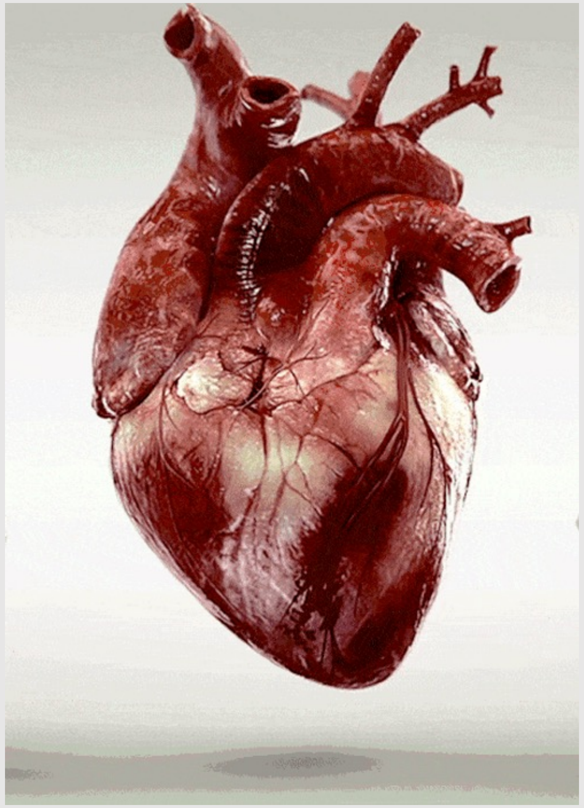
A beginners guide to cardiac modelling

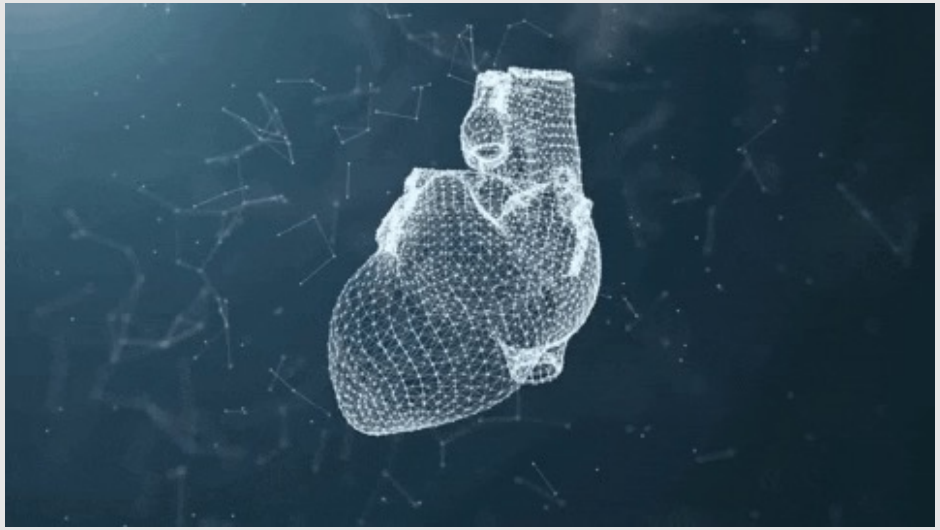
Henrik Finsberg
Simula Summer Festival 06.06.24

simula

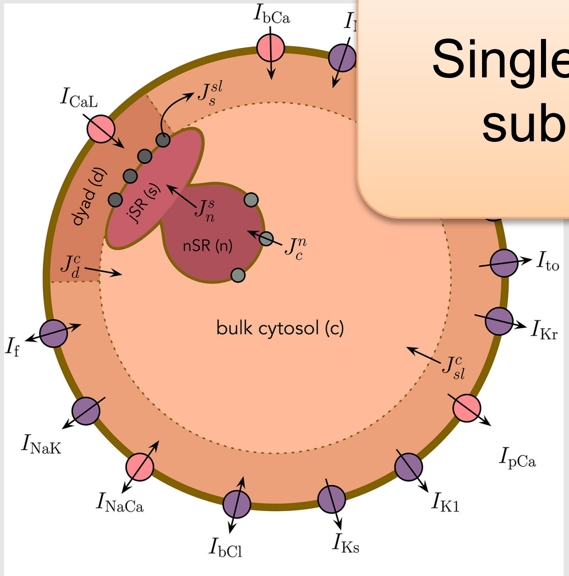
What do you think cardiac modeling is all about?



https://gifdb.com/gif/beating-human-heart-3d-real-animation-ndugdstfj863rnow.html



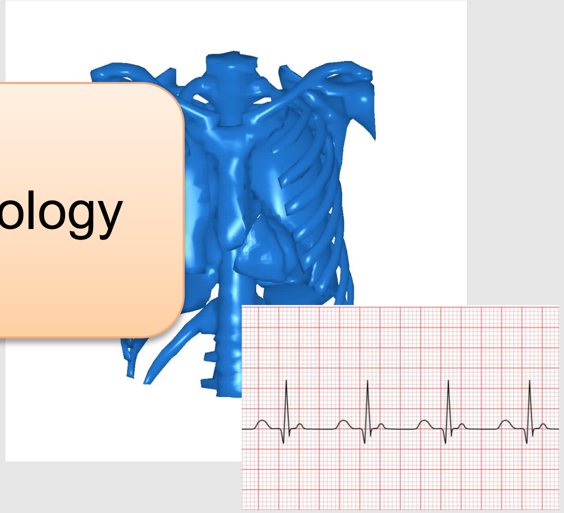
https://insilicotrials.com/working-on-a-new-european-project-that-will-leverage-simulation-to-help-fight-cardiovascular-disease/



Single cells (and sub-cellular)

Tveito, Jæger, Finsberg, Wall

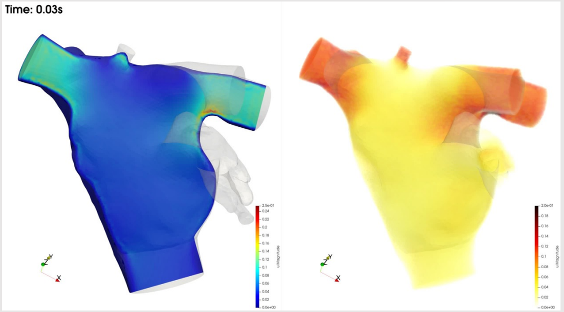
Uv, Tveito, & Arevalo



Electrophysiology

People in ComPhy are working on different aspects of cardiac modelling

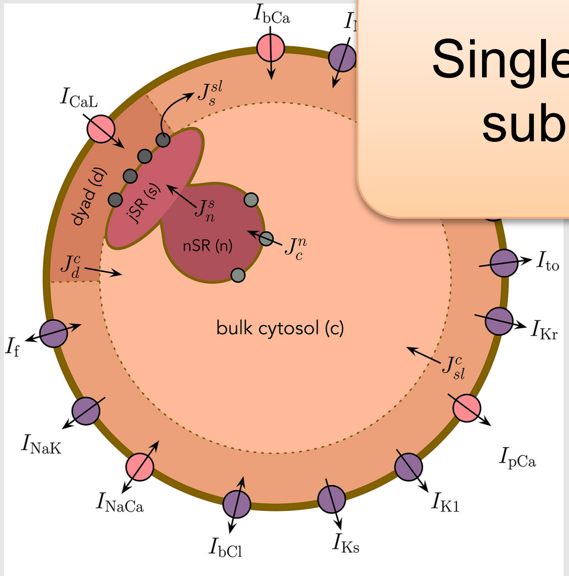
Blood flow



Valen-Sendstad, Khalili, Kjeldsberg

Mechanics

Finsberg, Sundnes, Wall



Single cells (and sub-cellular)

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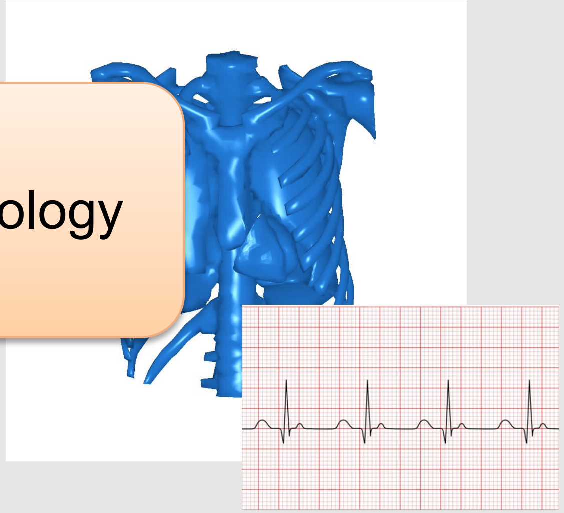
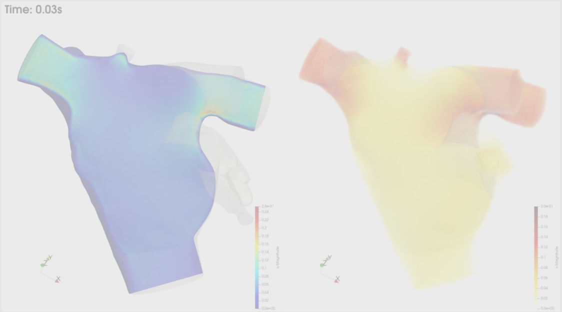


Electrophysiology

I am primarily work with cell-models, electrophysiology and mechanics

Blood flow



Valen-Sendstad, Khalili, Kjeldsberg

Mechanics

Finsberg, Sundnes, Wall

I am not a biologist

- 2014: Master: NTNU – Applied mathematics
- 2014-2017: PhD Scientific computing – Cardiac modeling (CaMO) at Simula – Patient specific computational modeling of cardiac mechanics
- 2017-2021: Research engineer
- 2021-present: Senior Research Engineer

