Computational Biology

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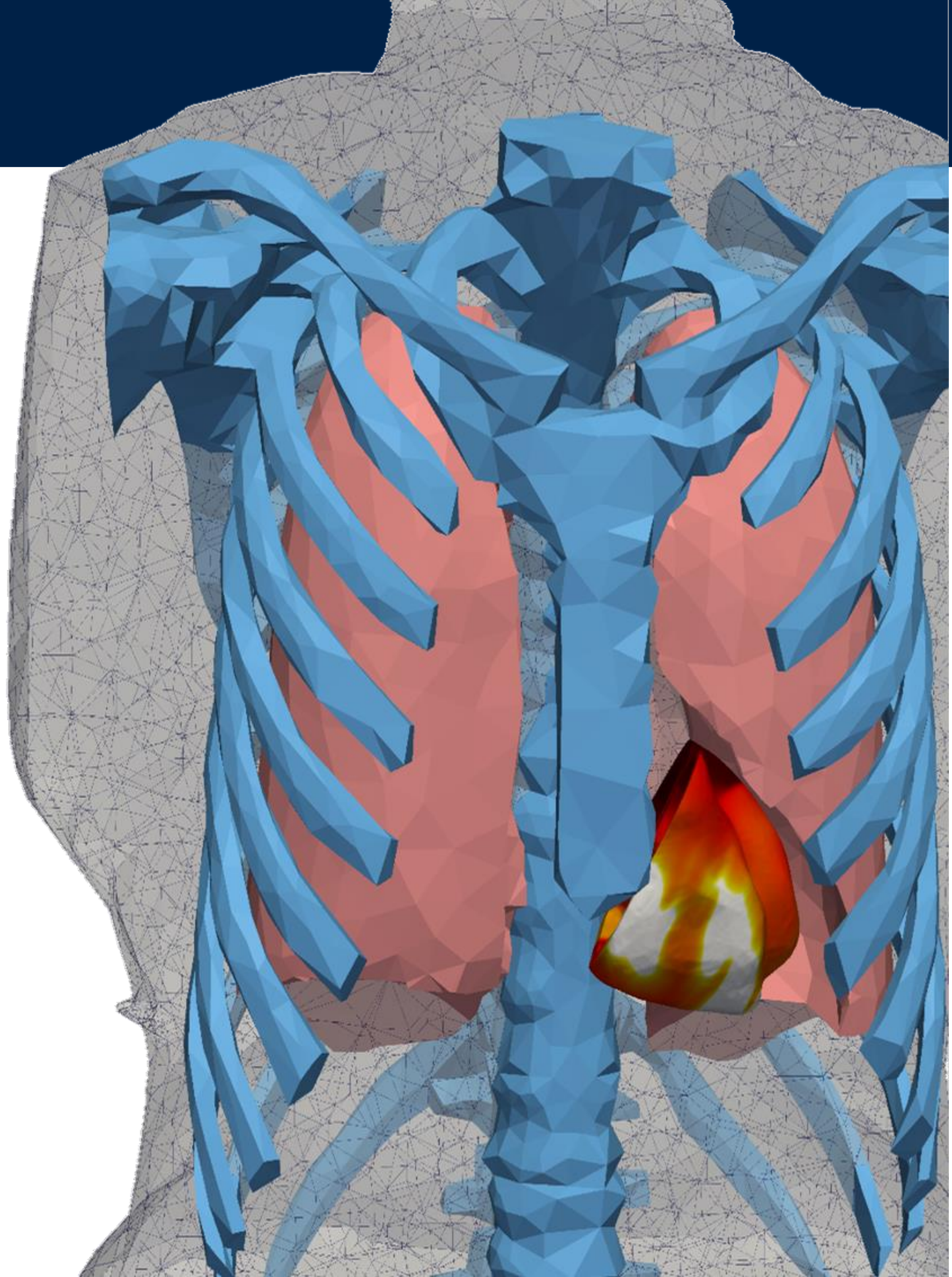
UNIVERSITY OF OXFORD

DEPARTMENT OF COMPUTER SCIENCE



Outline

Royal Institution Masterclasses in Computer Science: Year 10, 2021

Computational Biology

Part I

1) 9.30-9.45: Introduction
Computational Biology and Computer Models of the Action Potential
1) 9.45-10.45: Hands-on
The Hodgkin & Huxley model

