HPC simulations for in-silico trials in humans: therapeutic strategies in acute myocardial ischemia

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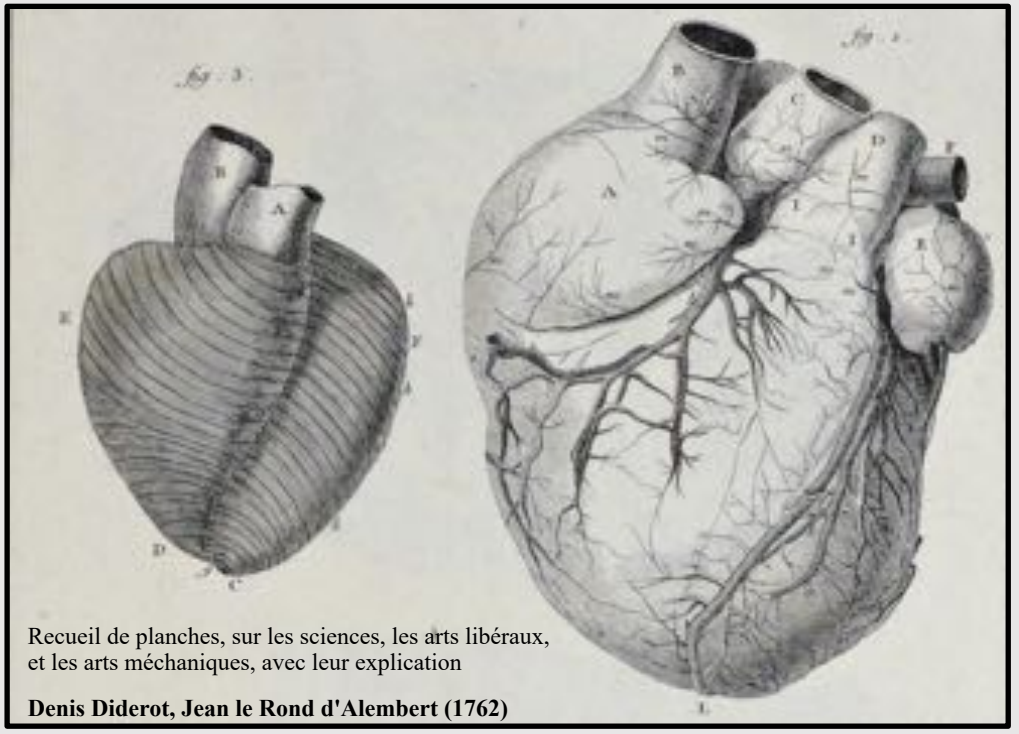


Recueil de planches, sur les sciences, les arts libéraux, et les arts méchaniques, avec leur explication

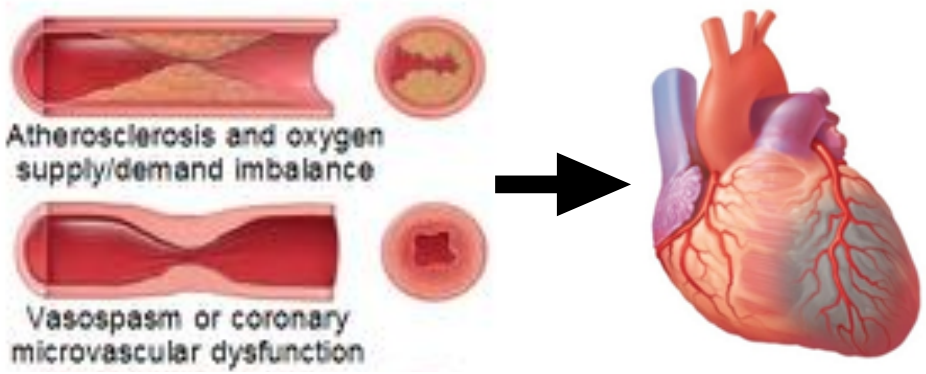
Denis Diderot, Jean le Rond d'Alembert (1762)