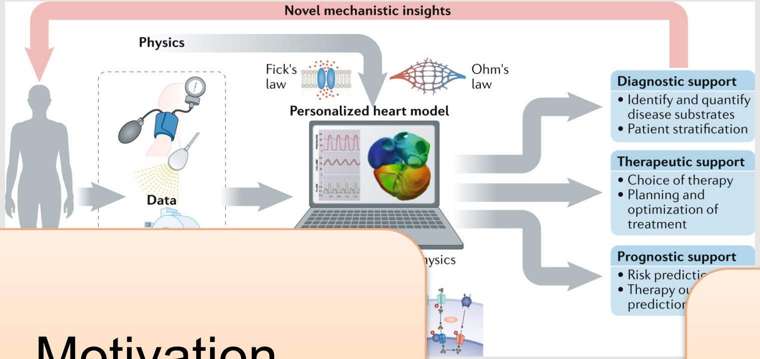
CENTER FOR CARDIOLOGICAL **INNOVATION**

Berkeley UNIVERSITY OF CALIFORNIA

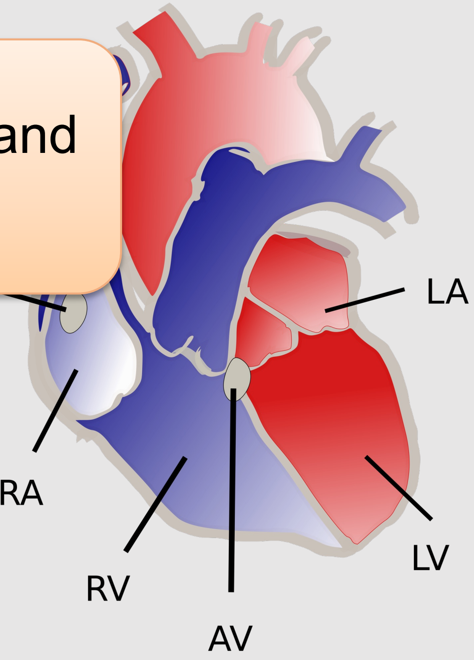
ORGANOS

SIM CARDIO TEST

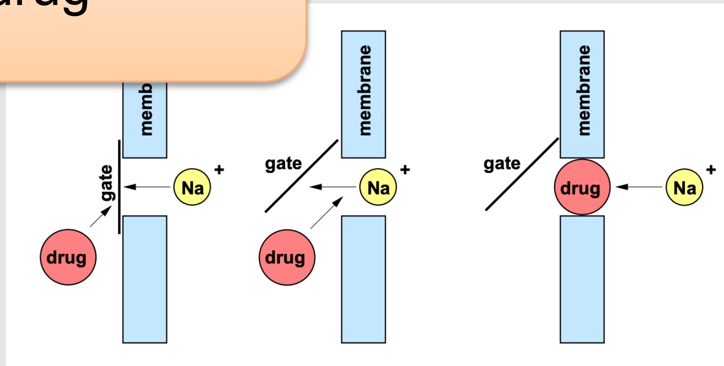
Motivation



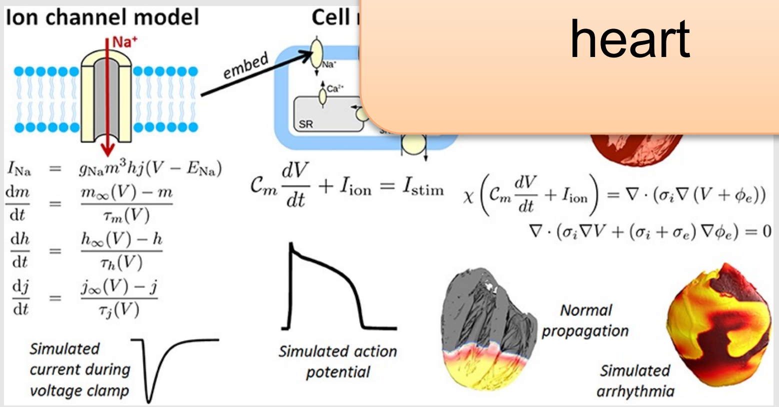
Basic anatomy and physiology



How to model a drug

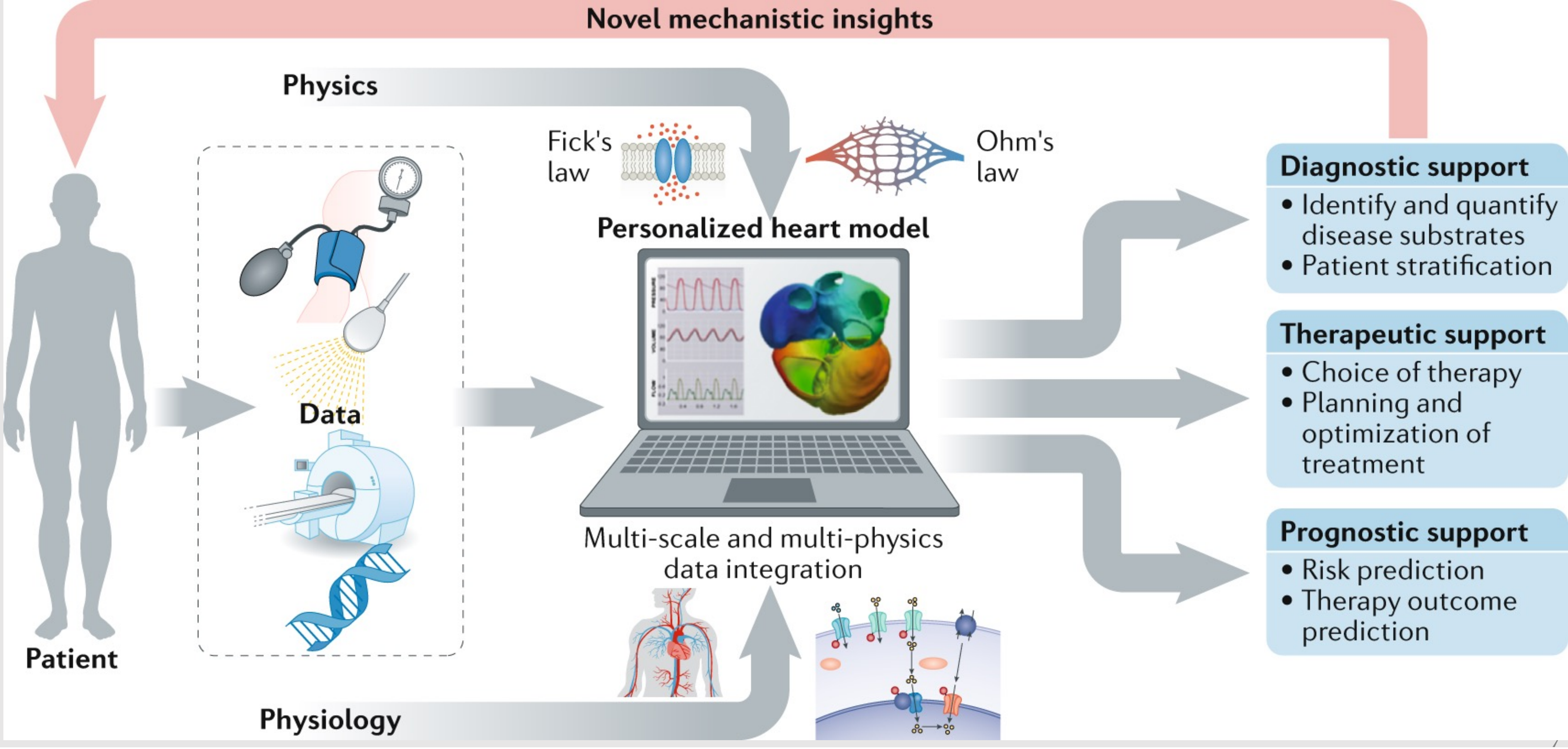


How to model the heart



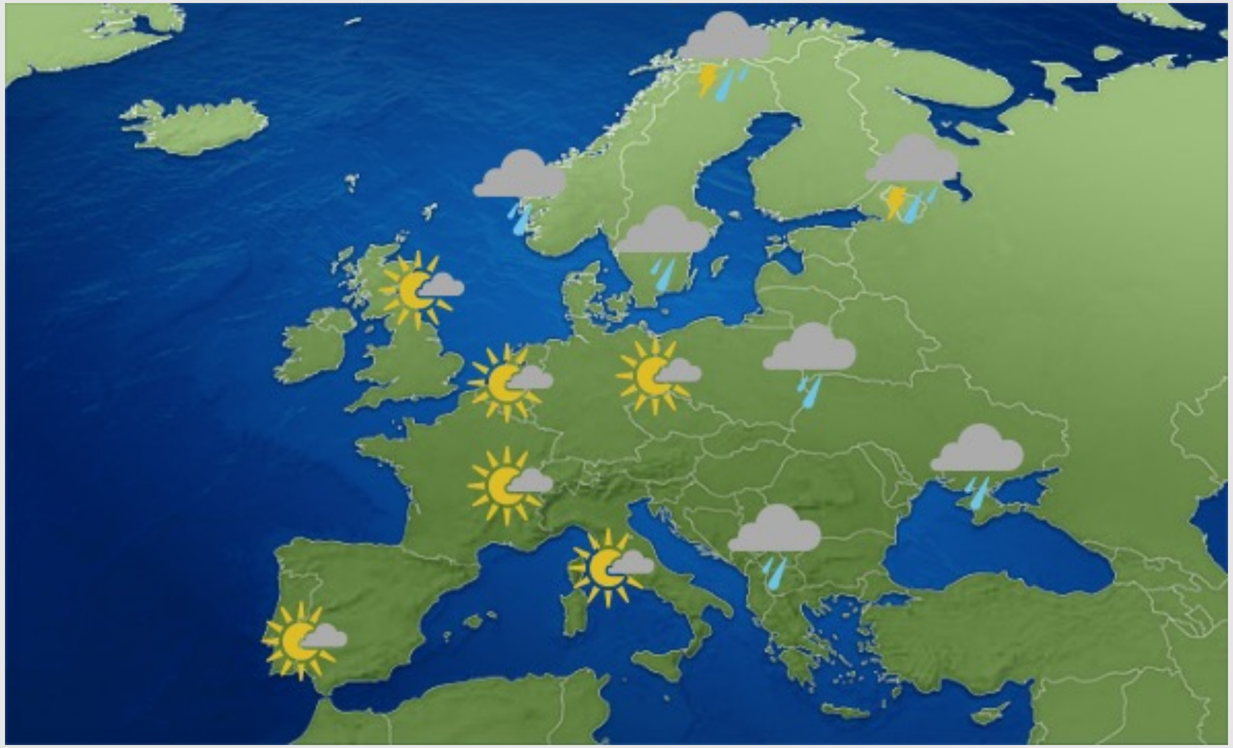
Which tools we use

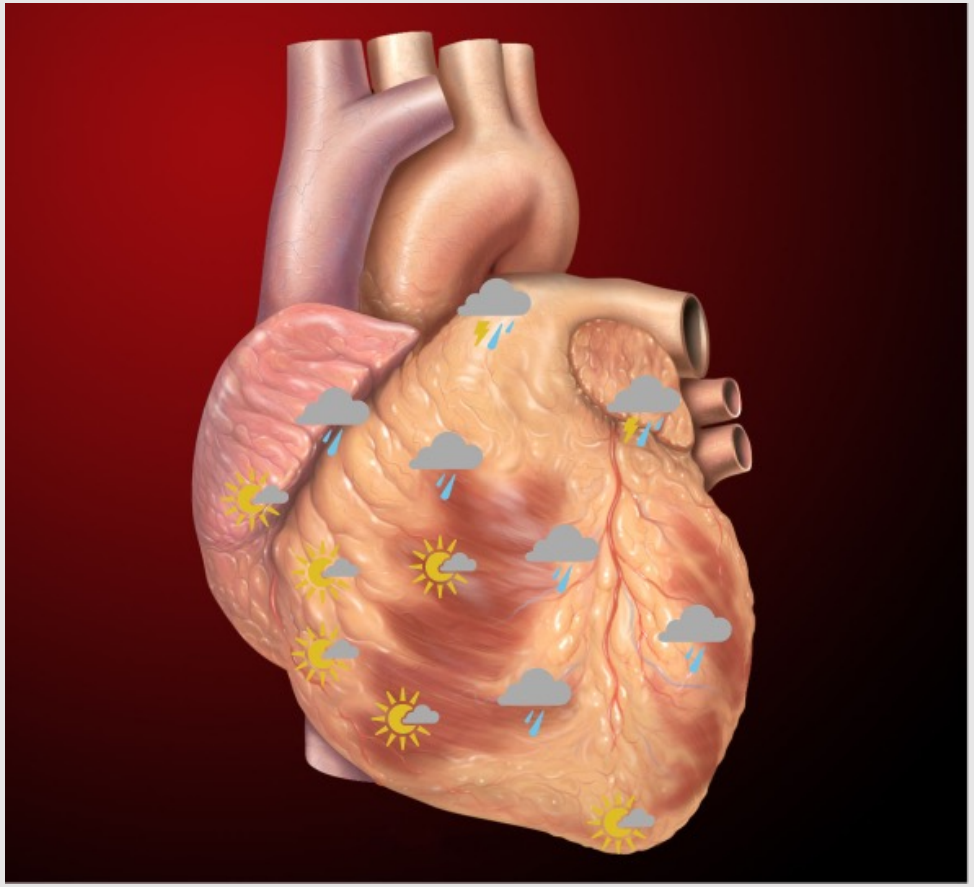
The long term goal is to use models to assist clinicians in the descision making



Niederer, Steven A., Joost Lumens, and Natalia A. Trayanova. "Computational models in cardiology." *Nature reviews cardiology* 16.2 (2019): 100-111.

We can forecast the weather, but would we be able to do the same with the heart?



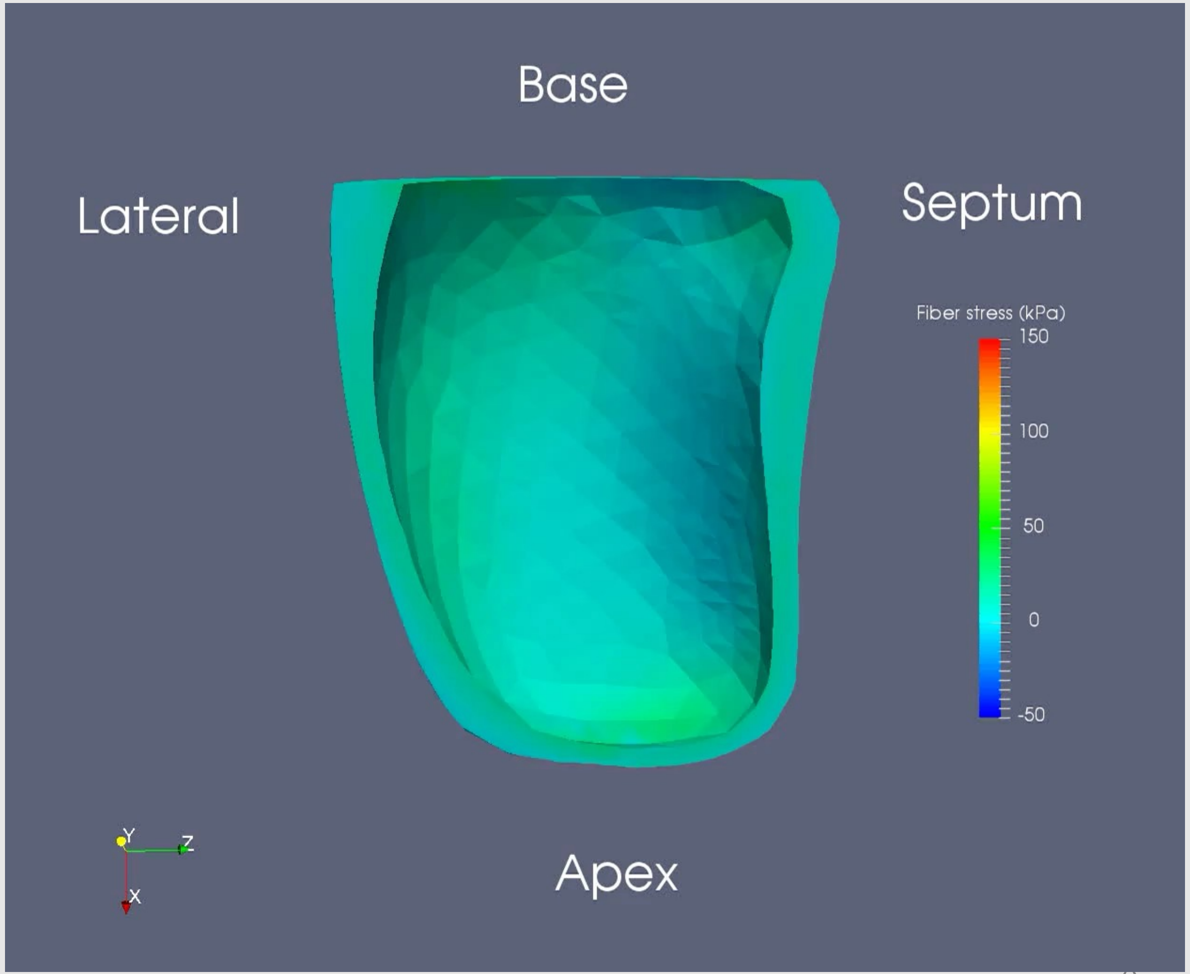


Models can be used to compute quatities that are difficult / impossible to measure

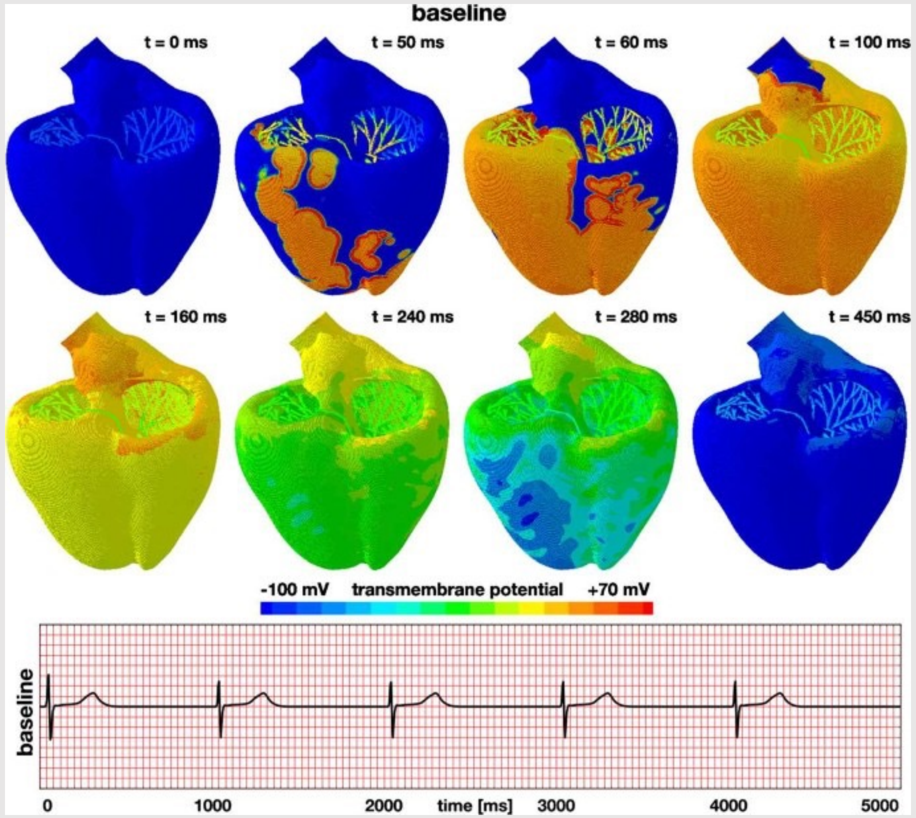
For example: forces / stresses in the heart

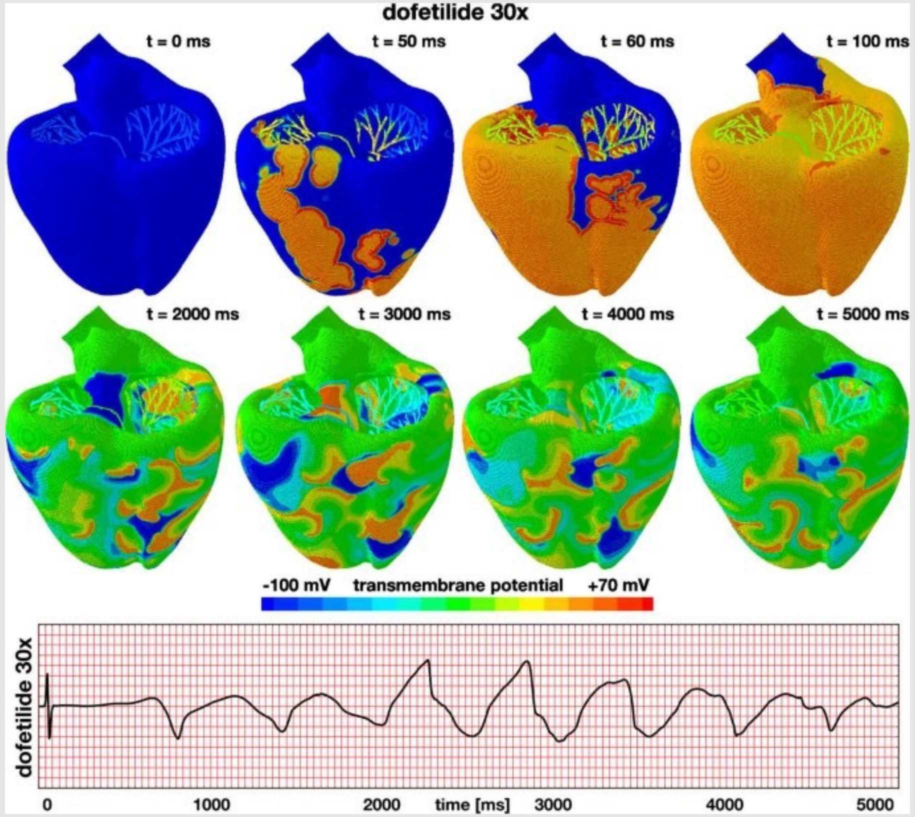
Validation is hard

Development of new biomarkers



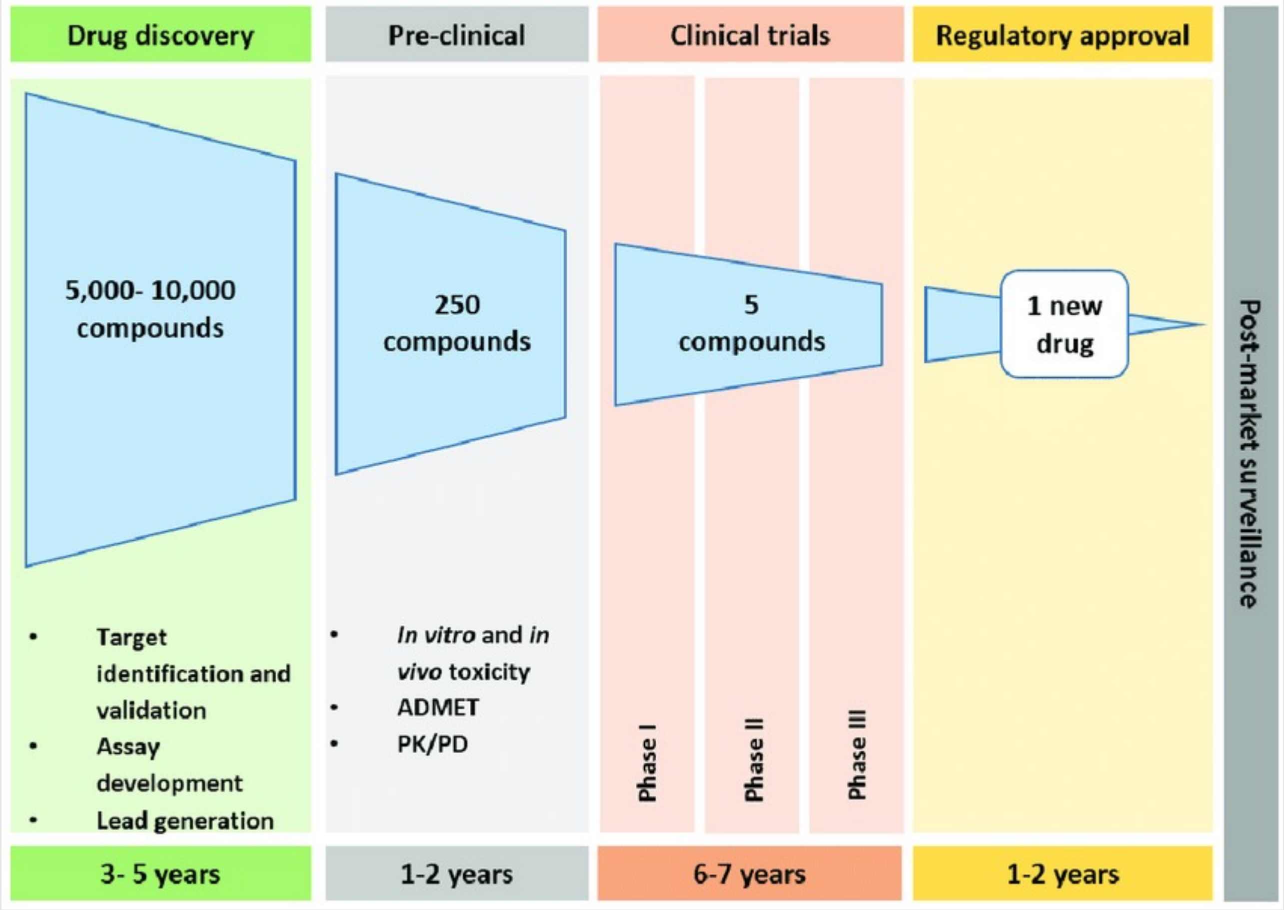
Models can be used to test if a drug is safe / efficient





Kügler, Philipp. "Modelling and simulation for preclinical cardiac safety assessment of drugs with human iPSC-derived cardiomyocytes." *Jahresbericht der Deutschen Mathematiker-Vereinigung* 122.4 (2020): 209-257.