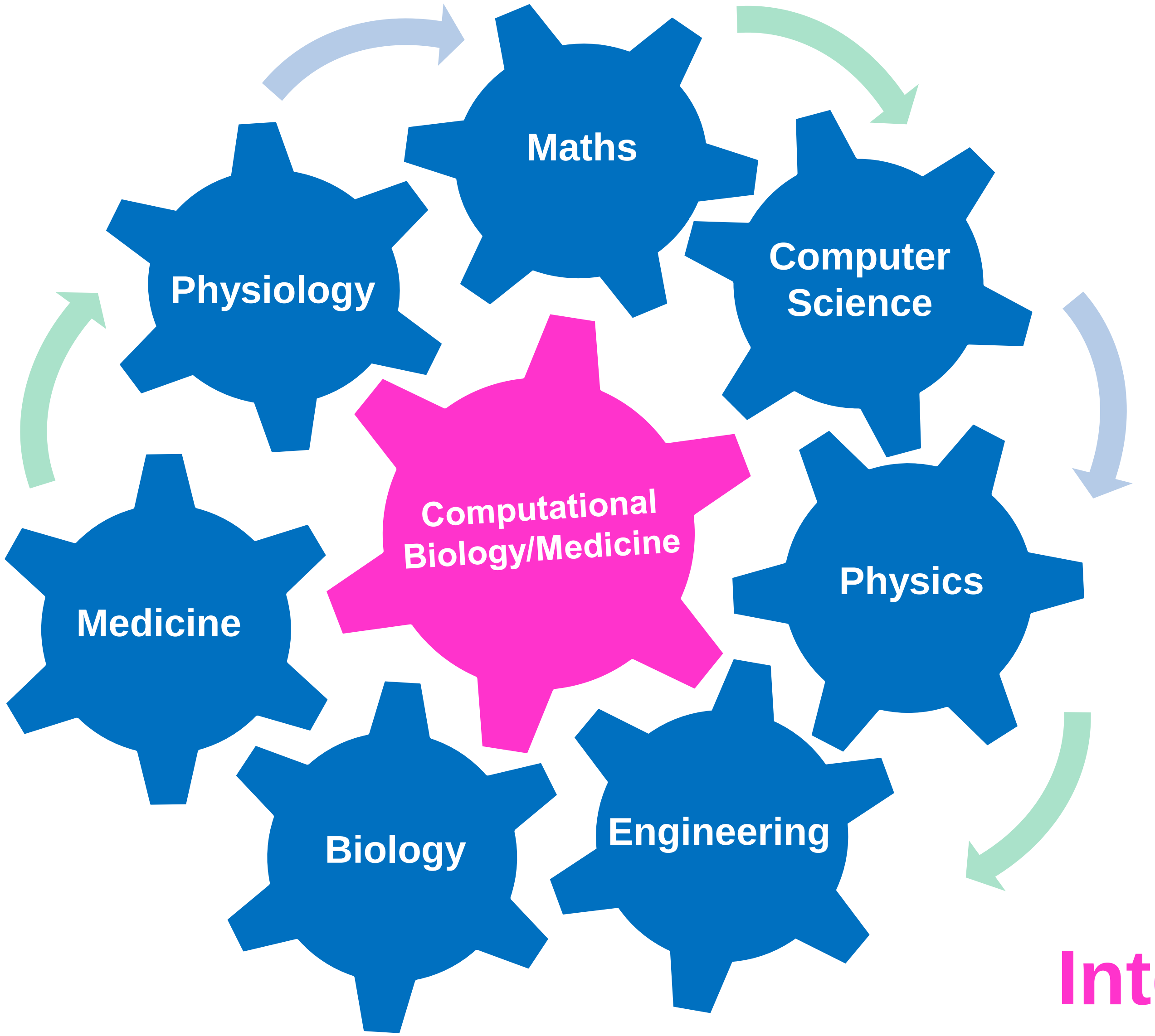
Break (15 mins)

Part II

1) 11:00-11:15: Introduction
Computer Models of the Heart and Drug Safety Testing
1) 11.15-11:45: Hands-on
Human in Silico Drug Trials

Summary and Conclusions

What is Computational Biology/Medicine?



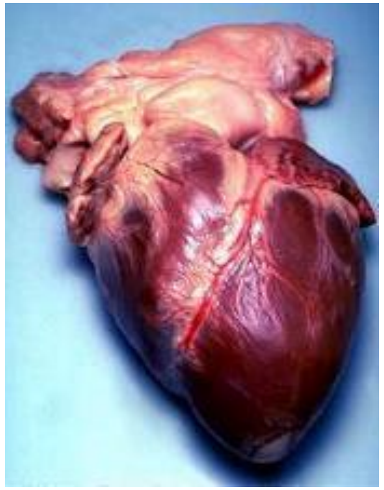
slido

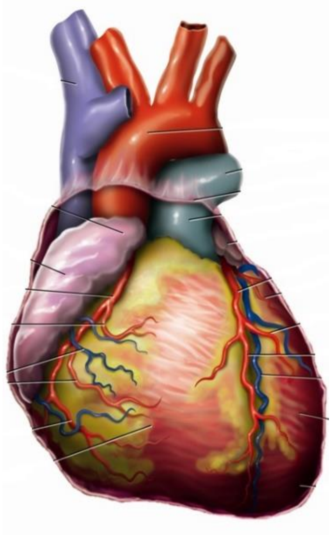
Interdisciplinary!

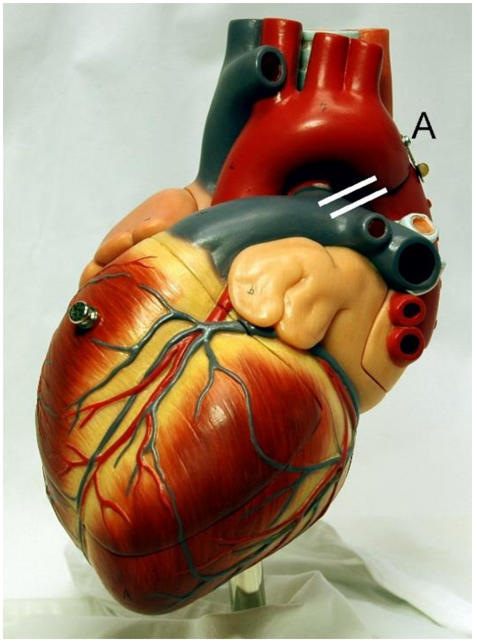
What is a Model?

- **Simplified representation of reality**
  - ✓ not TOO detailed
  - ✓ not TOO simple

  …level of detail based on purpose







- **What for?**
  - ✓ to learn/understand better what is going on
  - ✓ to formulate and test new hypotheses

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Image Credits: Stanwhit607, Nevit Dilmen, Tvanbr, Ekko

What is a Model?

