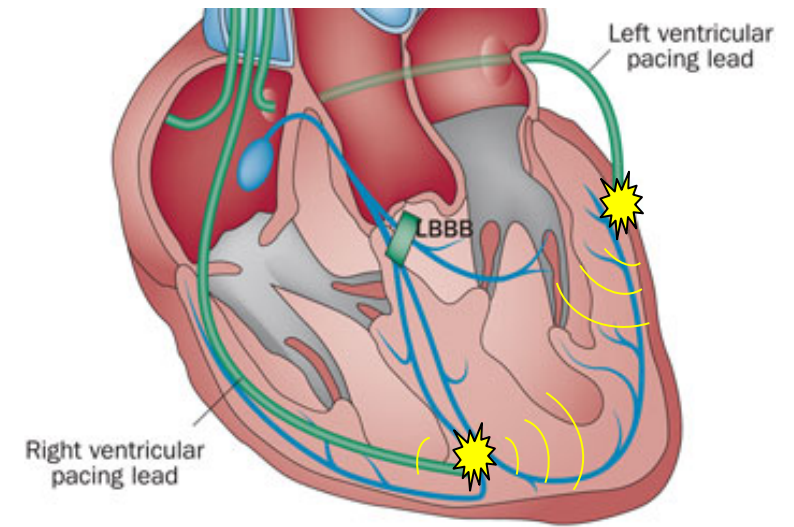


CardioInsight device

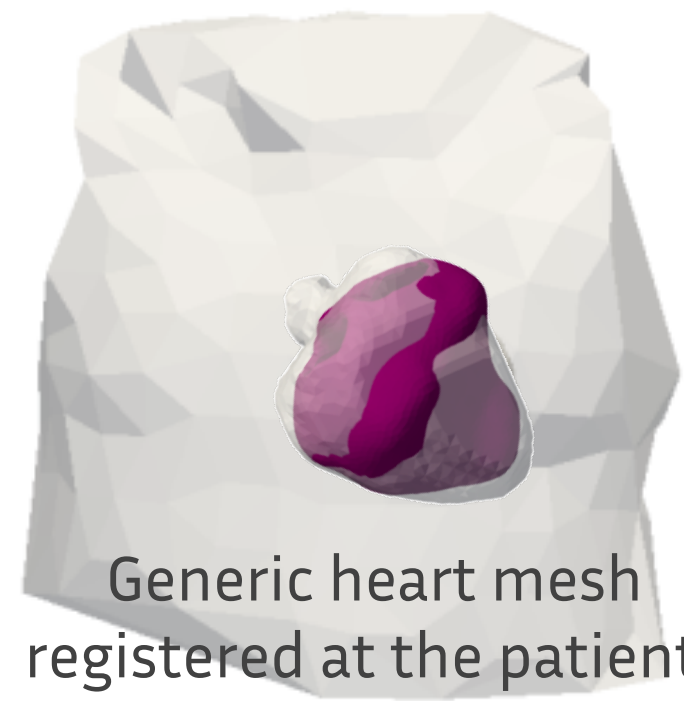


Segmented geometries from
X-ray scanner

- 69 year-old
- female
- complete heart block
- non-ischemic
- LBBB



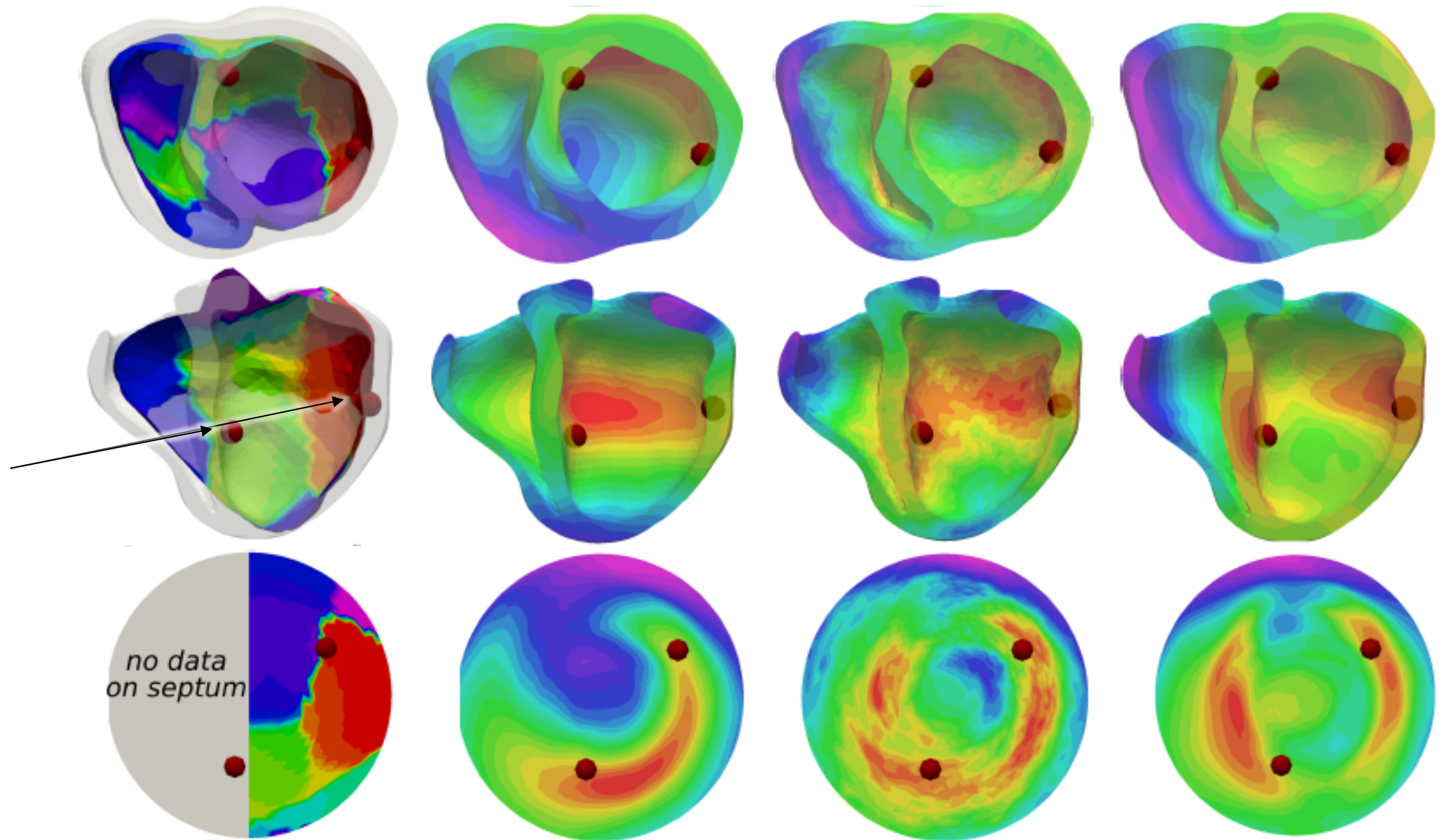
Stimulation leads
(simultaneous pacing)