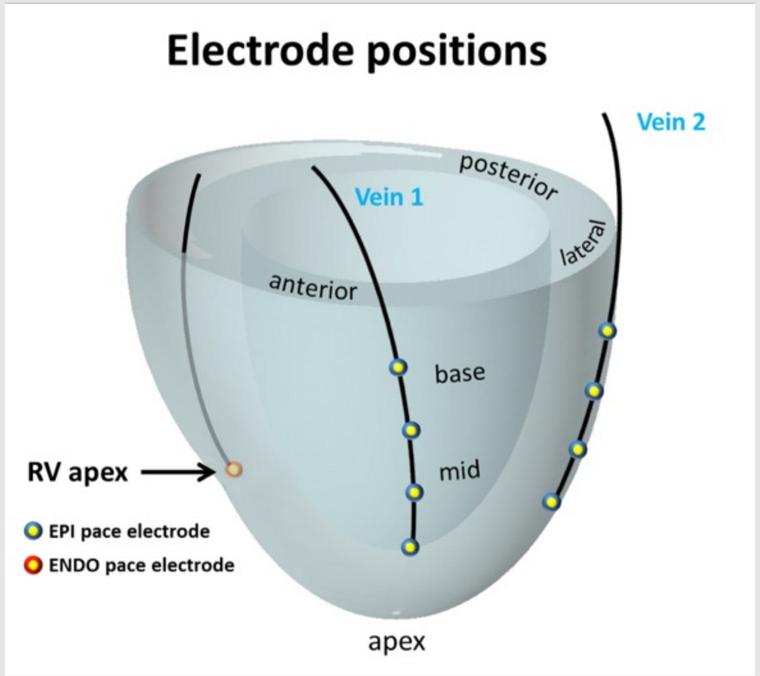
Development of drugs is a costly and time consuming process

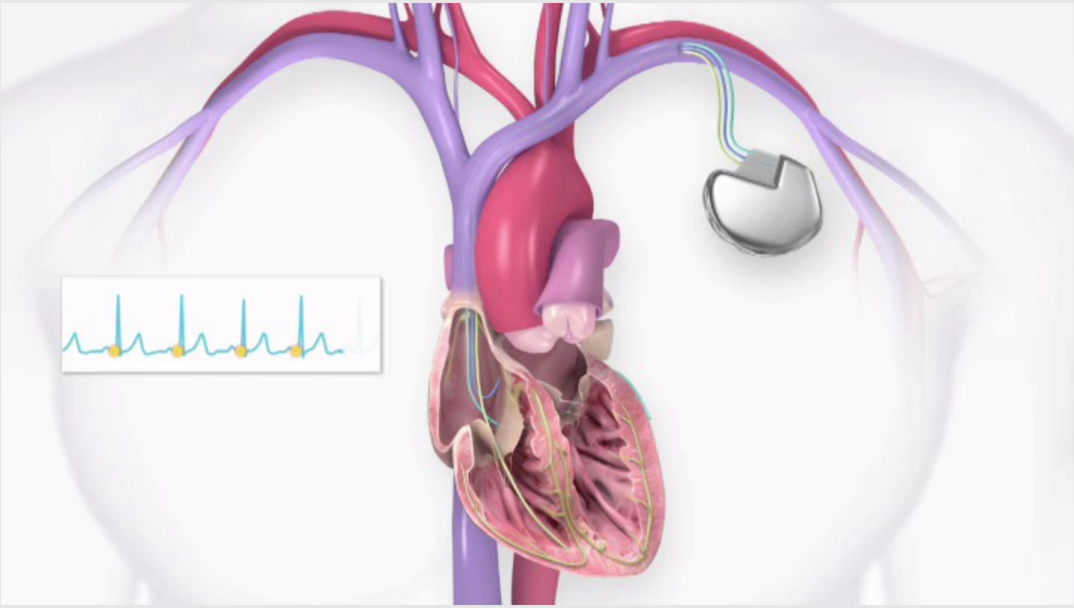


Matthews, Holly & Hanison, James & Nirmalan, Niroshini. (2016). "Omics"-Informed Drug and Biomarker Discovery: Opportunities, Challenges and Future Perspectives. Proteomes. 4. 2. 10.3390/proteomes4030028.

Models can be used to test different theraphies and optimize treatment

- Find optimal electrode positions for pacemakers





The heart has four chambers

SA: Sino Atrial node

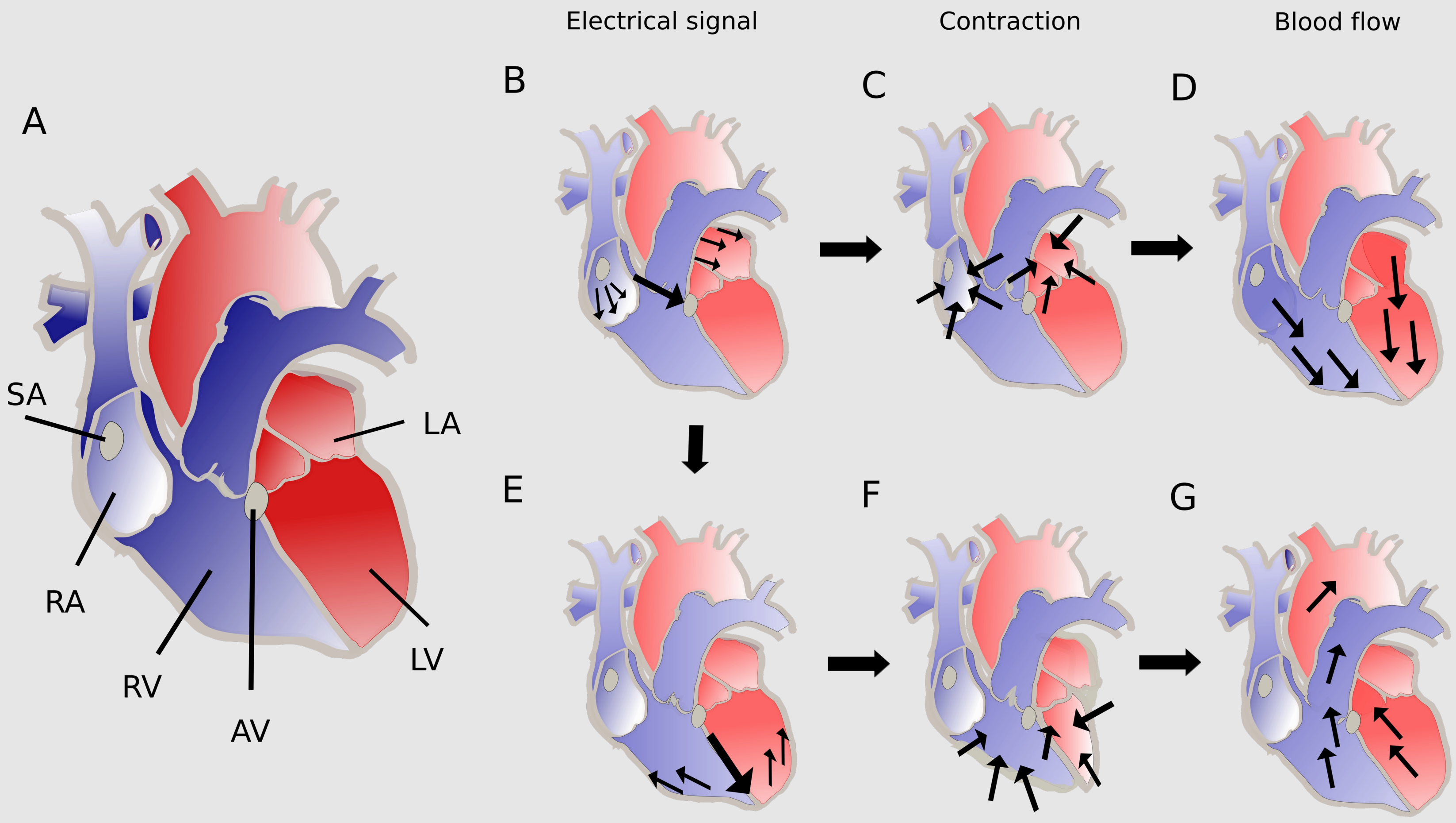
AV: Atrioventricular node

RA: Right Atrium

RV: Right ventricle

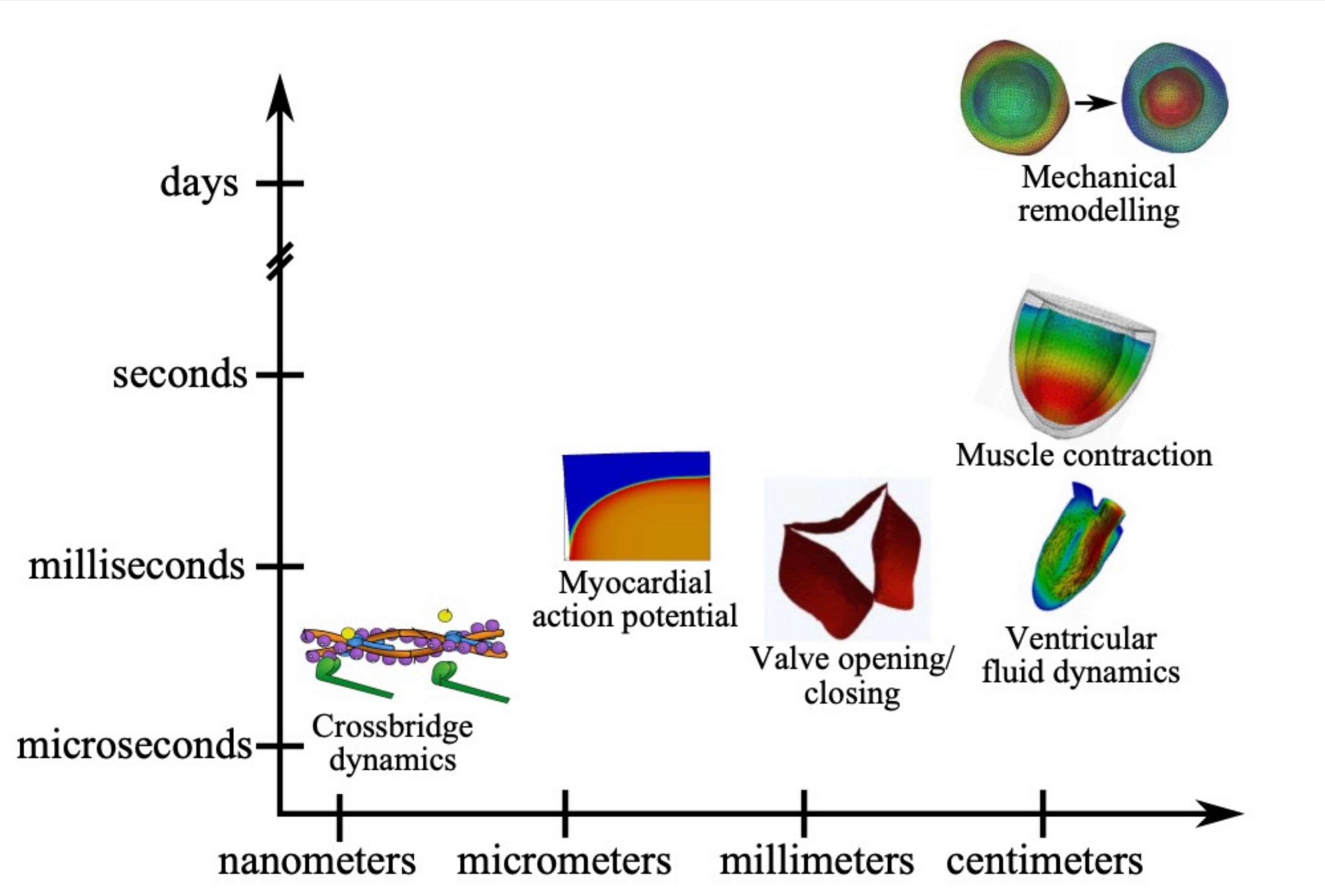
LA: Left Atrium

LV: Left ventricle



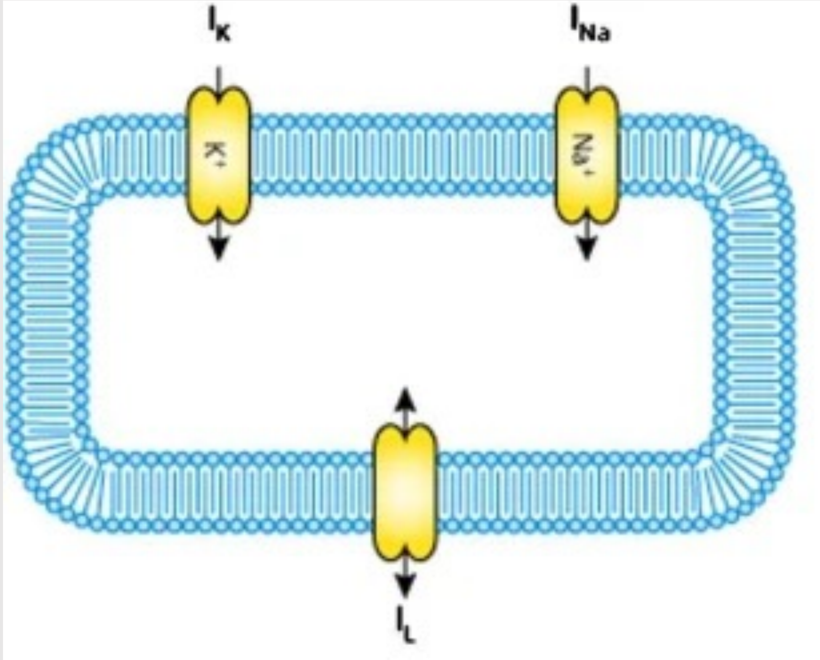
Telle, Åshild. "Modeling cardiac mechanics on a microscale: Mechanical modeling and analysis of cardiomyocytes and cardiac micromuscles." (2022).

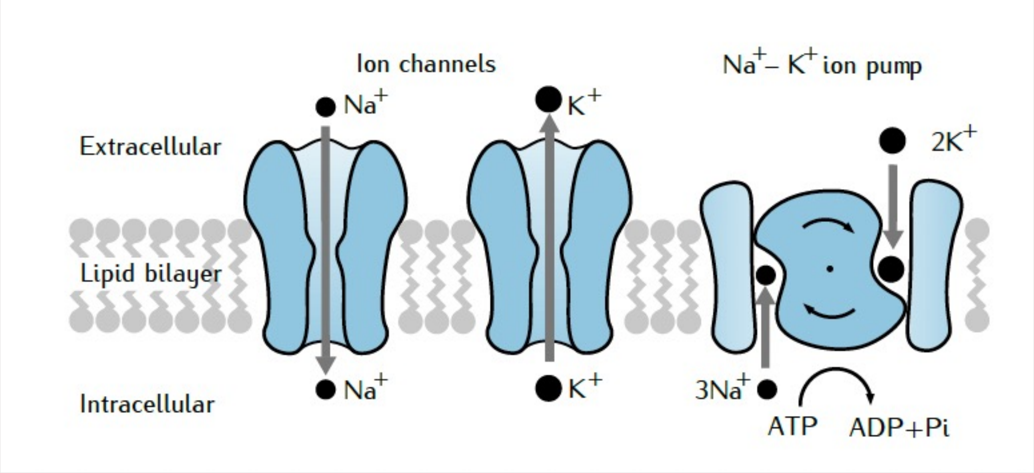
The heart is operating on different spatial and temporal scales



Quarteroni, Alfio, et al. "Integrated heart—coupling multiscale and multiphysics models for the simulation of the cardiac function." *Computer Methods in Applied Mechanics and Engineering* 314 (2017): 345-407.

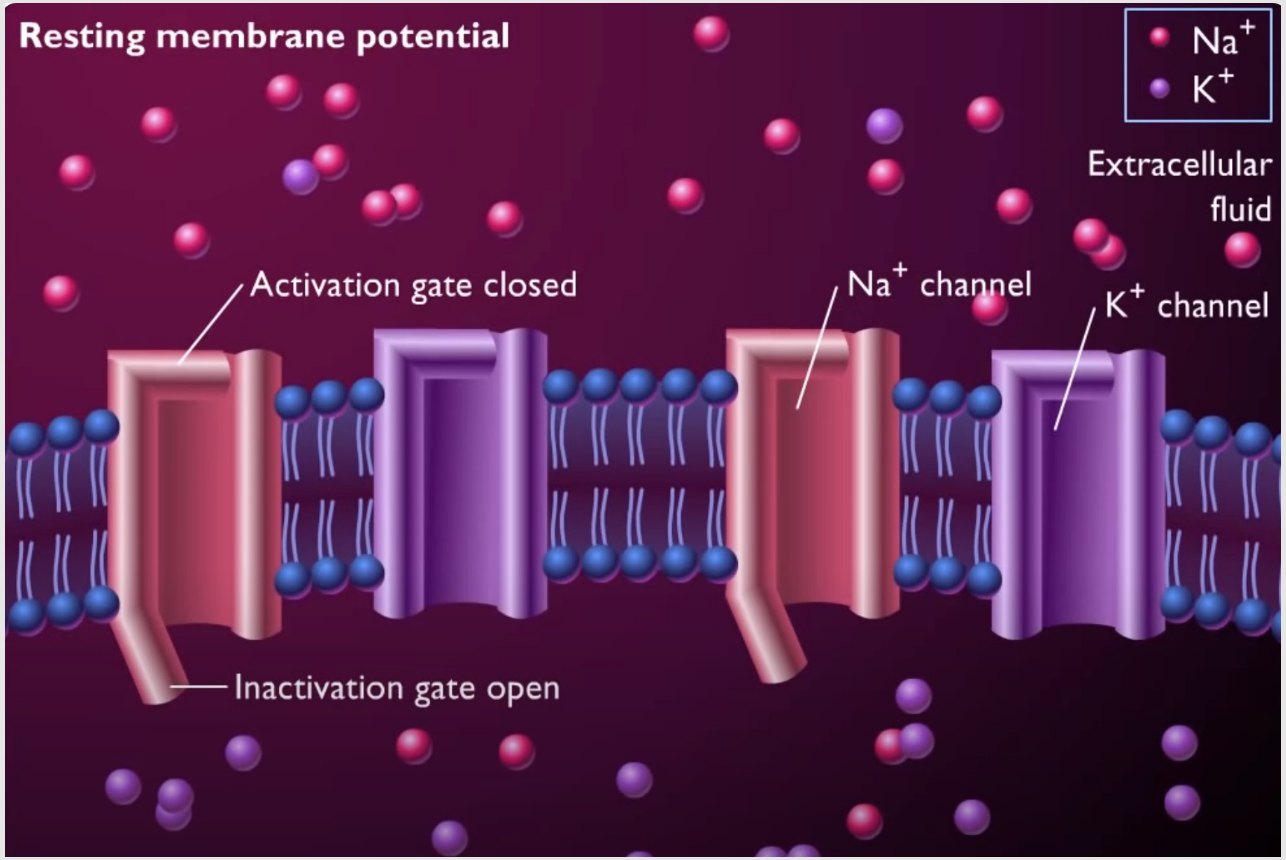
A cell consits of two spaces separated by a membrane