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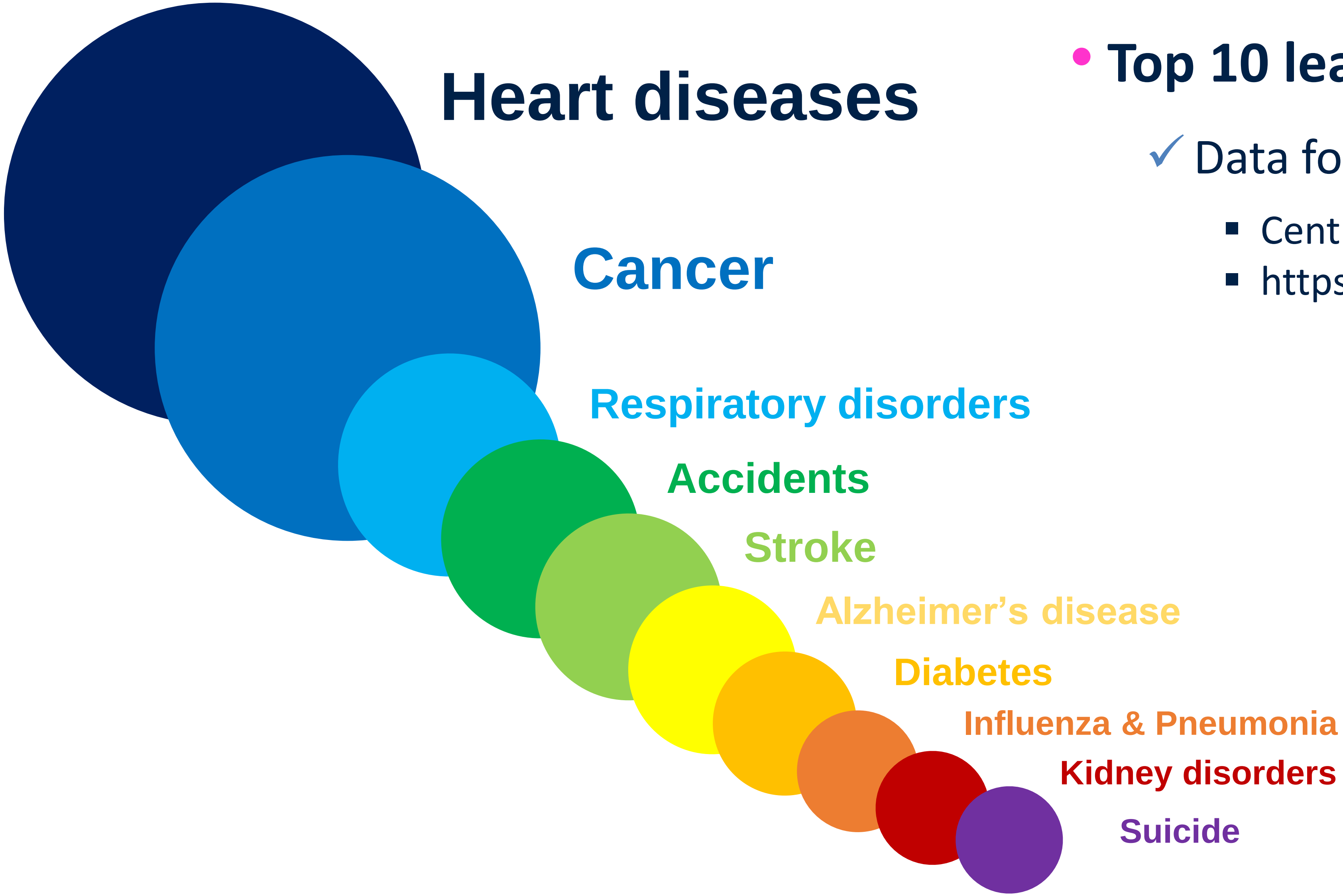
Representation   Tool for Discovery

slido

All MODELS are WRONG… but some of them are useful!
George Box

Image Credit: Fritz Jörn

Why the Heart? The Heart Matters ♥



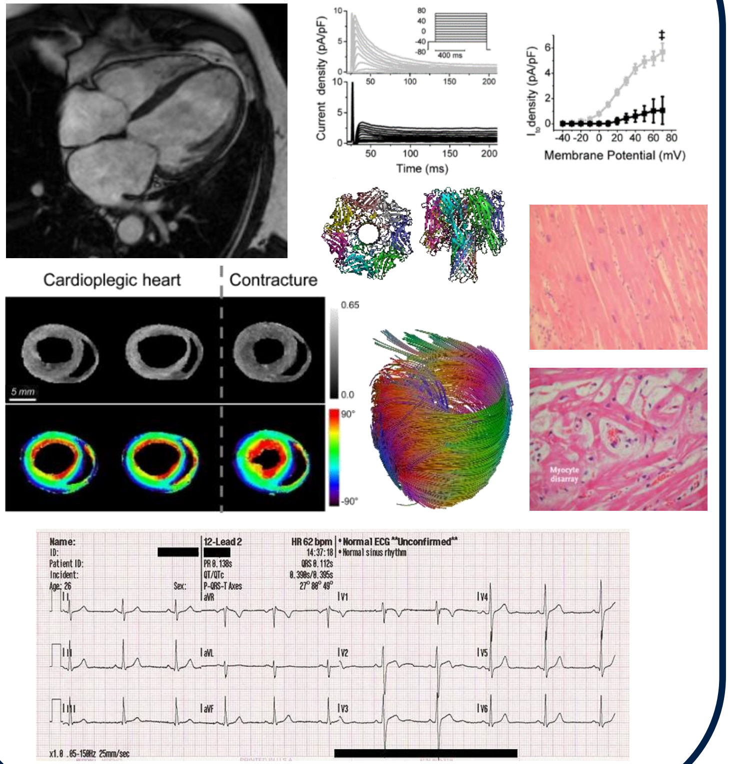
- **Top 10 leading causes of death**
  - ✓ Data for US population **1980-2015**
    - Centre for Disease Control and Prevention
    - https://www.cdc.gov

Computational Medicine for the Heart

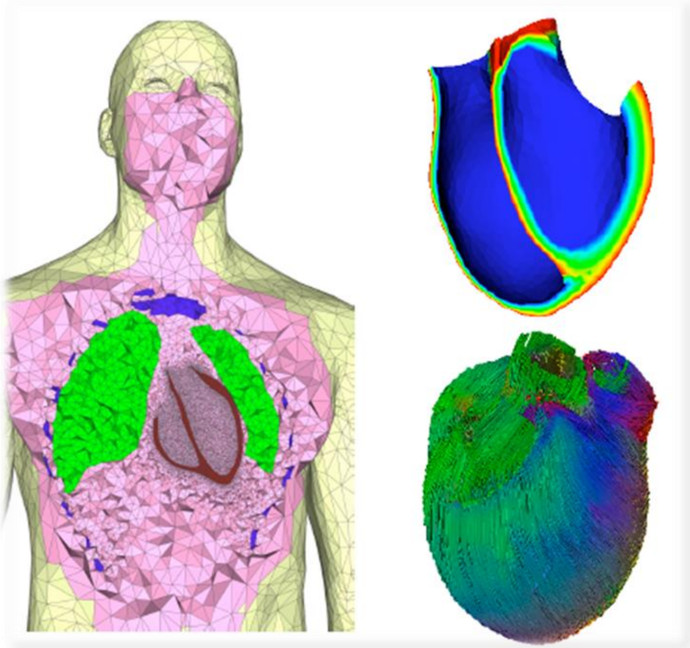
Heterogeneous

Multiscale

Experimental Data



The Virtual Heart



- **What can we do?**
  - ✓ Improve the current knowledge of heart and heart diseases
  - ✓ Improve diagnosis and therapies
    - Help to identify patients at risk
    - Plan and test possible treatments

