Bad luck, Drug or Heart - Computational models to the rescue

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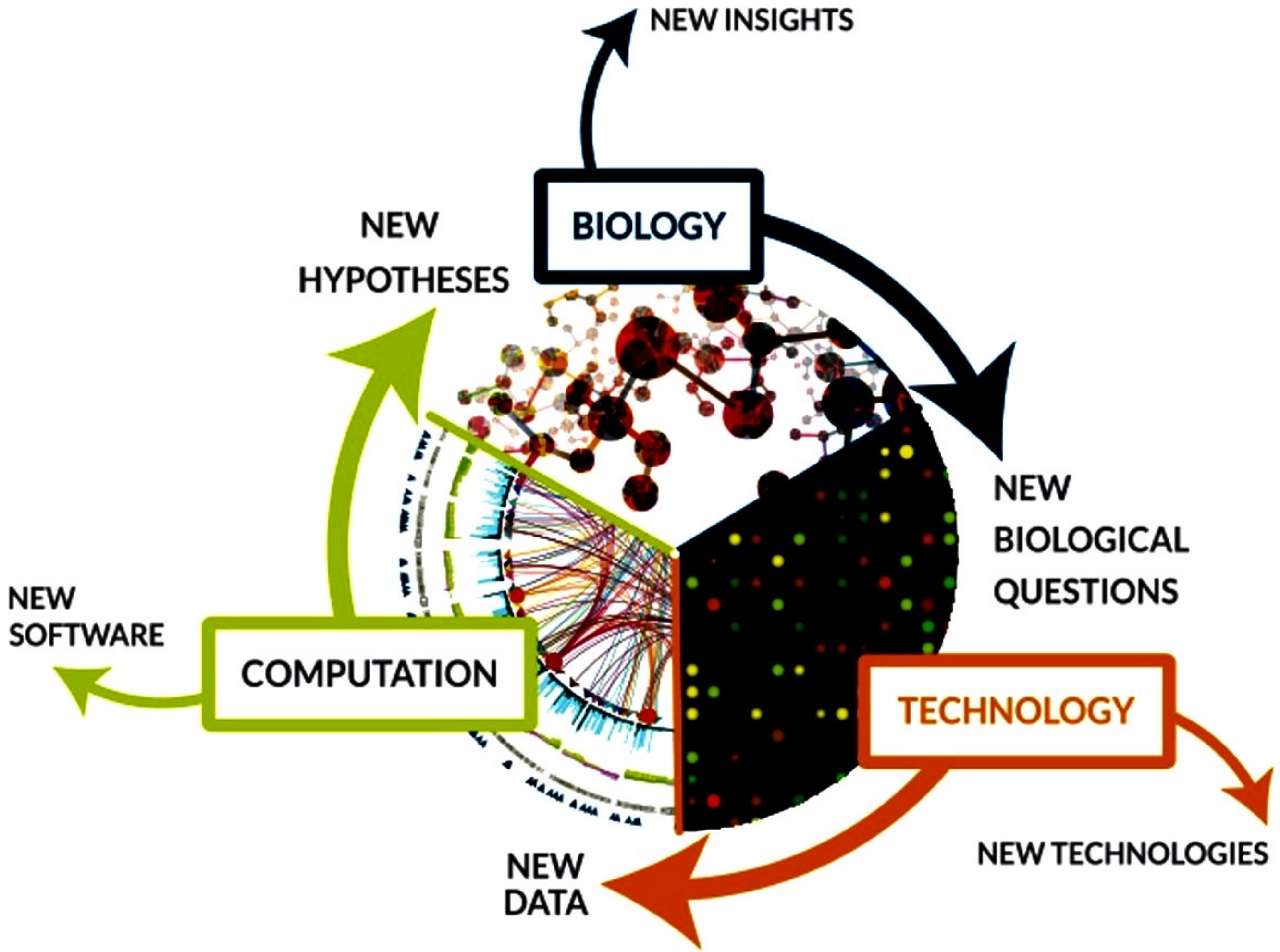
Simula Research Laboratory

Friday 13 January 2023

Computational modelling in biology and healthcare

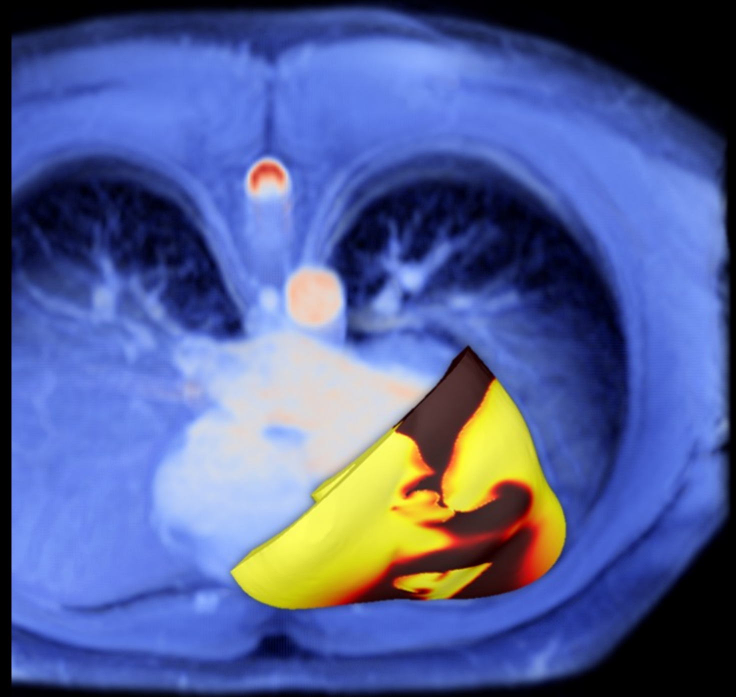


National Institute of Biomedical Imaging and Bioengineering

https://www.nibib.nih.gov/science-education/science-topics/computational-modeling

Outline

- Why?
- How?
- Try it yourself
- New software
- Wrap-up

Computational Physiology Department

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Mission Statement

To use mathematical modeling to gain insight into human health, disease, and treatment.

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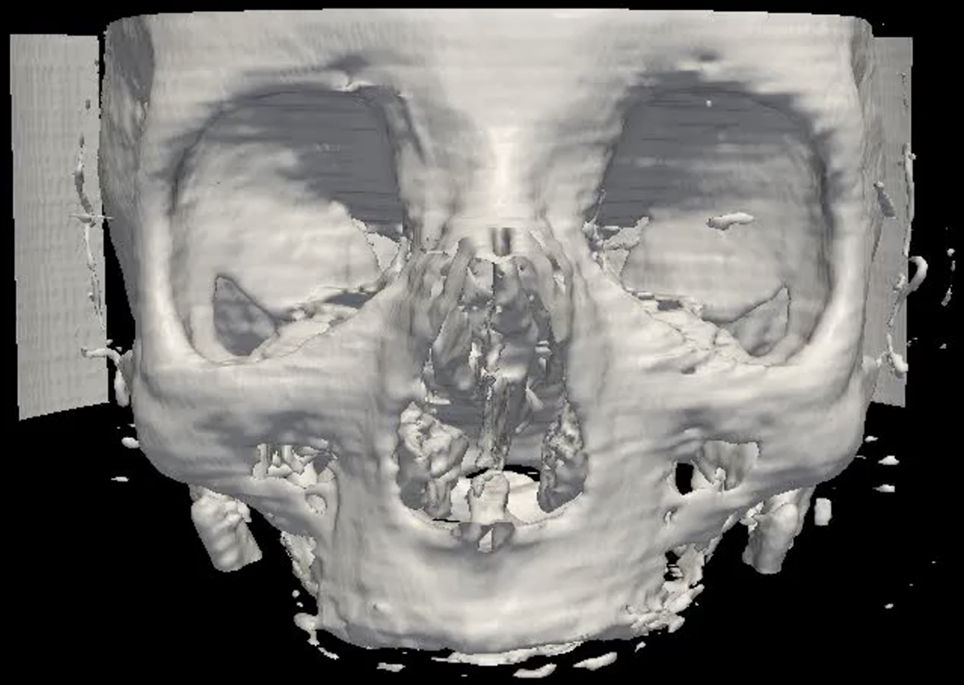
Cerebral Circulation Modeling

Predict Patient Risk of Aneurysm Rupture



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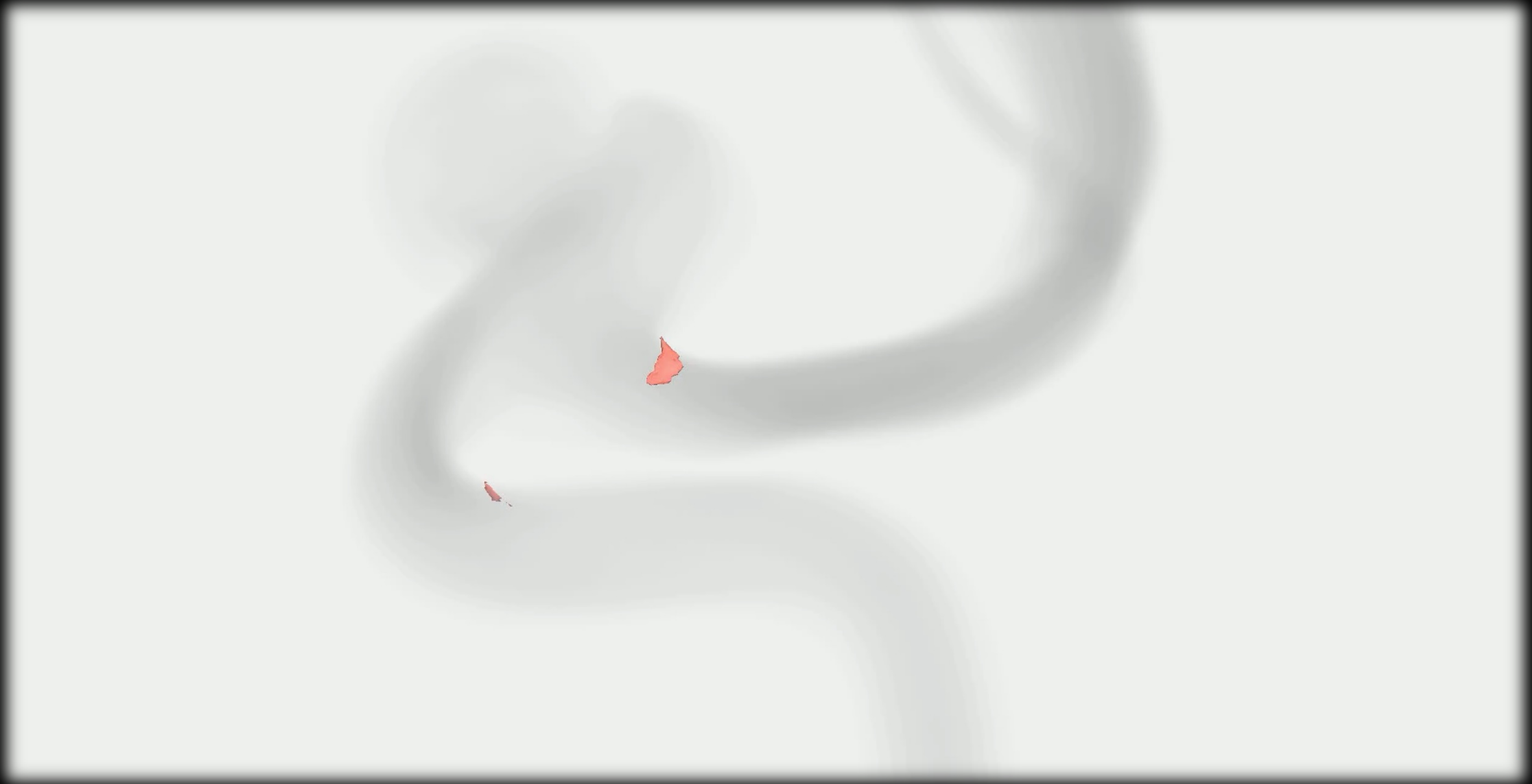
Cerebral Circulation Modeling

Predict Patient Risk of Aneurysm Rupture



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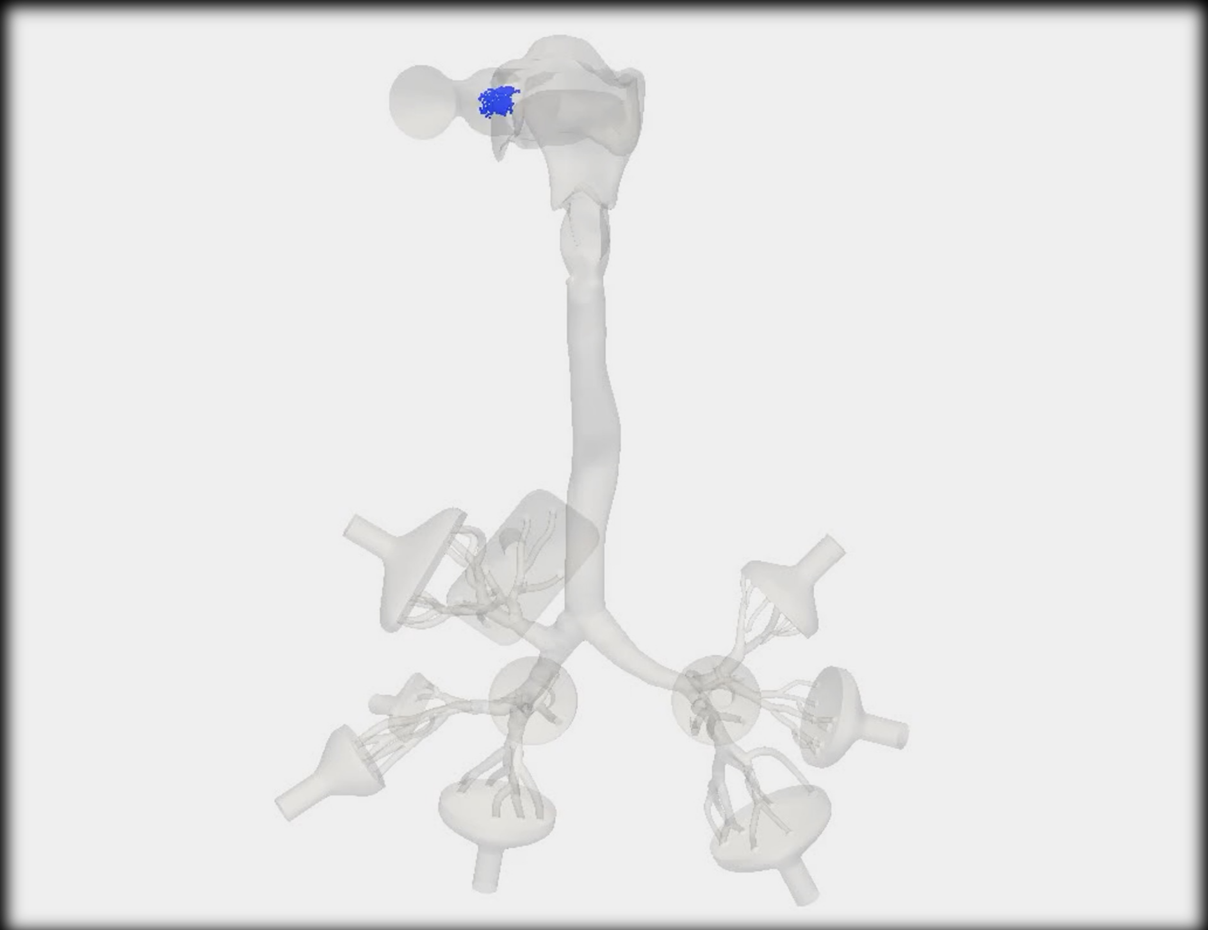
Respiratory Modeling