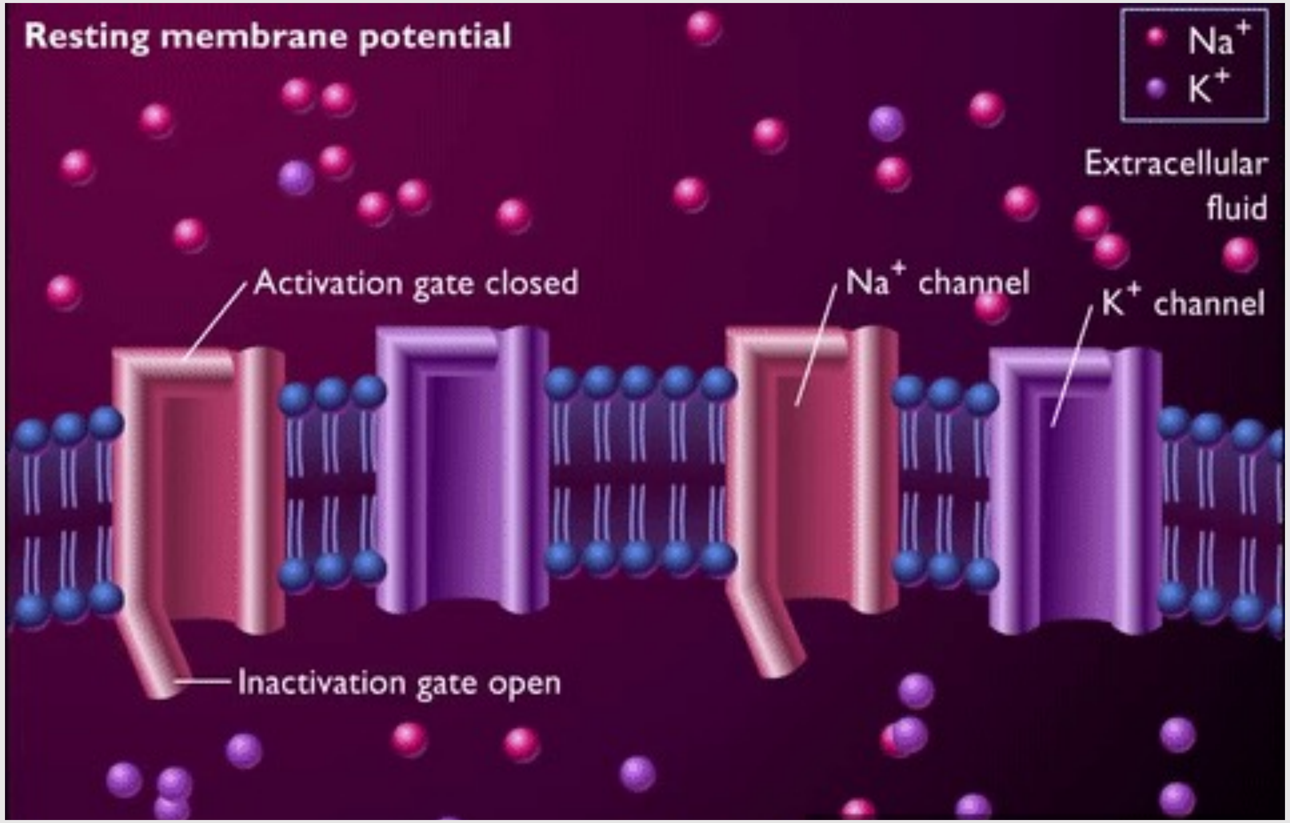
Ions can flow through specialized channels than can open and close in response to changes in voltage

A single ion channel can be open or closed by one or more gates



https://www.youtube.com/watch?v=kxnb_TSqmFY&t=2s

A single ion channel can be open or closed by one or more gates



https://www.youtube.com/watch?v=kxnb_TSqmFY&t=2s

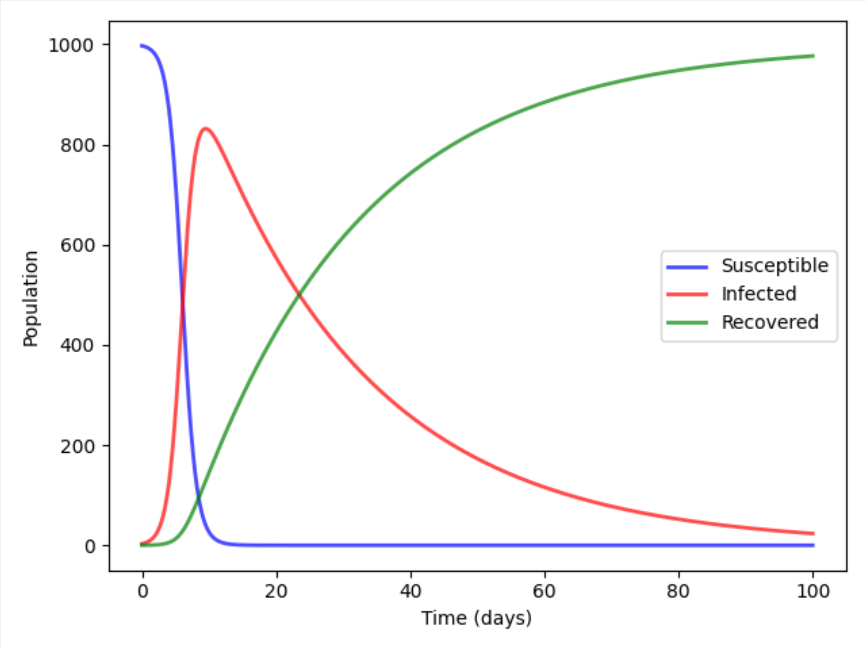
We can model a single cardiac cell using a system of ordinary differential equations (ODE)

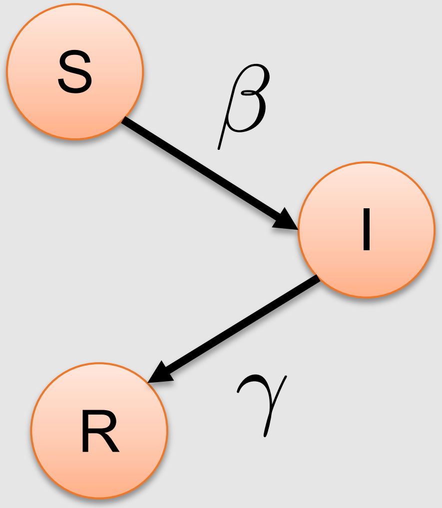
- An system of ordinary differential equation described how a variables changes over time
- For example a pandemic (using the SIR model)

$$\frac{dS}{dt} = -\beta S I$$

$$\frac{dI}{dt} = \beta S I - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$





To solve the ODEs we use General Ode TRANslator (Gotran(x))

- Domain Specific Language (DSL) for ODEs
- Describe ODEs in DSL
- Generate code in different programming languages for solving

https://github.com/finsberg/gotranx

https://github.com/ComputationalPhysiology/gotran

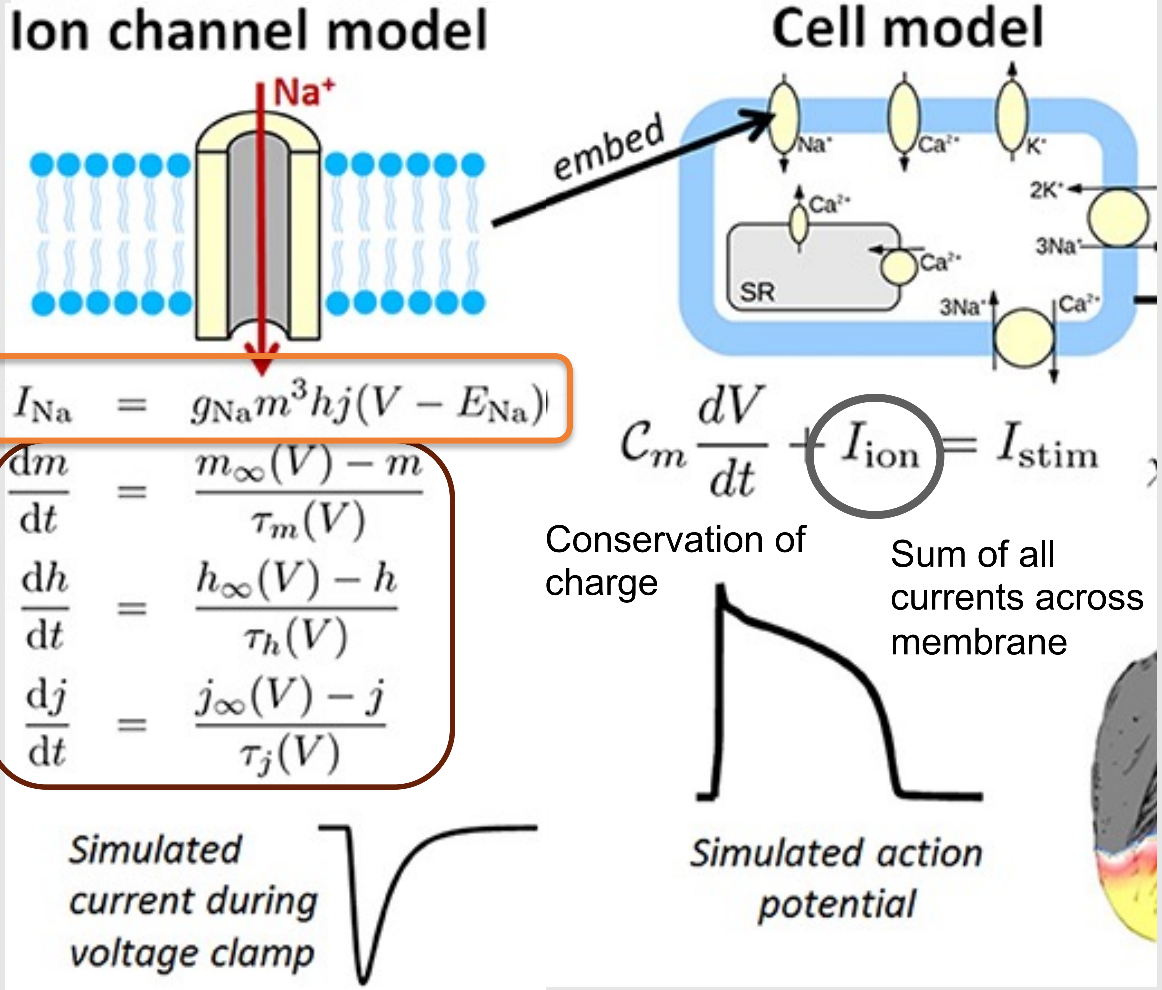
sandbox > sir > sir.ode

```
parameters(
        beta=0.001,
        gamma=0.04
)

states(
        S=997,
        I=3,
        R=0
)

dS_dt = -beta * S * I
dI_dt = beta * S * I - gamma * I
dR_dt = gamma * I
```

Typical state variables are ionic concentrations, state that controls channel opening and the voltage



Total current through one channel

Variables determining wether a channel is open or closed

Conservation of charge

Sum of all currents across membrane

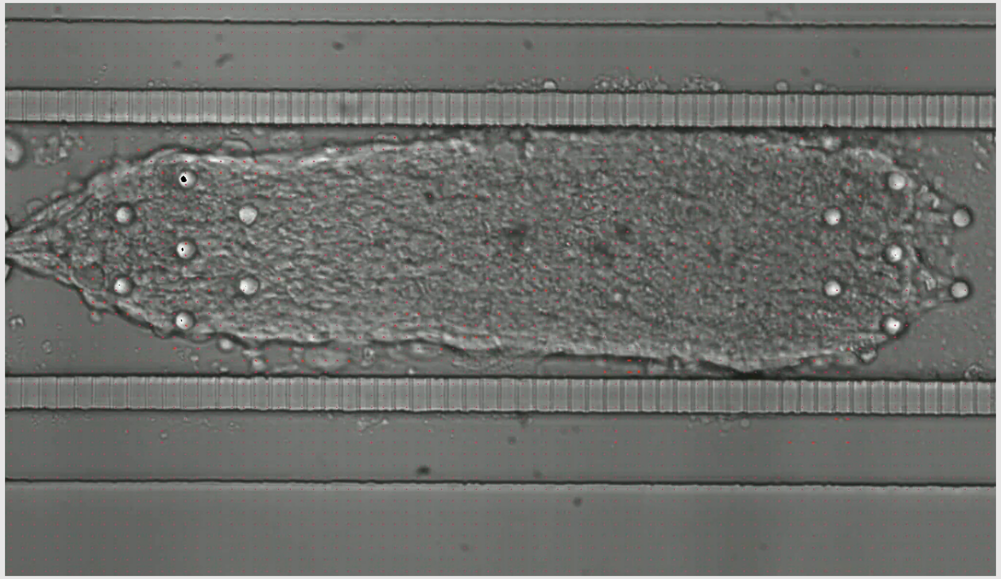
Nguyen, Thanh Danh, Olufemi E. Kadri, and Roman S. Voronov. "An introductory overview of image-based computational modeling in personalized cardiovascular medicine." *Frontiers in Bioengineering and Biotechnology* 8 (2020): 529365.

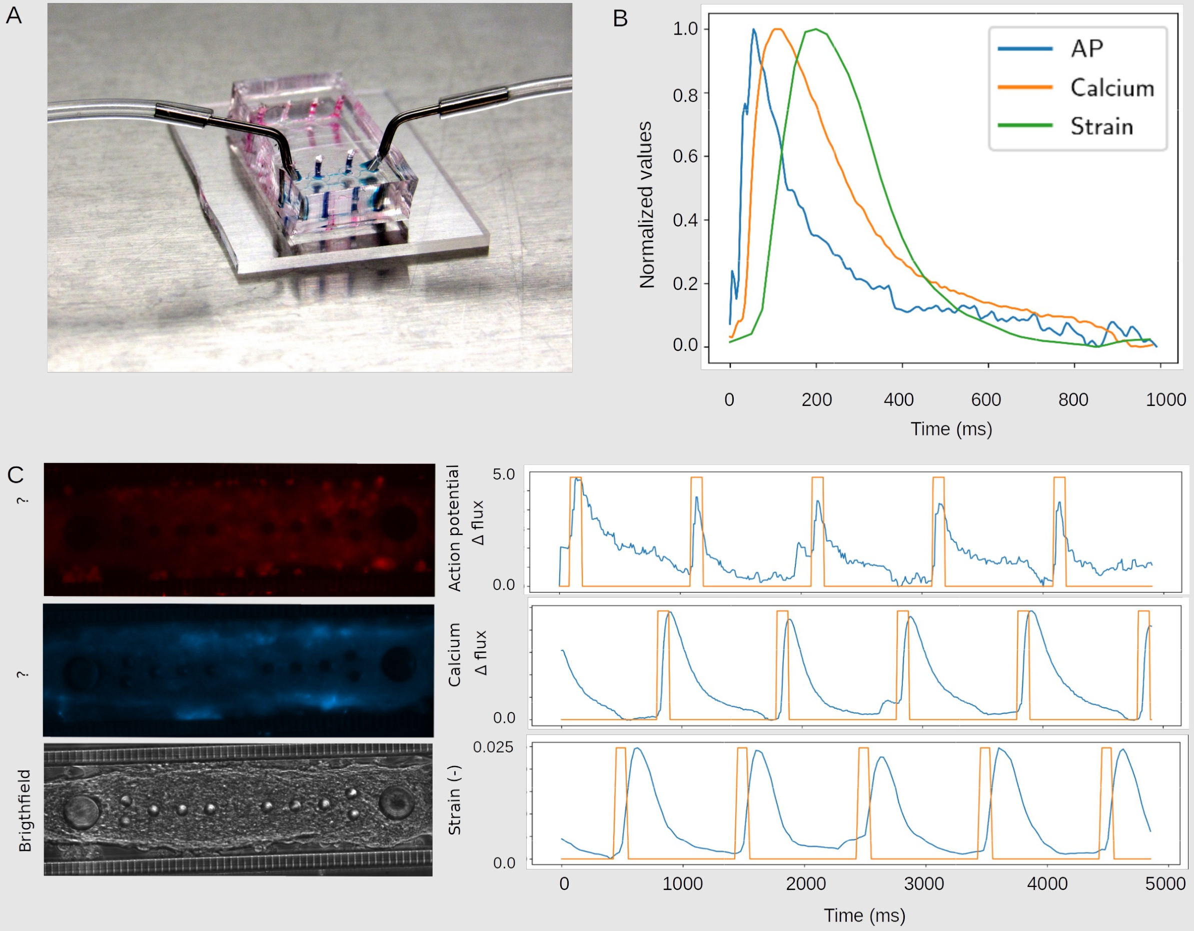
How can we determine model parameters?