Image credits: Doregan (cardiac MRI), Coppini et al. Circ Res. 2013 (ion current recordings), Bassophile (ion channel structure), Dr P.Hales/BBSRC University of Oxford (heart fibres), Lohezic et al. Prog Biophys Mol Biol. 2014 (cardiac DTI), Watkins et al. N Engl J Med 2011 (tissue images) , MoodyGroove (ECG), Zemzemi et al. British J Pharm. 2012

Why do we need a model?

- **The underlying biology is very complex**
- **Experimental data in humans are extremely rare**
  - ✓ very invasive!!!
  - ✓ unhealthy hearts

The majority of experiments are still performed on animals

- **A human being is very different from a mouse,**

  a rabbit, a guinea pig, a dog, a goat...
  - ✓ Not always the translation works!

Image Credit: G. Scott Segler

Image Credit: H Schwadron for Reader's Digest

National Centre for the Replacement Refinement & Reduction of Animals in Research

A Brief Introduction to the Heart

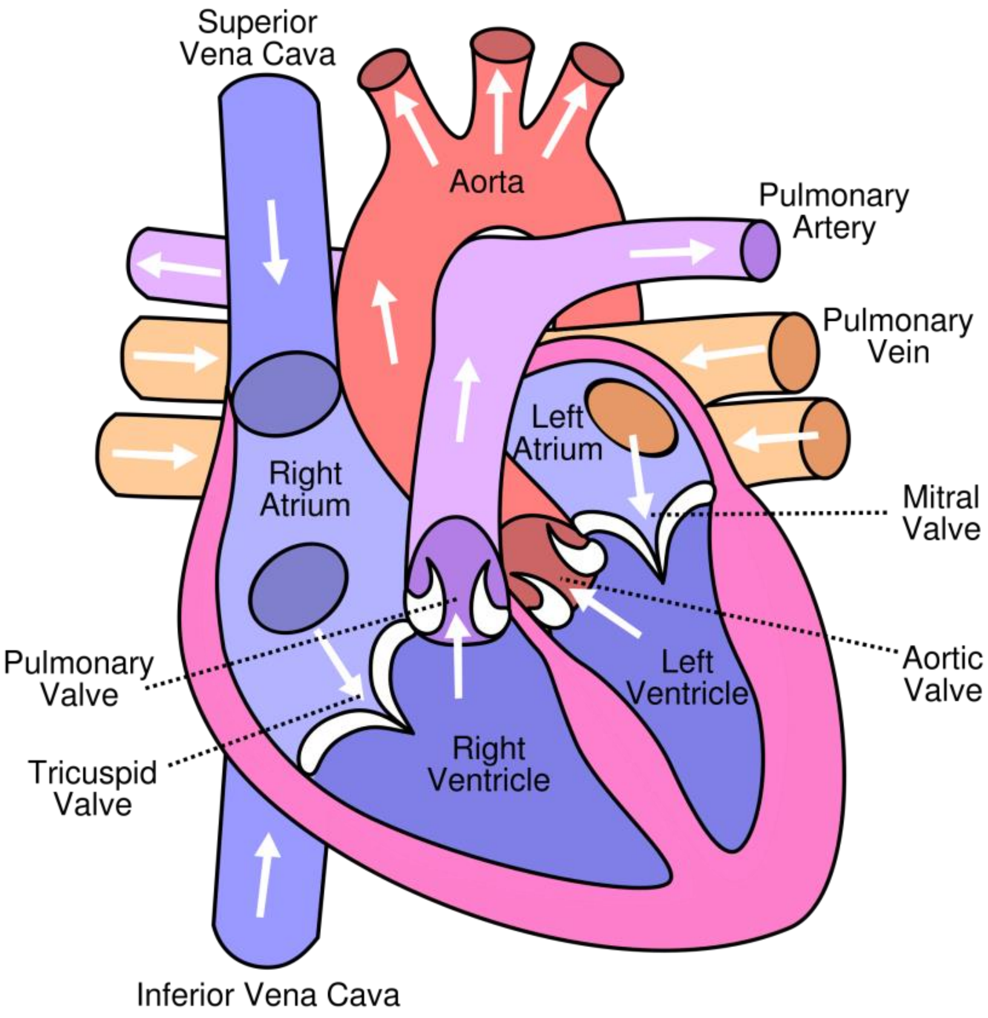
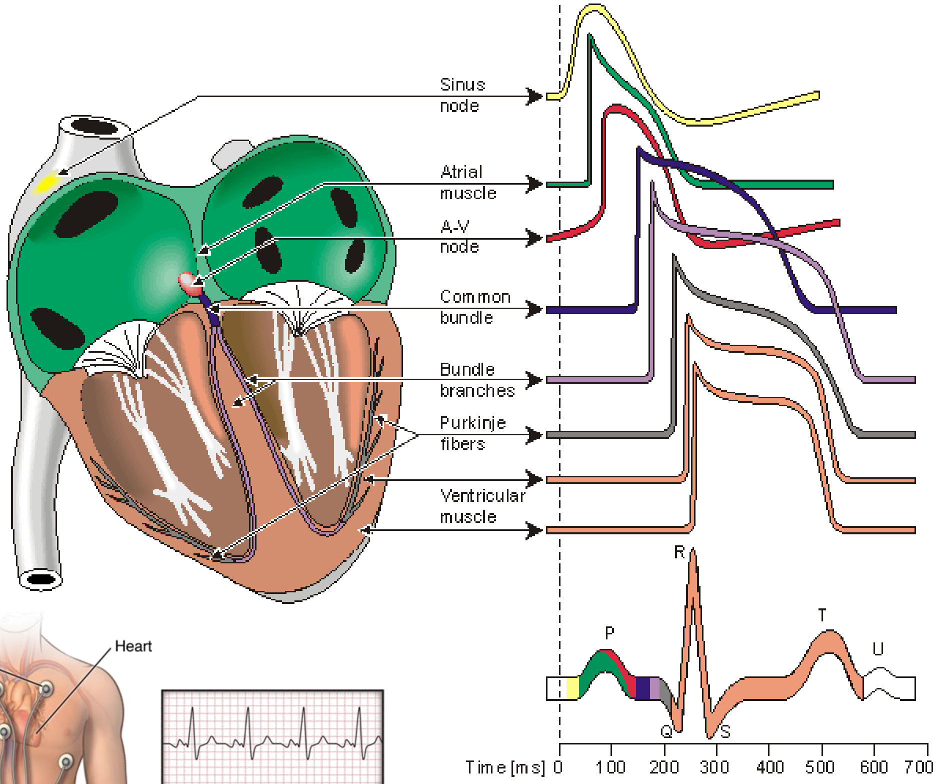