Designing Efficient Delivery of Inhaled Drugs



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Cardiac Modeling

Identify Diseased Tissue from MRI Data

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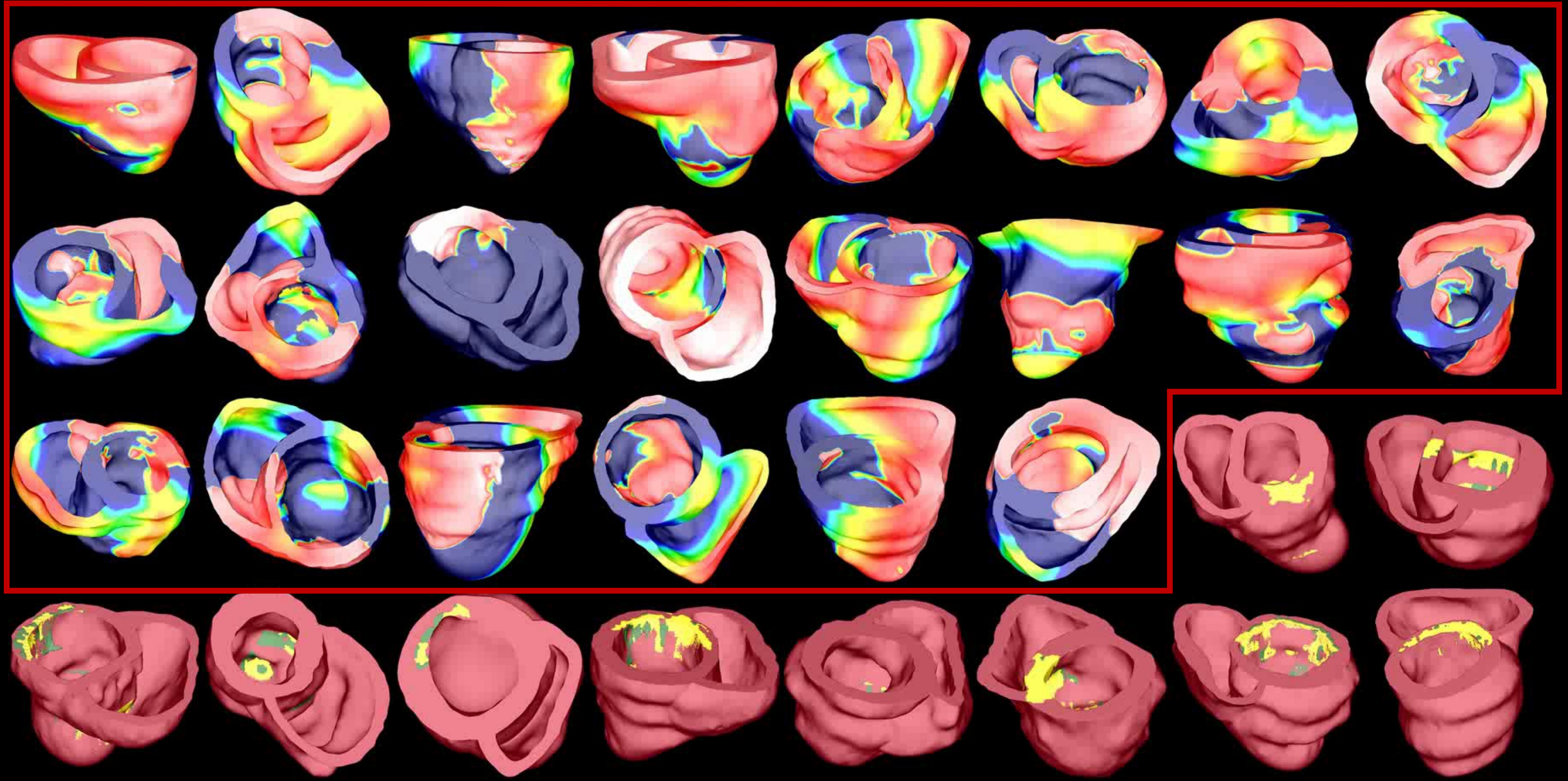
Personalized Cardiac Models

Identify Patients at Risk for Arrhythmias



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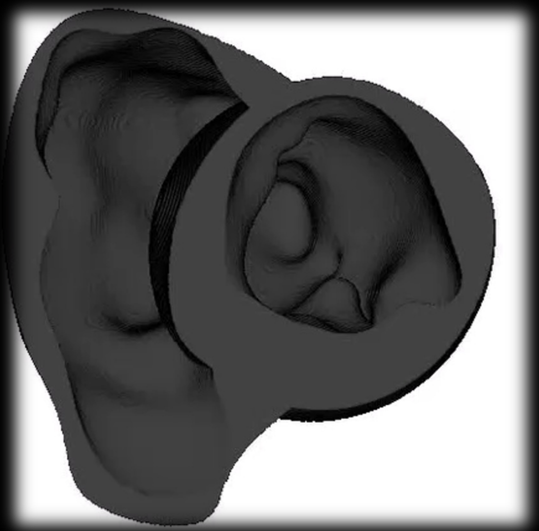
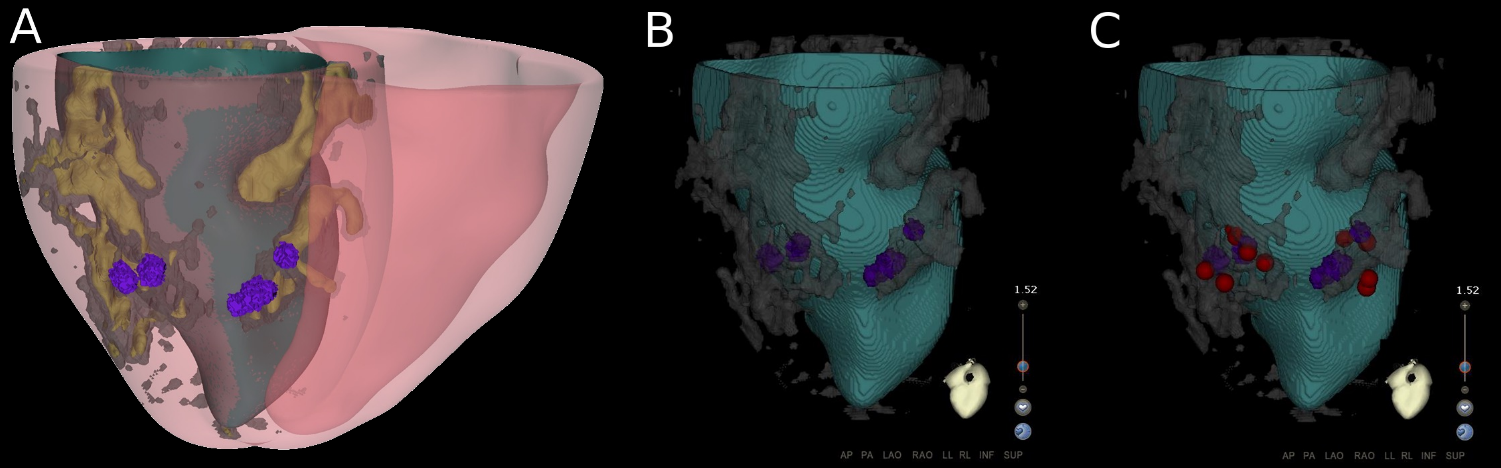
Personalized Cardiac Models

Guide Optimal Ablation of Ventricular Arrhythmias





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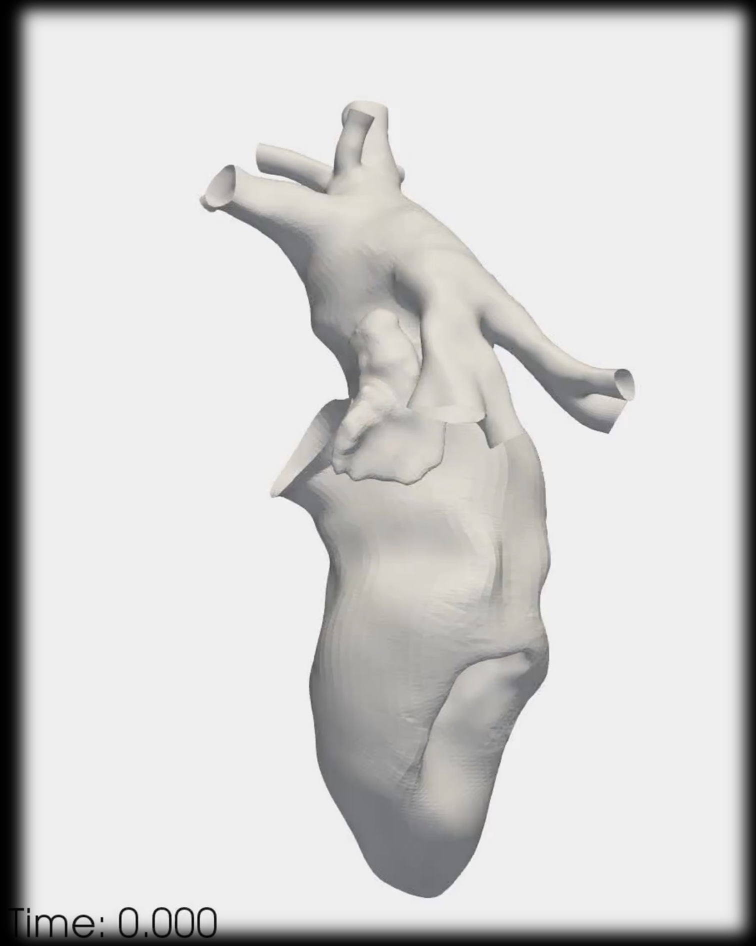
Personalized Cardiac Models

Predict Blood Clot Formation in the Left Atrial Appendage



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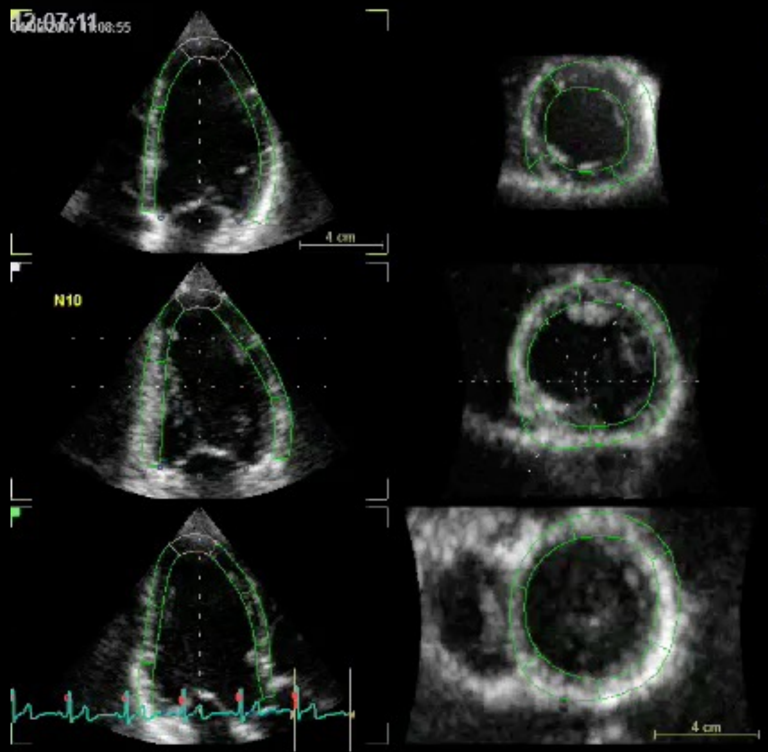
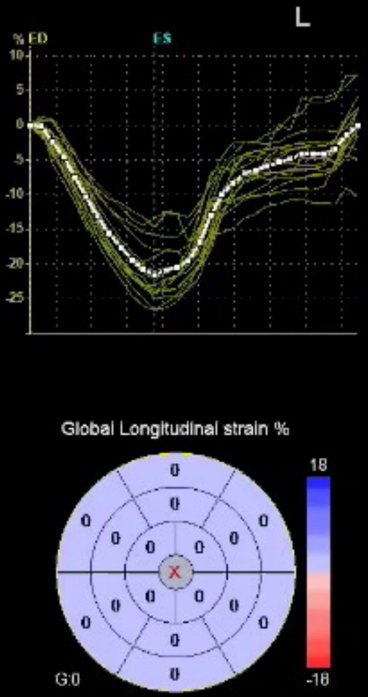
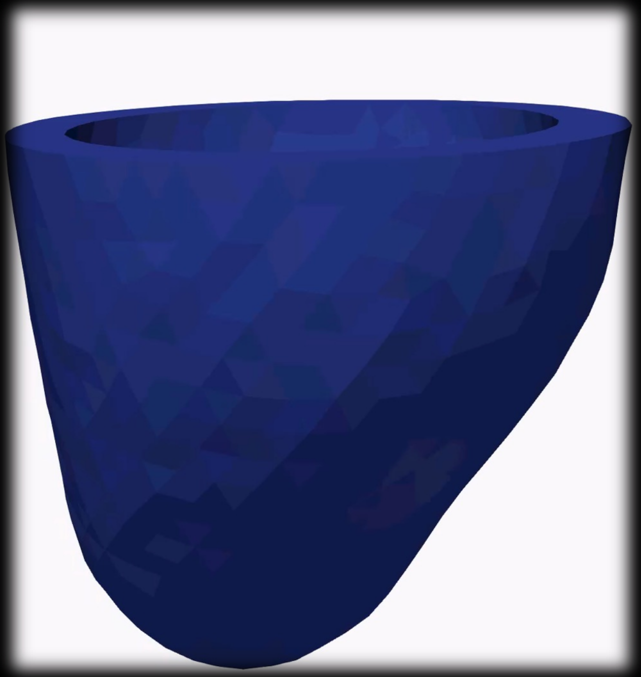
Personalized Cardiac Models

Improve Mechanical Function of Heart Failure Patients







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SimCardioTest

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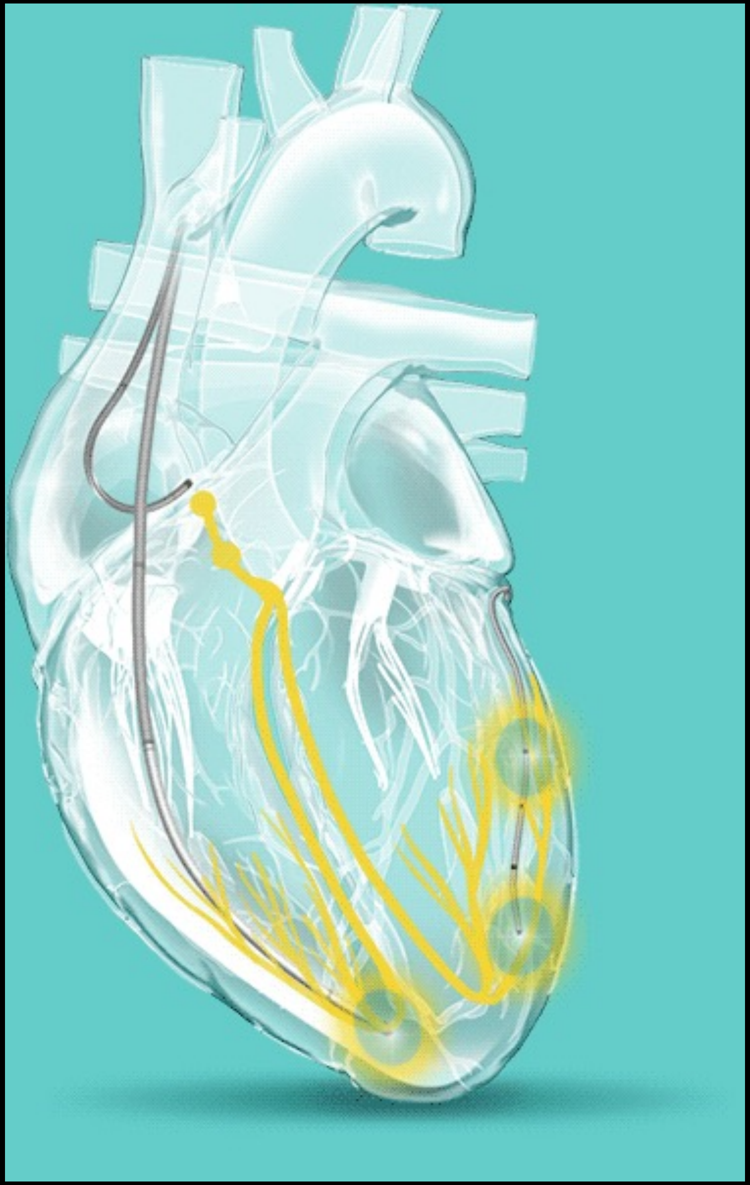
Simulation of Cardiac Devices & Drugs for in-silico Testing and Certification (SimCardioTest)

Goal

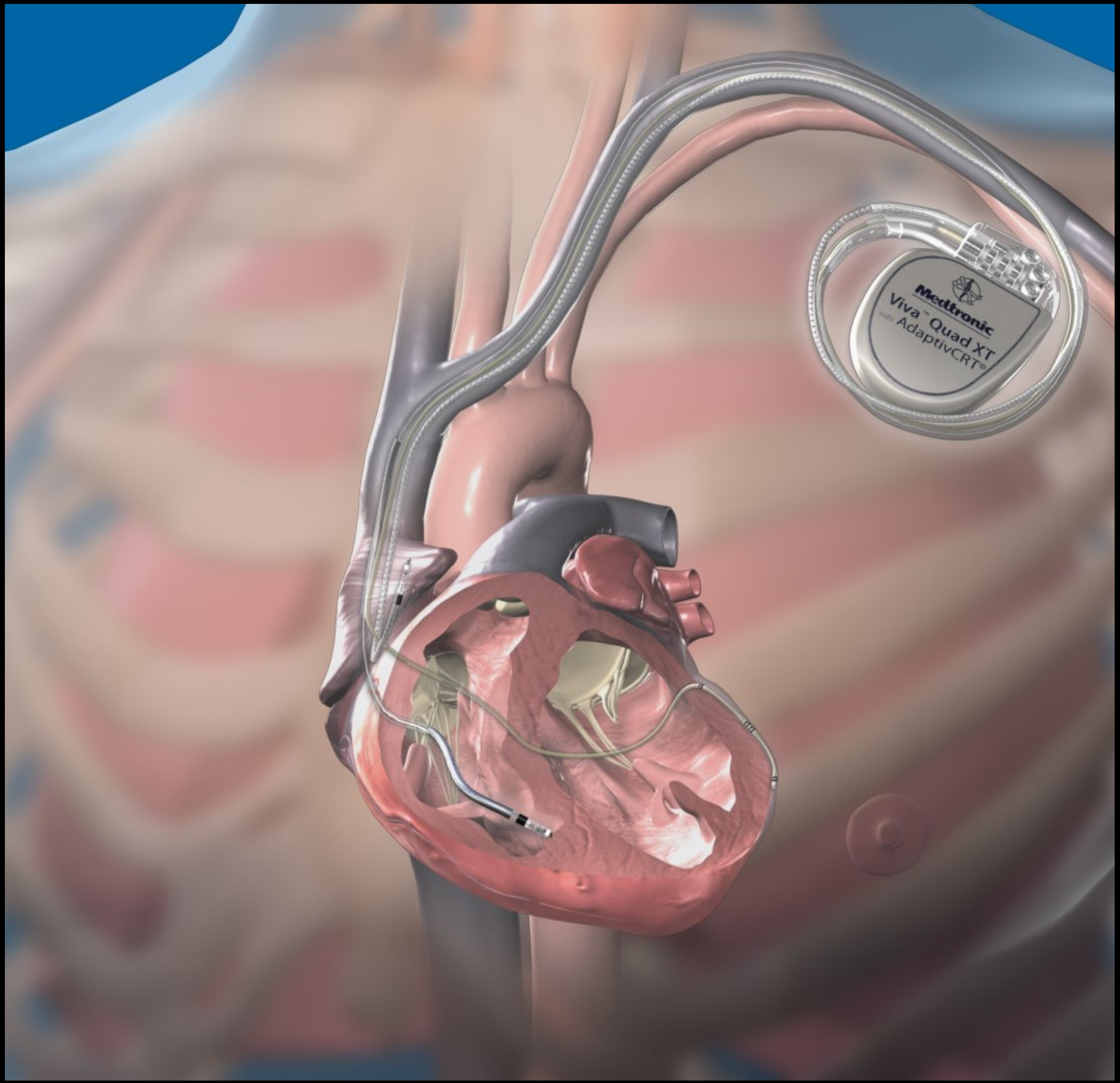
In this project, we selected a small number of cardiac devices and drugs that already have advanced results on the simulation side, and we will demonstrate how we can set up a standardised and rigorous approach for in silico clinical trials.