Acute myocardial ischemia

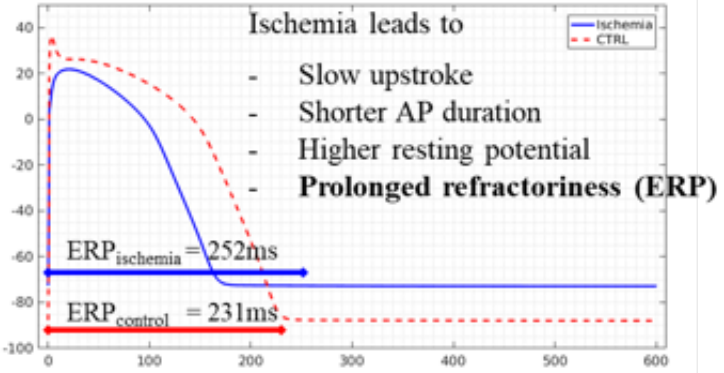
Coronary artery disease (CAD) is the most common cause of death globally [1]. There are 2.6 million people living in UK with CAD. About 73,000 die yearly [2].

[1] GBD 2015 Mortality and Causes of Death Collaborators (2016)
[2] https://heartuk.org.uk

Coronary occlusion causes myocardial ischemia

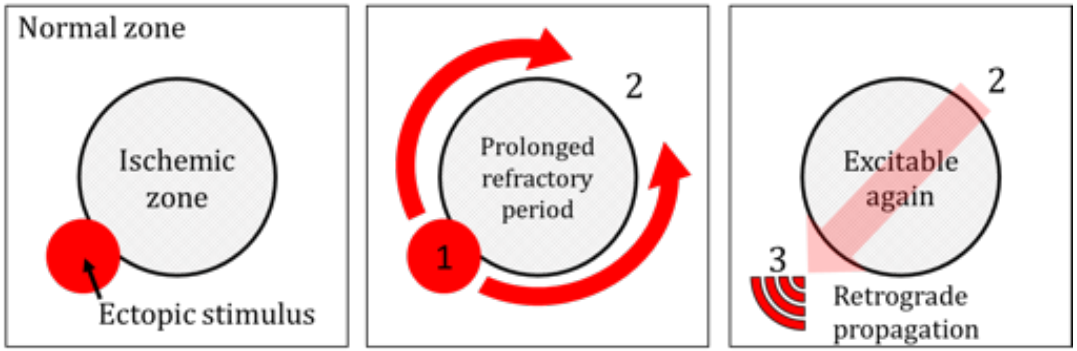


Electrophysiological heterogeneities



Most pro-arrhythmic stage:
10-15 min post occlusion

Formation of reentrant patterns



Janse et al.,1980

Aims

How does variability of the ischemic region affect arrhythmogenesis?

Can we use in-silico trials to explain the cardiotoxic effects of certain drugs?

Can we use the results to suggest new effective anti-arrhythmic strategies?

Computational models of cardiac electrophysiology

In-silico trials

- Based on human data: results translatable to human
- Suitable alternative when ethics or technical limitations

Drug development

- Early prediction of drug cardiotoxicity
- Reduction, refinement and replacement of animal experimenting

Major challenges to tackle

- High variability in drug response
- Variable diseased conditions
- Concomitant medications