Generic heart mesh
registered at the patient-
specific location

Example of result: biventricular pacing localisation

Ground
truth
onset
location
s



CardioInsight

Kernel ridge
regression

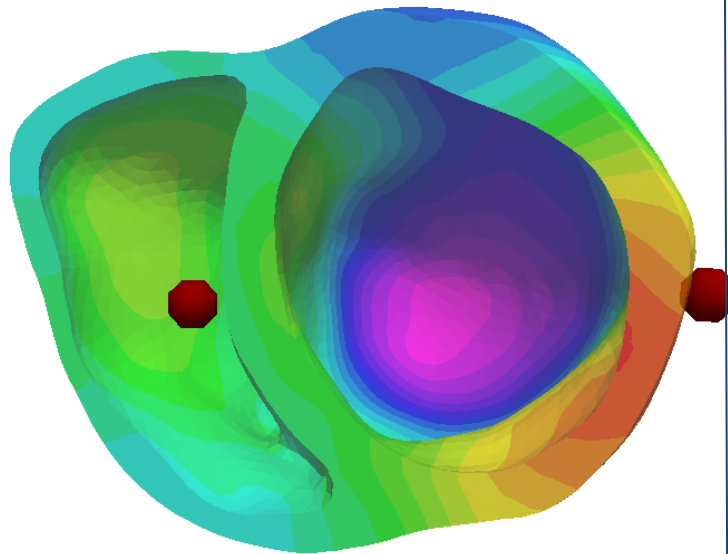
RVR

RVR reduced

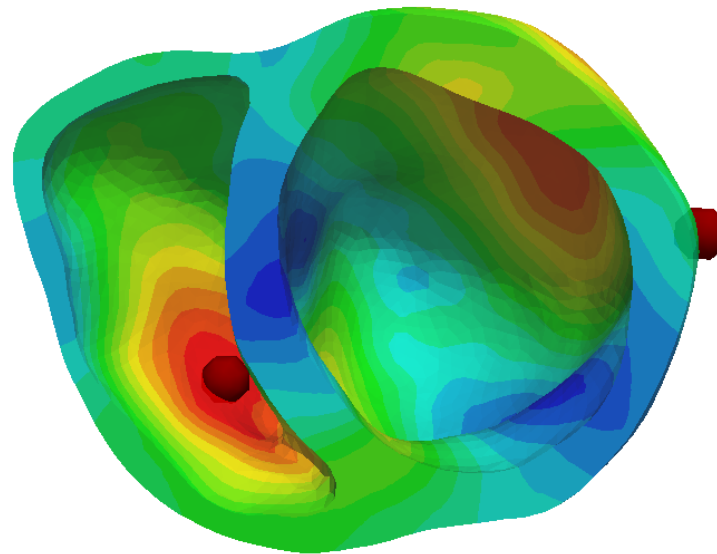
Activation time
Min  Max

Bipacing localisations: 3 other patients

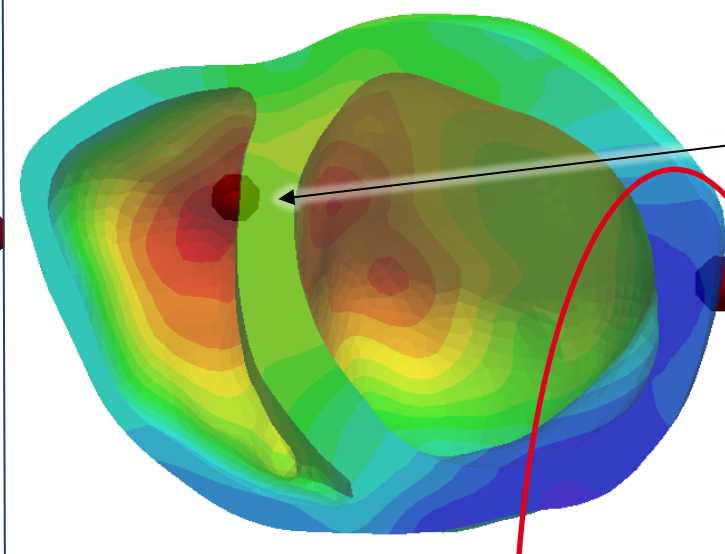
Patient #2



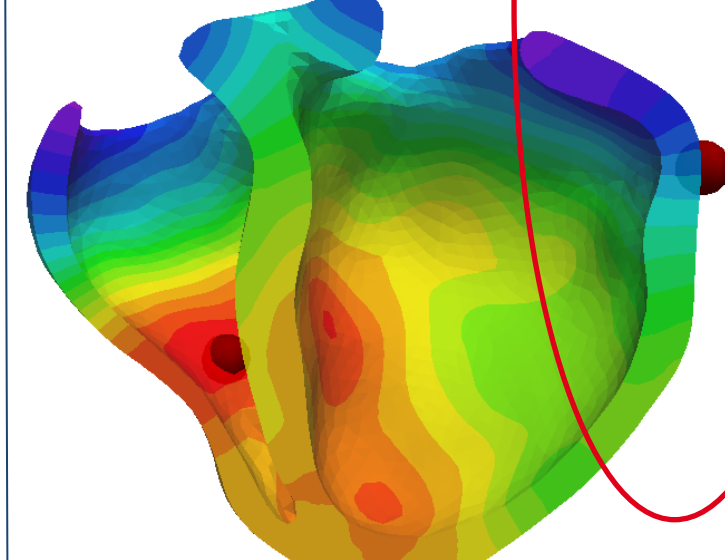
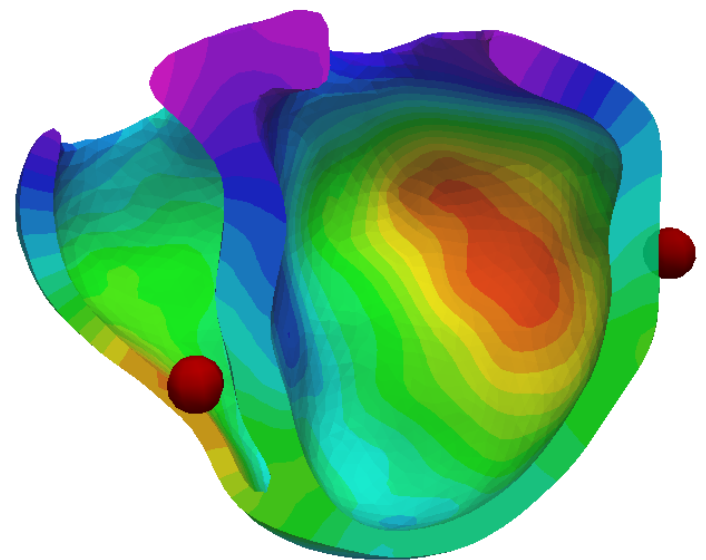
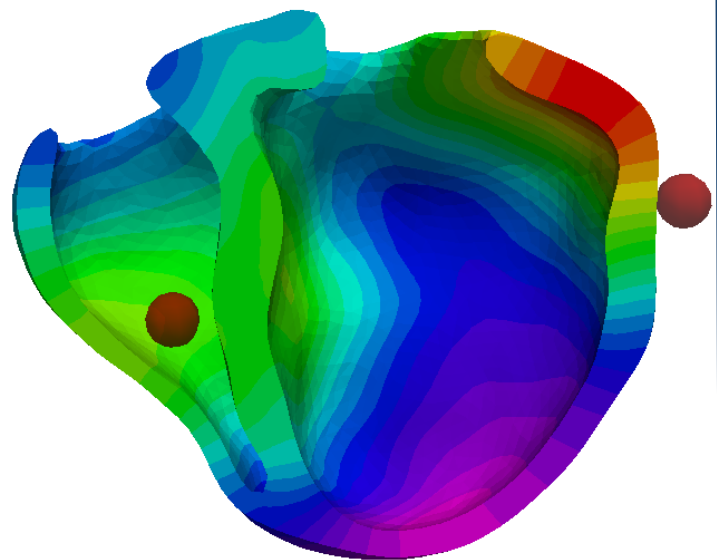
Patient #3



Patient #4



Ground
truth
onset
locations



Min
Activation time
Max

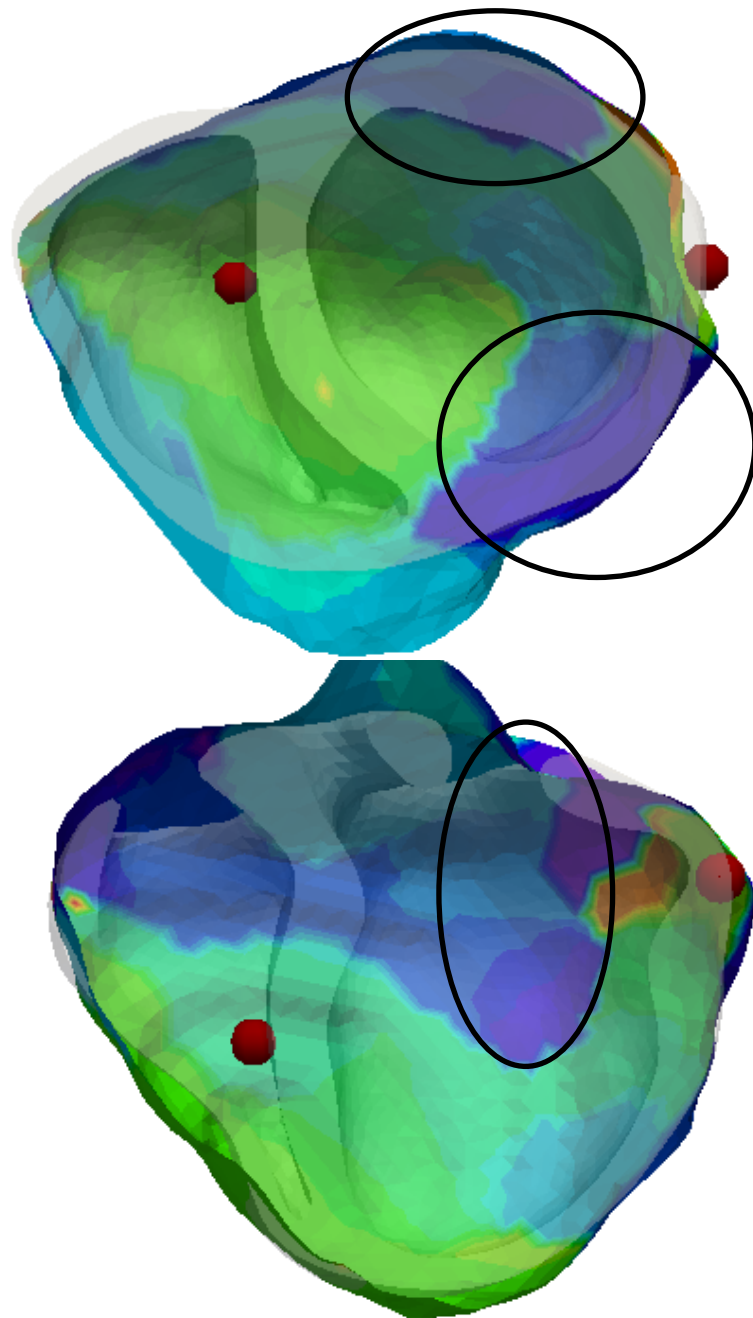
* The same generic heart mesh is used for 3 different patients