Use Case 1: Cardiac Resynchronization Therapy

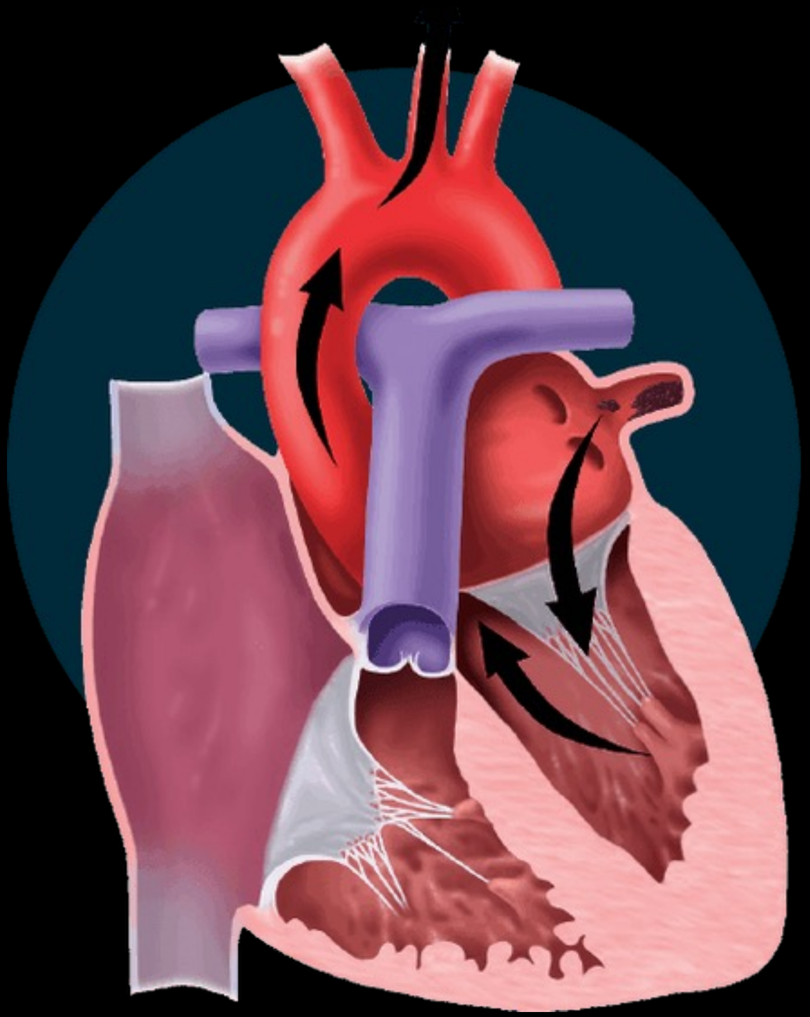
Background

- Restores normal rhythm of the heart
- New thinner catheters are coming to market
- Mechanical stability of leads are difficult to predict

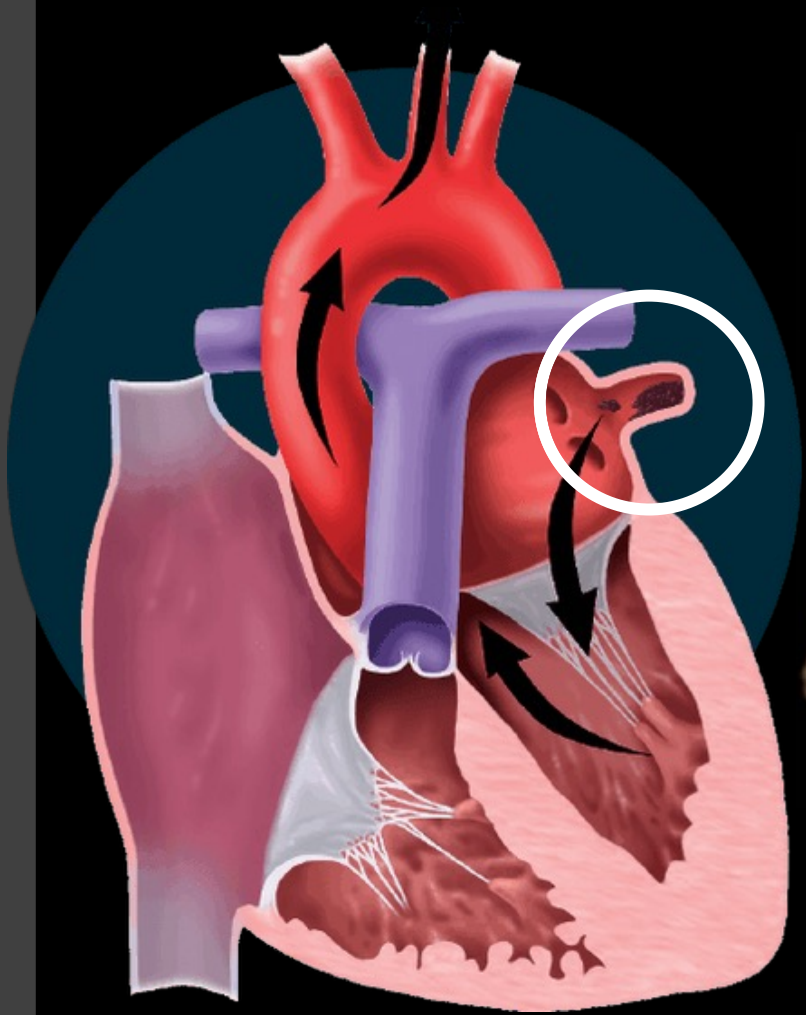


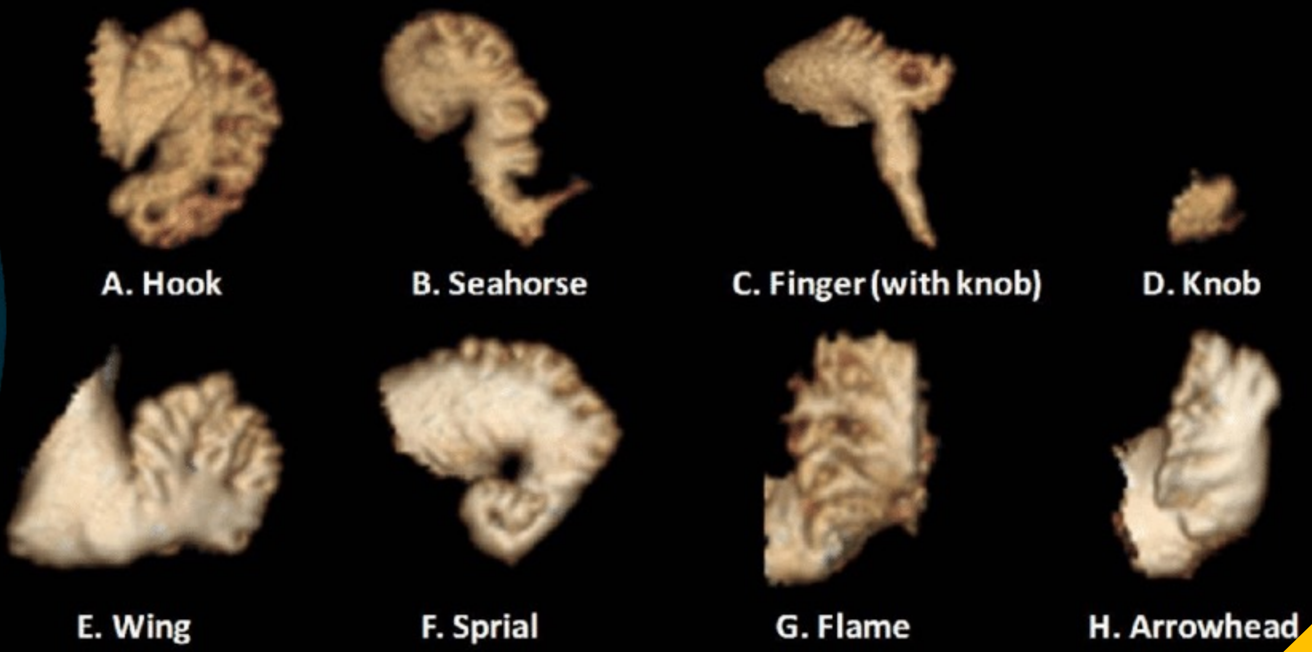
Objectives

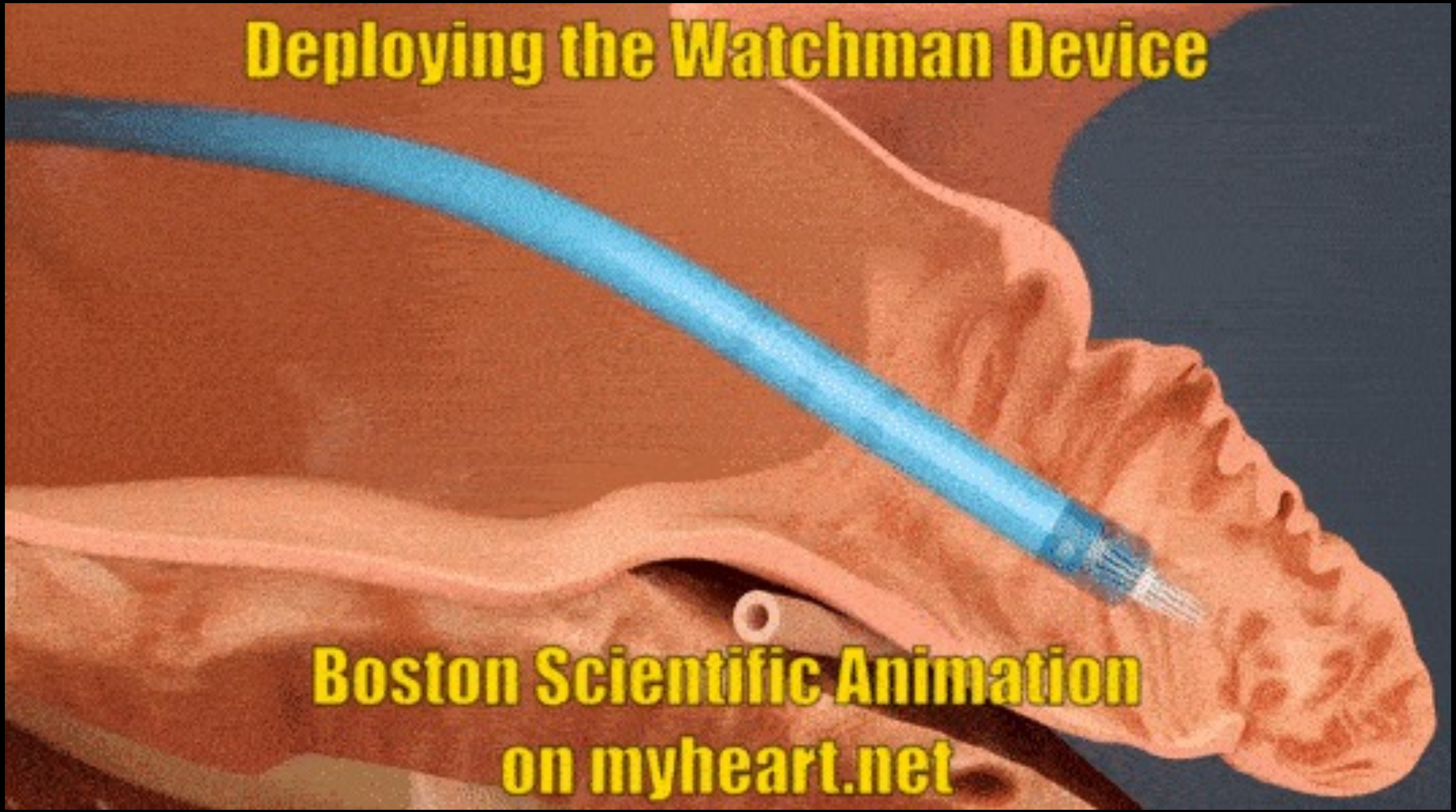
- Enable the validation with computational models of the navigation properties of (ultra-thin) catheters.
- Evaluate the pacing properties of such stimulating electrodes, and provide computational tools to help the design of cardiac pacing devices and protocols.
- Simulate the mechanical interactions between implanted pacing devices and cardiac tissue, including prediction of perforation and rupture by mechanical fatigue.