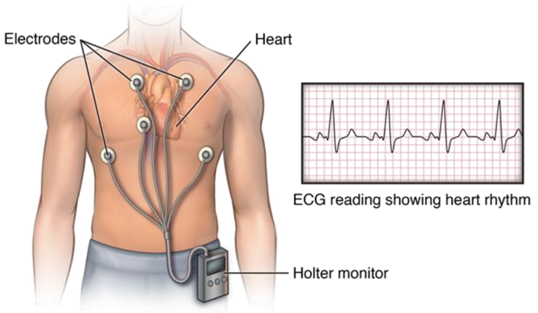
Image Credit: Wapcaplet

- **The heart is a pump**
  - ✓ it pumps oxygen-rich blood into the arteries to the tissues and organs
  - ✓ it pumps blood that needs oxygen to the lungs
- **The heart is a muscle**
  - ✓ it needs to contract for pumping the blood around
  - ✓ the contraction is driven by the electrical activity

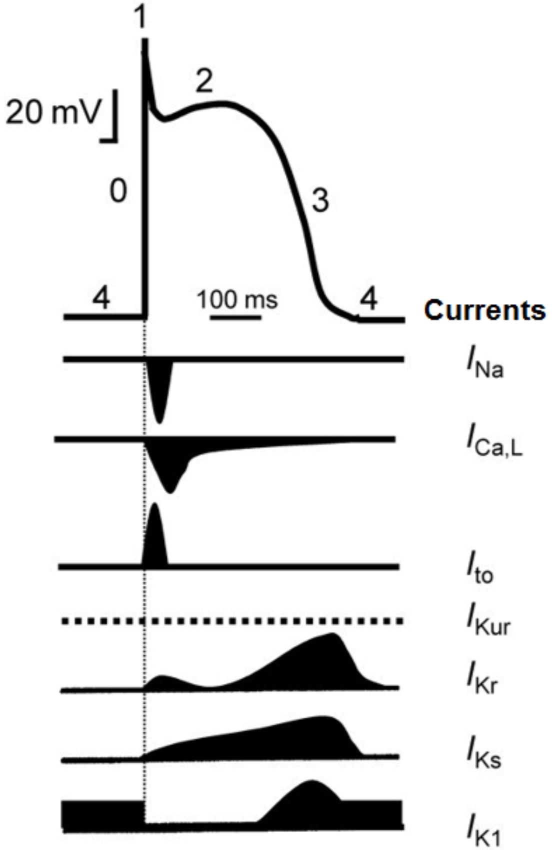
What do we model?

- **Cardiac Action Potential (AP)**
  Electrical signal of the heart at the **single cell level**