Bipacing localisations: 3 other patients

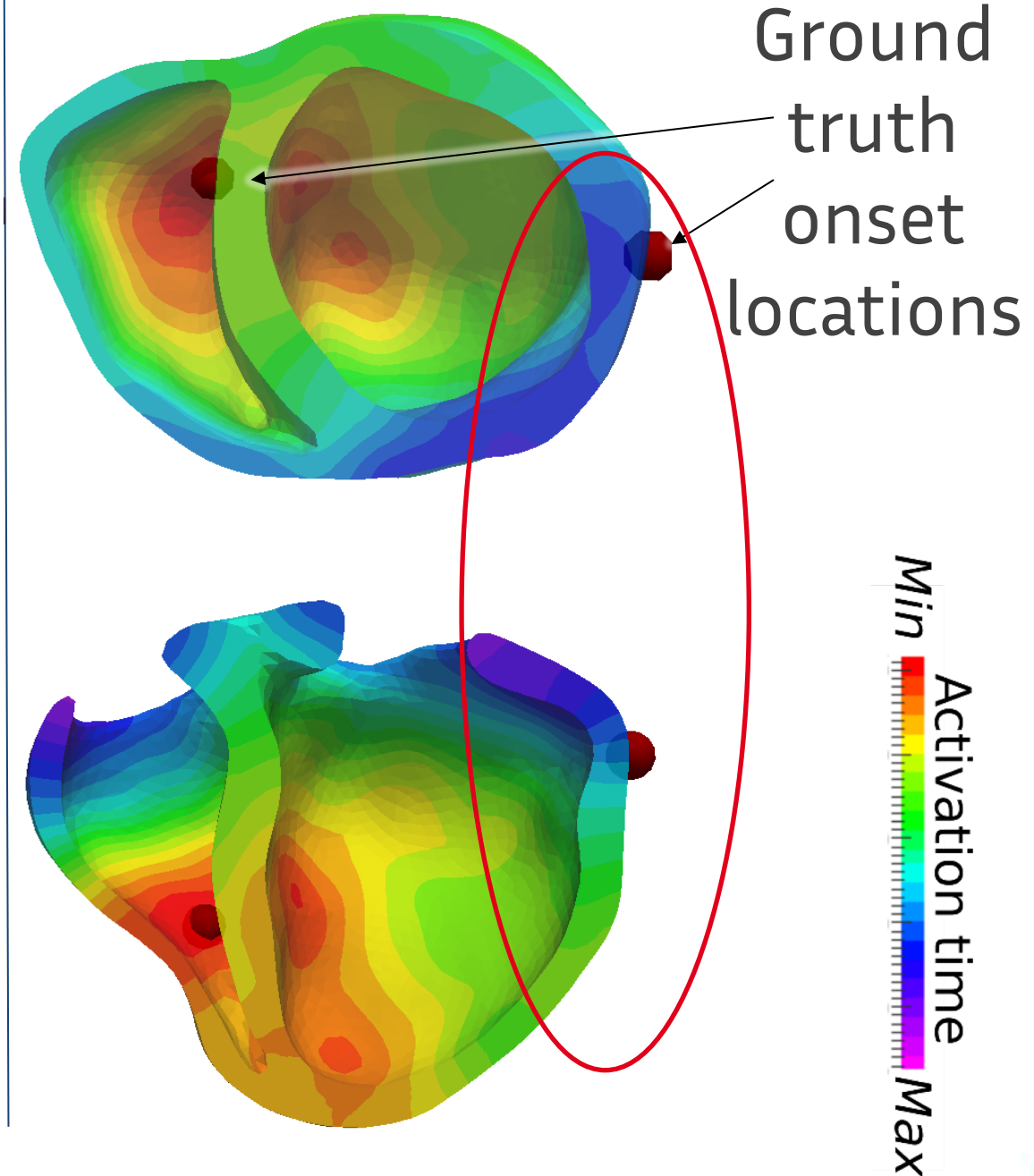
Patient #4:

Epicardial reconstruction (CardioInsight)

→ Infarcted patients:
include tissue
heterogeneity

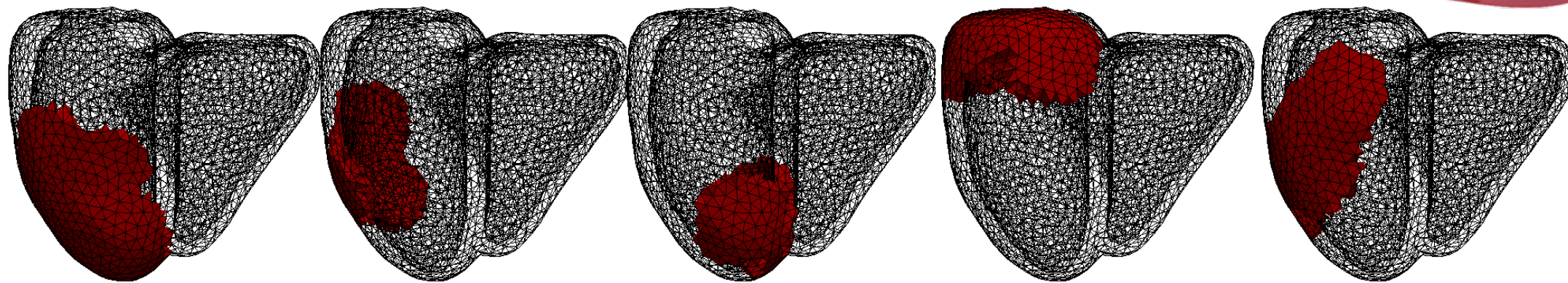
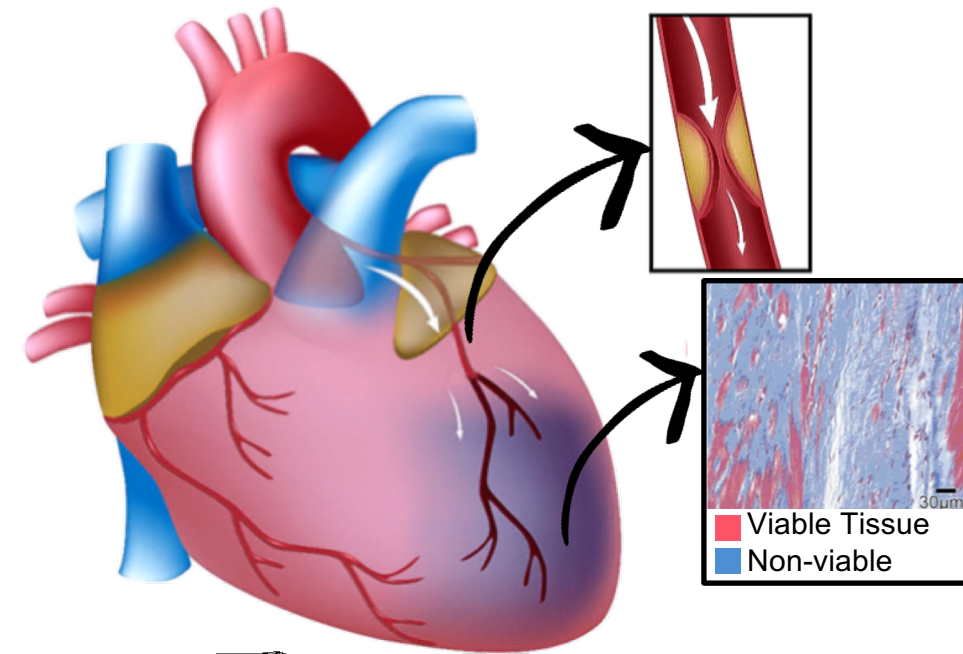


Patient #4

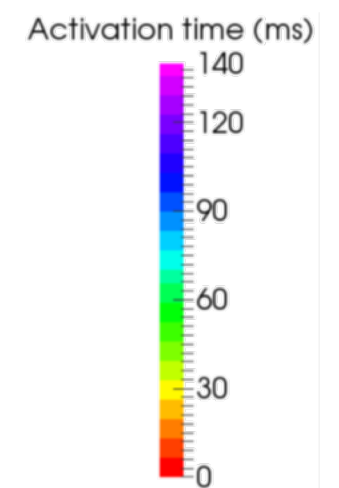
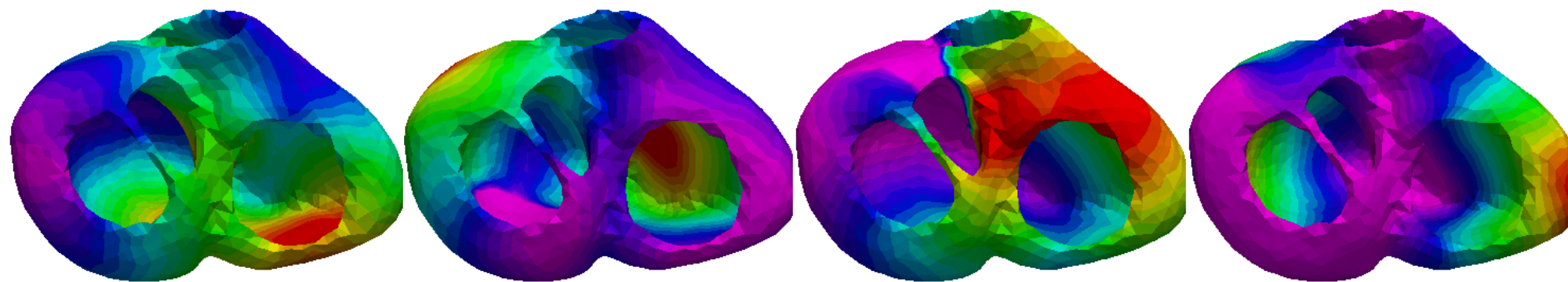


Include scar in the database

- Model realistic scar tissue
 - Random shape generation [1]
 - No reaction term + 80% diffusivity reduction



- 5000 simulations database
 - Left ventricle random scar (1/2 simulations)
 - Random global conduction velocity
 - Random onset activation locations



→ How to use a common (and not patient-specific) database?