Use Case 2: Left Atrial Appendage Occluder

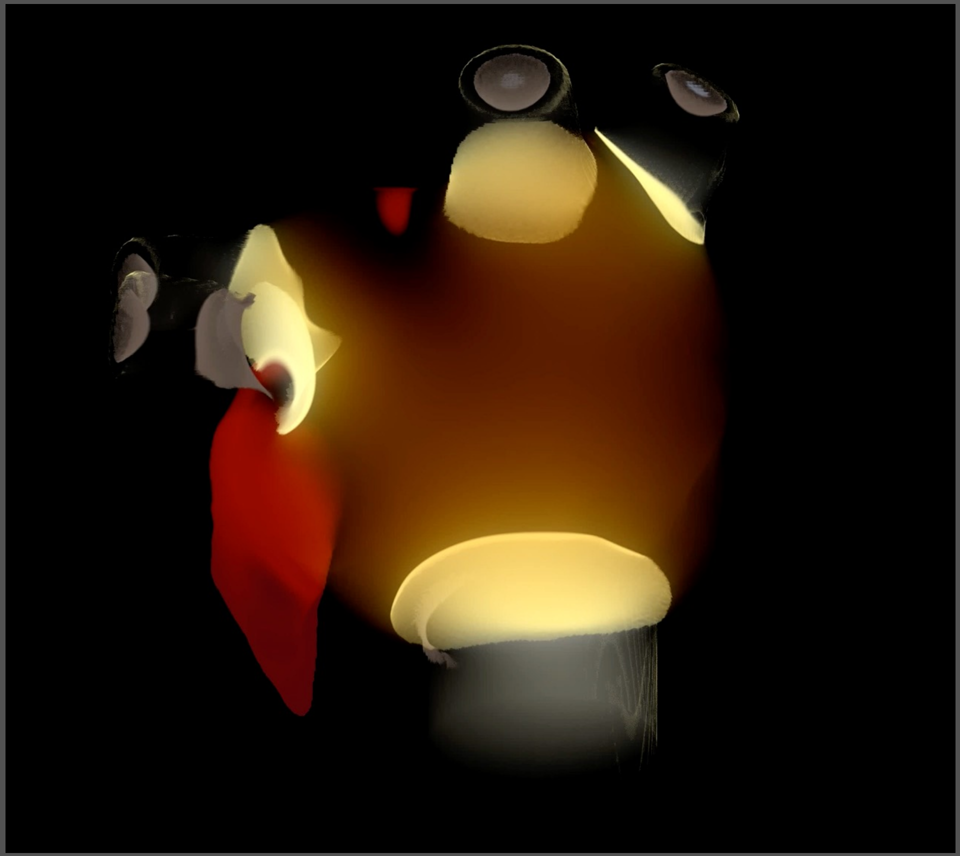


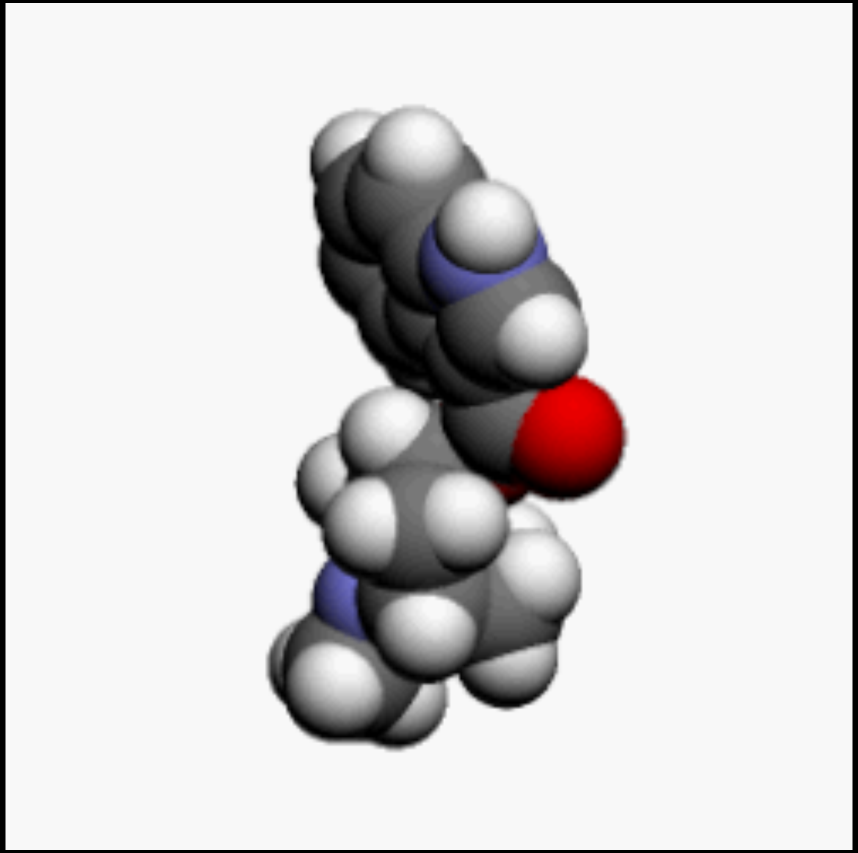

A. Hook
B. Seahorse
C. Finger (with knob)
D. Knob
E. Wing
F. Sprial
G. Flame
H. Arrowhead


Deploying the Watchman Device
Boston Scientific Animation
on myheart.net

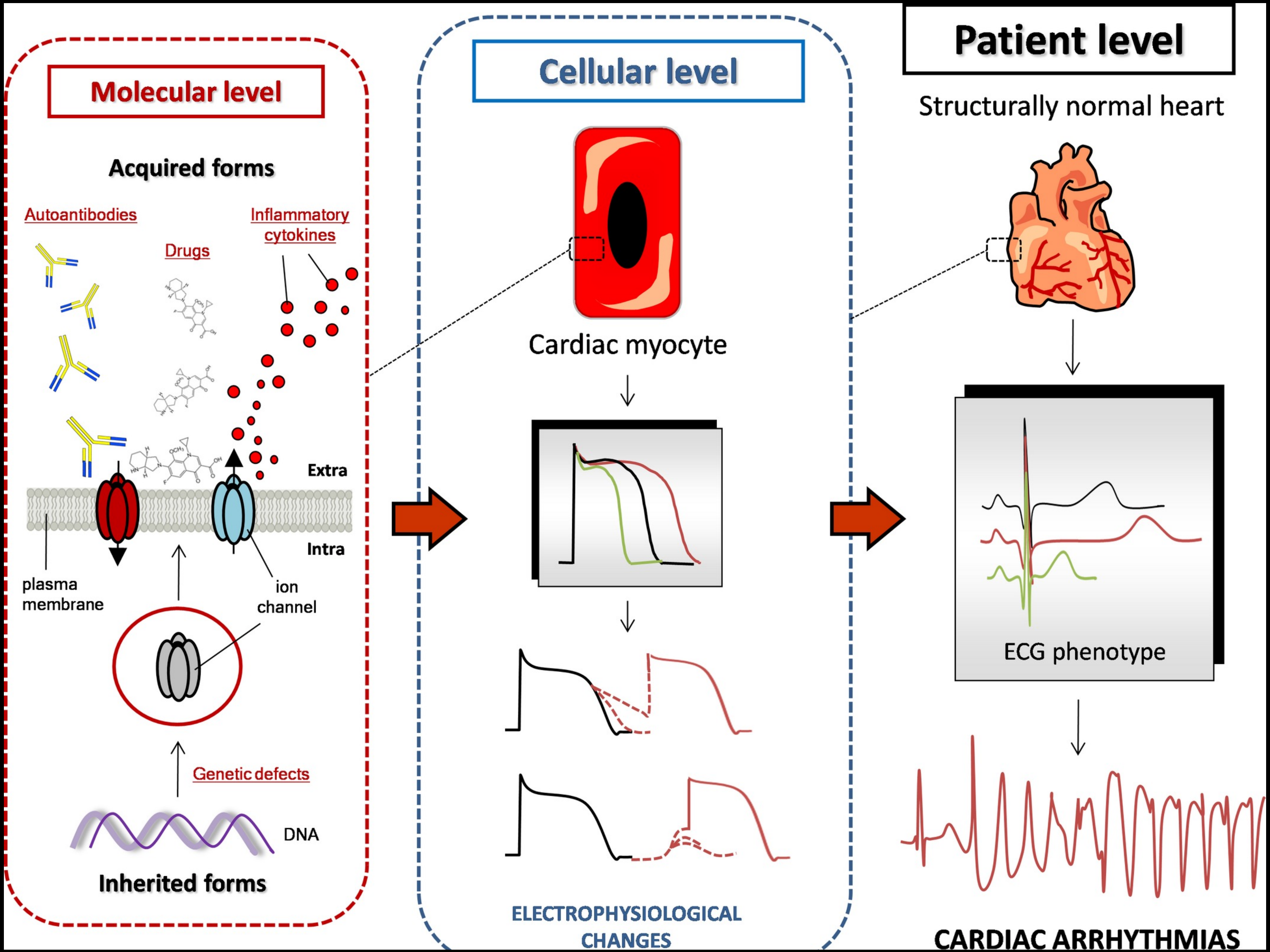
Objectives

- Develop pipeline for generating patient-specific meshes and patient-specific boundary conditions for large number of cases
- Sensitivity analyses and model calibration to determine optimal methodological choices in fluid simulations
- Derivation of in-silico haemodynamic indices to assess the risk of thrombus formation and predict the benefit of LAAO implantation

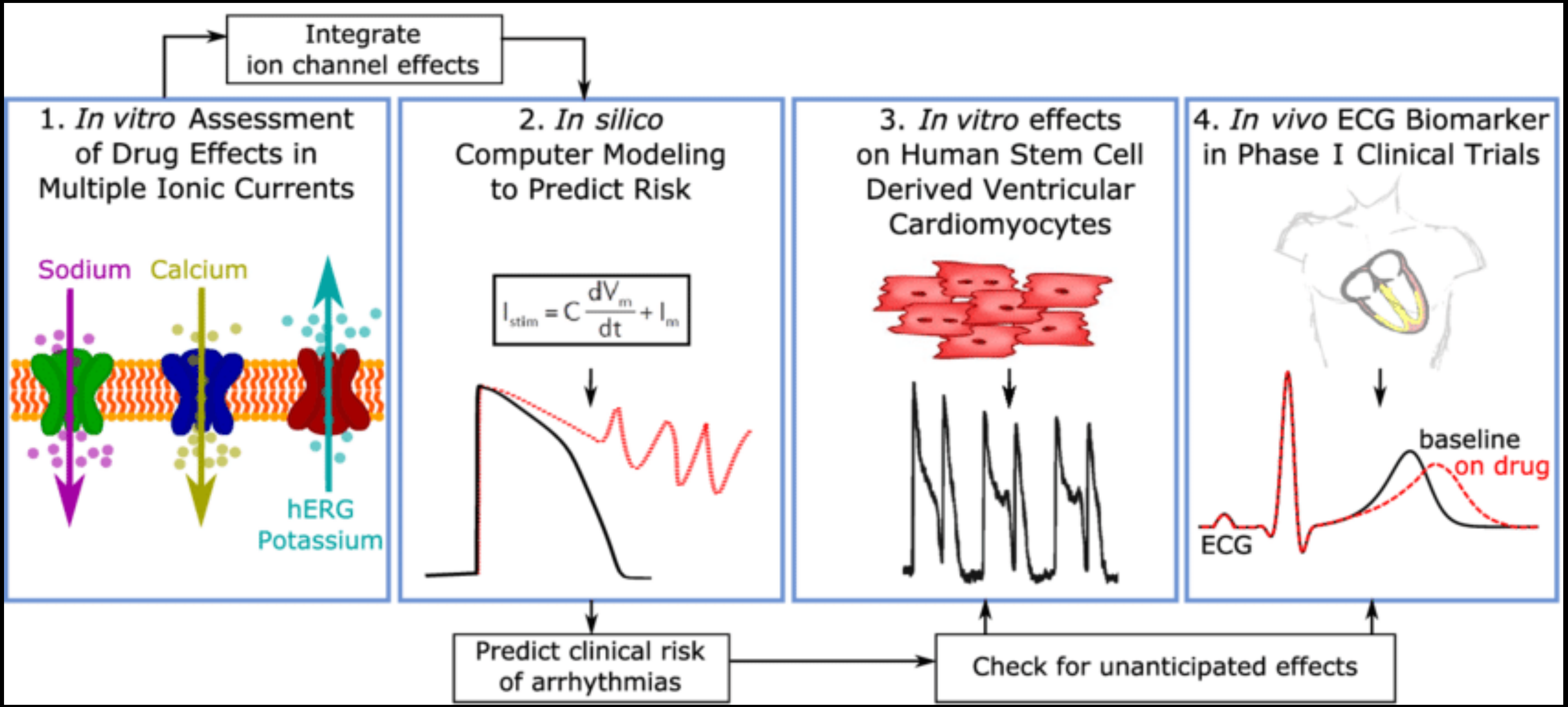




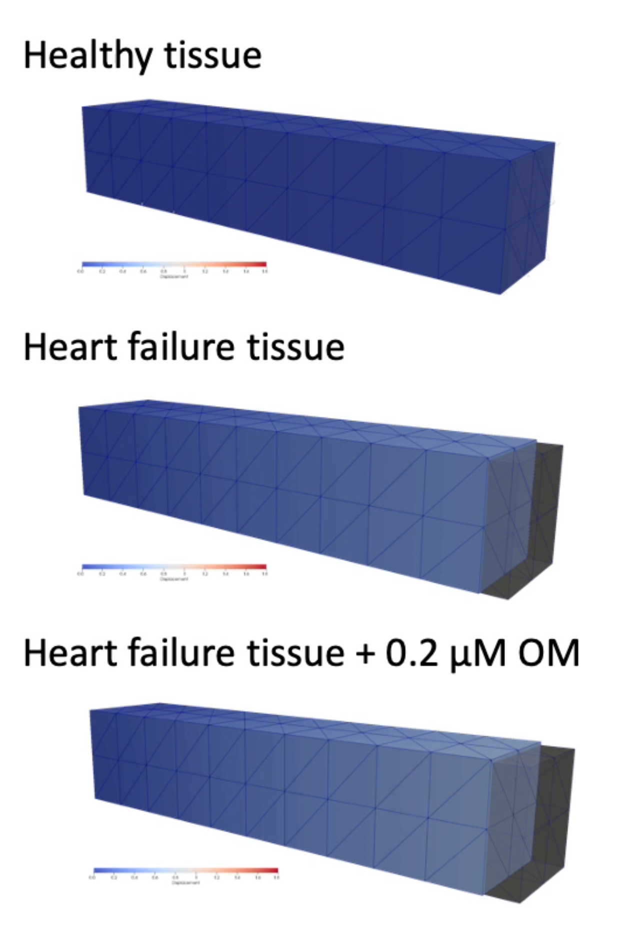
Use Case 3: Drug Efficacy and Toxicity

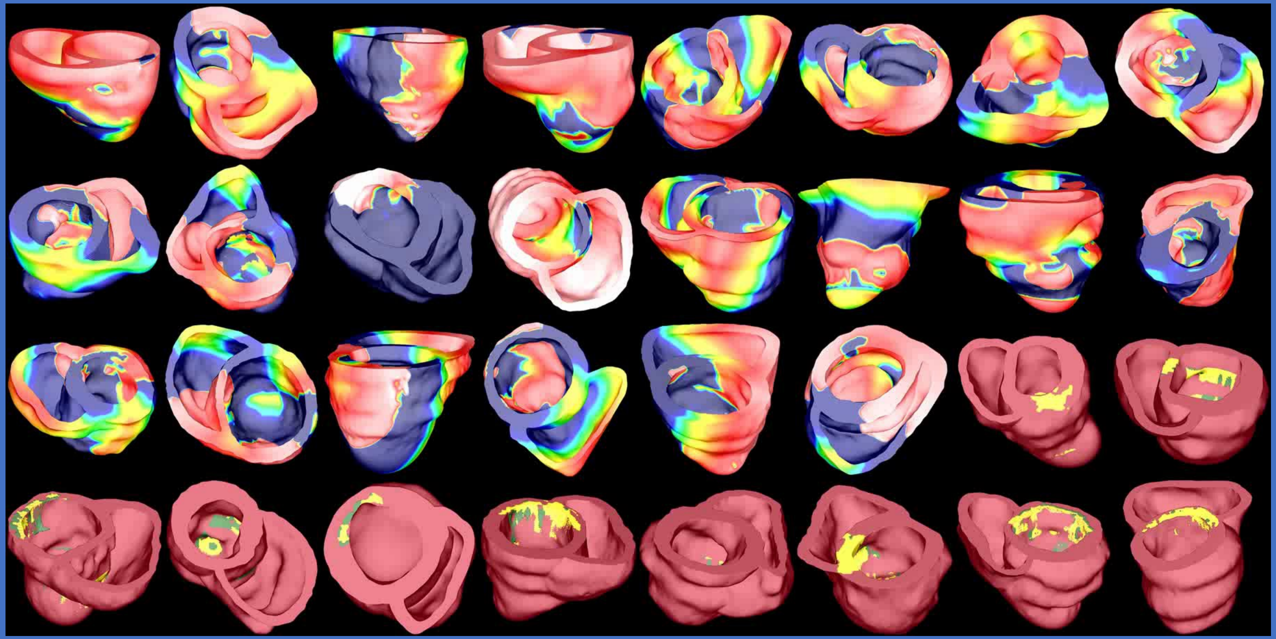


Molecular level
Acquired forms
Autoantibodies
Drugs
Inflammatory cytokines
Extra
Intra
plasma membrane
ion channel
Genetic defects
DNA
Inherited forms
Cellular level
Cardiac myocyte
ELECTROPHYSIOLOGICAL CHANGES
Patient level
Structurally normal heart
ECG phenotype
CARDIAC ARRHYTHMIAS



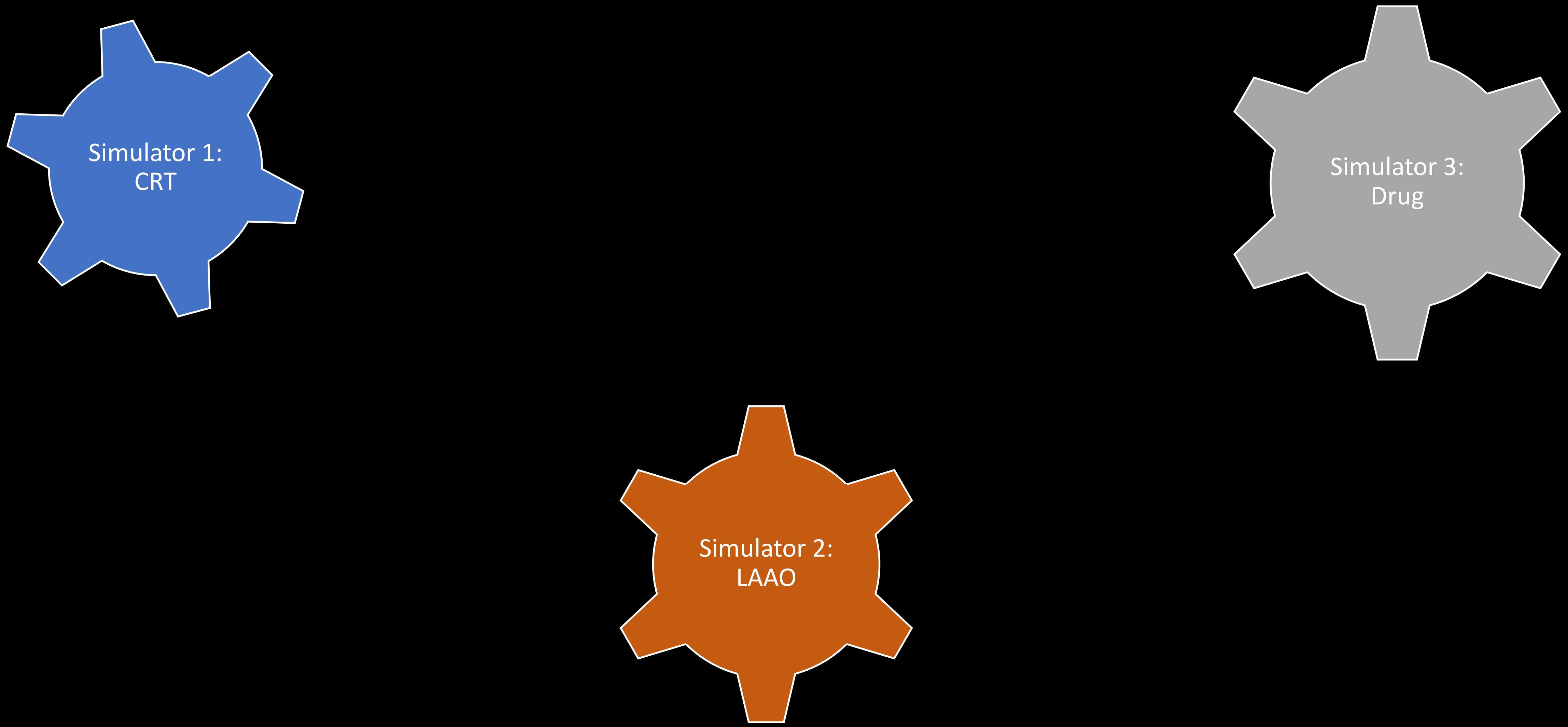
Comprehensive in vitro Proarrhythmia Assay (CIPA)