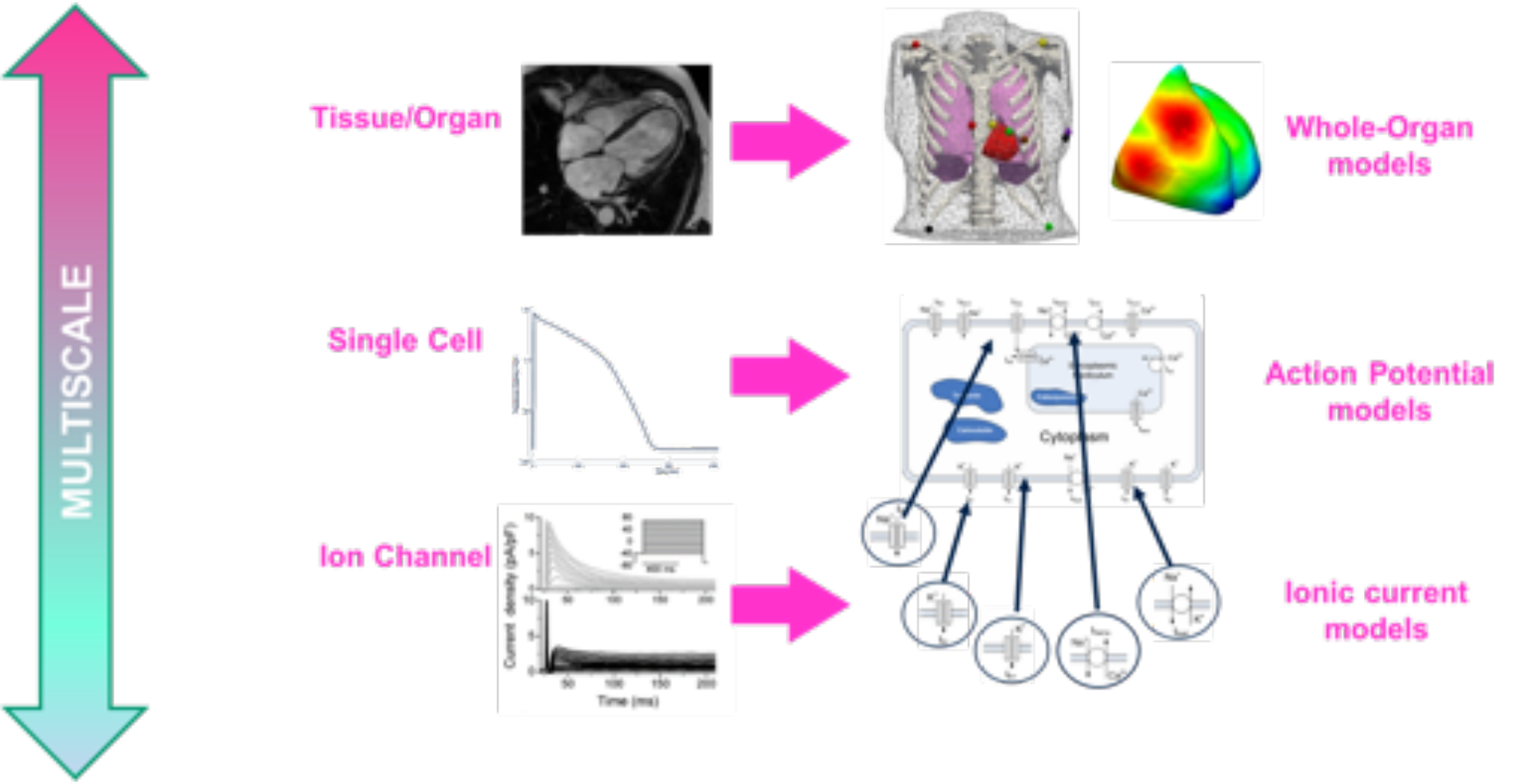
in-vitro testing

animal testing

clinical trials

in-silico trials

Computational models of cardiac electrophysiology

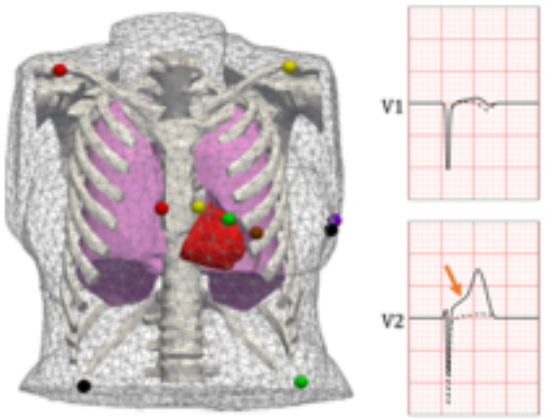


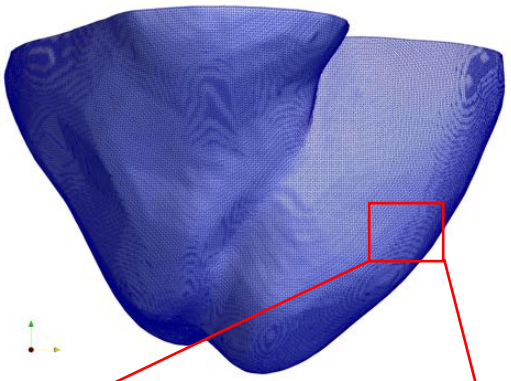
How is the whole organ model built?