Overview

- Cardiac Modelling & Machine Learning
 - Feature Augmentation
 - Data Augmentation
 - Transfer Learning

Reference Geometry → Domain Adaptation

- 20 patients with same device (CardioInsight)
- Majority of scarred patients

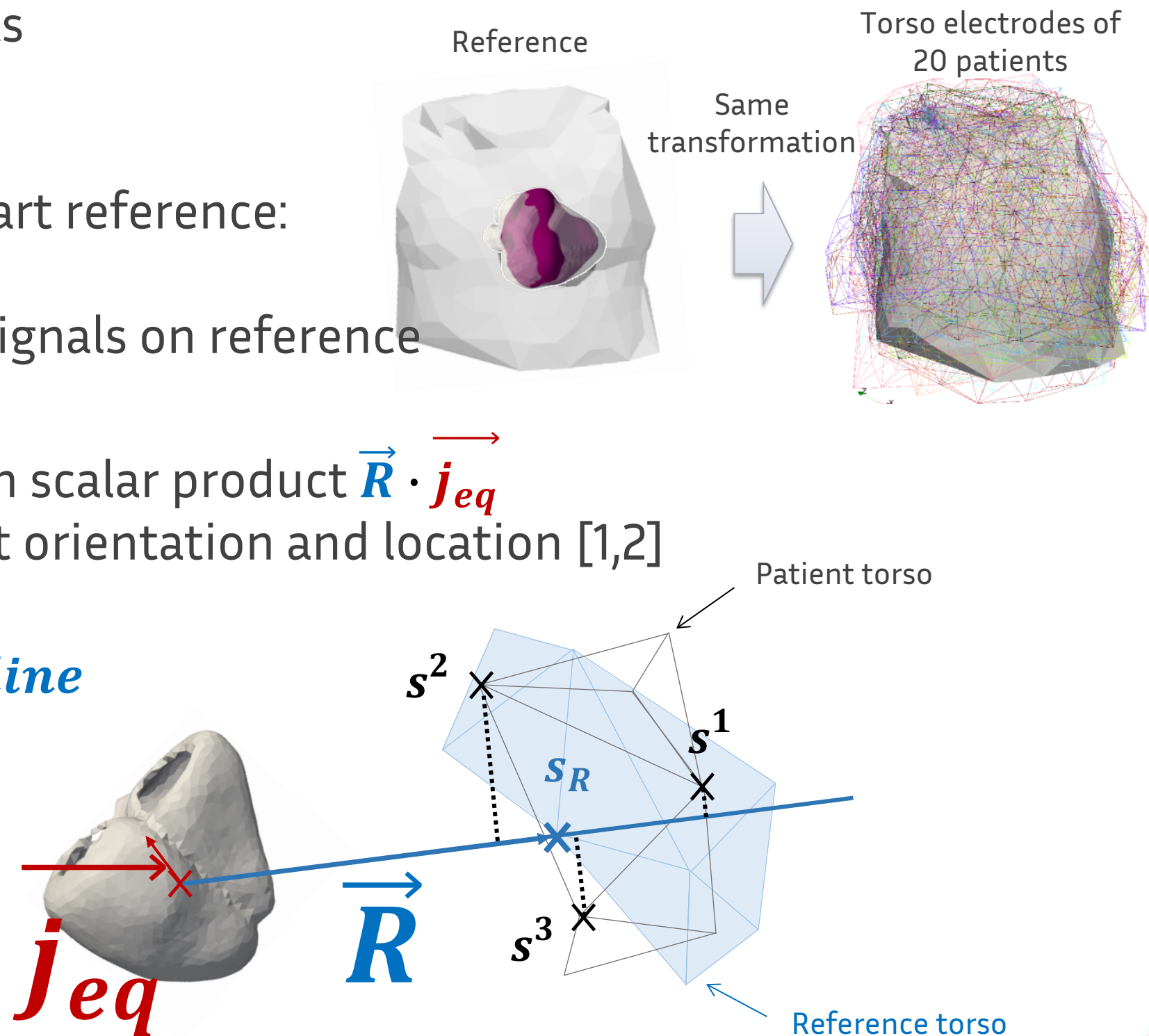
1) Rigidly register heart to heart reference:

2) How to interpolate BSPM signals on reference electrodes?

- Dipole formulation based on scalar product $\vec{R} \cdot \vec{j}_{eq}$
- ECG signal sensitive to heart orientation and location [1,2]

→ Preserve $\vec{R}$ direction

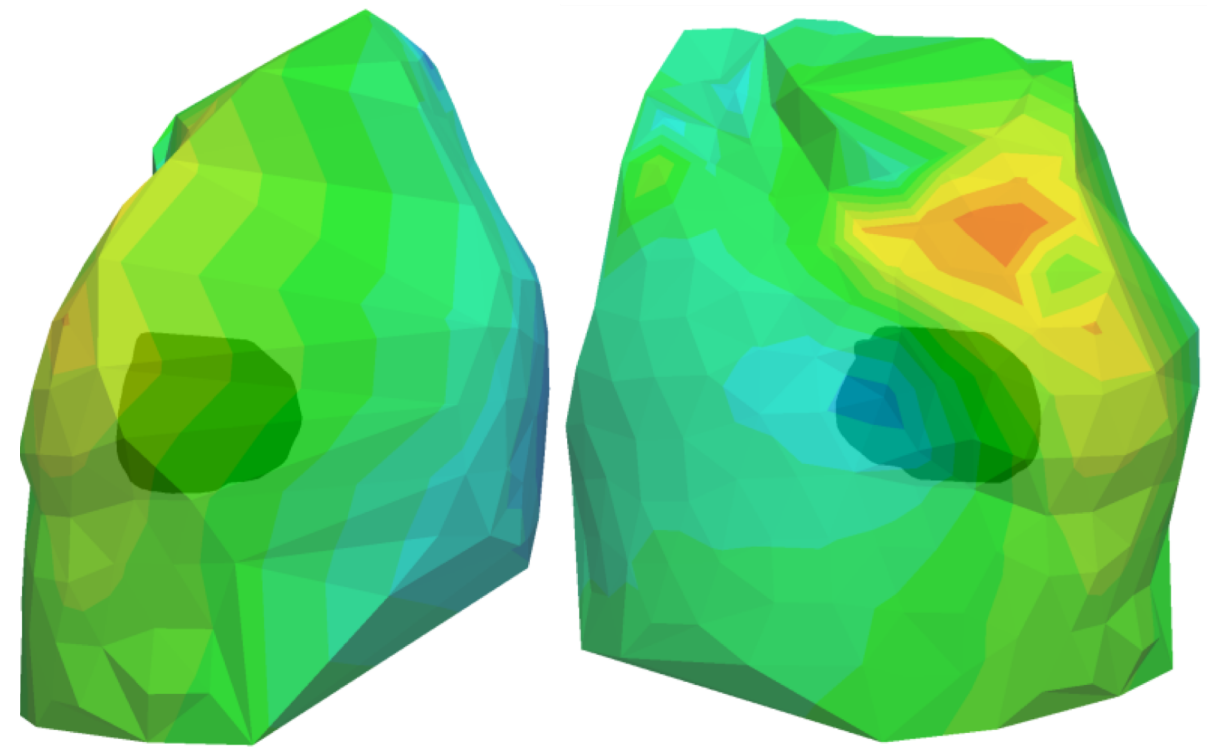
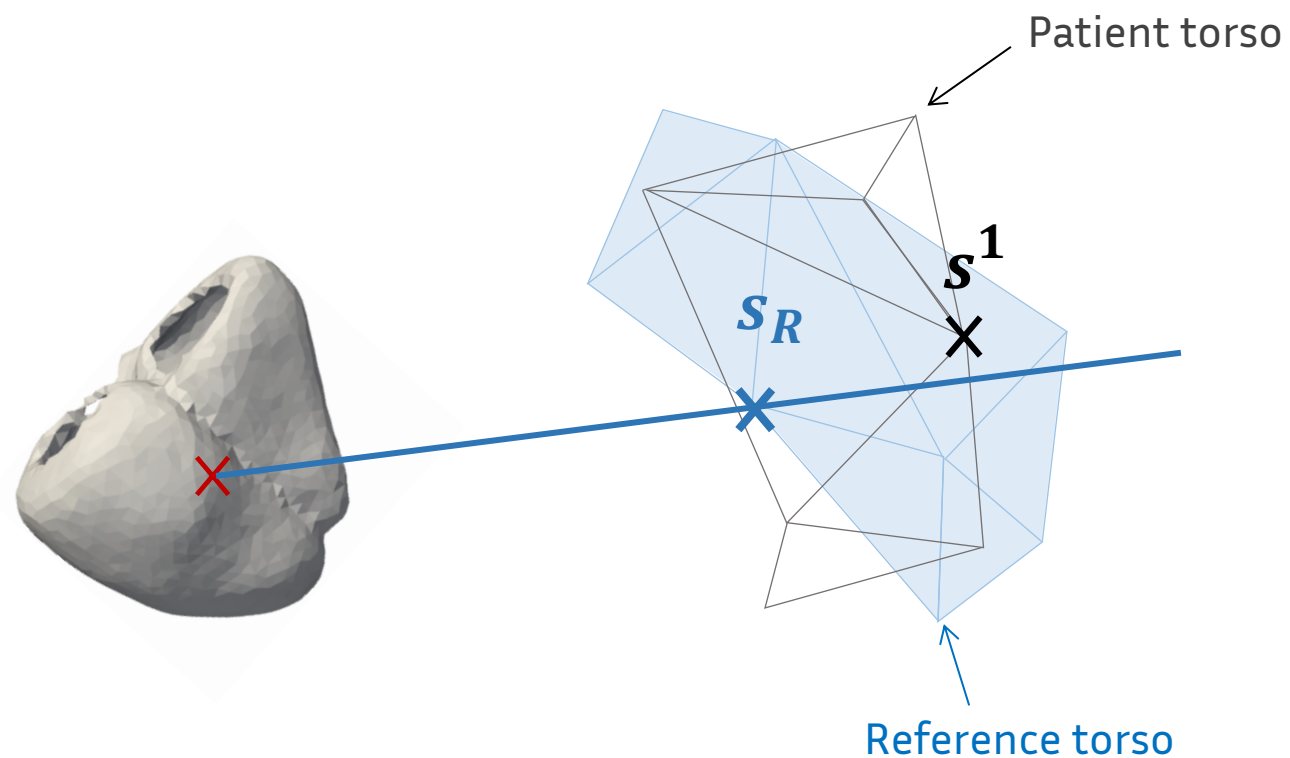
→ Minimize distance to **blue line**