Healthy tissue
Heart failure tissue
Heart failure tissue + 0.2 μM OM

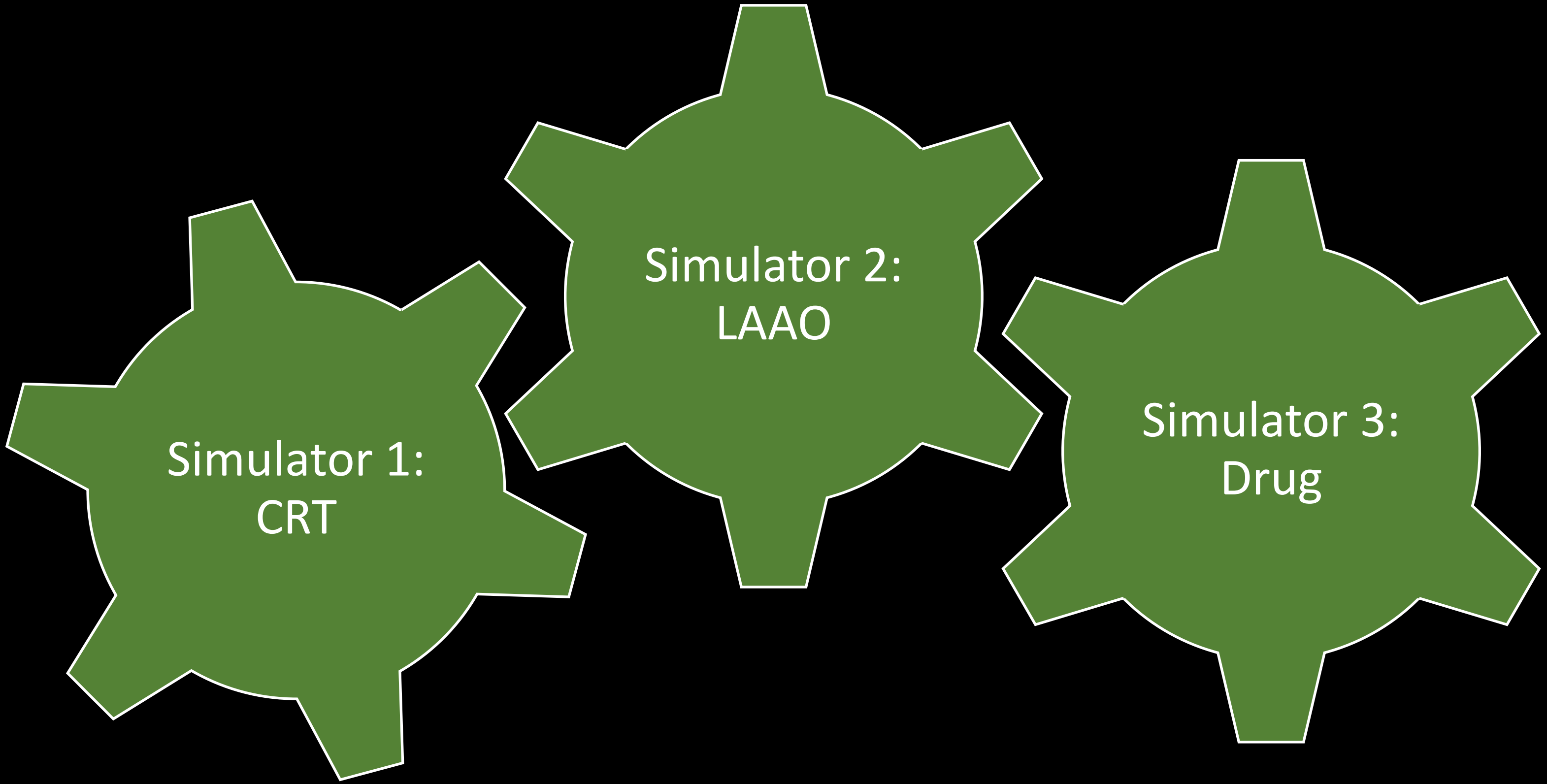


Objectives

- Development of drug ion channel interaction models and assess drug effects at the cellular level in healthy and pathological virtual populations
- Assessment of the effects of drugs in validated, anatomically-based multi-scale predictive cardiac models for healthy and patient-specific disease conditions
- Identification of selective and specific biomarkers to improve prediction of drug efficacy and safety

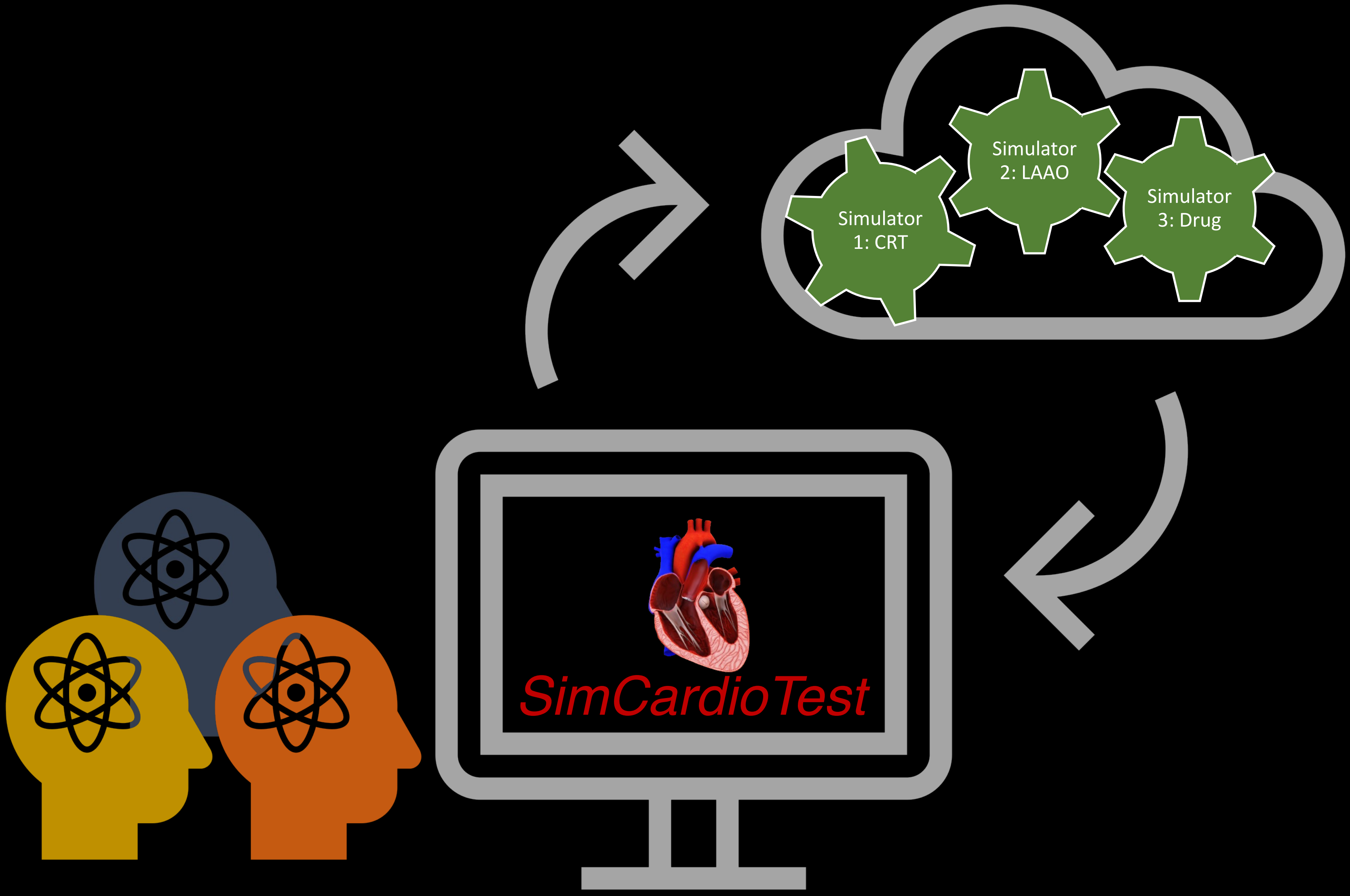


Use Case Pipelines



Validate and Verify Simulation Predictions

Implementation of Standards



Platform refinement

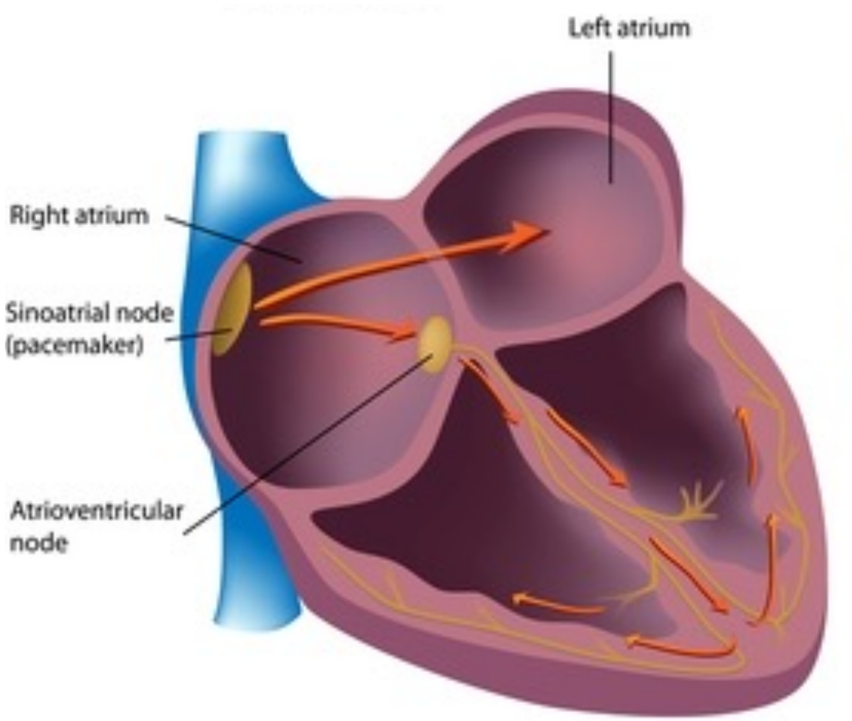
Cardiac modelling in practice

- Internships
- Master thesis
- Simula Summer School in Computational Physiology

Resources: https://github.com/ComputationalPhysiology/uio-digital-scholarship-days

- Bad luck:
  - Model (component) does not exist
  - Simulation cannot finish due to solver
- Bad drug:
  - Drug is causing unwanted (side) effects
  - Concentration dependent effects
  - Drug has an unpredictable effect
- Bad heart:
  - Heart disease
  - Unknown or unpredictable side effects
  - Influence of other organs
- **None of the above**