- For example we need to determine the conductance for each channel

$$I_{\mathrm{Na}} = g_{\mathrm{Na}} m^3 h j (V - E_{\mathrm{Na}})$$

We can use data from optical measurements



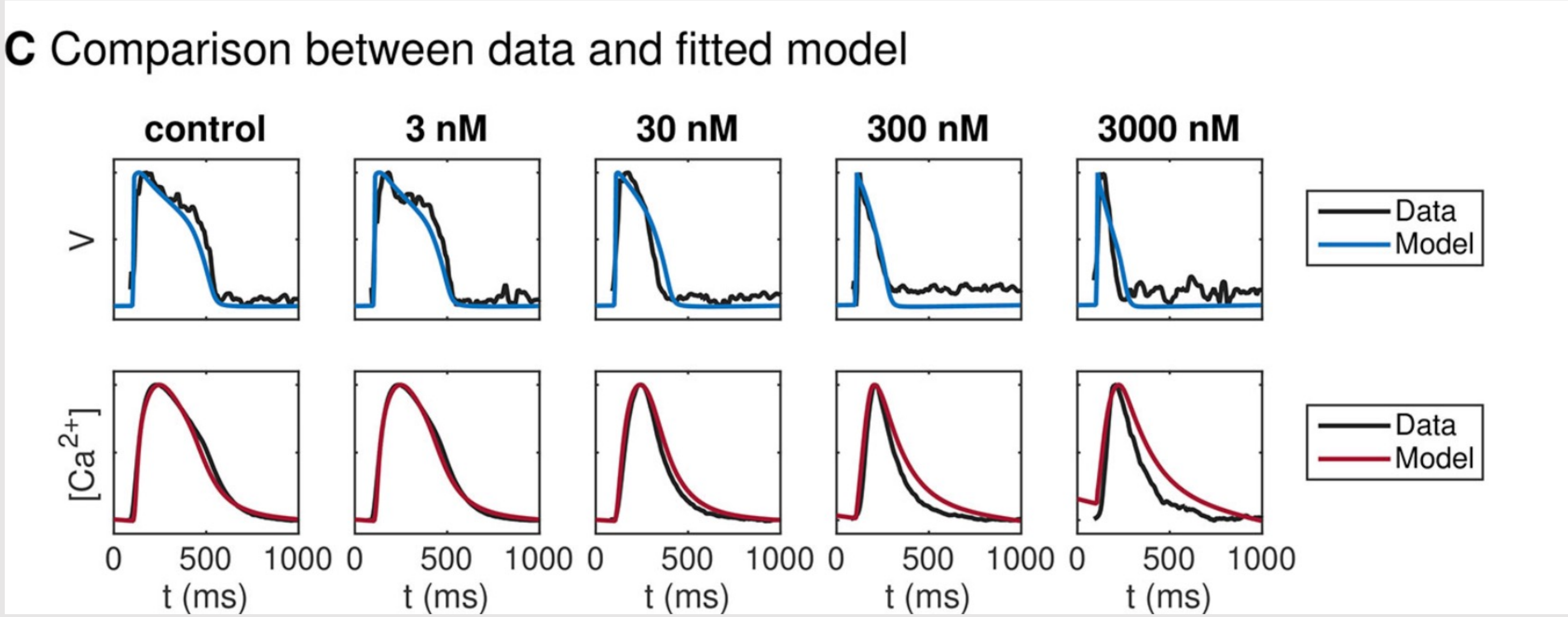


We can mesure the membrane potential and calcium concentration inside the cell using optics

Telle, Åshild. "Modeling cardiac mechanics on a microscale: Mechanical modeling and analysis of cardiomyocytes and cardiac micromuscles." (2022).

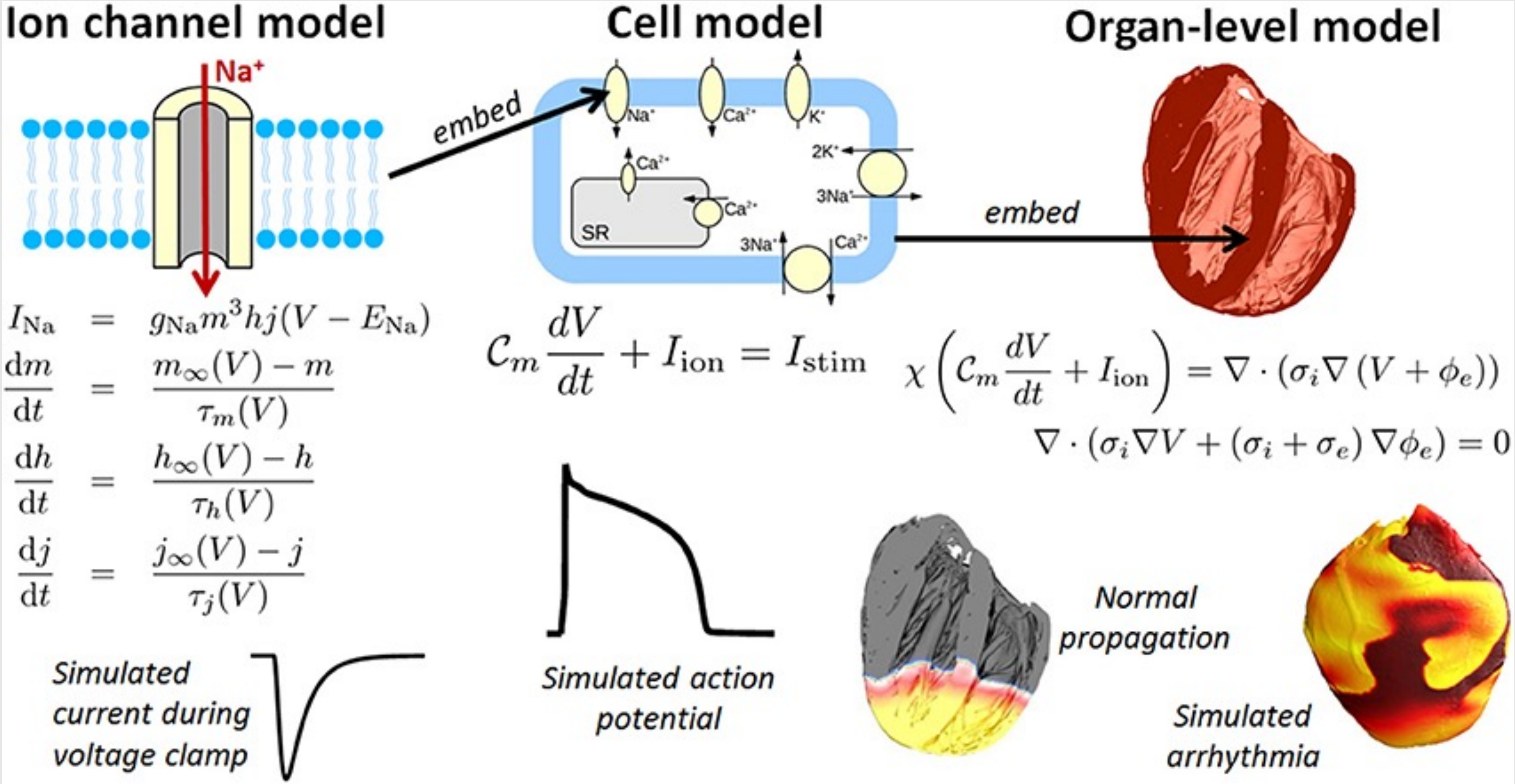
We select a few parameters in the model and tune them to fit data

$$I_{\text{Na}} = g_{\text{Na}} m^3 hj(V - E_{\text{Na}})$$



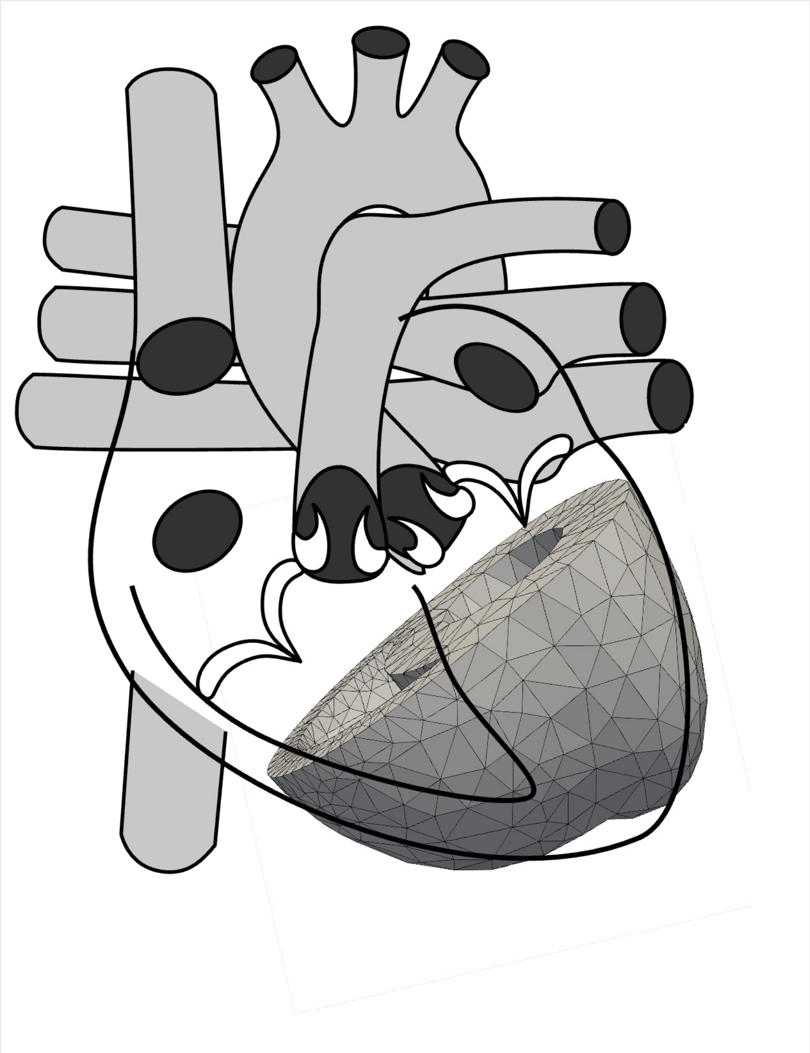
Jæger, Karoline Horgmo, et al. "Improved computational identification of drug response using optical measurements of human stem cell derived cardiomyocytes in microphysiological systems." *Frontiers in Pharmacology* 10 (2020): 498937.

We embed the cell model into the organ-level model by having one different cell in each point

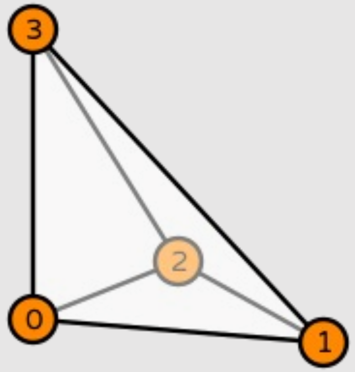


Nguyen, Thanh Danh, Olufemi E. Kadri, and Roman S. Voronov. "An introductory overview of image-based computational modeling in personalized cardiovascular medicine." *Frontiers in Bioengineering and Biotechnology* 8 (2020): 529365.

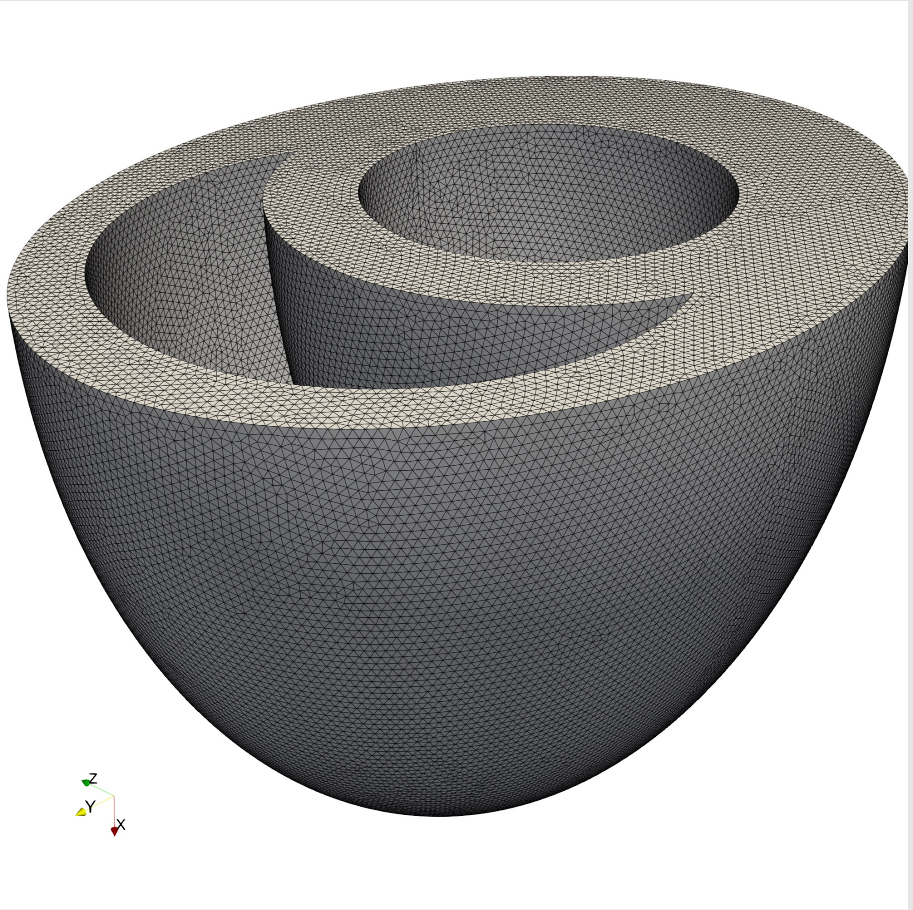
We discretize the geometry into tetraheadra and assign one heart cell to each node



https://gmsh.info

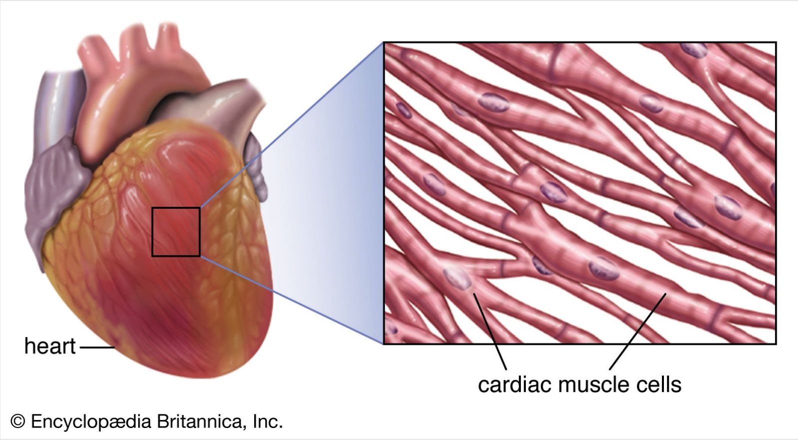


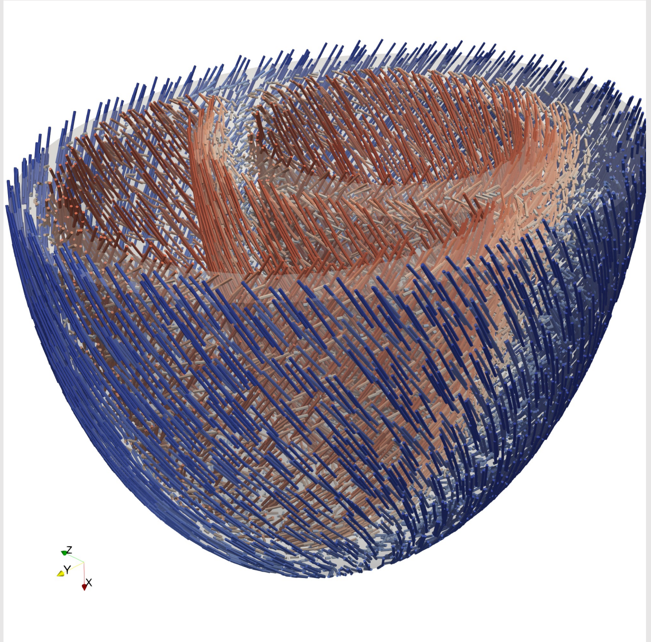
https://defelement.com/elements/lagrange.html



https://github.com/ComputationalPhysiology/cardiac_geometries

We also need vectors that assigns the direction of the muscle fibers in the heart

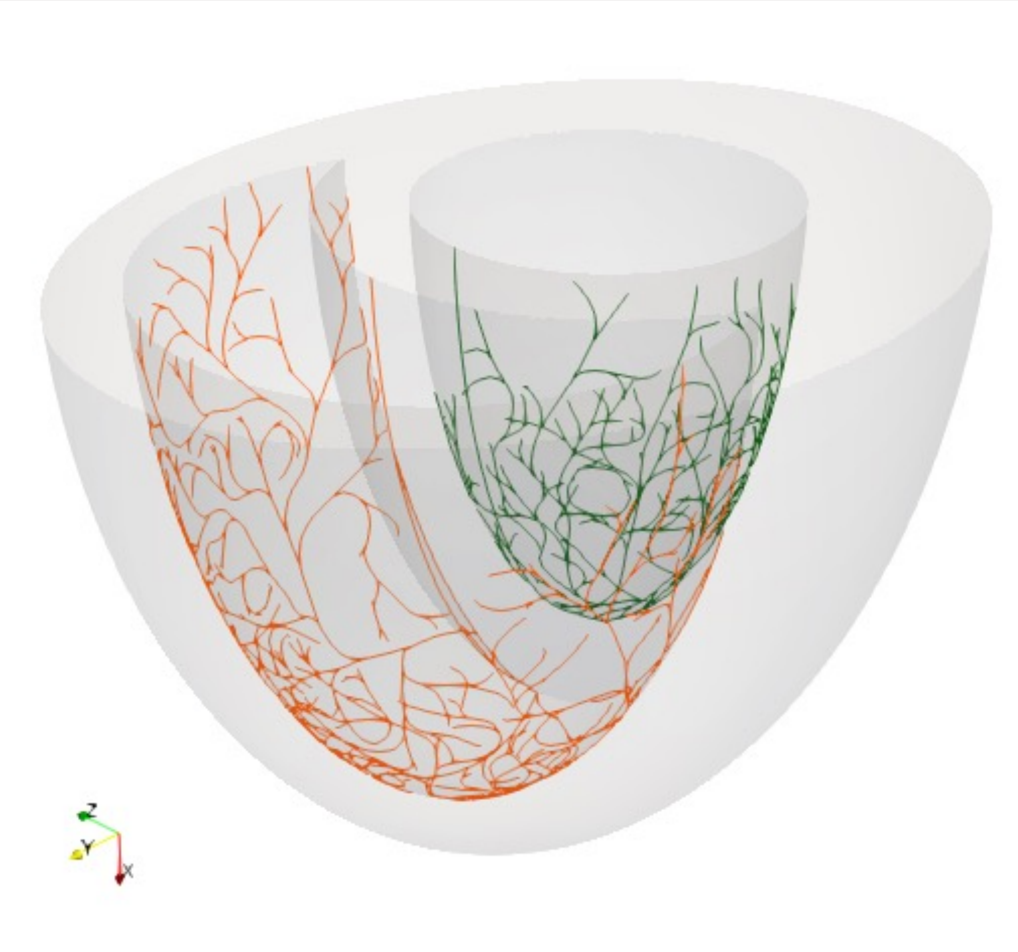


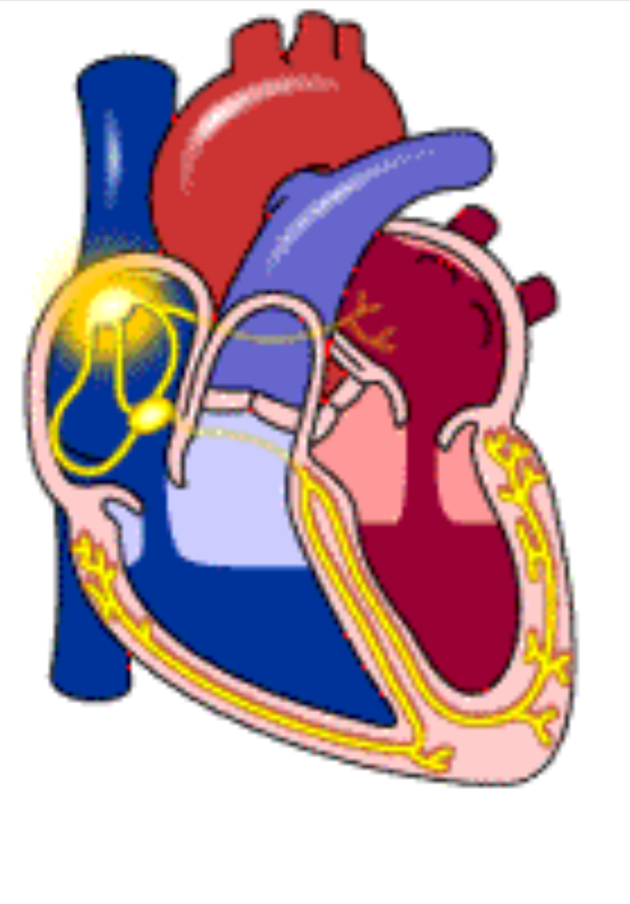


https://github.com/finsberg/ldrb

- Electrical current travels faster along the fibers
- Heart tissue is stiffer along the fibers
- The tissue contracts in the direction of the fibers