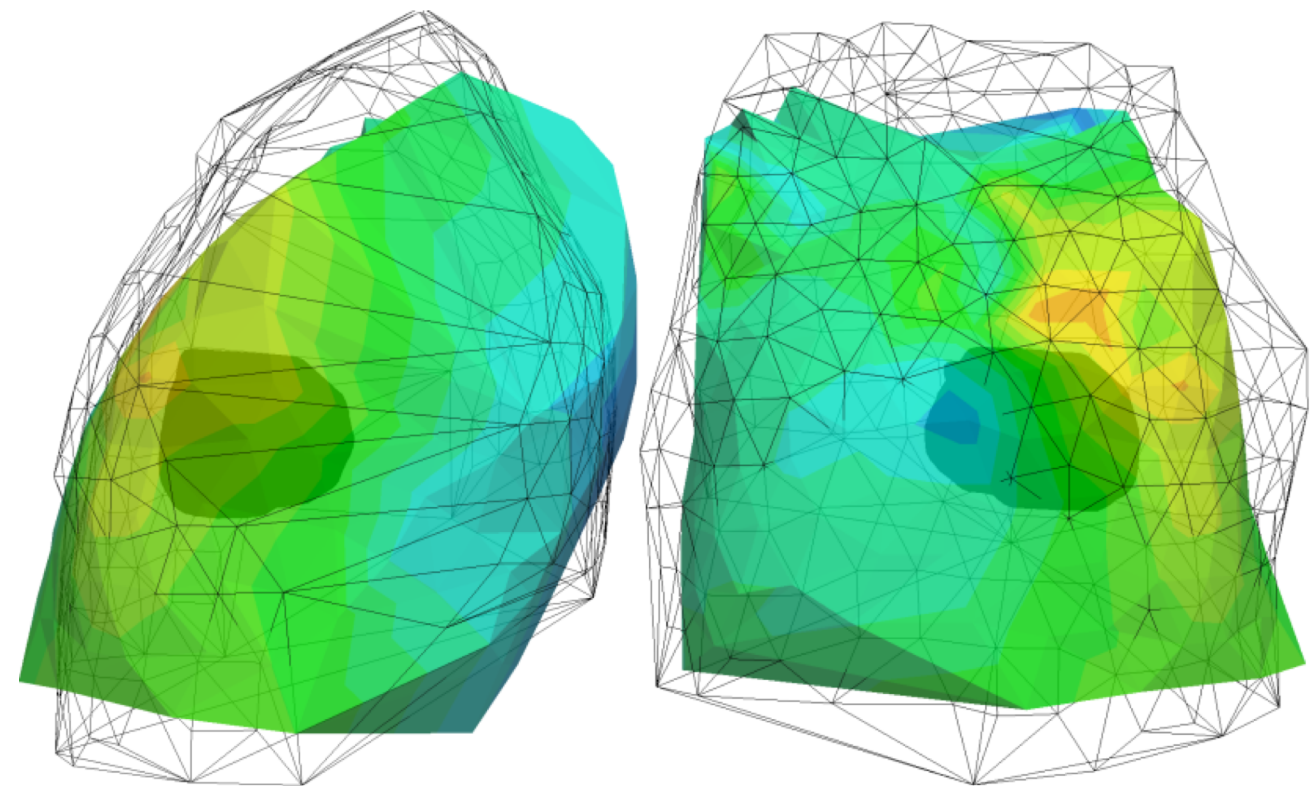
Reference Geometry

Matching of measured BSPM signals

$$\Psi(\mathbf{s}_R) = \Psi(\mathbf{s}^1)$$

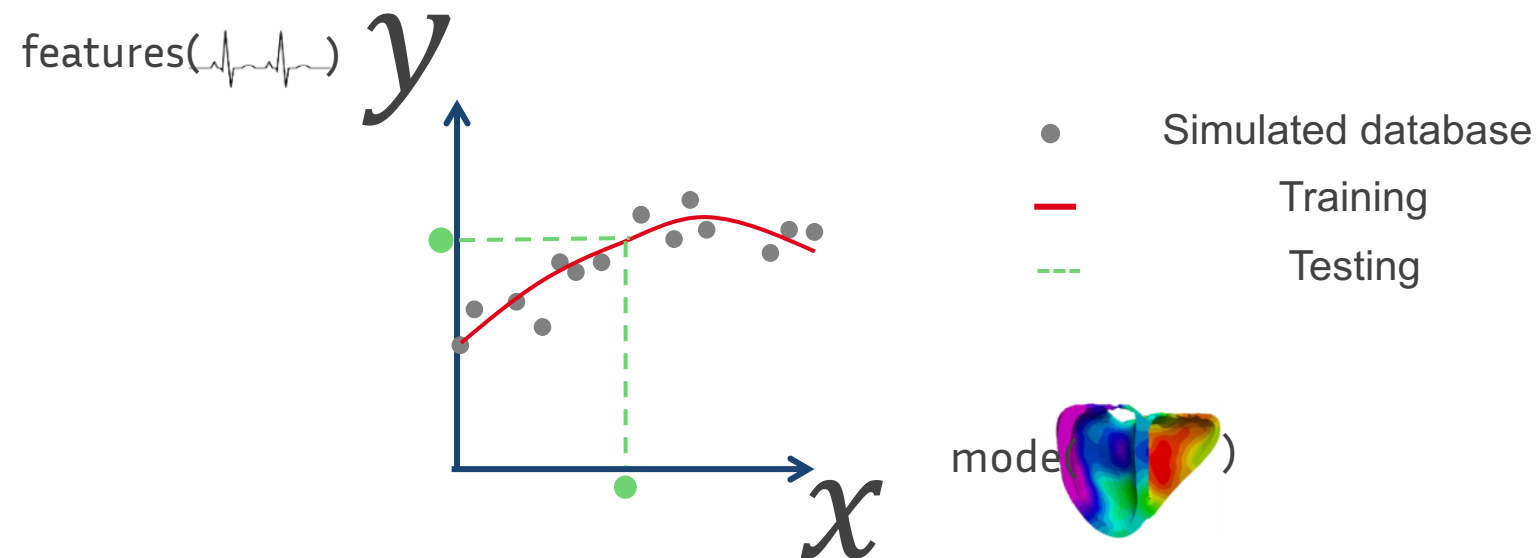


Measured BSPM on one patient at time t

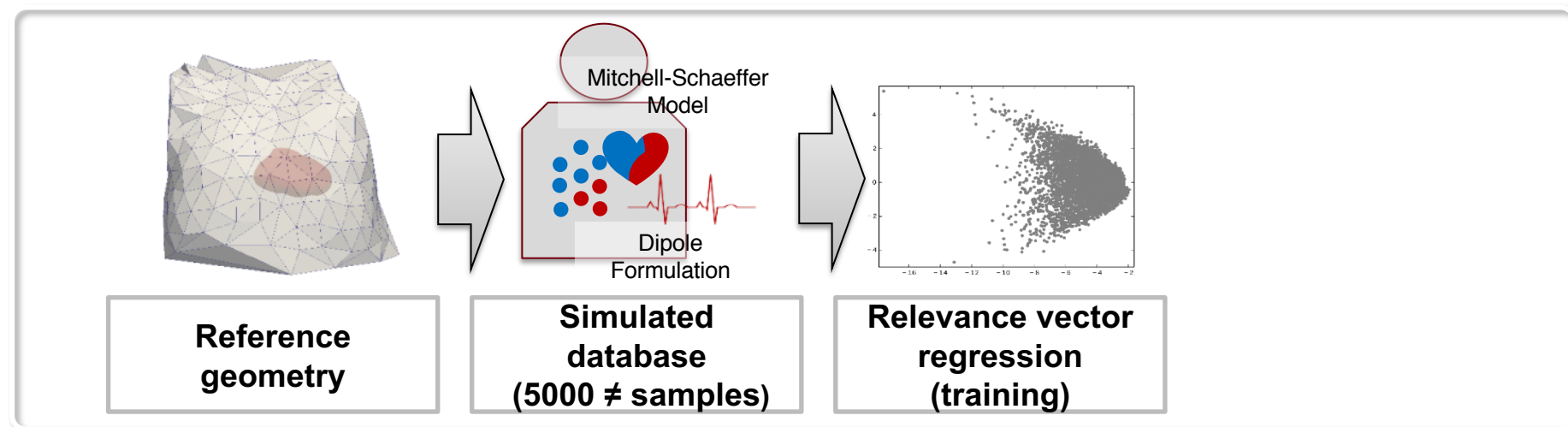


Projection of the BSPM on the reference torso

Reference Geometry Personalisation Pipeline

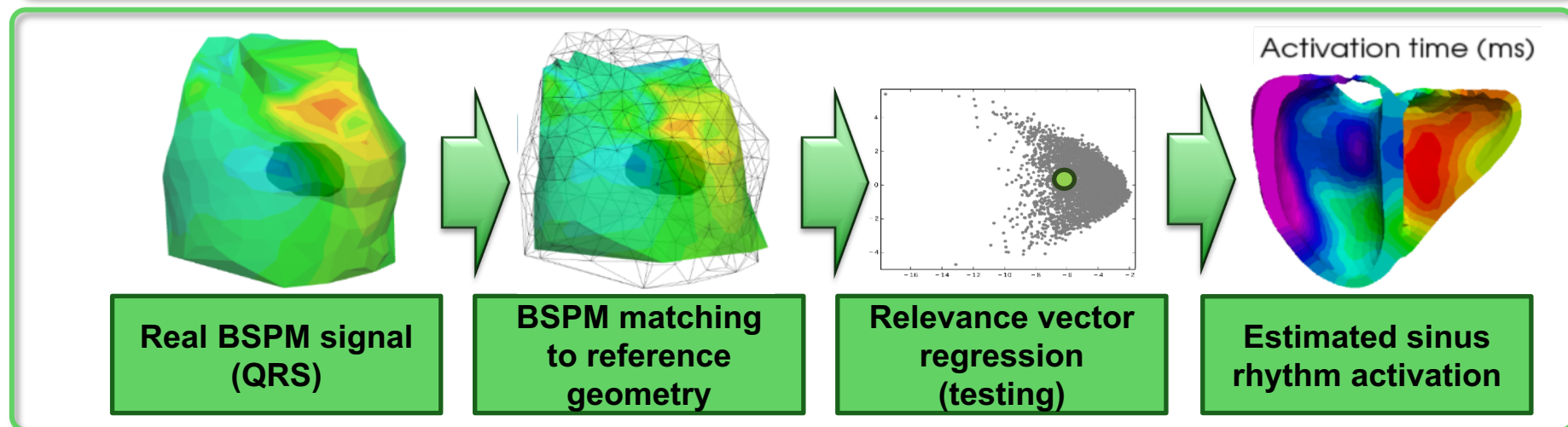


GENERIC
(OFFLINE)



Training:
6 hours

PATIENT-SPECIFIC
(ONLINE)

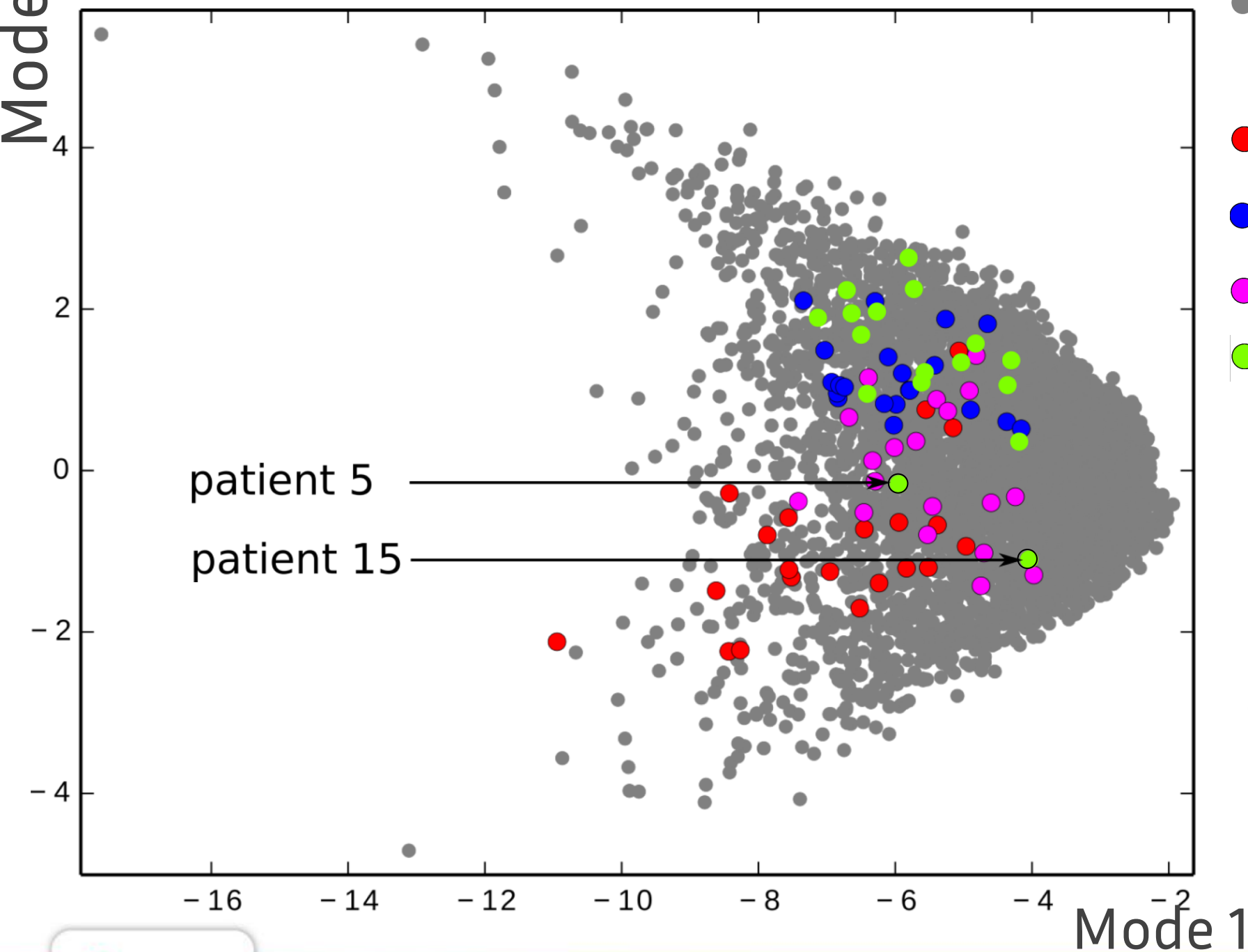


Testing:
2 min