- Ventricular/torso mesh based on more than **3.2 million nodes** from CT scans.

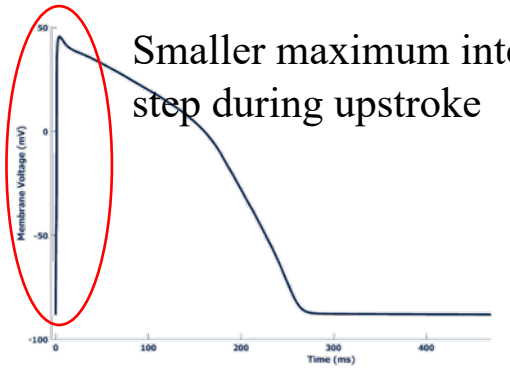
- Each node in the ventricles' domain is an **instance of the ORd** cardiac cell model.
  2.5 million ORd instances coupled to each other.

- Electrical propagation equations solved with **FEM** using a **adaptative integration** method.





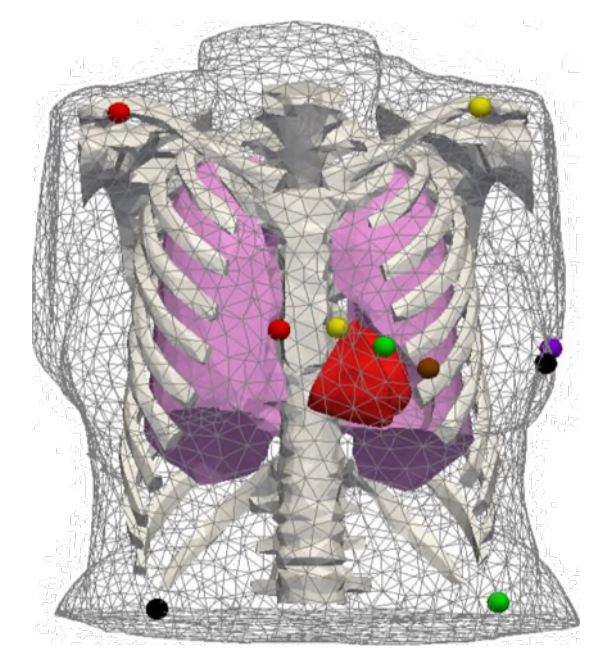
Chaste



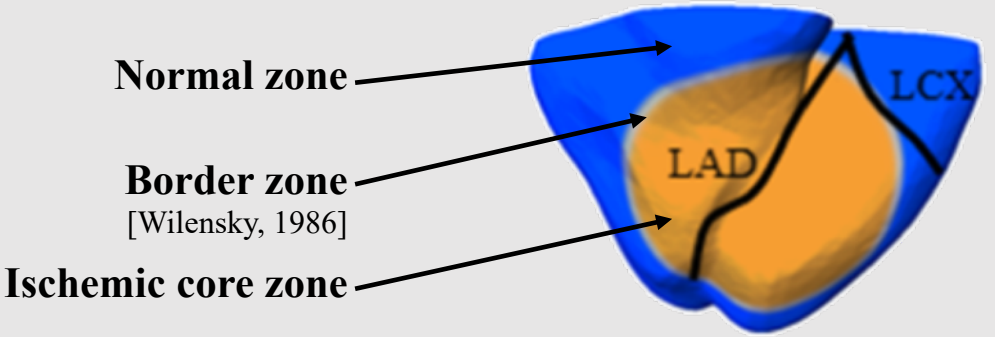
Smaller maximum integration step during upstroke

Methods

Human biventricular model of acute ischemia



- Fibre orientation.
- Transmural and apicobasal heterogeneities.
- Realistic activation sequence.
- Realistic conduction velocities.