Electrical signal triggers contraction

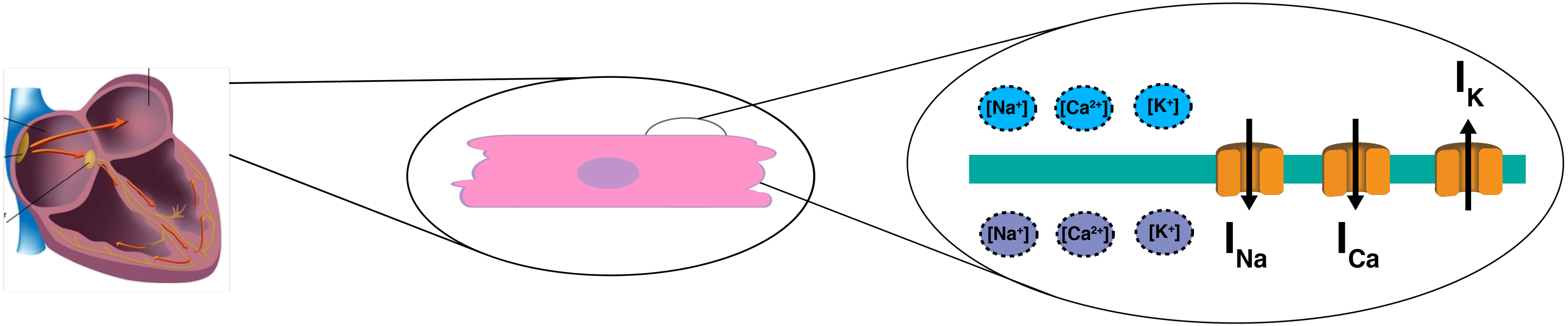


ECG signal

atrial contraction

ventricular contraction

Multi-scale

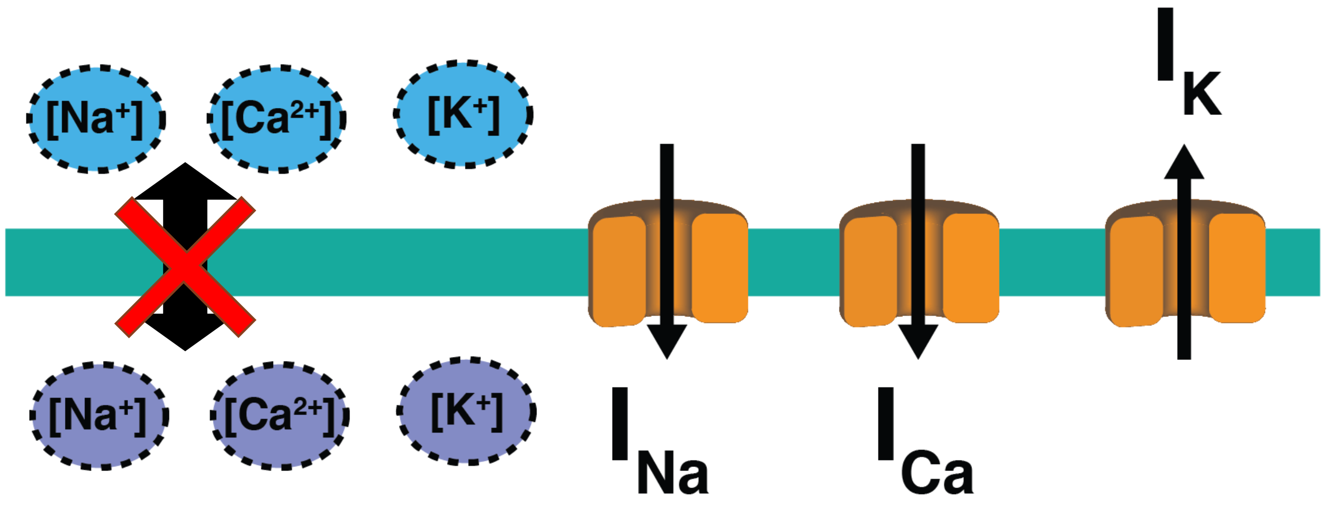


Heart

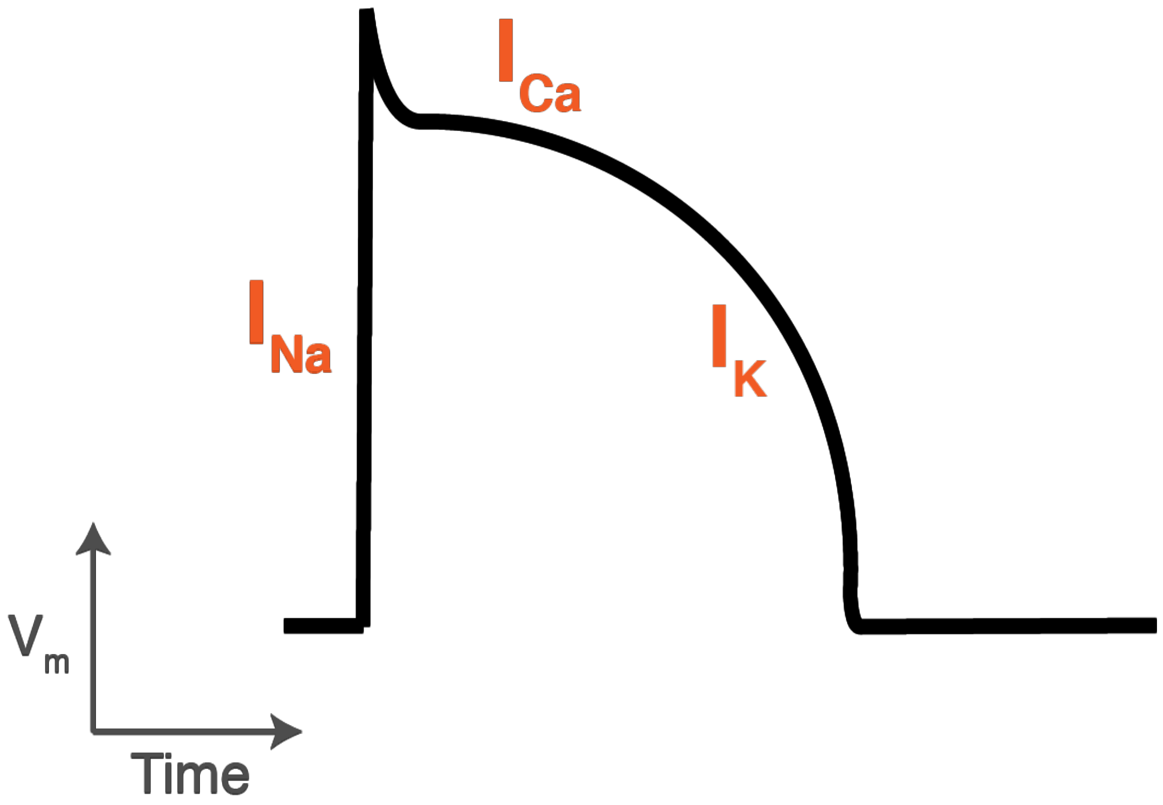
Cell

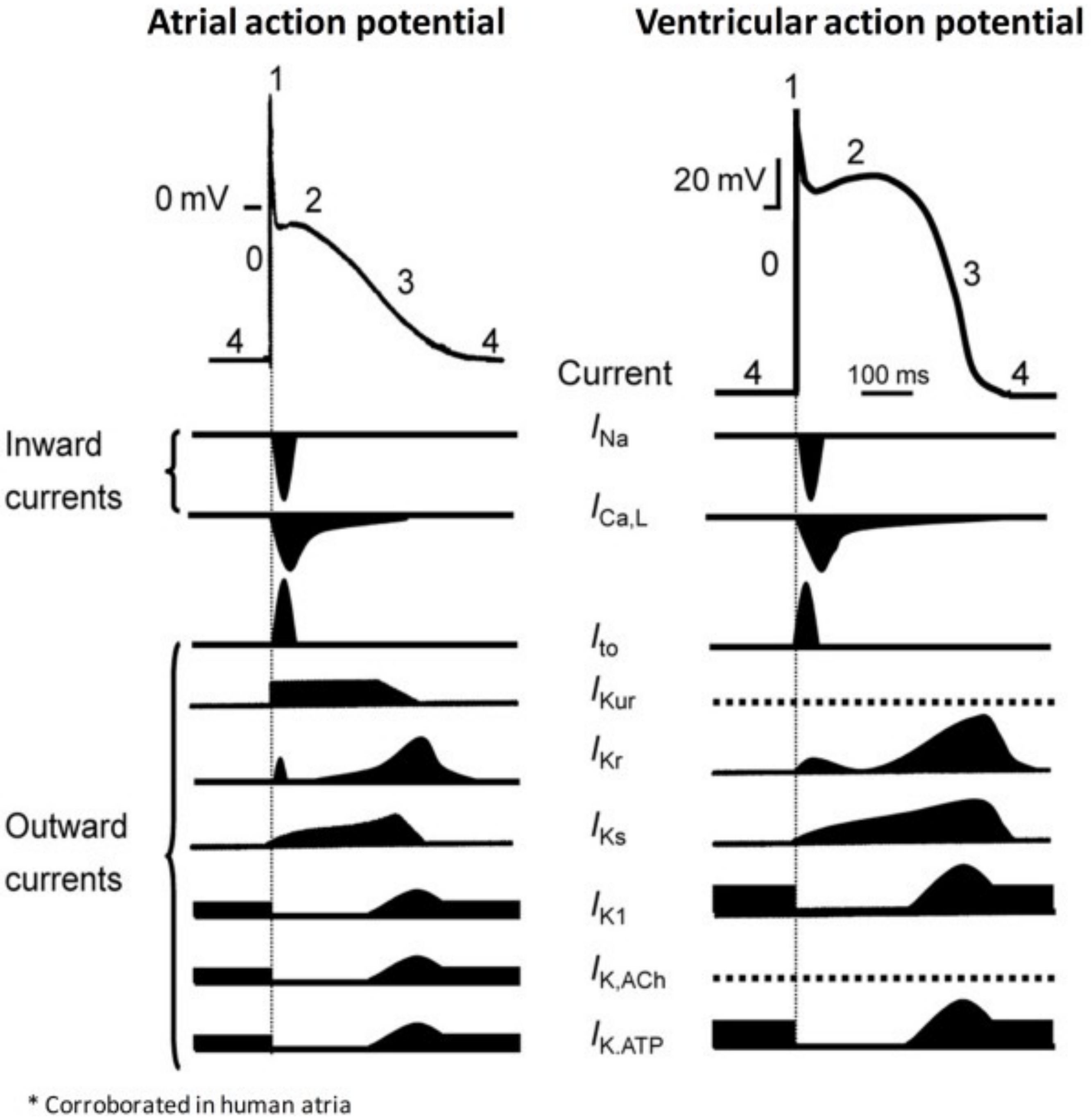
Membrane

Cell membrane limits movement of charged ions



Electrical signal of single cell: Action potential

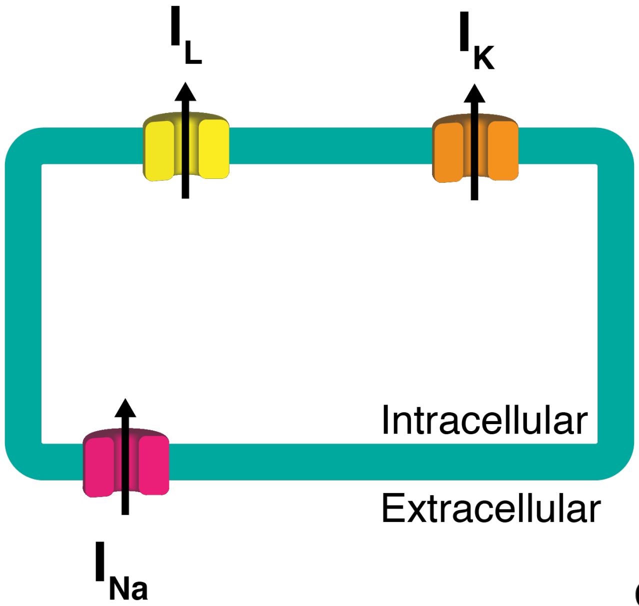


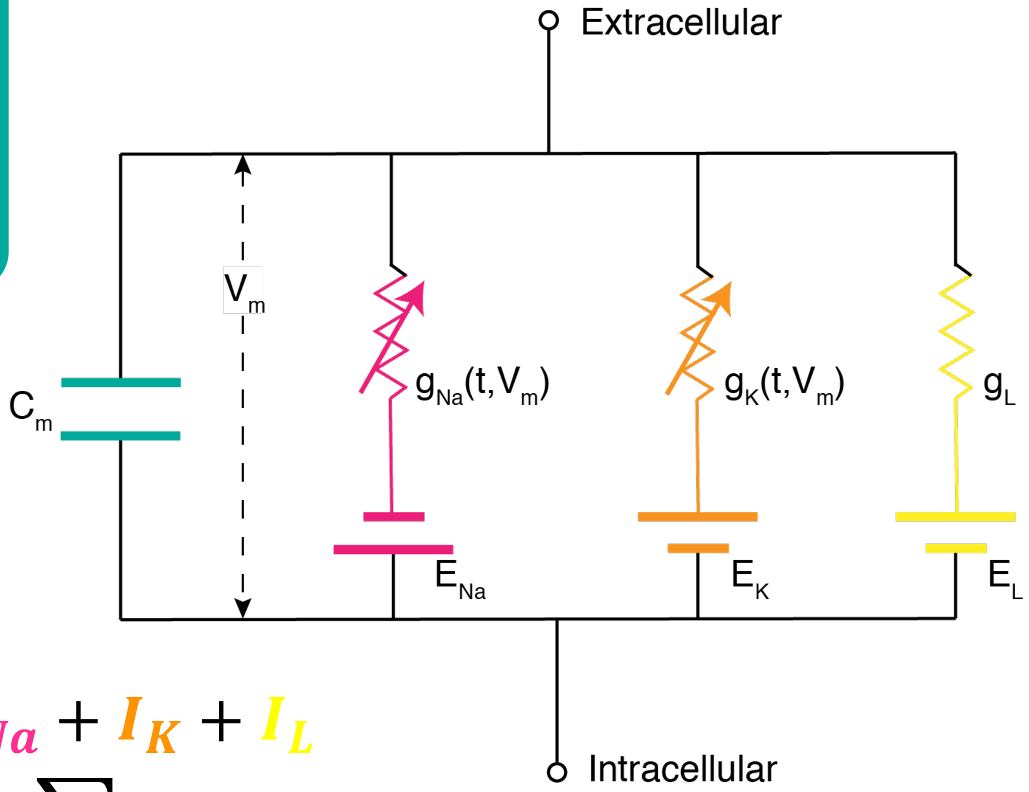


Modified from Moreno et al.; 2012; Frontiers in physiology

How can a computer replicate this?

Hodgkin and Huxley described the membrane as an electric capacitor





$$I = I_{Na} + I_K + I_L$$
$$= \sum I_x$$

Hodgkin and Huxley; 1952; The Journal of Physiology

Hodgkin and Huxley described the membrane as an electric capacitor

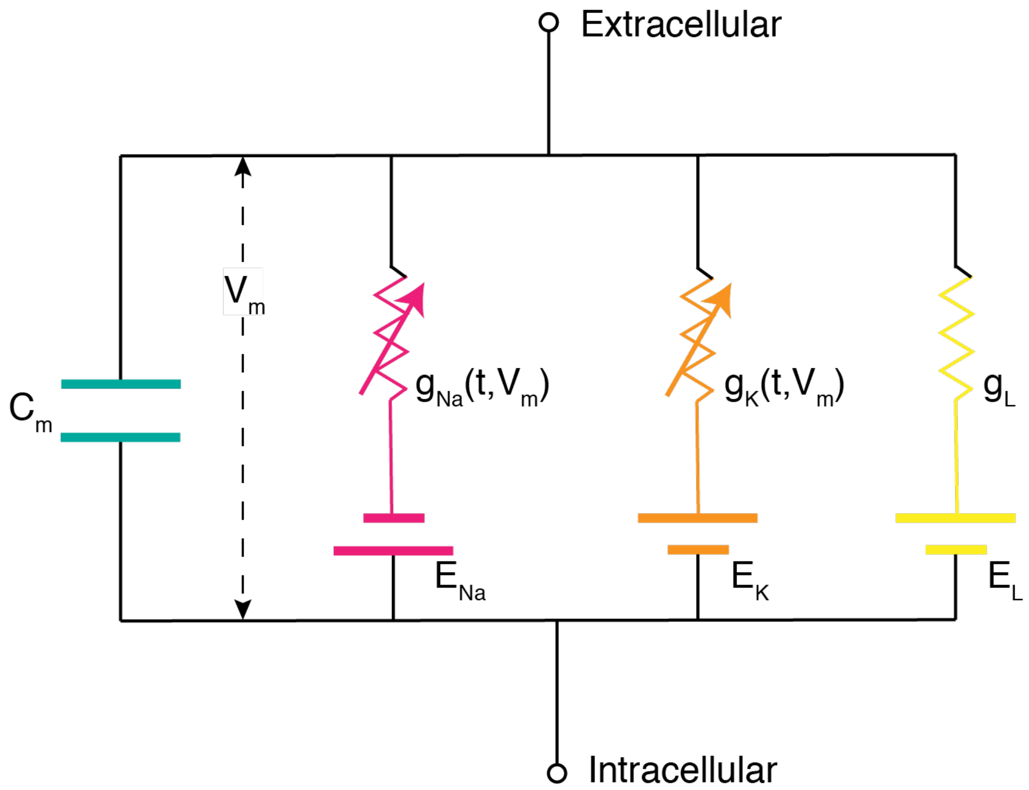
ODEs (ordinary differential equations)

$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + \bar{g}_{\mathrm{K}} n^4 (V_m - V_K) + \bar{g}_{\mathrm{Na}} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l)$$

$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

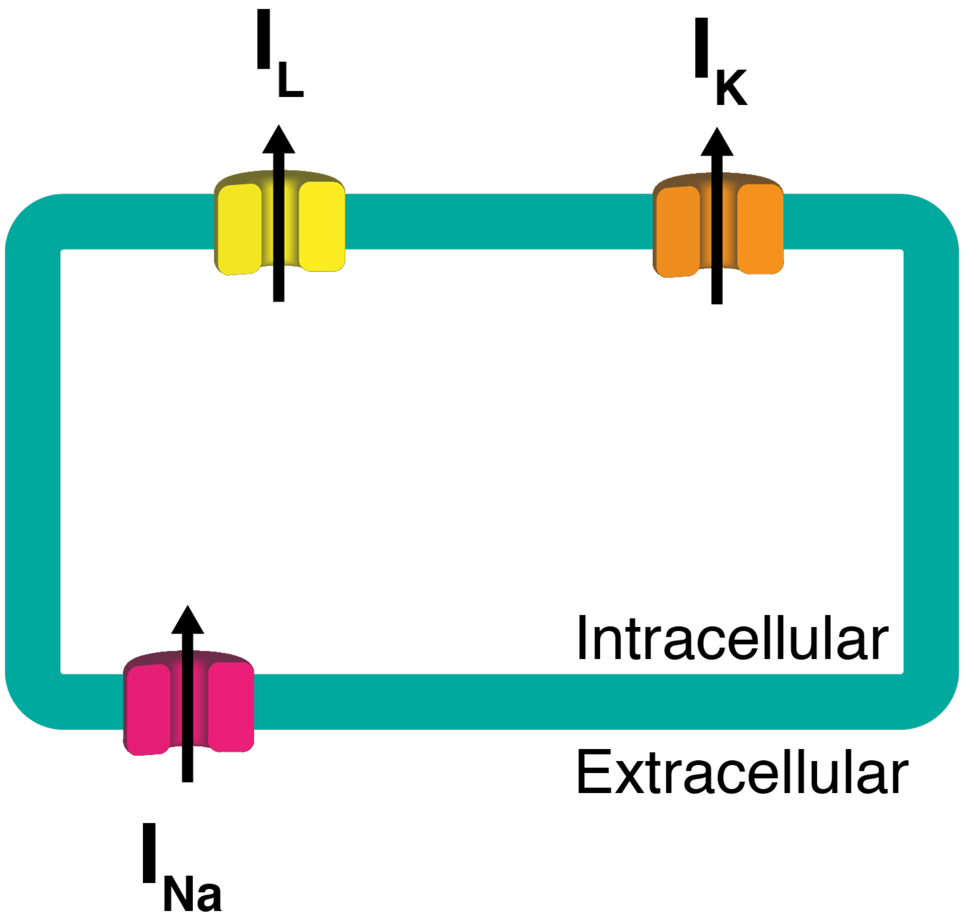
$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$