Interpatient study: how to combine information

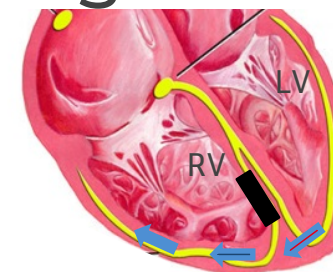
- 20 patients
- 80 BSPM recordings

Mode 2



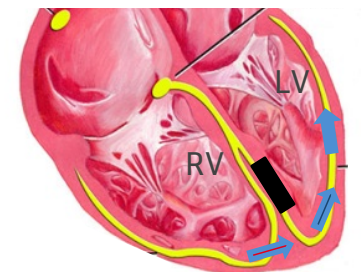
- simulations from training
 - LV only
 - RV only
 - simultaneous
 - sinus rhythm
- } different pacing

right BBB



patients
5 and 15

left BBB

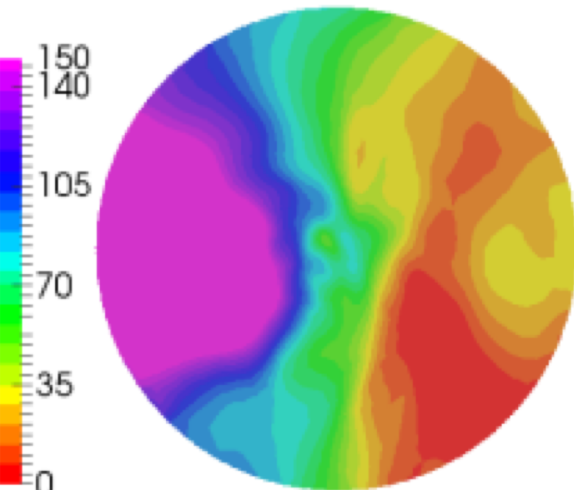
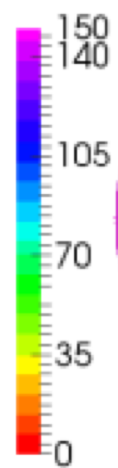


all other
patients

Sinus rhythm estimated activation map

- Ex. on one infarcted patient (#9)
- Local conduction velocity [1]? → from thresholding the SR estimation