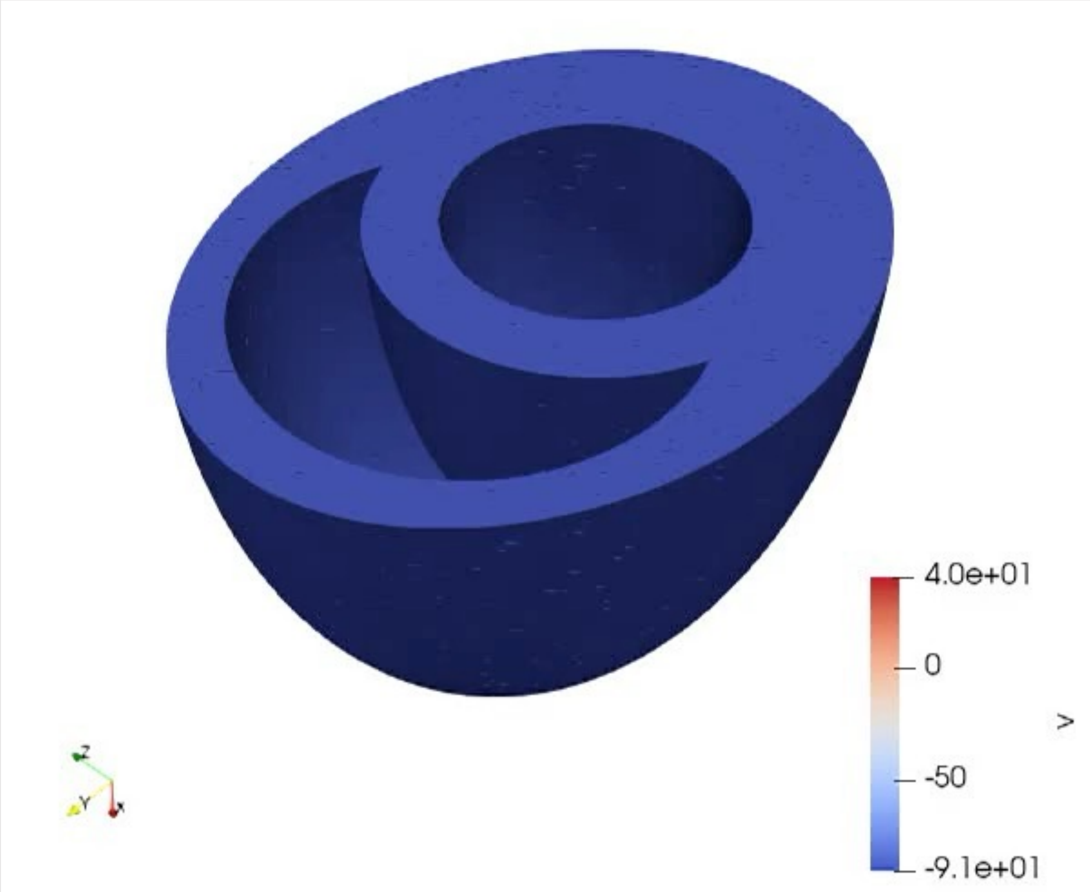
The heart tissue is stimulated by specialized cells (called purkinje cells) where the conduction is faster

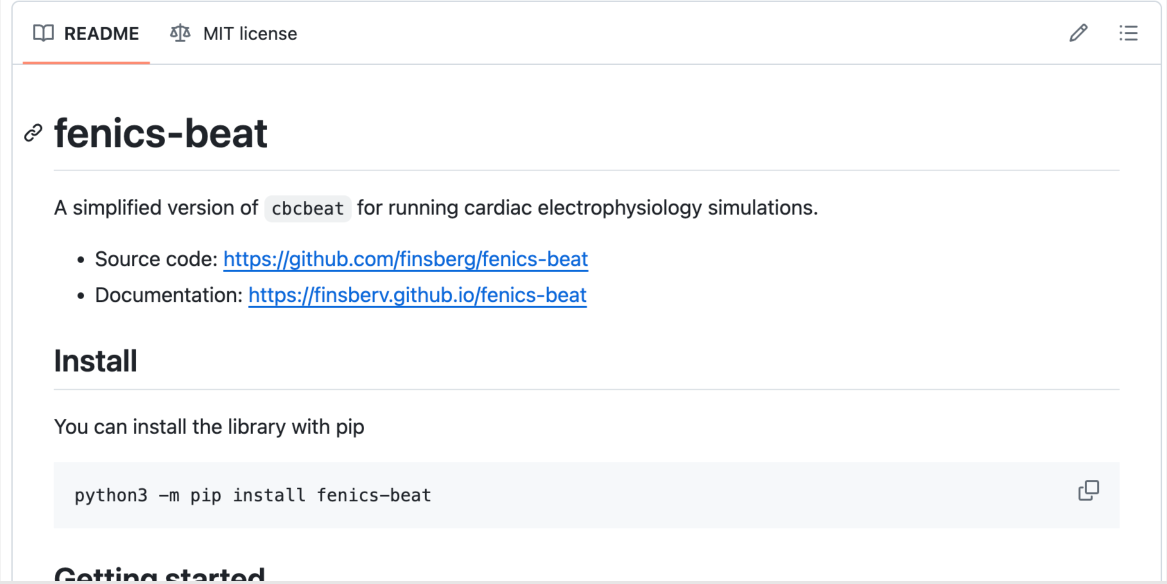




https://github.com/finsberg/fractal-tree

Now we can simulate the electrical propagation





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fenics-beat

A simplified version of `cbcbeat` for running cardiac electrophysiology simulations.

- Source code: https://github.com/finsberg/fenics-beat
- Documentation: https://finsberv.github.io/fenics-beat

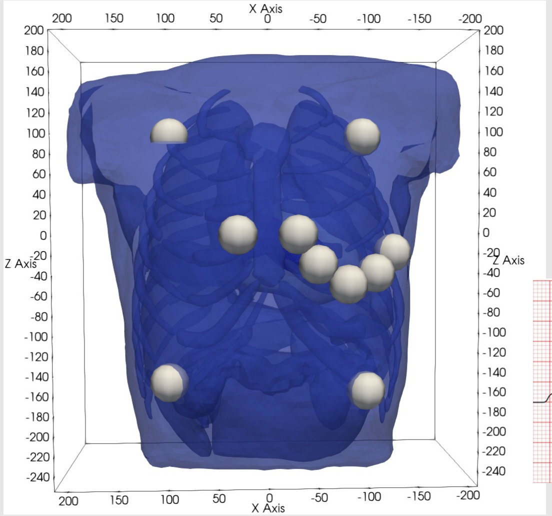
Install

You can install the library with pip

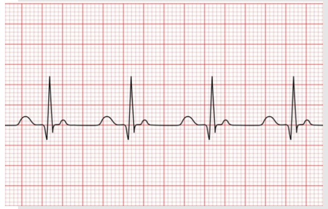
```
python3 -m pip install fenics-beat
```

Getting started

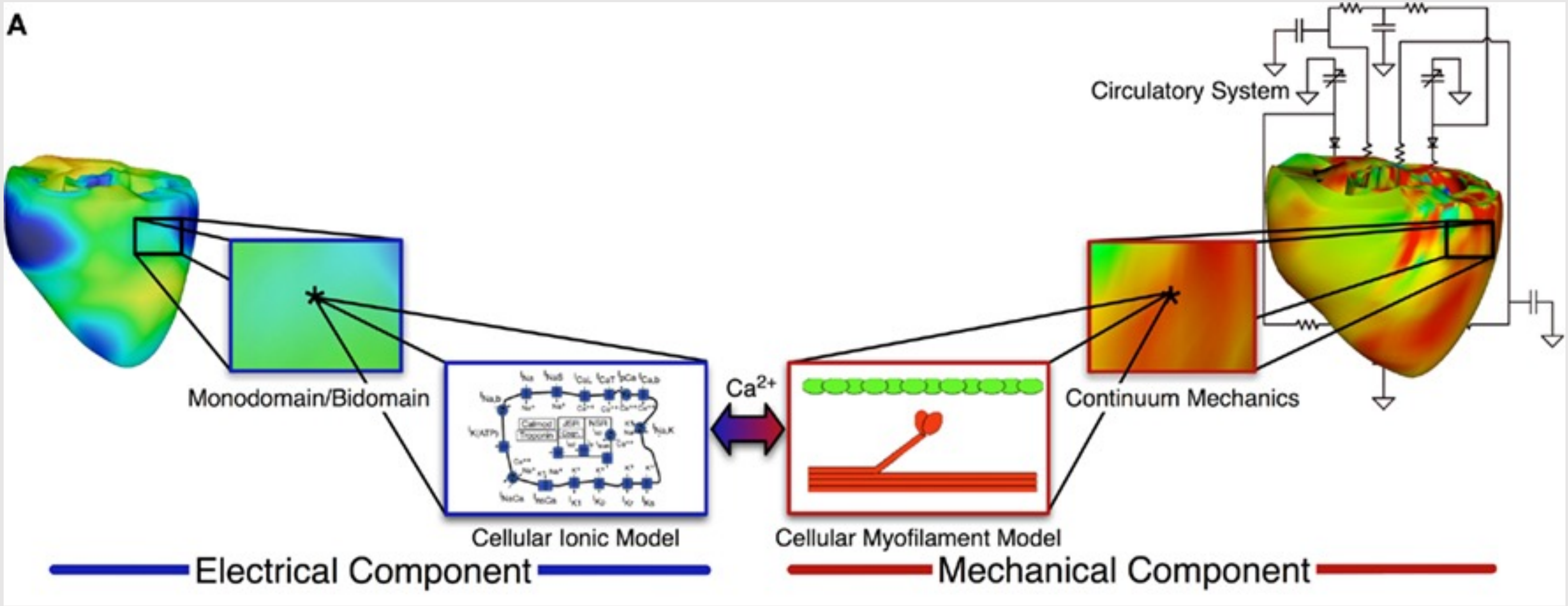
https://github.com/finsberg/fenics-beat



And Compute ECG

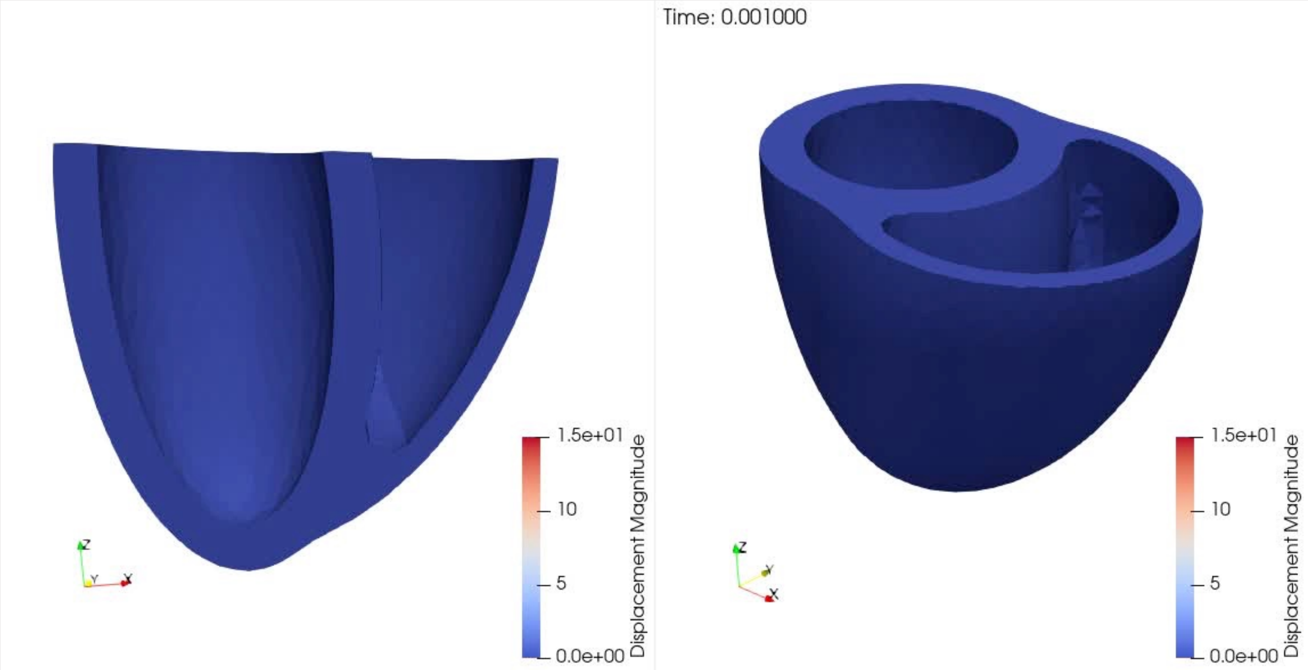


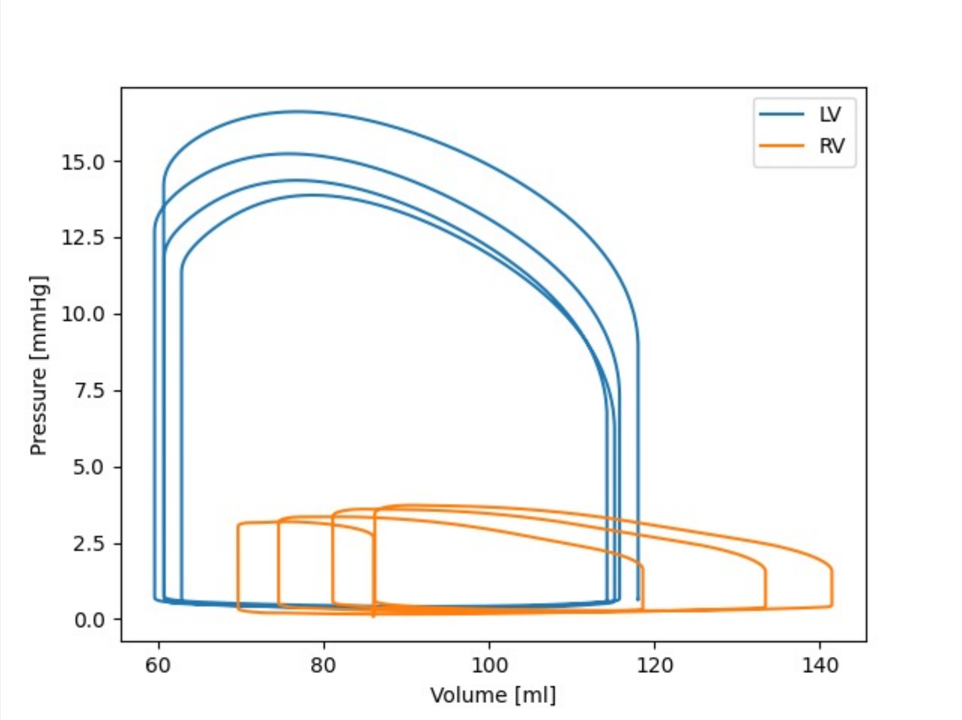
From the electrical model we can compute the calcium concentration which drives the mechanics



Trayanova, Natalia A., and John Jeremy Rice. "Cardiac electromechanical models: from cell to organ." *Frontiers in physiology* 2 (2011): 43.