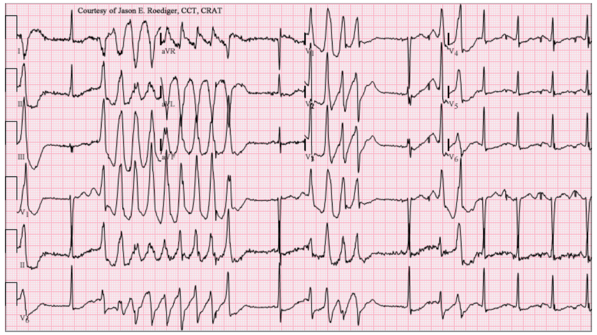


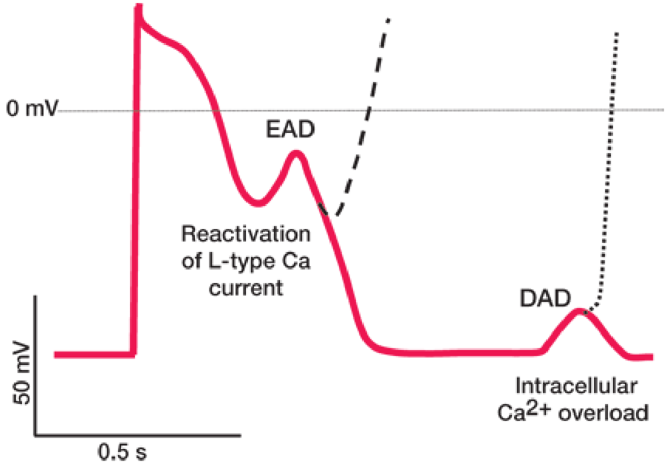
{J. Malmivuo and R. Plonsey 1995}



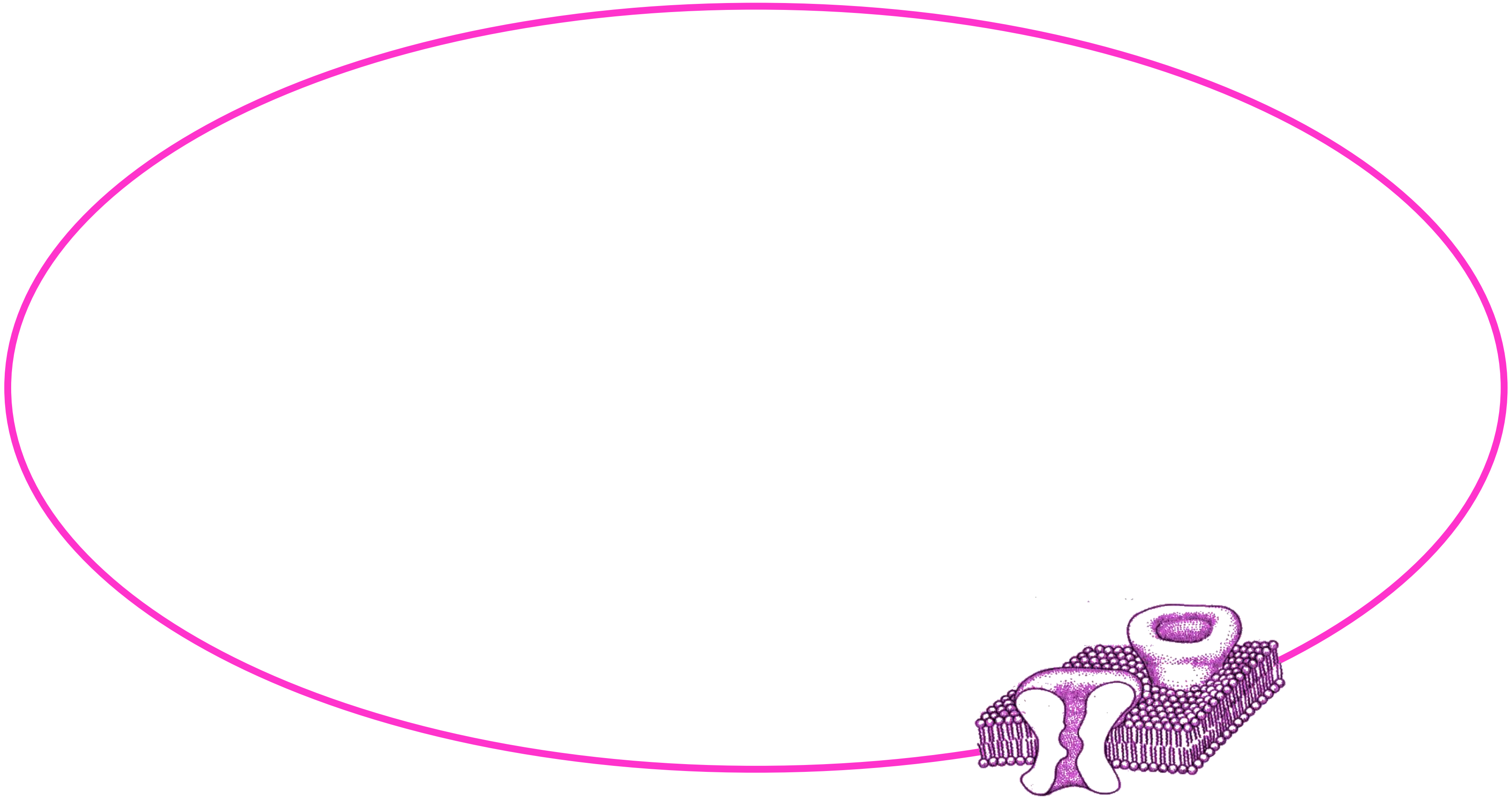
{U. Ravens and E. Cerbai Europace 2008}

- Torsade de Pointes (**TdP**)





IN and OUT the cell: ions and ionic currents



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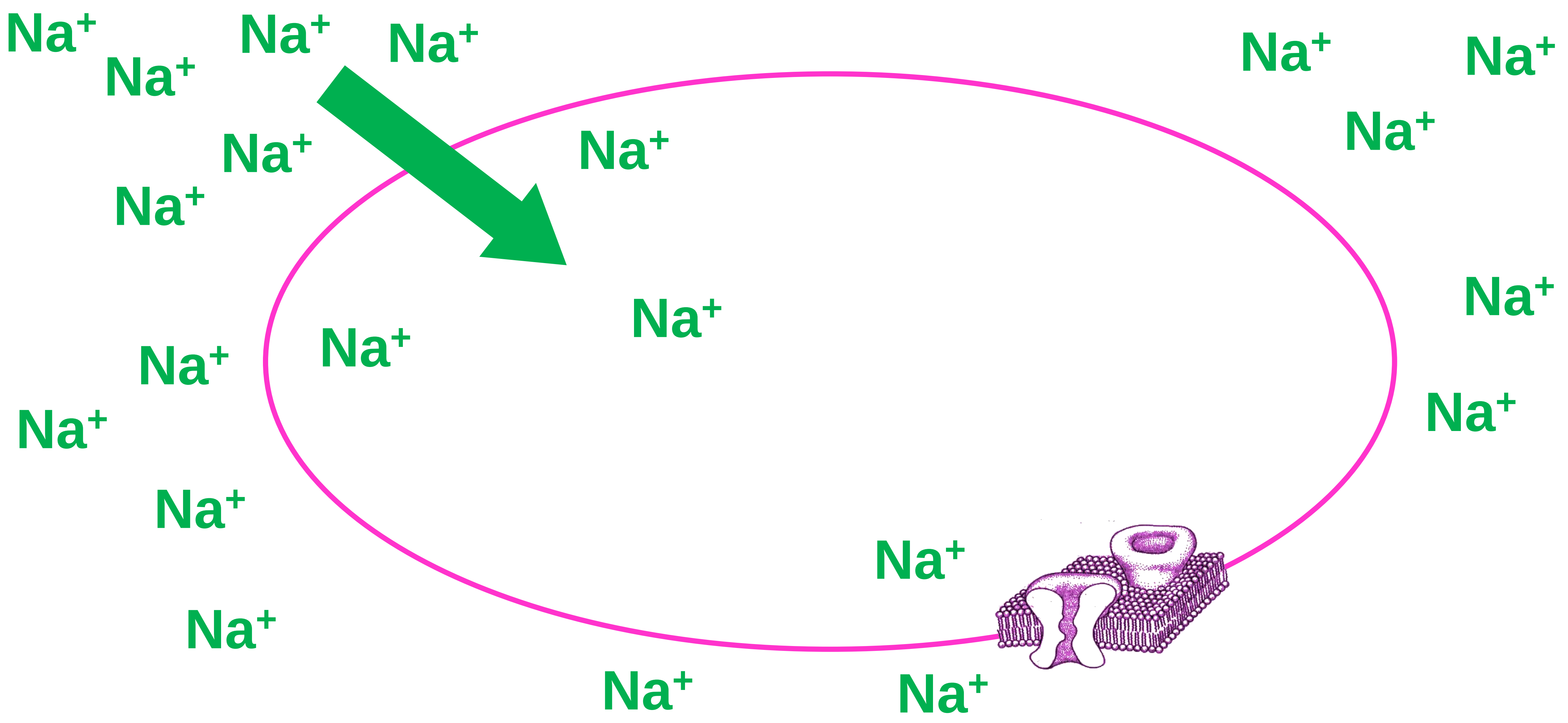