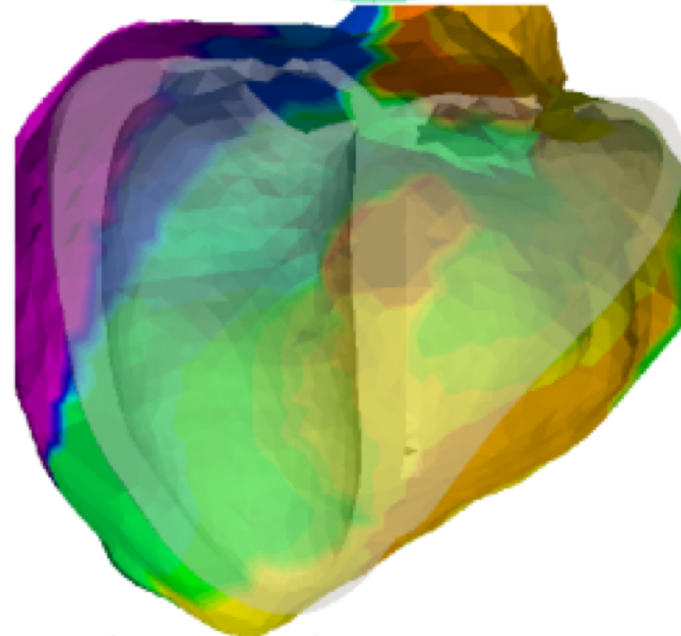
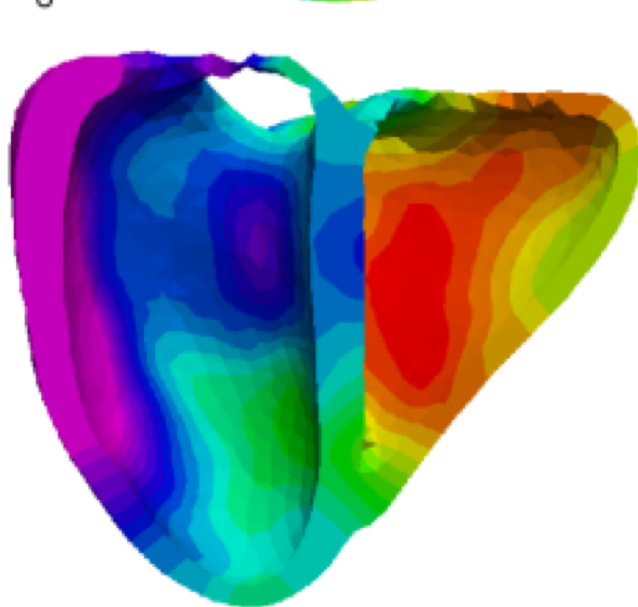
Activation time (ms)



RVR estimation
(using reference model)

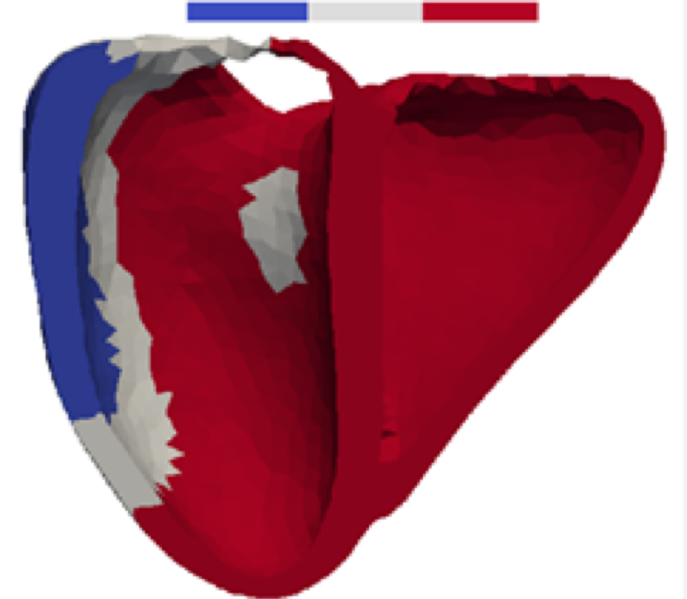


CardioInsight estimation



Conduction velocity (m/s)

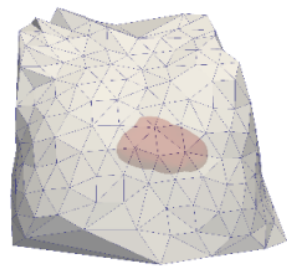
0.2 0.3 0.5



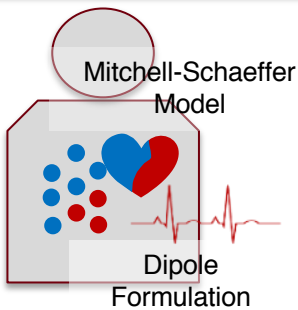
Personalised conduction
velocity (thresholding)

Personalised Pacing Predictions

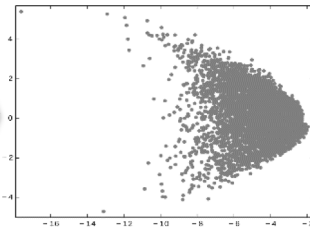
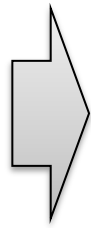
OFFLINE



Reference geometry

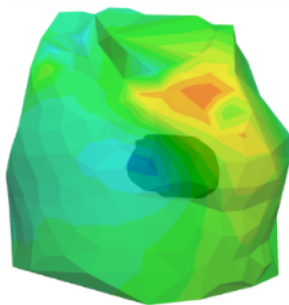


Simulated database
(5000 $\neq$ samples)

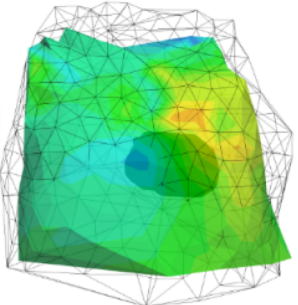


Relevance vector regression
(training)

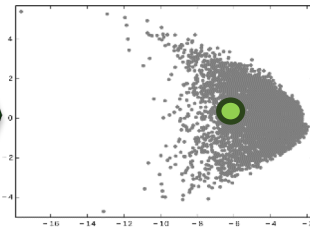
PATIENT-SPECIFIC



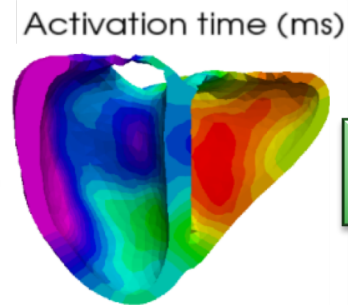
Real BSPM signal
(QRS)



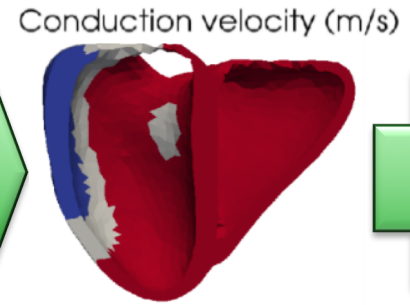
BSPM matching to reference geometry



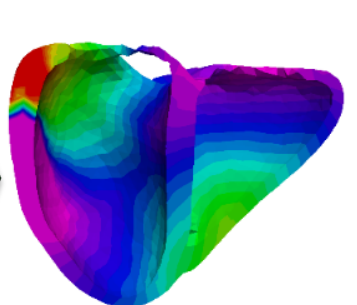
Relevance vector regression
(testing)