Hodgkin and Huxley; 1952; The Journal of Physiology

First cardiac cell model: Noble



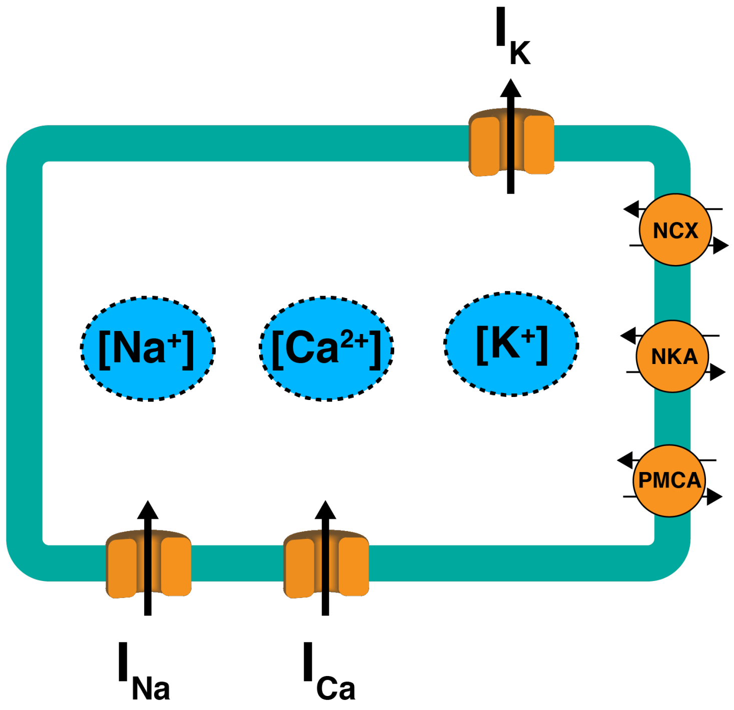
- Try it yourself
    - Noble model

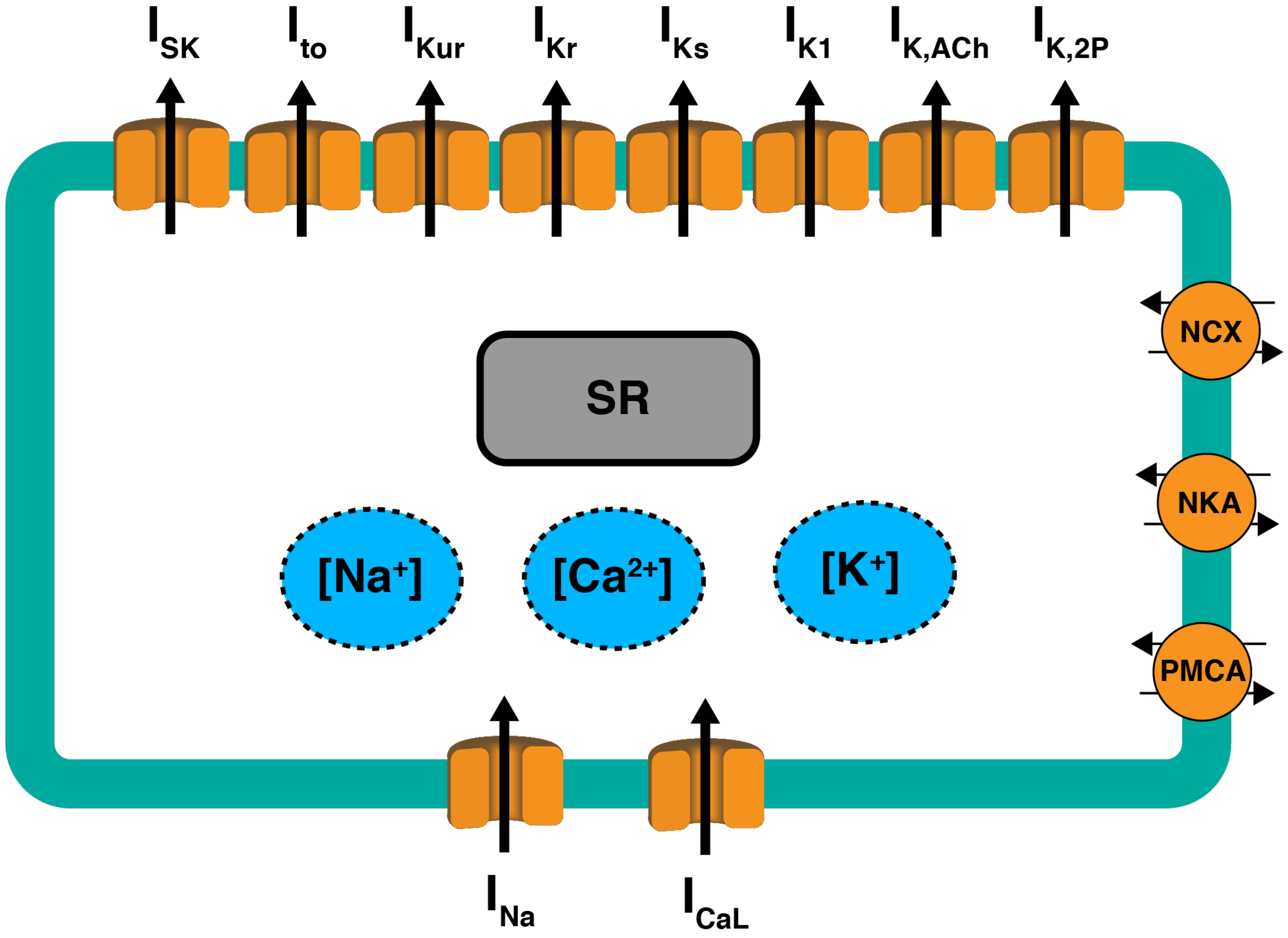
https://github.com/ComputationalPhysiology/uio-digital-scholarship-days

- Changes in dt can change the result
- Change parameter g_L

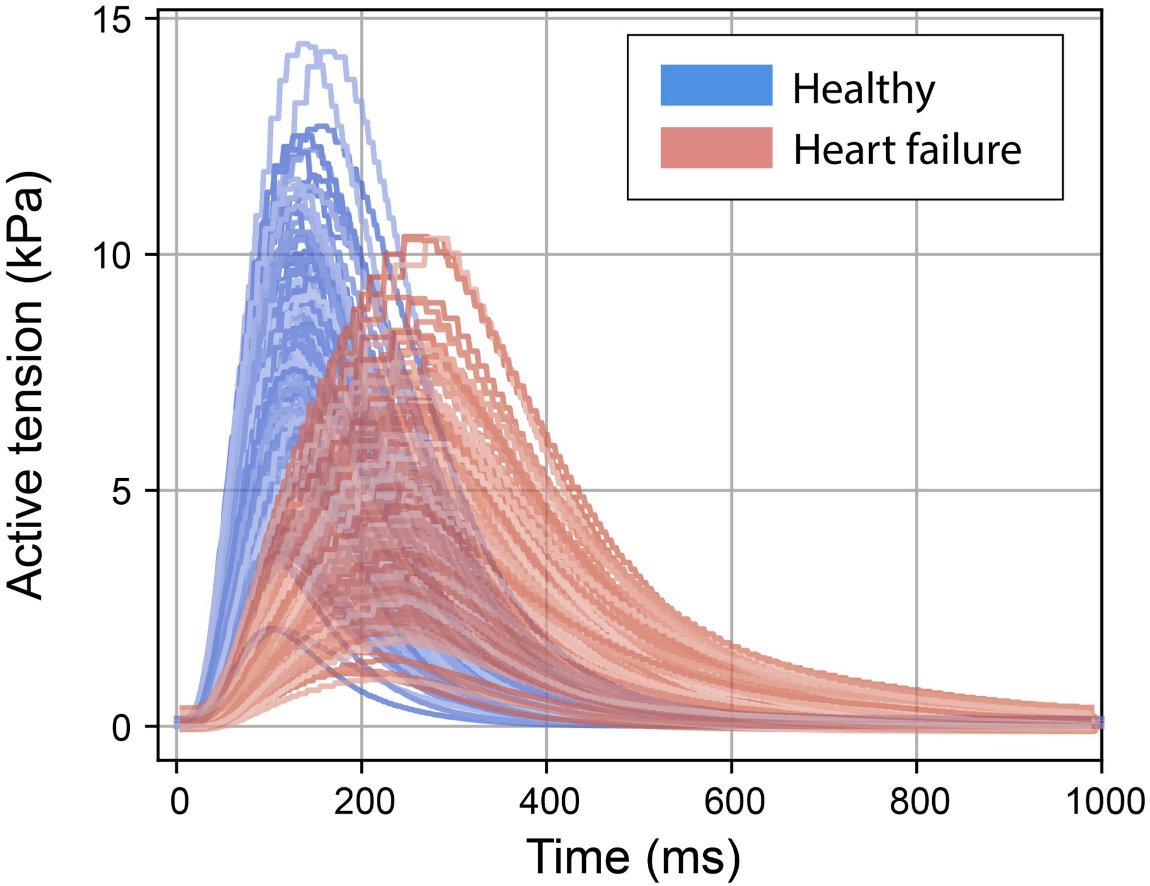
More complex models

- More accurate representation of cardiac cell
- Complex equations to solve
- Larger number of equations to solve




I_{SK}
I_{to}
I_{Kur}
I_{Kr}
I_{Ks}
I_{K1}
$I_{K,ACh}$
$I_{K,2P}$
SR
NCX
NKA
PMCA
$[Na^+]$
$[Ca^{2+}]$
$[K^+]$
I_{Na}
I_{CaL}

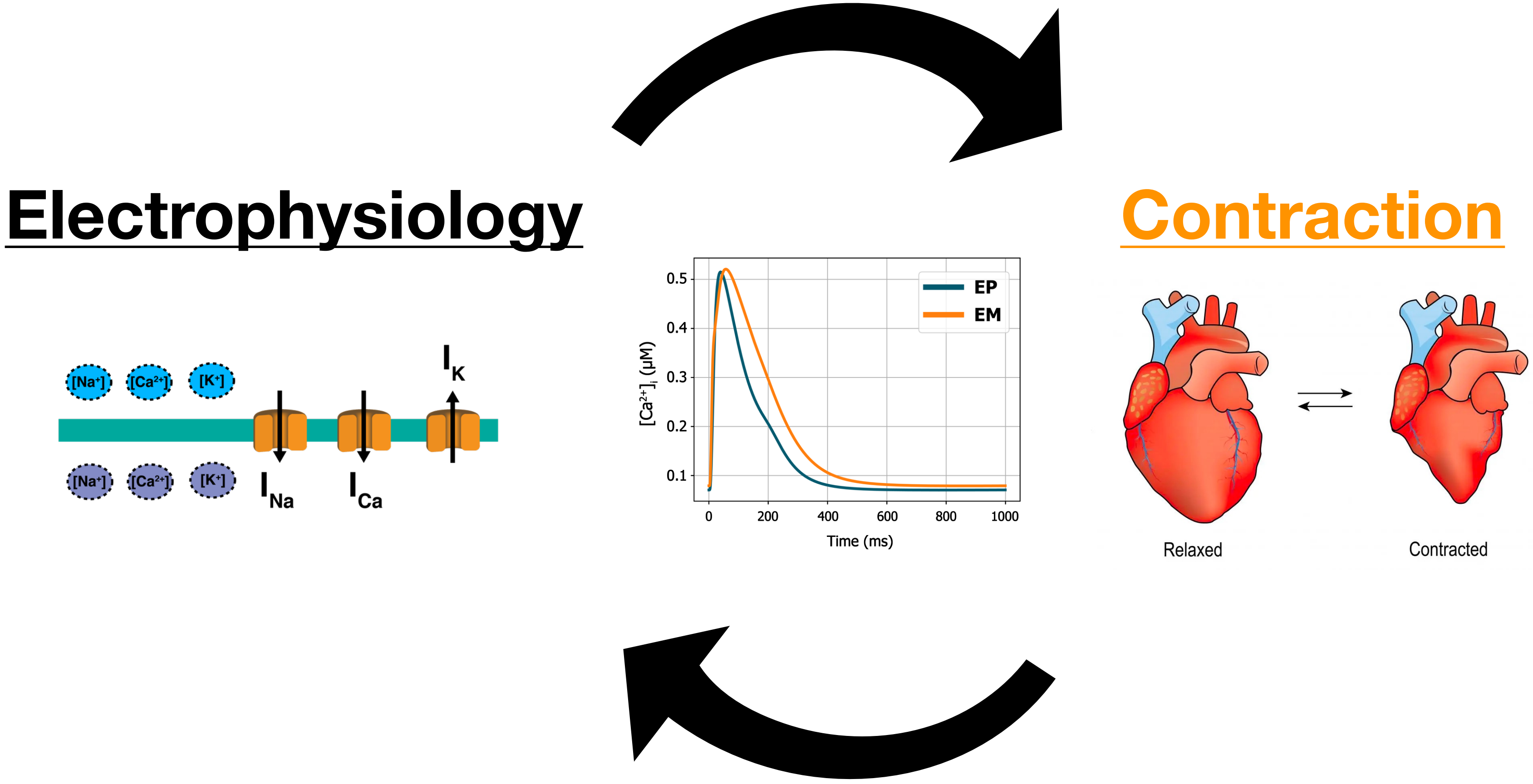
Example of bad heart



- Try it yourself
    - O'Hara Rudy Land model (until stretch)

https://github.com/ComputationalPhysiology/uio-digital-scholarship-days

Electro-mechanics: coupling two models



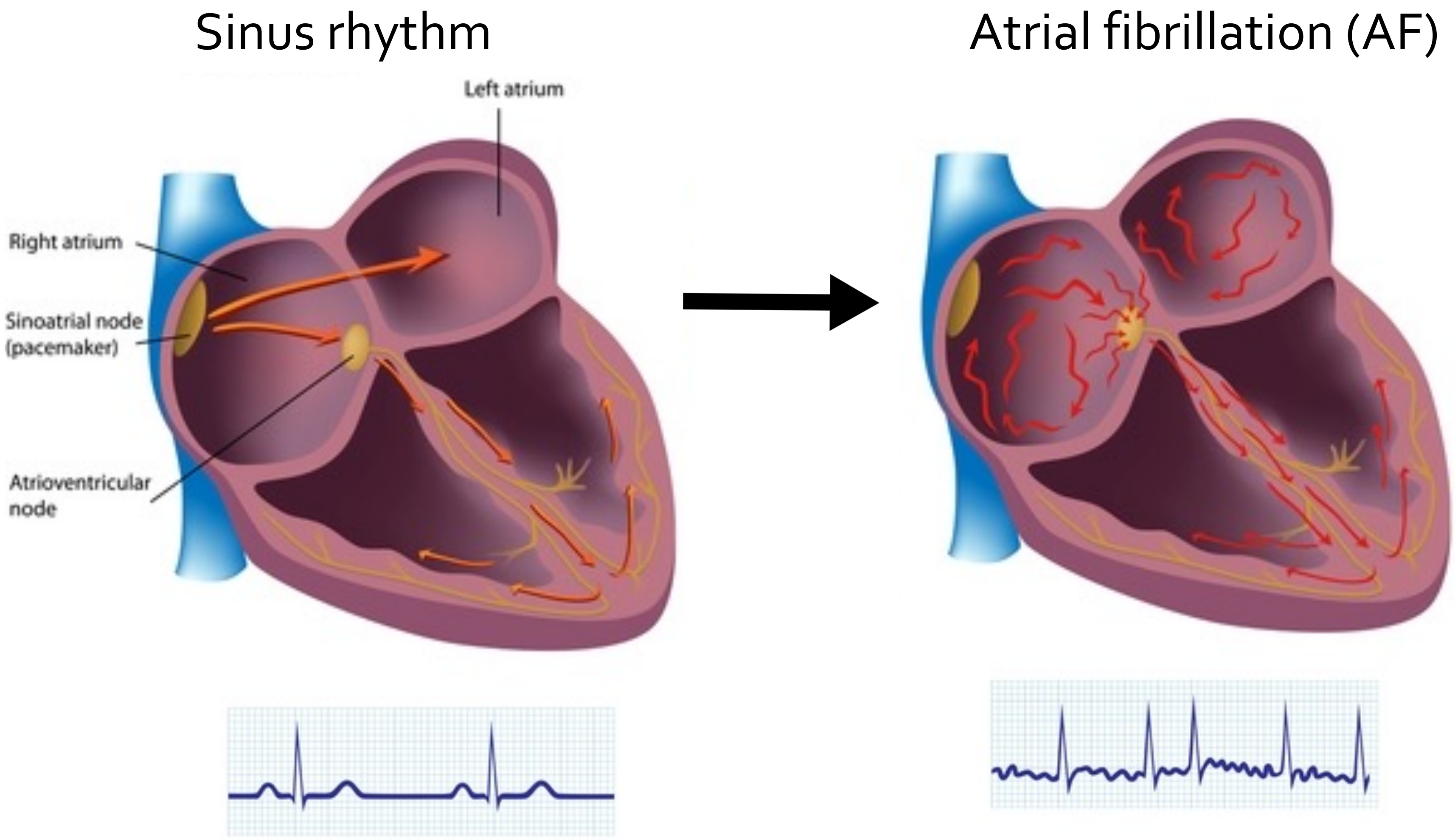
- Try it yourself
  - O'Hara Rudy Land model

https://github.com/ComputationalPhysiology/uio-digital-scholarship-days

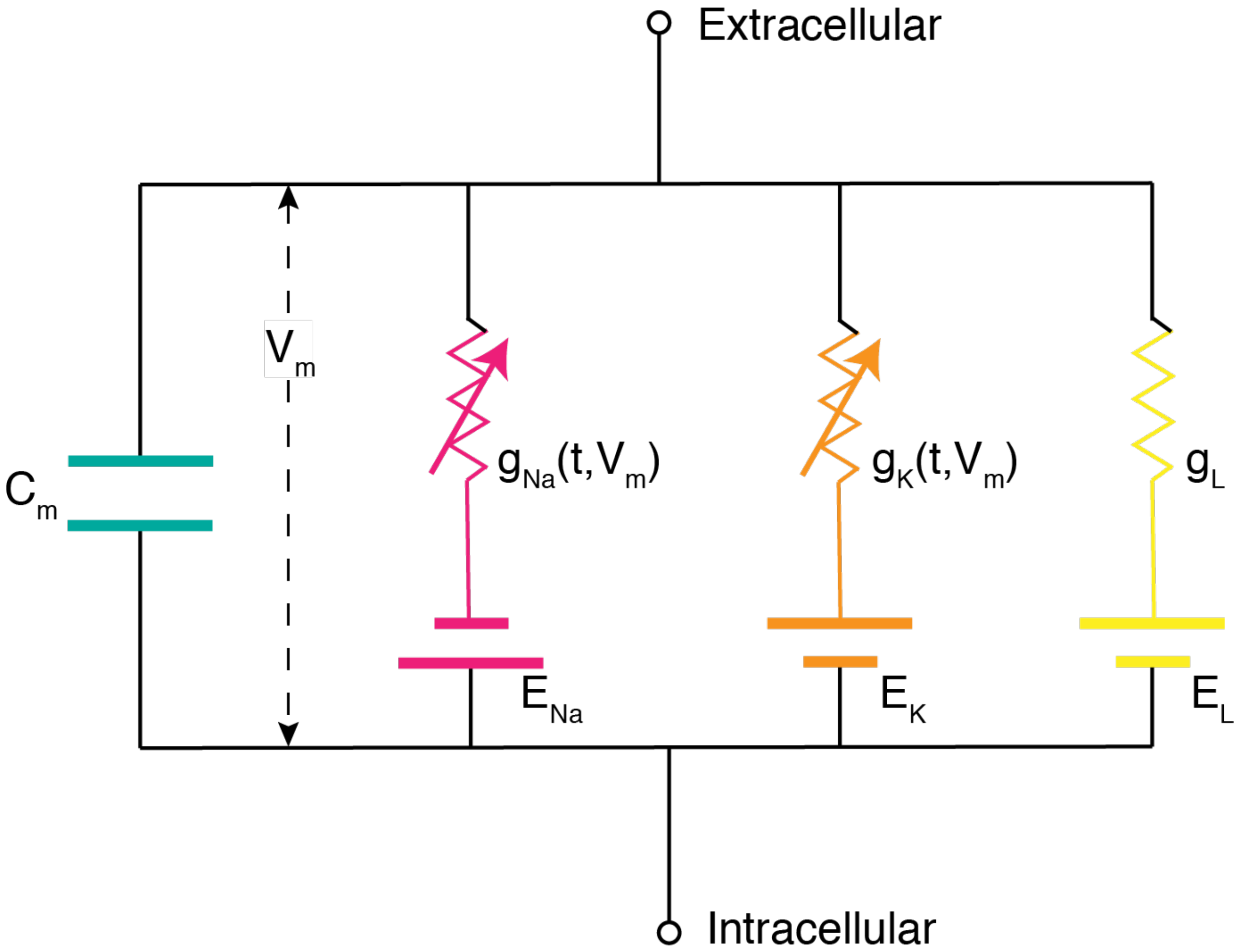
- Steady state
- Extract ion currents
- Membrane voltage and ion currents
- Stretching