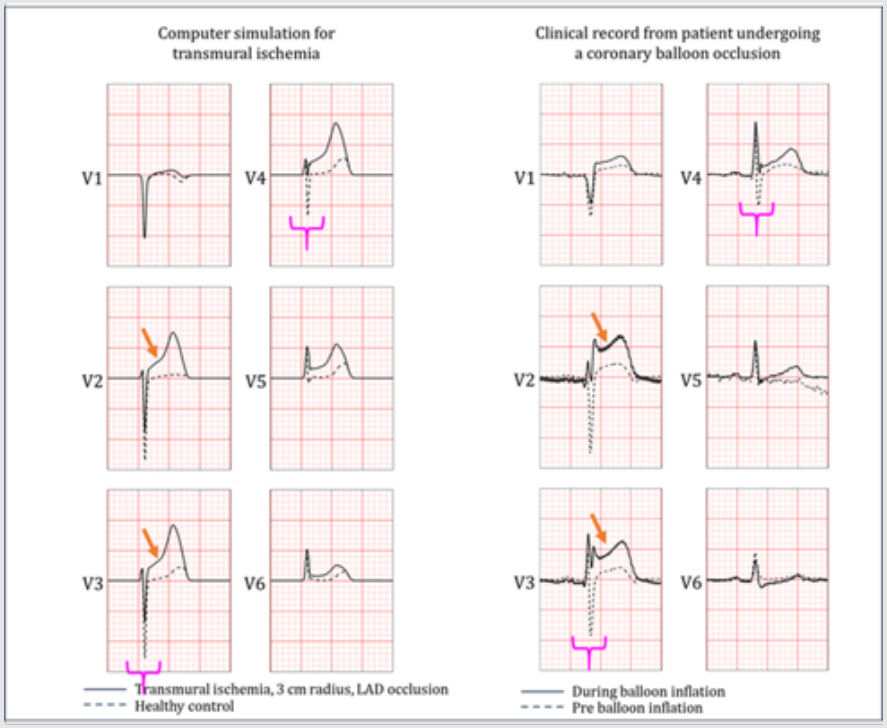
Design of **multiple scenarios** simulating variability in the ischemic region.

Validation

Cell/tissue level [Dutta 2017]

- Action potential shortening
- Refractoriness prolongation
- Conduction velocity reduction

in agreement with human measurements [Taggart 2000]



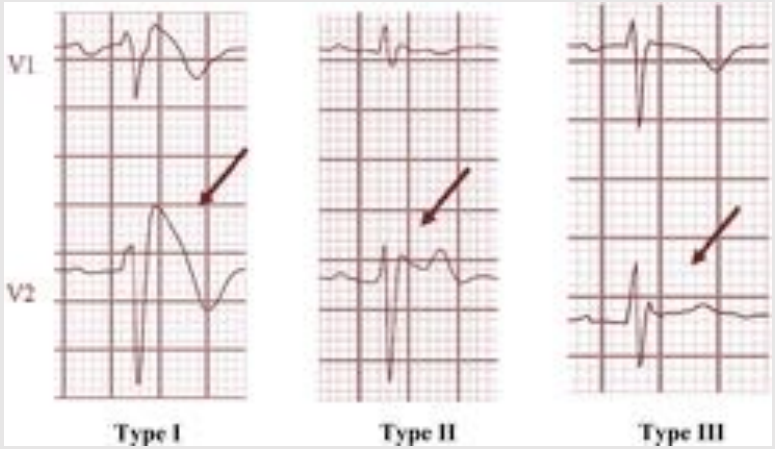
Whole organ level [Martinez-Navarro 2019]

Comparison of the simulated ECG obtained from the model under transmural ischemia conditions and records from a patient in the STAFF III database.