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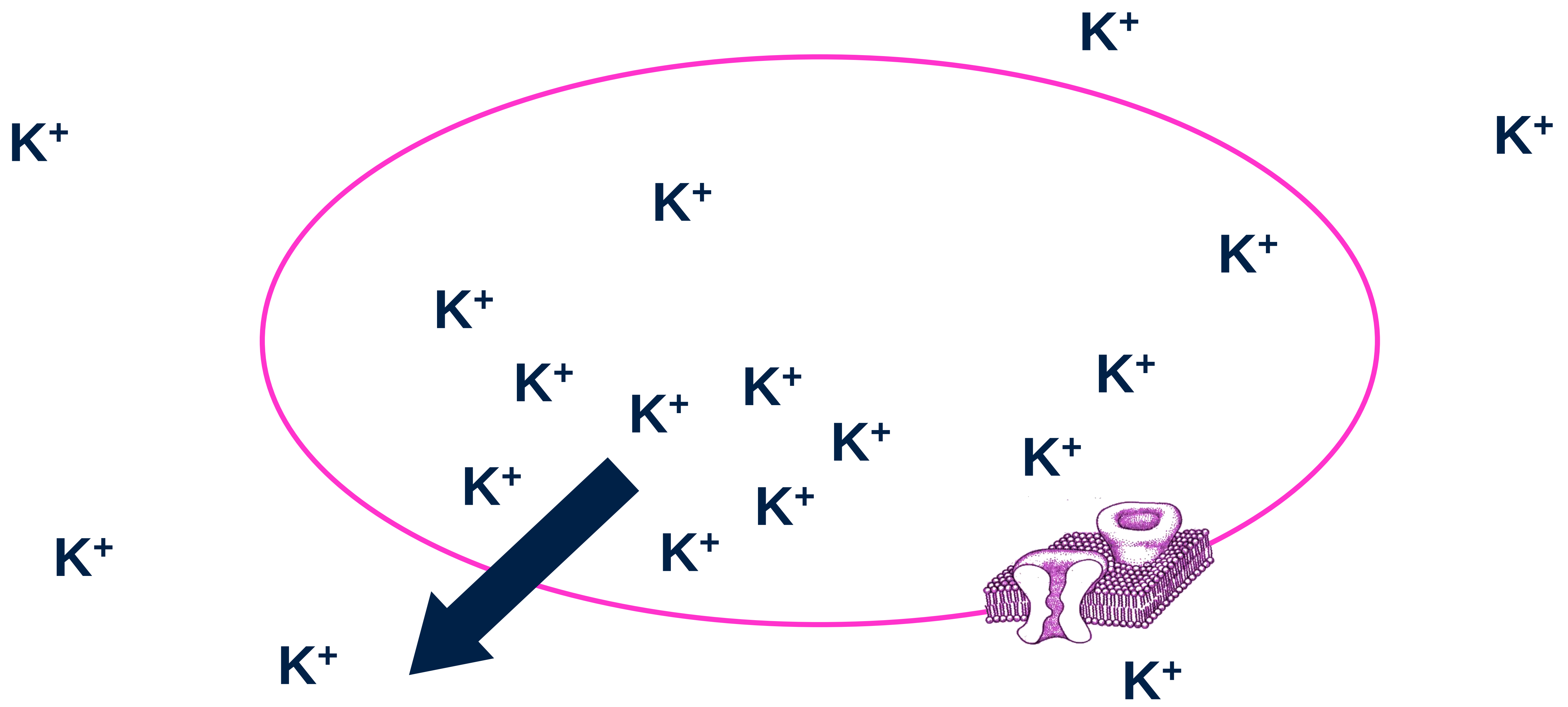