Drug interactions

Why?: Atrial fibrillation is characterized by rapid and irregular beating of atria

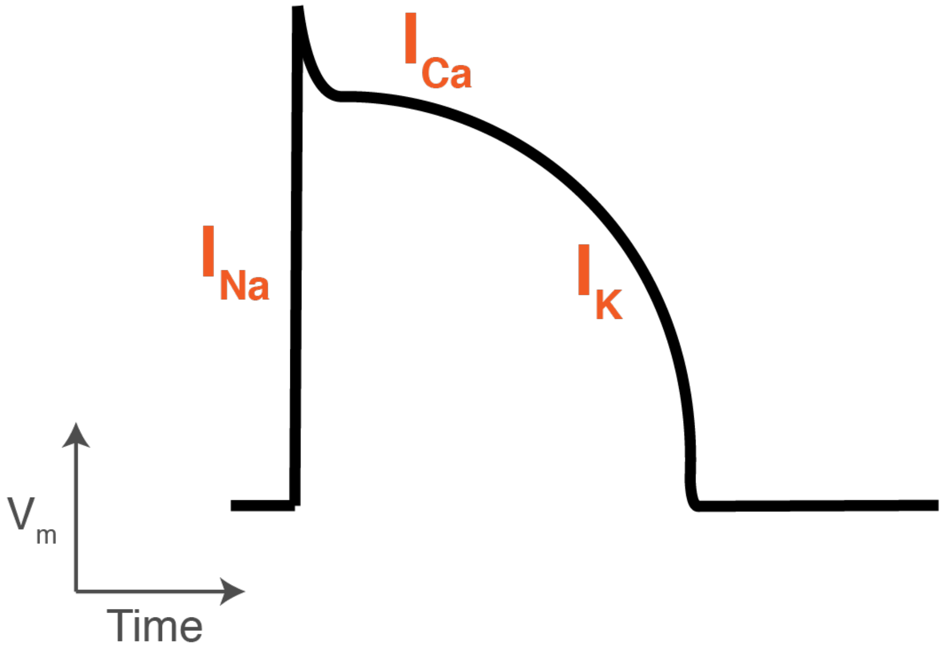


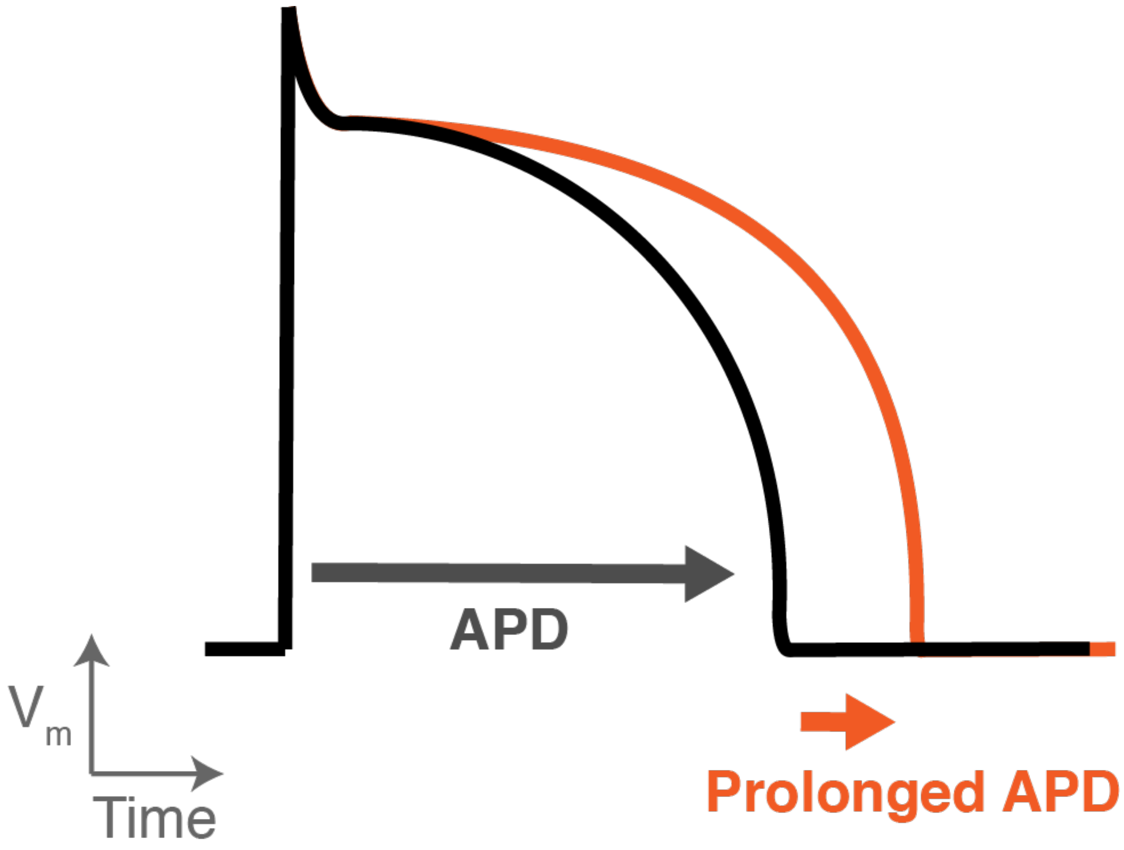
Drug interactions in the model: scaling factors



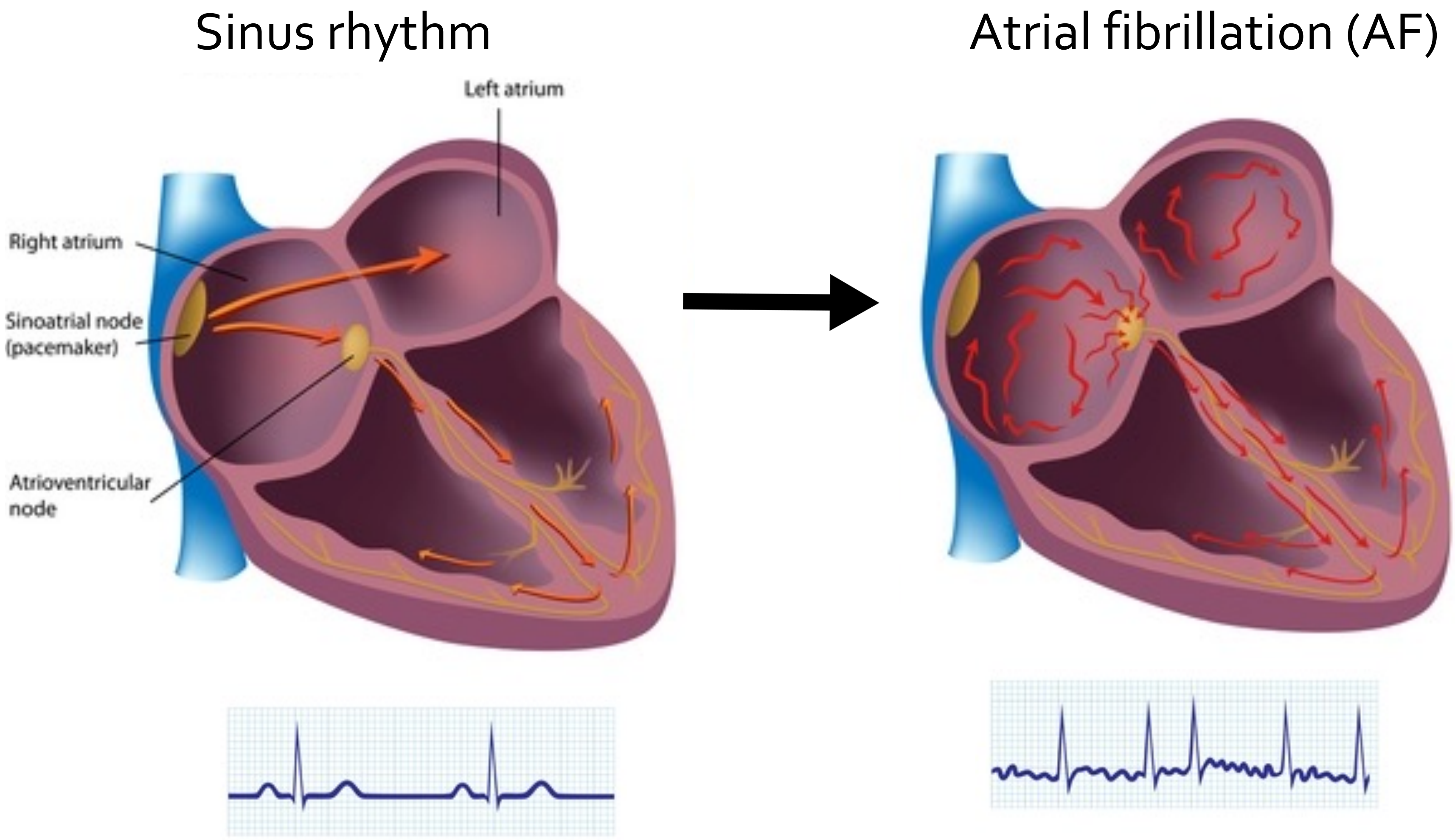
Drugs target different (and sometimes multiple) ion channels

Drug	Target
Flecainide, Propafenone	Na^+-channels
Ranolazine	Na^+, Ca^{2+}, K^+-channels
Amiodarone, Dronedarone, Ibutilide, Vernakalent, Dofetilide, Sotalol	K^+-channels
Cardiac glycosides	NKA pump




APD
Vm
Time
Prolonged APD

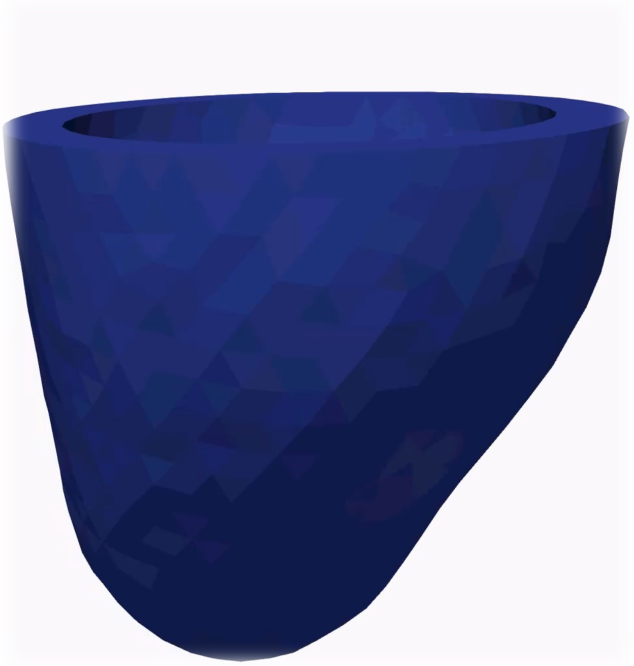
Why?: Atrial fibrillation is characterized by rapid and irregular beating of atria



- Try it yourself
    - Modeling drug effects

https://github.com/ComputationalPhysiology/uio-digital-scholarship-days

- Dofetilide
- Concentration dependence



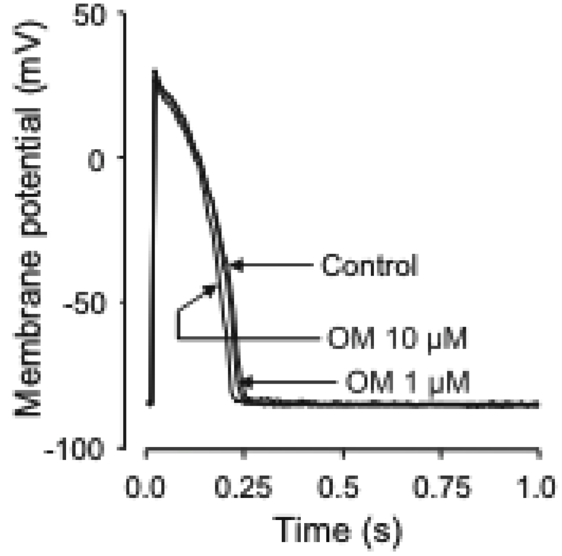
New software: SimCarDEMS

Couple electrophysiology and mechanics

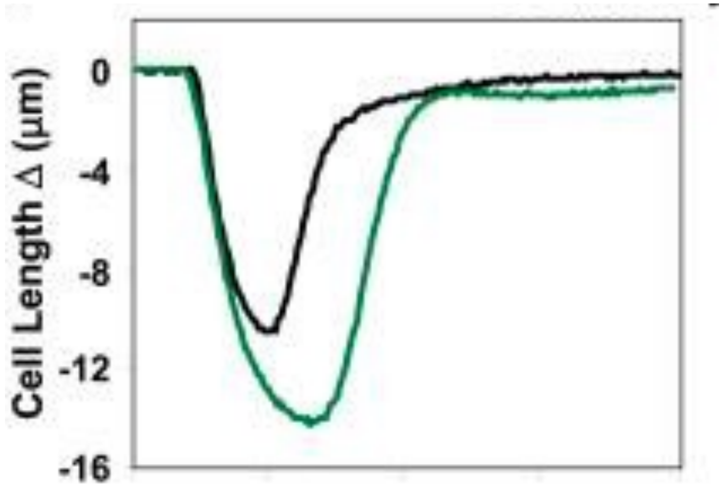
Omecamtiv Mecarbil

- Diseases and drugs that target the contraction of the heart, but not the electrophysiology

Action potential



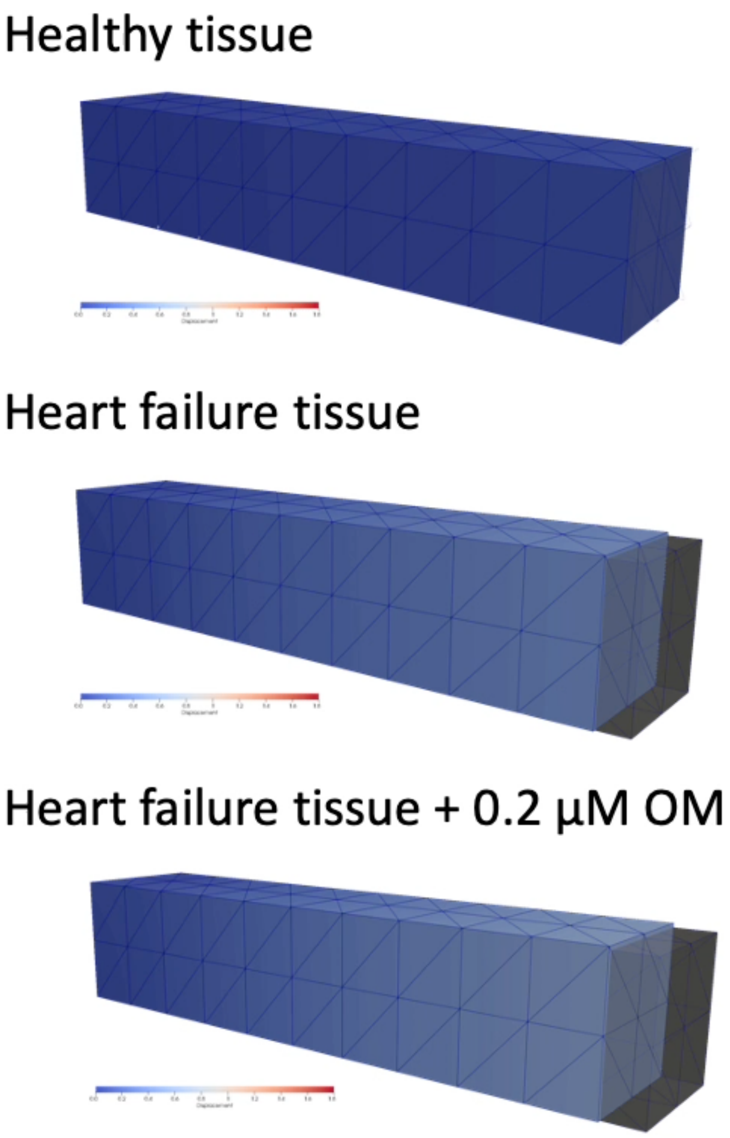
Cell length



Horvath et al. 2017

Malik et al. 2011
Gao et al. 2020
Abi-Gerges et al. 2021

Simulate contracting cardiac tissue



www.github.com/ComputationalPhysiology/simcardems

Wrap up

Bad luck, Drug or Heart - Computational models to the rescue

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Simula Research Laboratory

Friday 13 January 2023

Feedback

Give feedback on this workshop and the UiO Digital Scholarship days

at: nettskjema.no/a/dsc-days

More information

- Github: ComputationalPhysiology/uio-digital-scholarship-days

- Simula: www.simula.no

- Simula Summer School: www.simula.no/education/courses/summer-school-computational-physiology/2023-summer-school