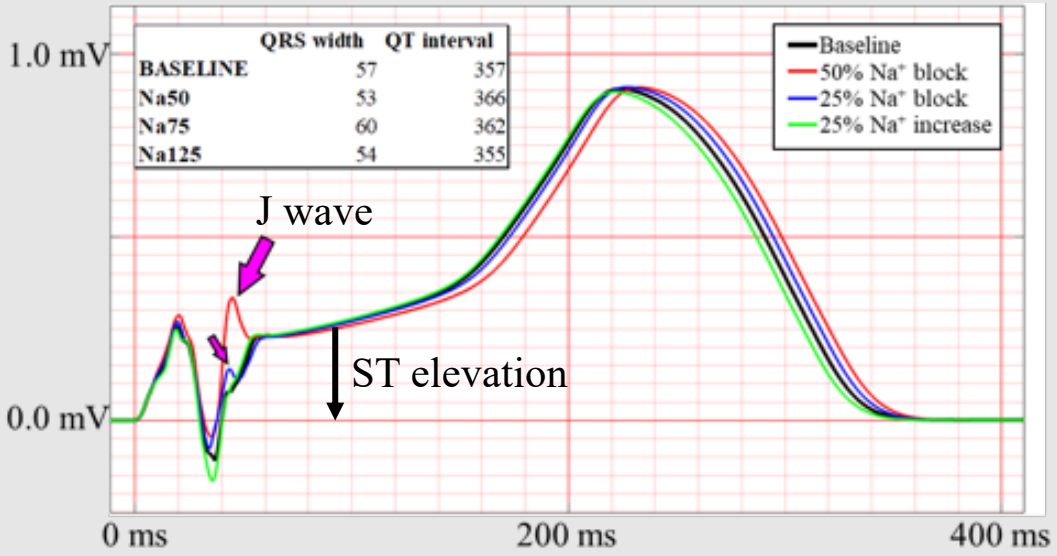
Validation

ECG signature of SCN5A mutations leading to Na^+ channel block

Type I II III Brugada syndrome, Sethi et al. (2014)



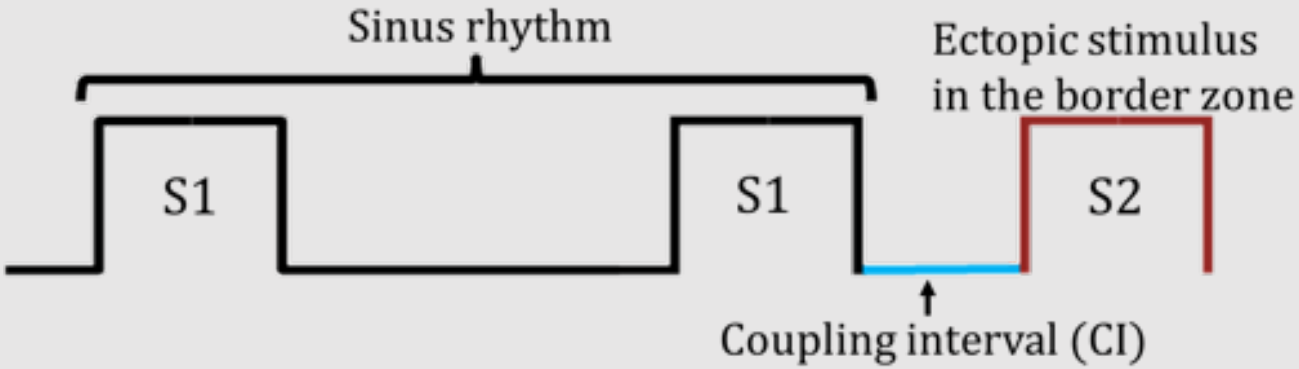
Computer simulations of ischemia co-existing with varying Na^+ channel alterations



The model reproduces

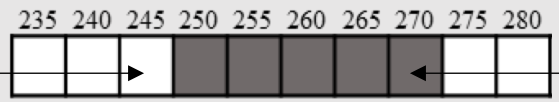
- Realistic ECG morphology
- Ischemia induced ST elevation
- J waves under Na^+ block conditions