Estimated sinus rhythm activation



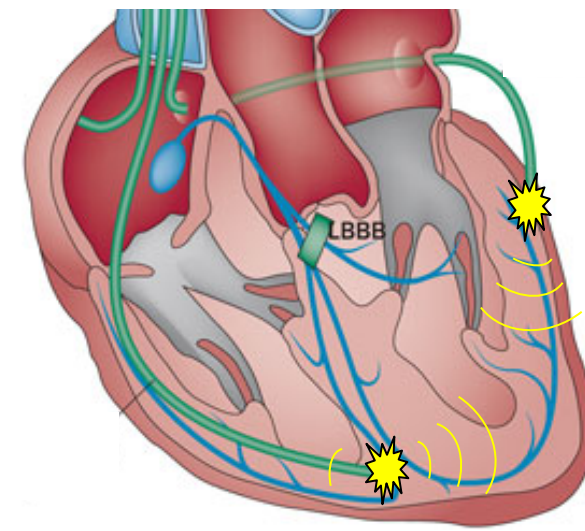
Personalised local CV parameters



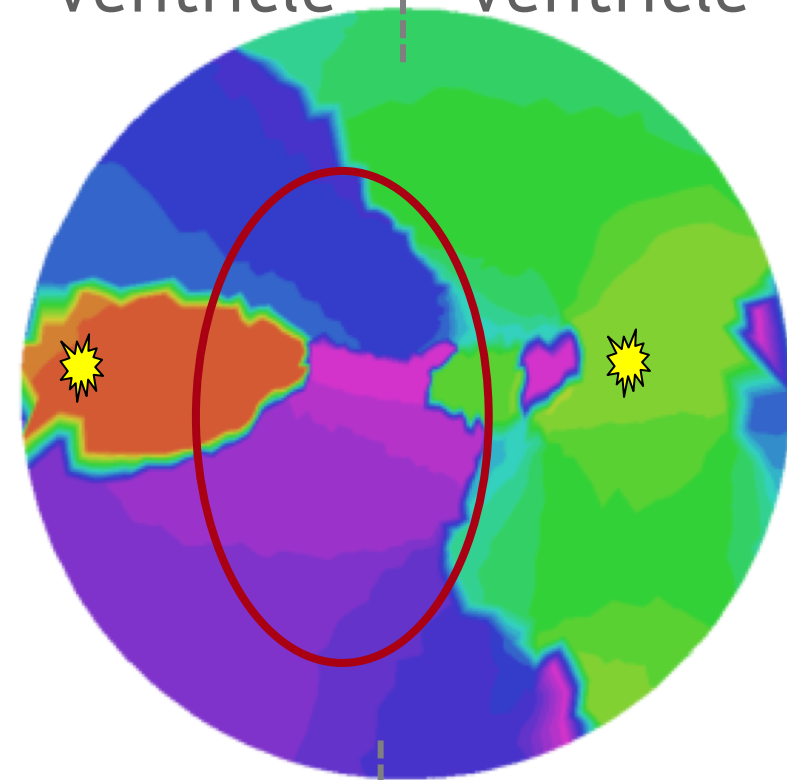
Prediction of $\neq$ pacing activations

Personalised Pacing Predictions

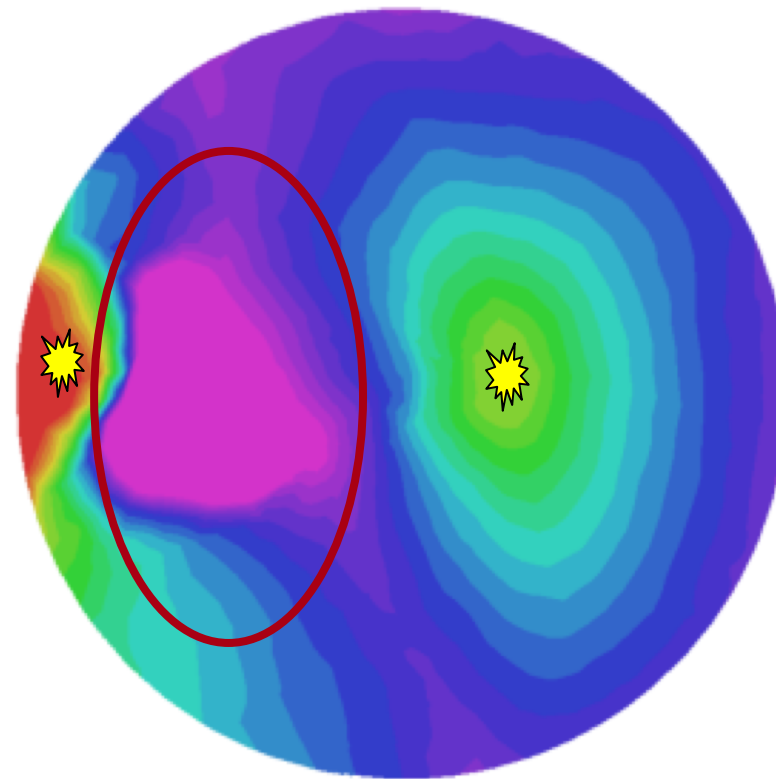
- Ex. on one infarcted patient (#9)
- Biventricular pacing: LV 40ms



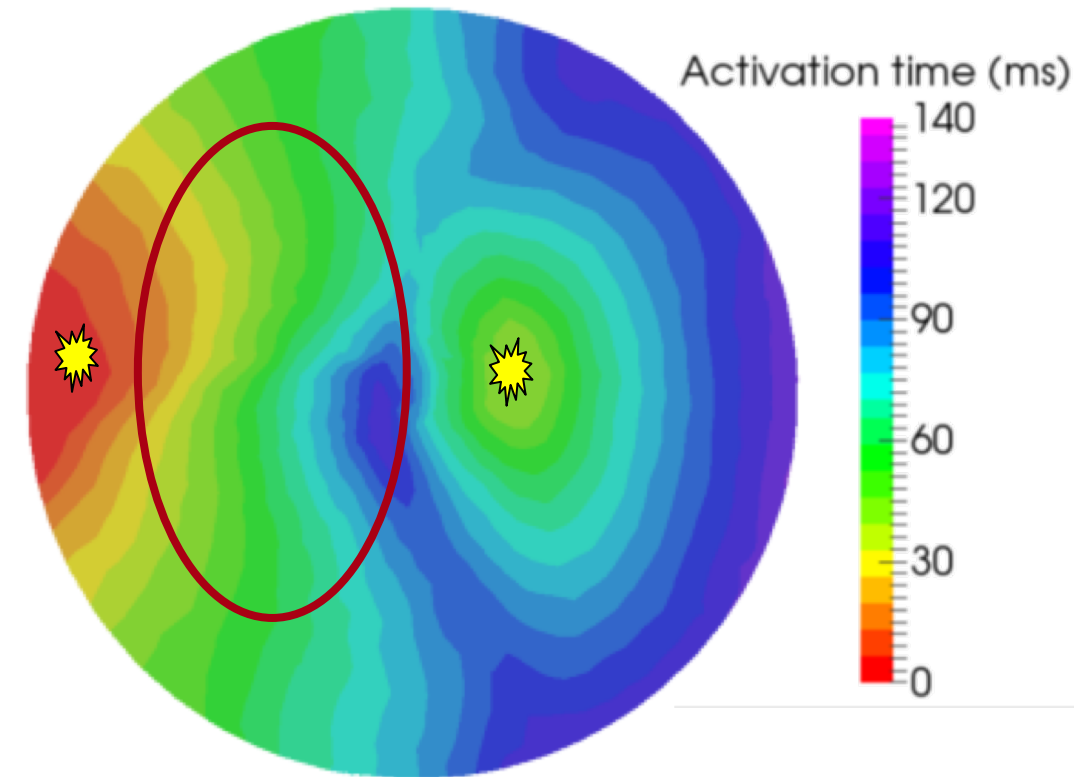
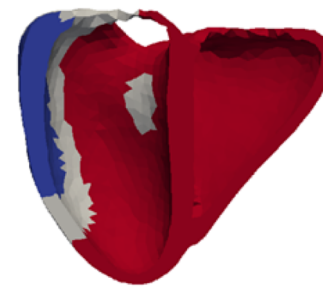
Left ventricle | Right ventricle



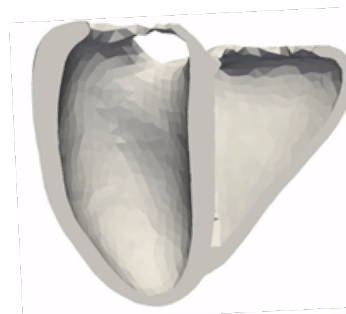
CardioInsight solution
(from actual recordings)



Prediction from personalised
parameters from sinus
rhythm



Prediction from
homogeneous conduction
velocity



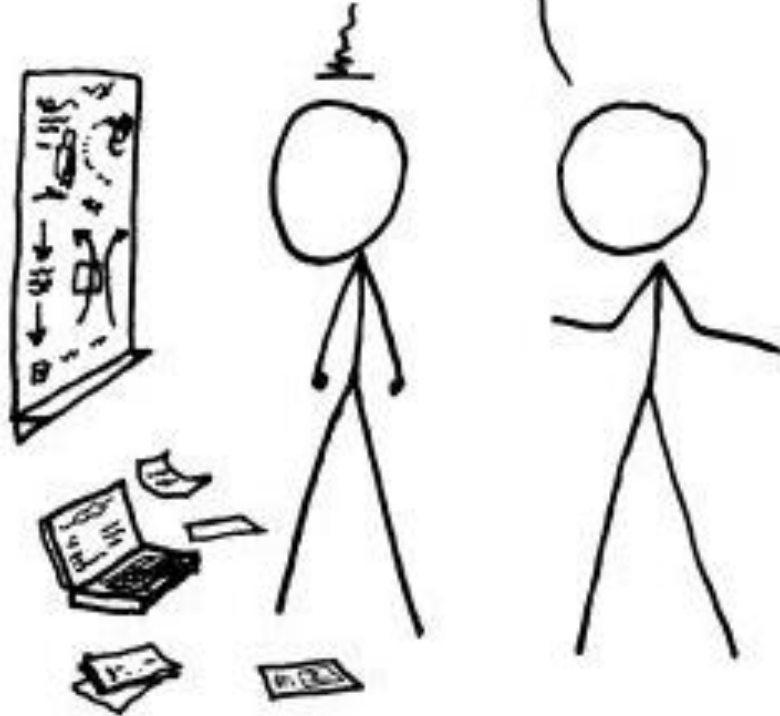
Conclusion

- Healthcare data is often sparse and noisy
- Large labelled databases is a challenge
- Simulation is a way to augment data and features
- Many different ways to combine machine learning and biophysical modelling
- Learning and modelling could also be directly integrated (PDE-net...)

YOU'RE TRYING TO PREDICT THE BEHAVIOR
OF <COMPLICATED SYSTEM>? JUST MODEL
IT WITH A DEEP NETWORK AND THEN ADD
SOME REGULARIZATION TO ACCOUNT FOR
<COMPLICATIONS I JUST THOUGHT OF>.

EASY, RIGHT?

SO, WHY DOES <YOUR FIELD> NEED
A WHOLE JOURNAL, ANYWAY?



LIBERAL-ARTS MAJORS MAY BE ANNOYING SOMETIMES,
BUT THERE'S *NOTHING* MORE OBNOXIOUS THAN
PROGRAMMERS ENCOUNTERING A NEW SUBJECT.

**Thank you for your attention.
Any question?**

Maxime Sermesant
Inria, Epione team
Sophia Antipolis, France
`maxime.sermesant@inria.fr`