And we can use this to simulate a beating heart

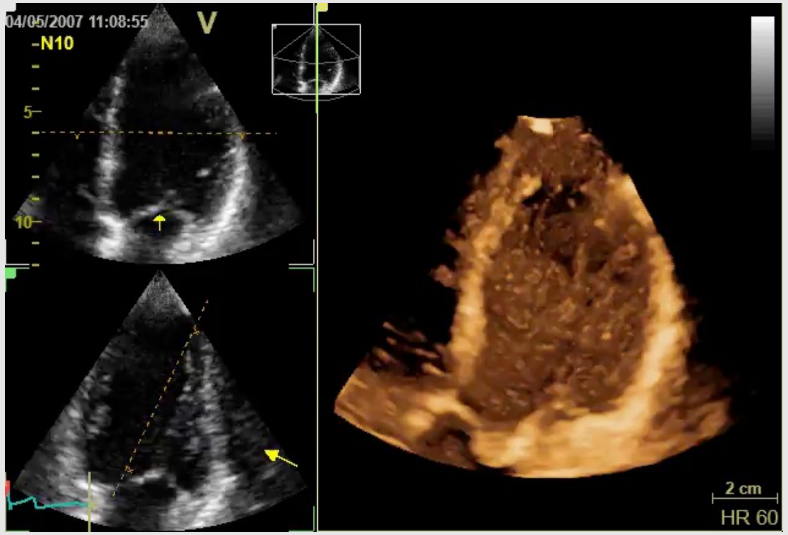




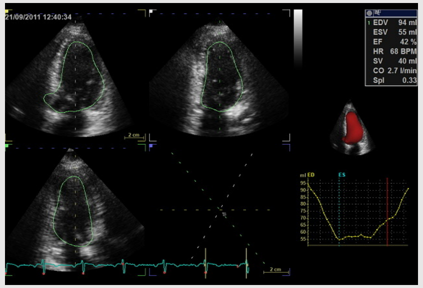
https://github.com/marchirschvogel/ambit/tree/master
https://github.com/finsberg/pulse

Plot of Pressure vs Volume inside the two chambers

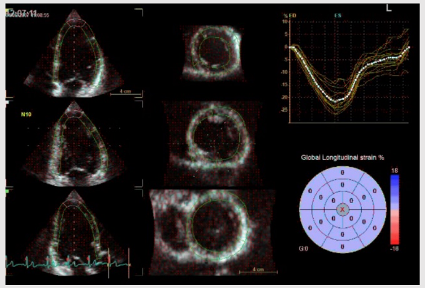
My PhD was about building patient specific computational models of the heart

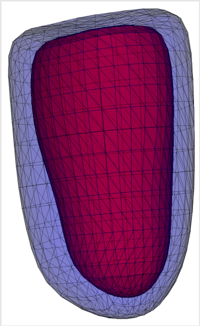


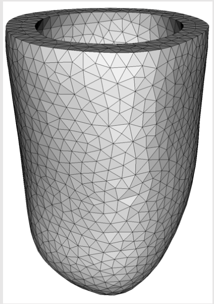
Volume

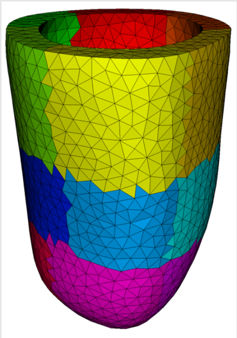


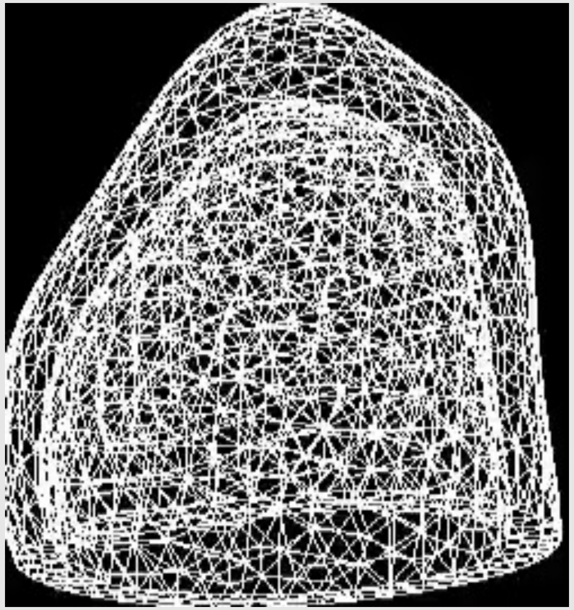
Regional strain



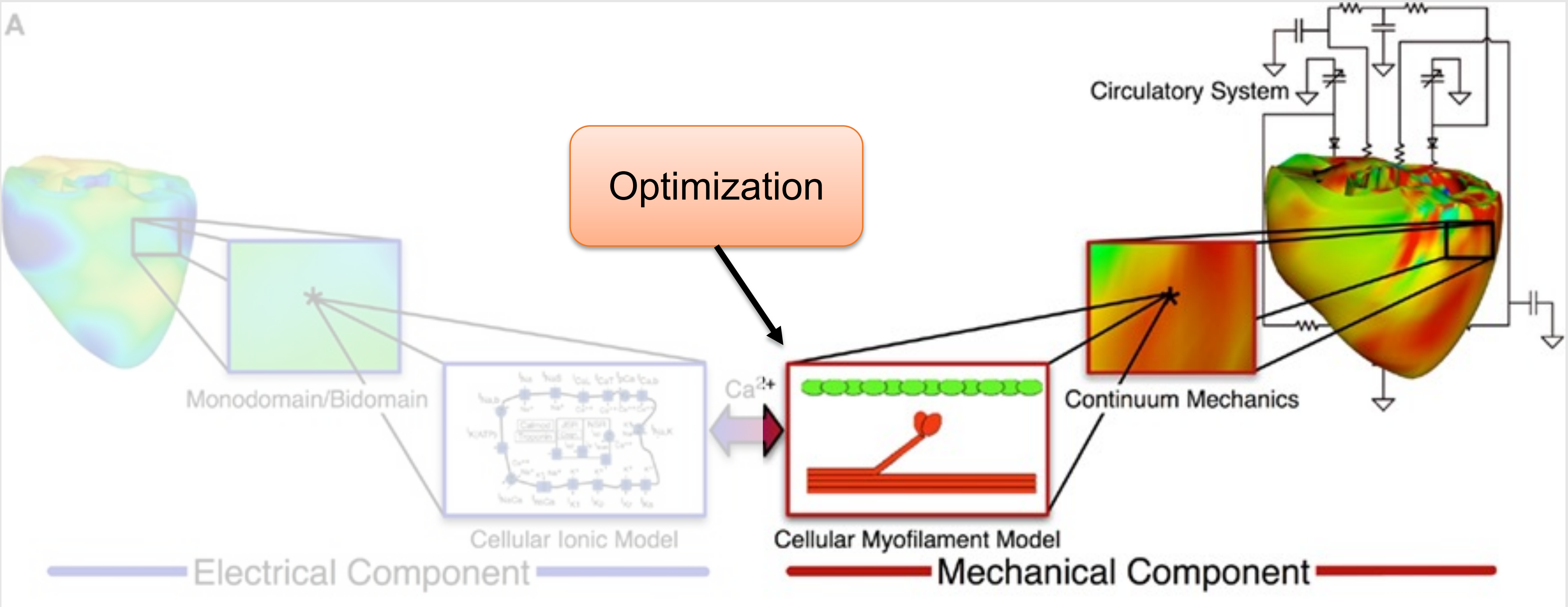






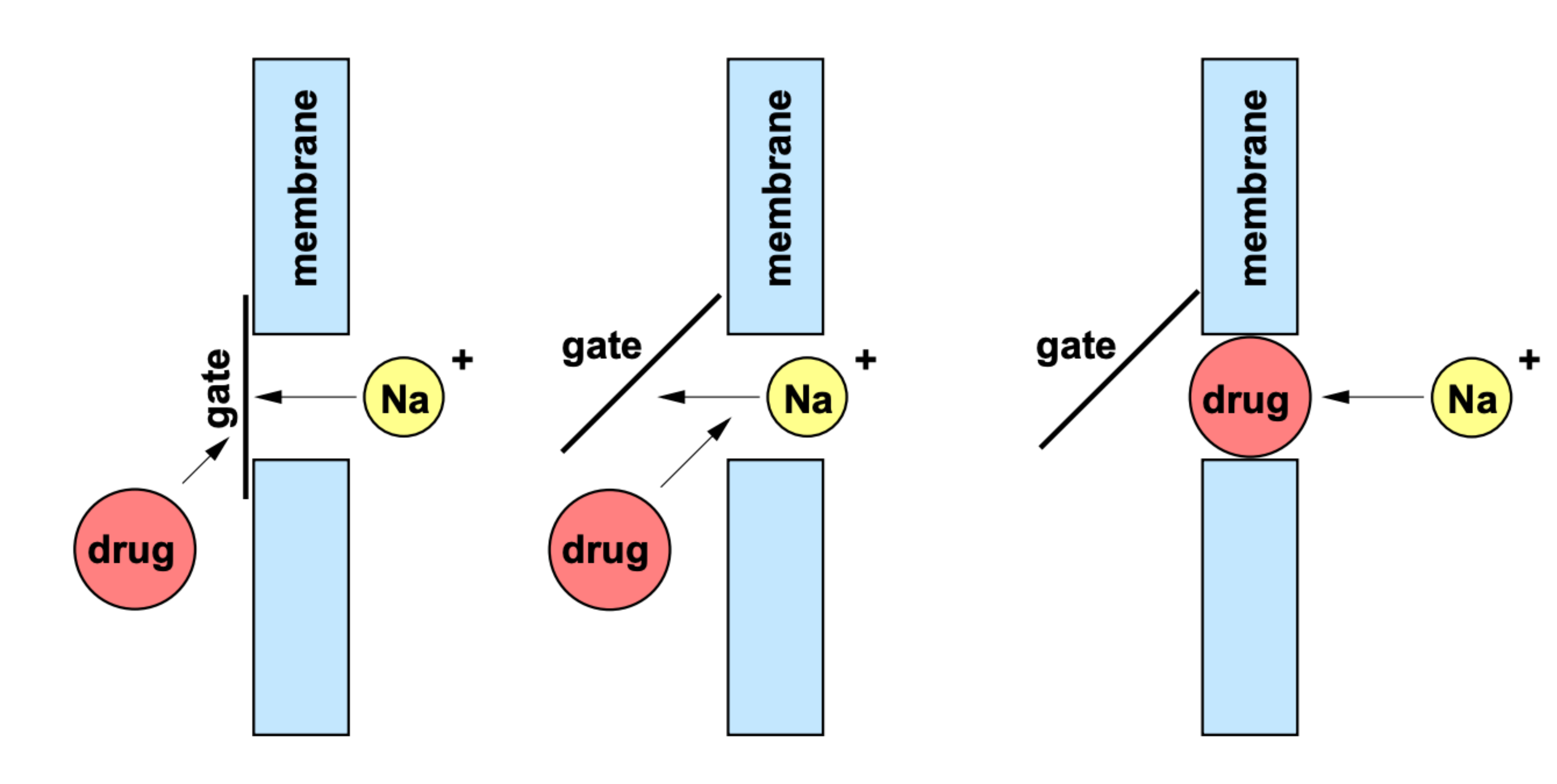


In that case we used optimization to find how much contraction we needed to fit the data



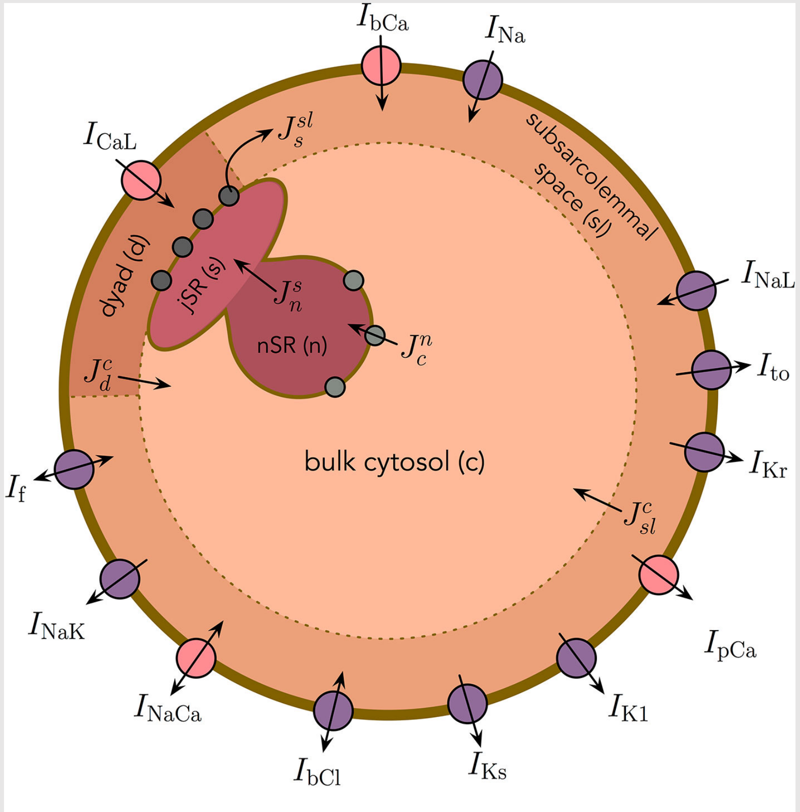
Trayanova, Natalia A., and John Jeremy Rice. "Cardiac electromechanical models: from cell to organ." *Frontiers in physiology* 2 (2011): 43.

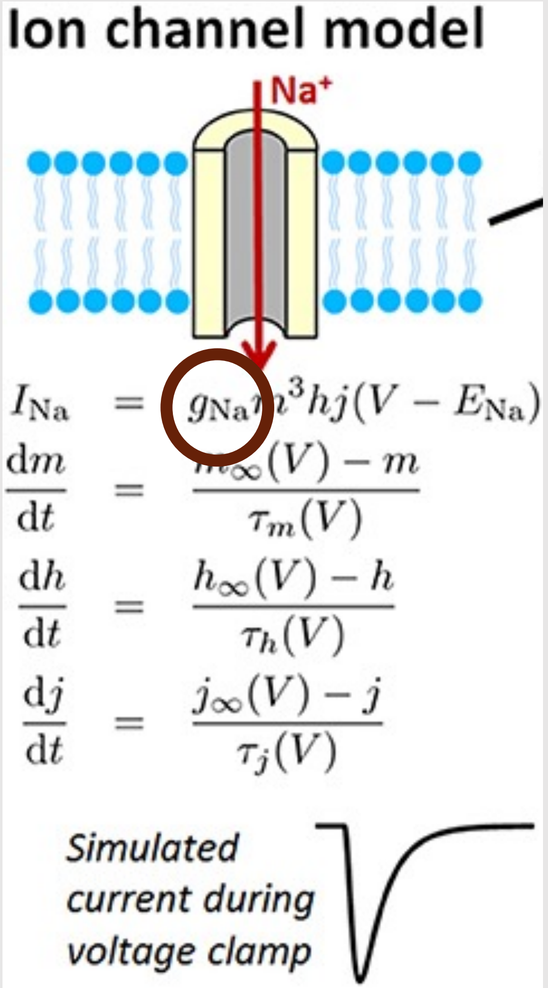
To model a drug effect we can block one of these channels

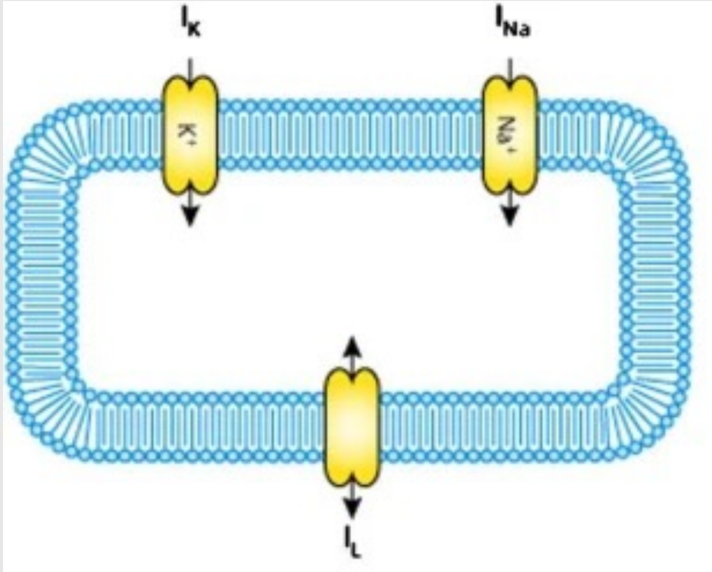


Starmer, C. Frank. "How antiarrhythmic drugs increase the rate of sudden cardiac death." *International Journal of Bifurcation and Chaos* 12.09 (2002): 1953-1968.