Stimulation protocol to assess reentry vulnerability

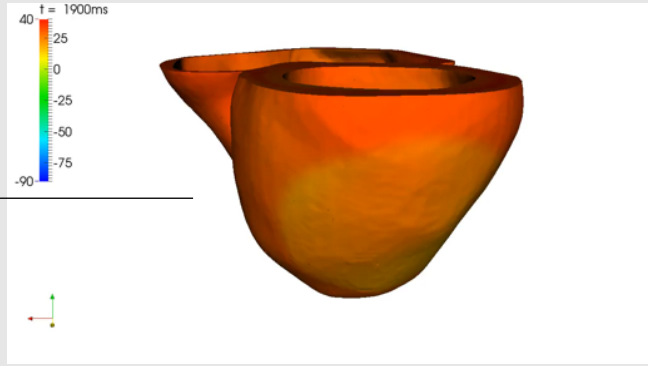


NO REENTRY

Vulnerability window



REENTRY

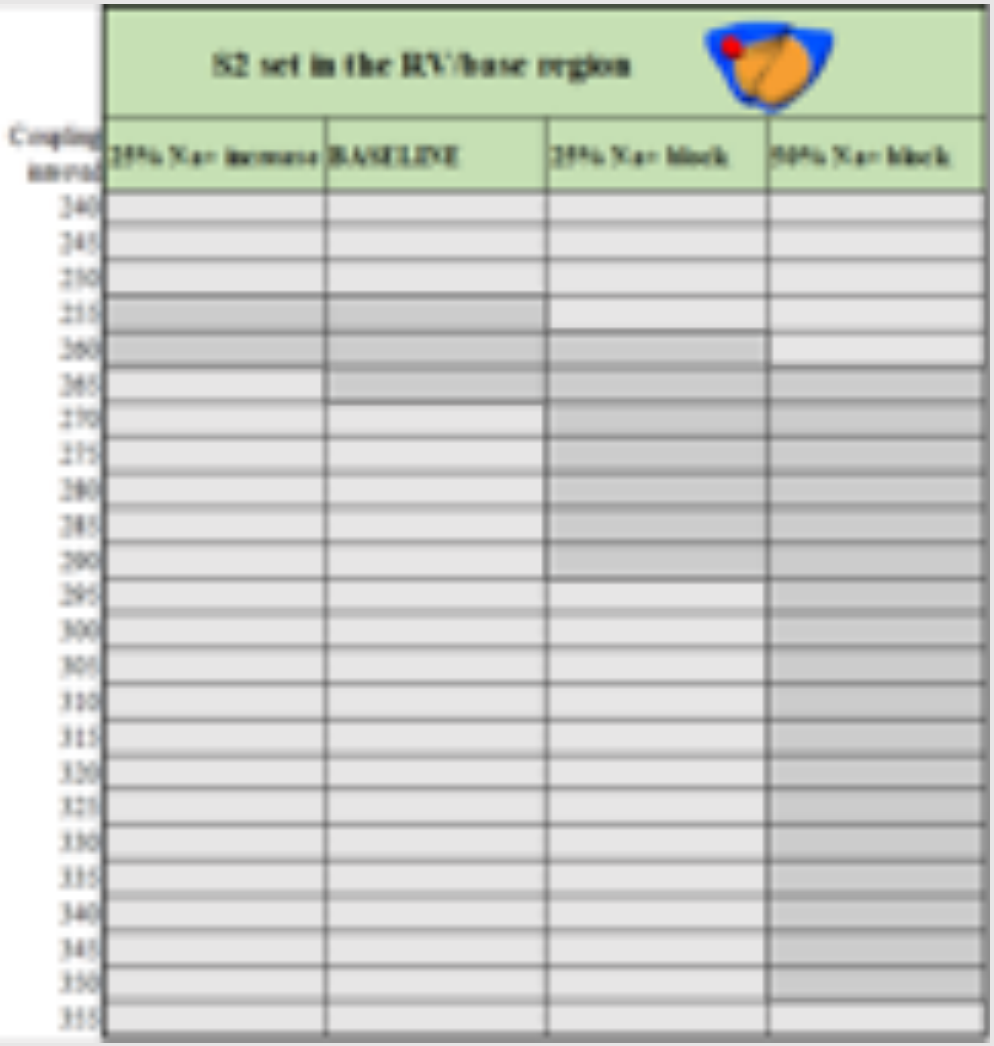


Approx. 500 simulations, each of them using 720 cores, 3-12h
Results: ~80 GB each simulation

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

archer

Results



Na^+ current availability is shown to have a crucial role in ischemia-induced arrhythmogenesis.

25% Na^+ increase
Gene therapy, such as SkM1 overexpression

BASELINE
Normal ionic conditions

25% Na^+ block
Na^+ channel blockers, such as flecanide or encanide

50% Na^+ block
SCN5A mutations, such as BrS or Lenègre's disease

Conclusions

- **Computer models of cardiac electrophysiology**
  - ✓ **Human-based** and **multiscale**
  - ✓ **Population of models** take into account inter-subject variability
- **Human in-silico drug trials**
  - ✓ Early prediction of **clinical risk of drug-induced arrhythmias**
  - ✓ Potential to replace pre-clinical animal experiments
- **3D whole-heart simulations**
  - ✓ Suitable for understanding arrhythmogenic mechanisms
  - ✓ Identification of therapy targets oriented to specific pathologies