To model a drug effect we can block on of these channels

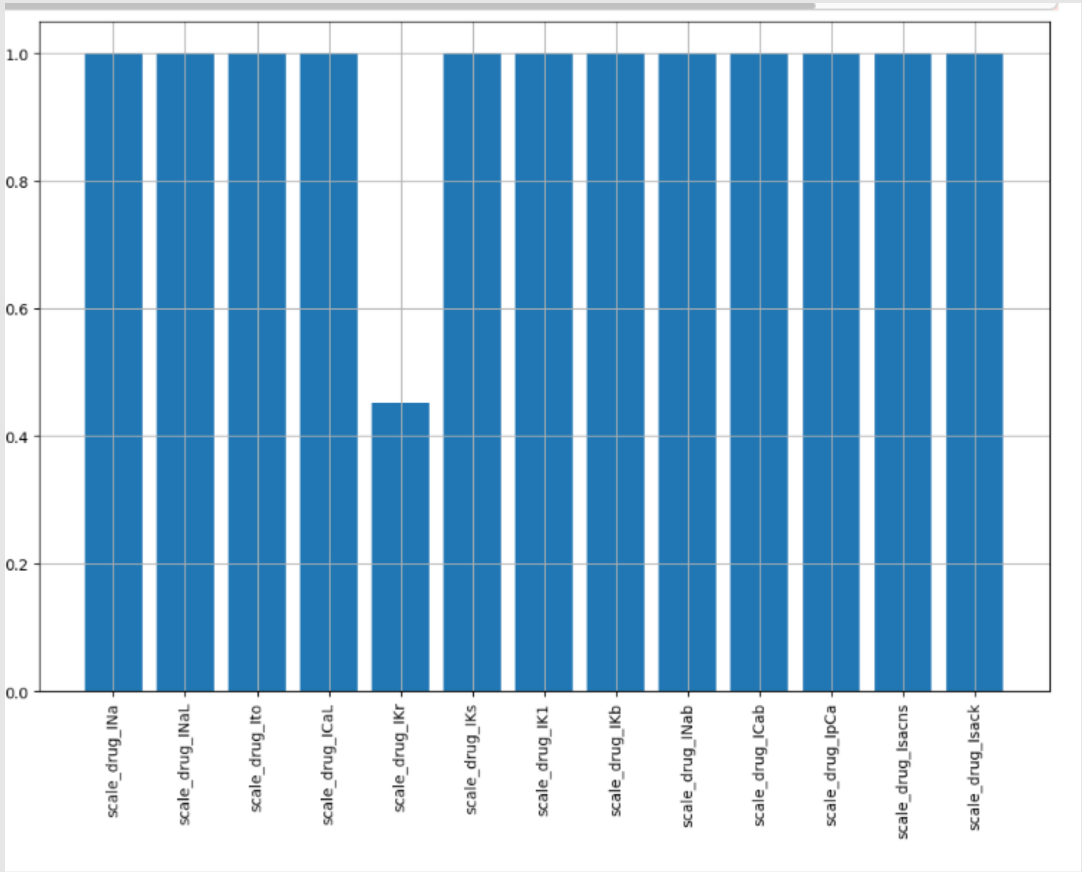


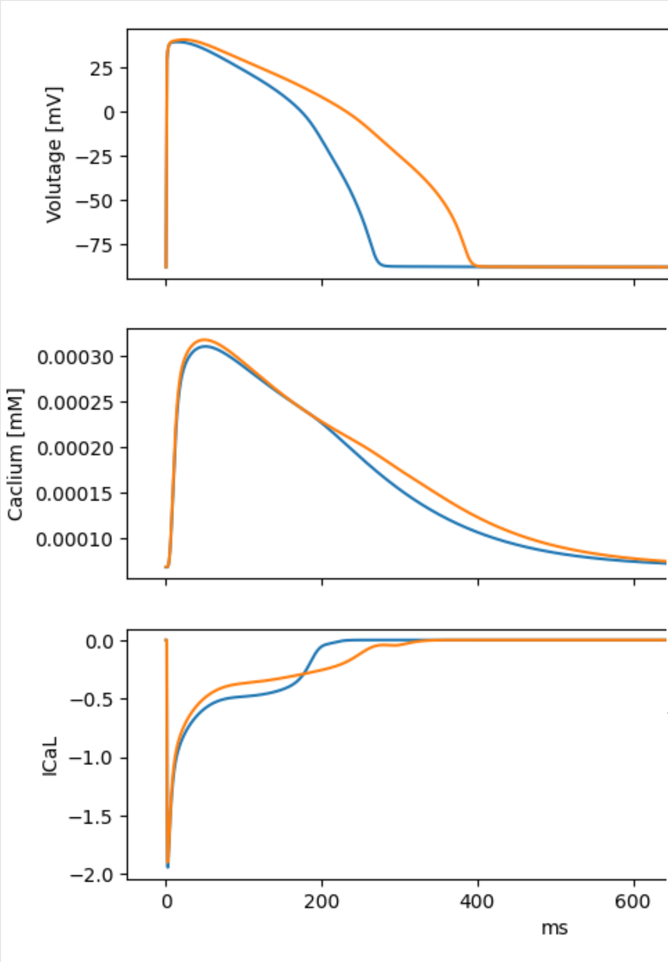


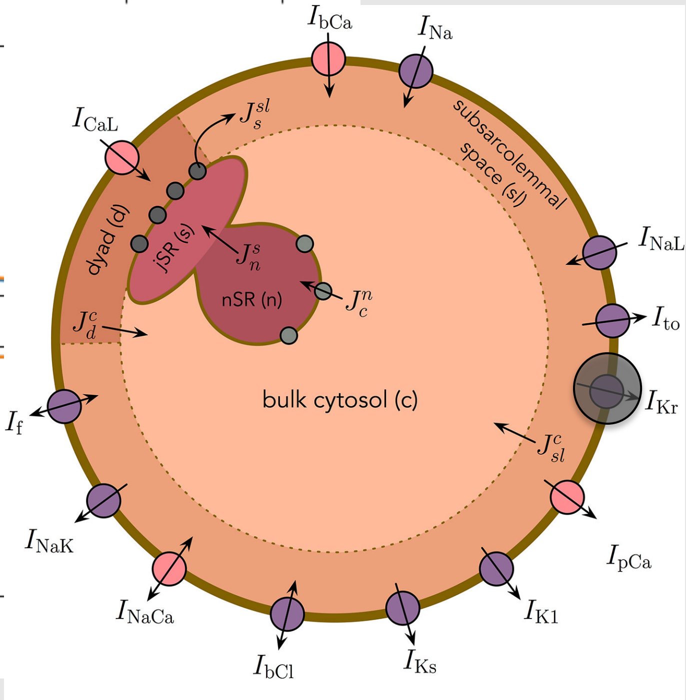


Modeling drug effect in a single cell modelling

Drug that block a single channel

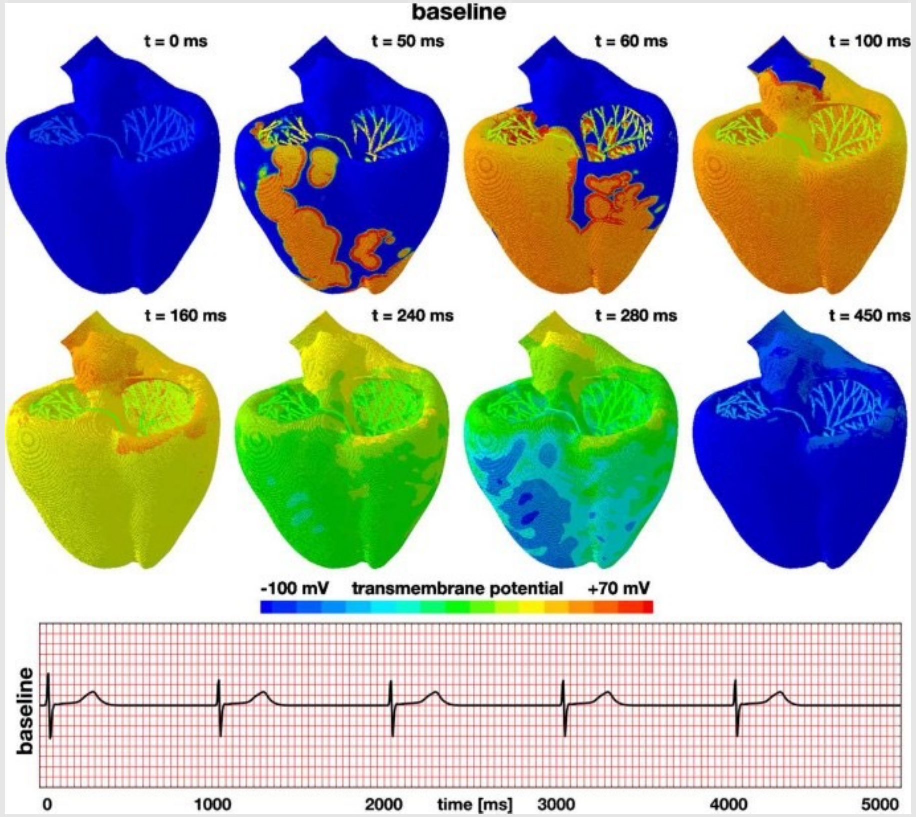


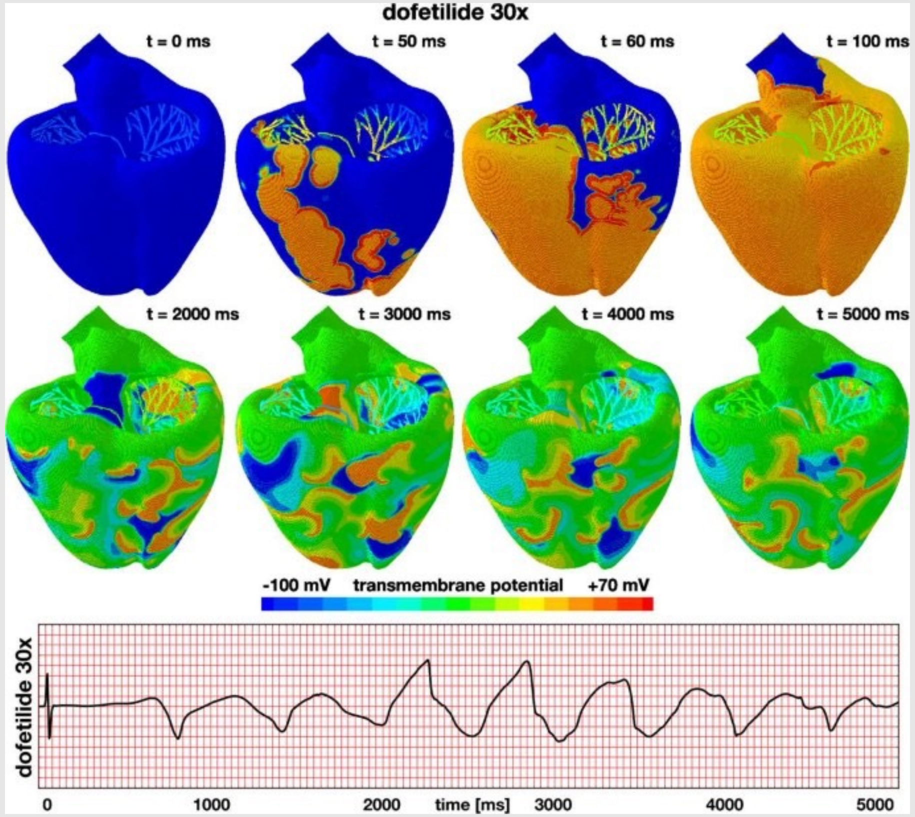




https://computationalphysiology.github.io/uio-digital-scholarship-days/single_cell/drug_effect.html

Now you can model a drug effect by simply changing a parameter in the cell model and rerunning the simulation





Kügler, Philipp. "Modelling and simulation for preclinical cardiac safety assessment of drugs with human iPSC-derived cardiomyocytes." *Jahresbericht der Deutschen Mathematiker-Vereinigung* 122.4 (2020): 209-257.

The equations are solved with FEniCS (dolfinx / dolfin)

$$a(u, v) = L(v) \qquad \forall v \in \hat{V}.$$

$$a(u, v) = \int_\Omega \nabla u \cdot \nabla v \, \mathrm{d}x,$$

$$L(v) = \int_\Omega f v \, \mathrm{d}x.$$

```
a = ufl.dot(ufl.grad(u), ufl.grad(v)) * ufl.dx
L = f * v * ufl.dx
```

```
from dolfinx.fem.petsc import LinearProblem
problem = LinearProblem(a, L, bcs=[bc], petsc_options={"ksp_type": "preonly", "pc_type": "l
uh = problem.solve()
```

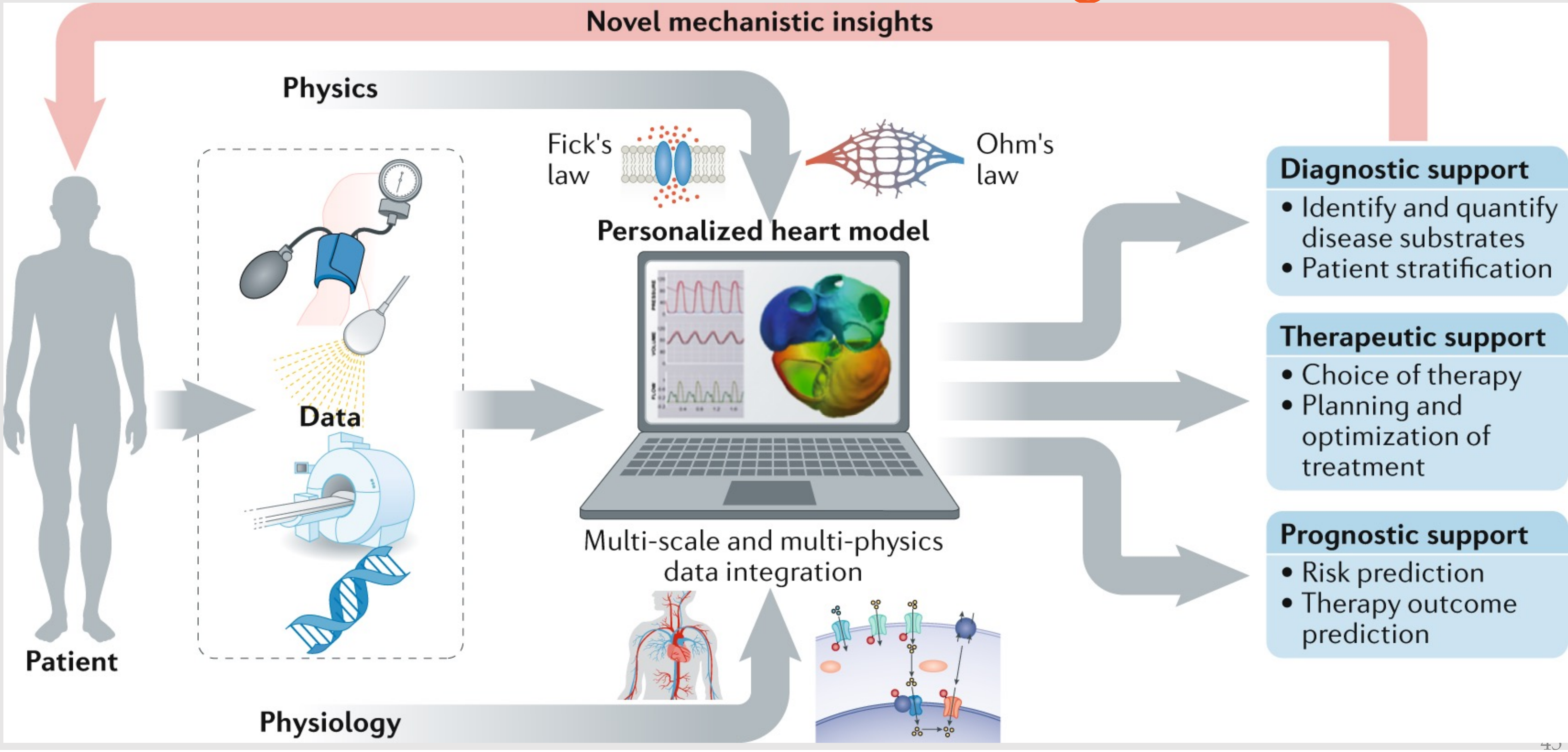
https://jsdokken.com/dolfinx-tutorial/

FEniCS is a library for solving partial differential equations with the finite element method

https://fenicsproject.org

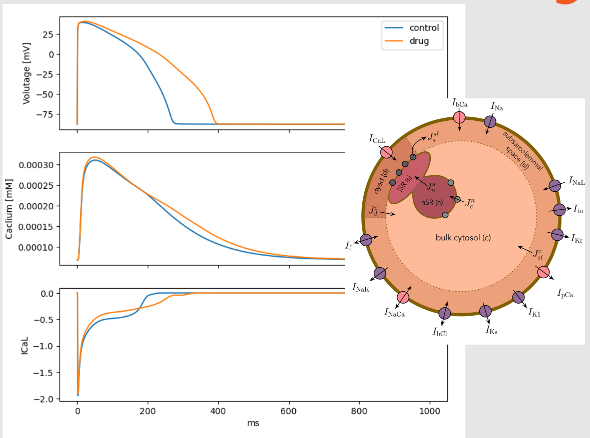
Presentation earlier today by Jørgen

The long term goal is to use models to assist clinicians in the descision making

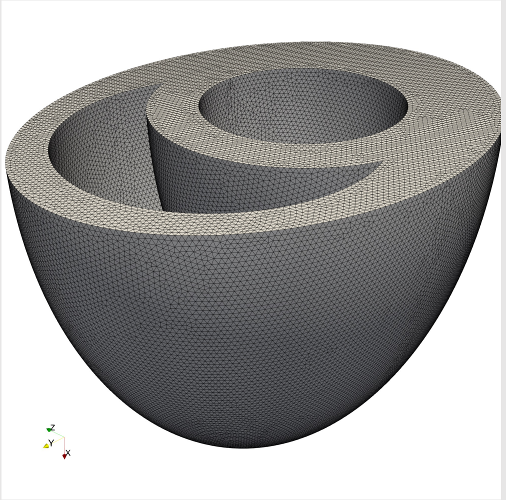


Niederer, Steven A., Joost Lumens, and Natalia A. Trayanova. "Computational models in cardiology." *Nature reviews cardiology* 16.2 (2019): 100-111.

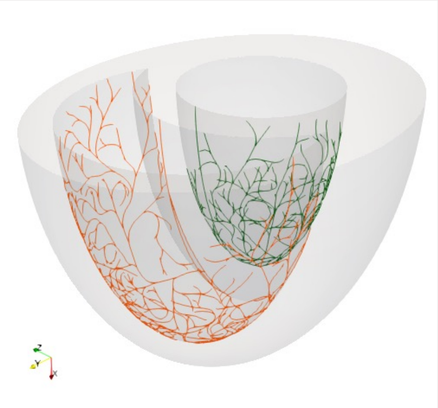
Summary



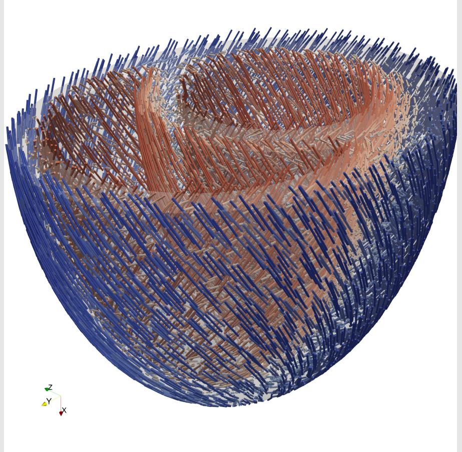
https://github.com/finsberg/gotranx



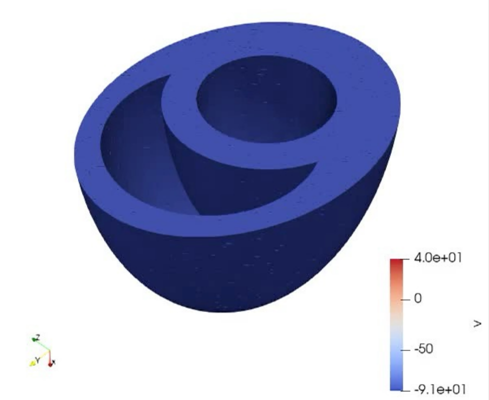
https://github.com/ComputationalPhysiology/cardiac_geometries



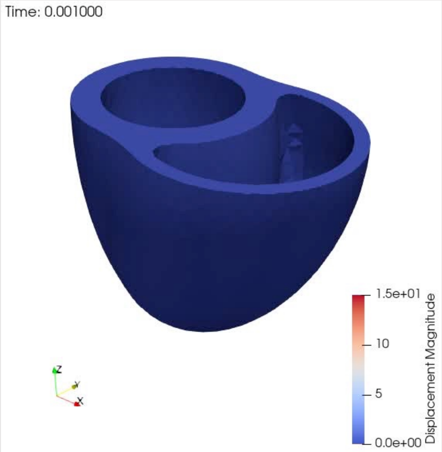
https://github.com/finsberg/fractal-tree



https://github.com/finsberg/ldrb



https://github.com/finsberg/fenics-beat



https://github.com/finsberg/pulse