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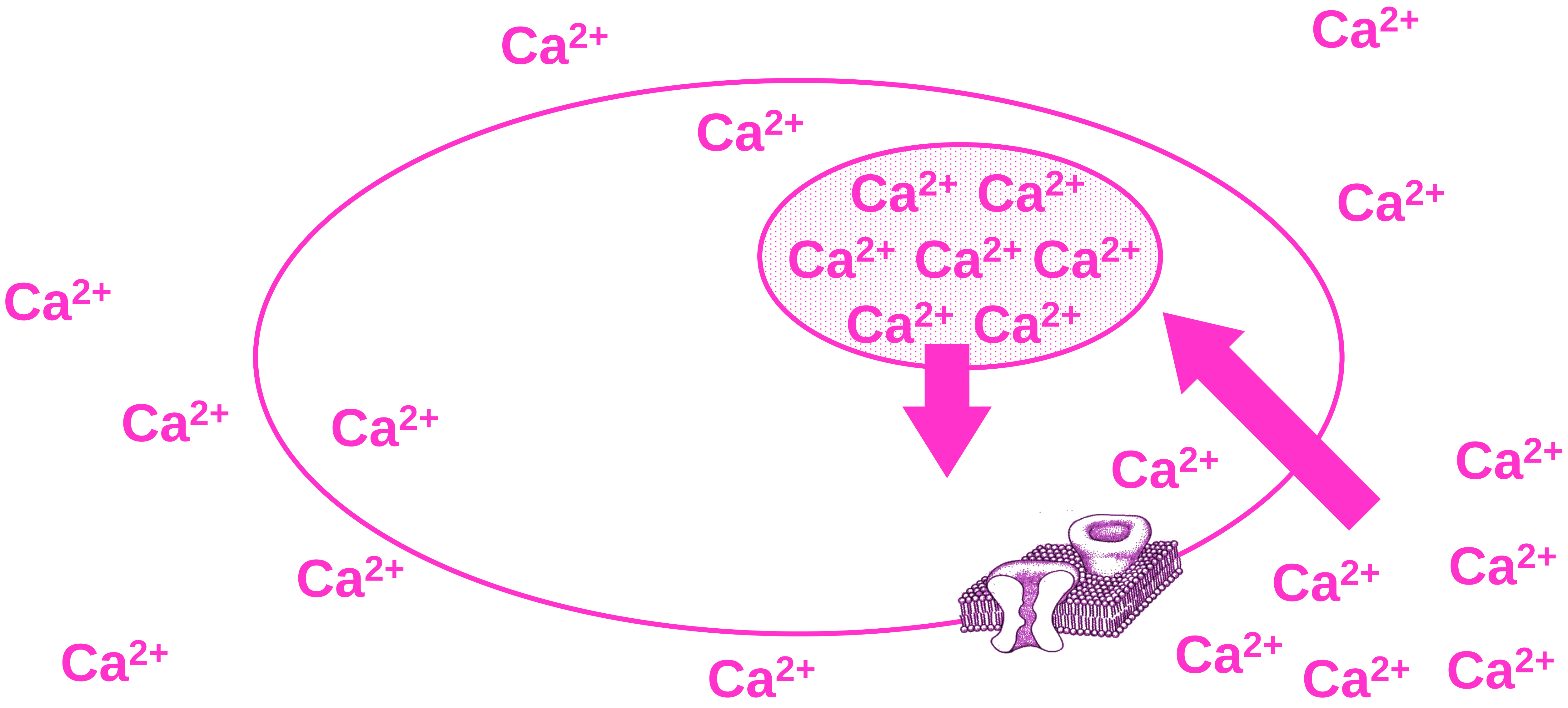

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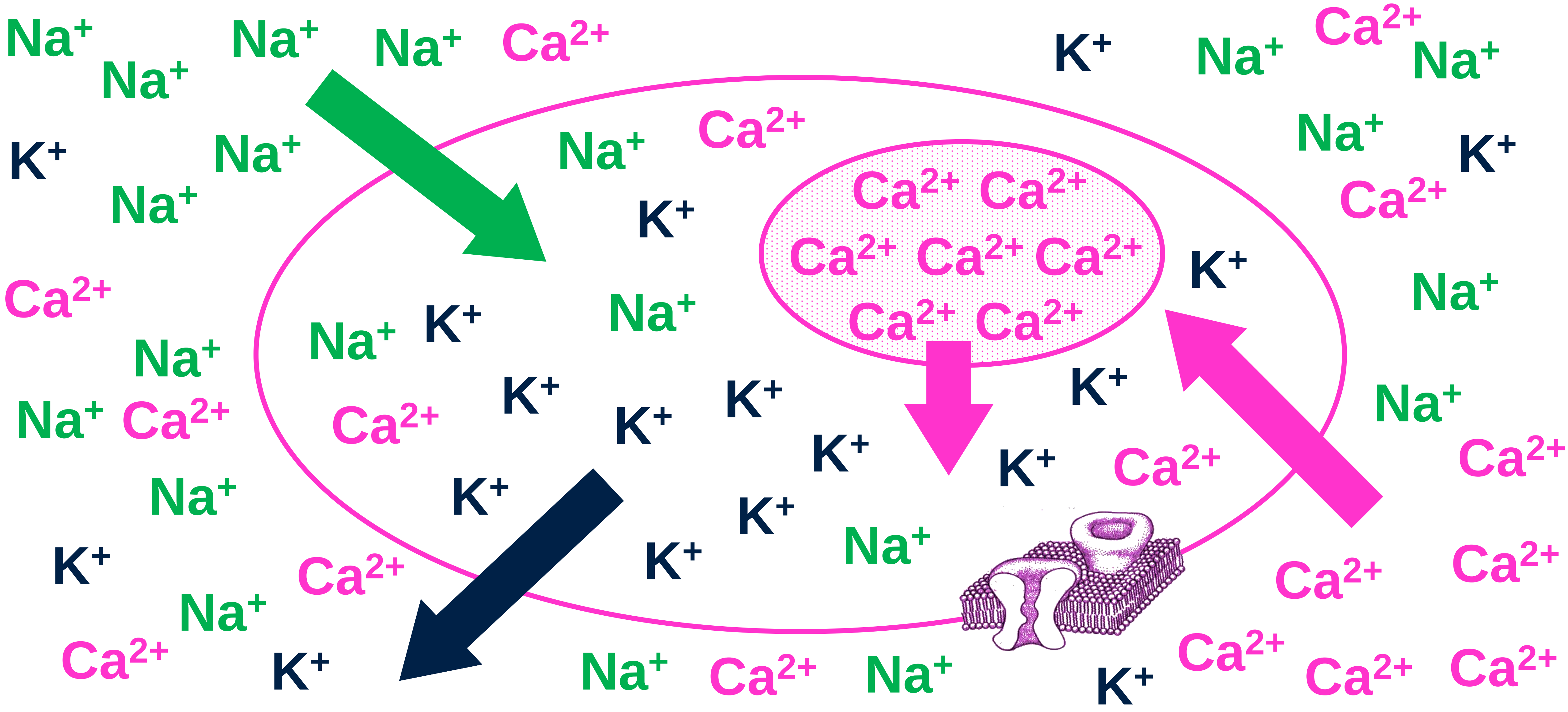

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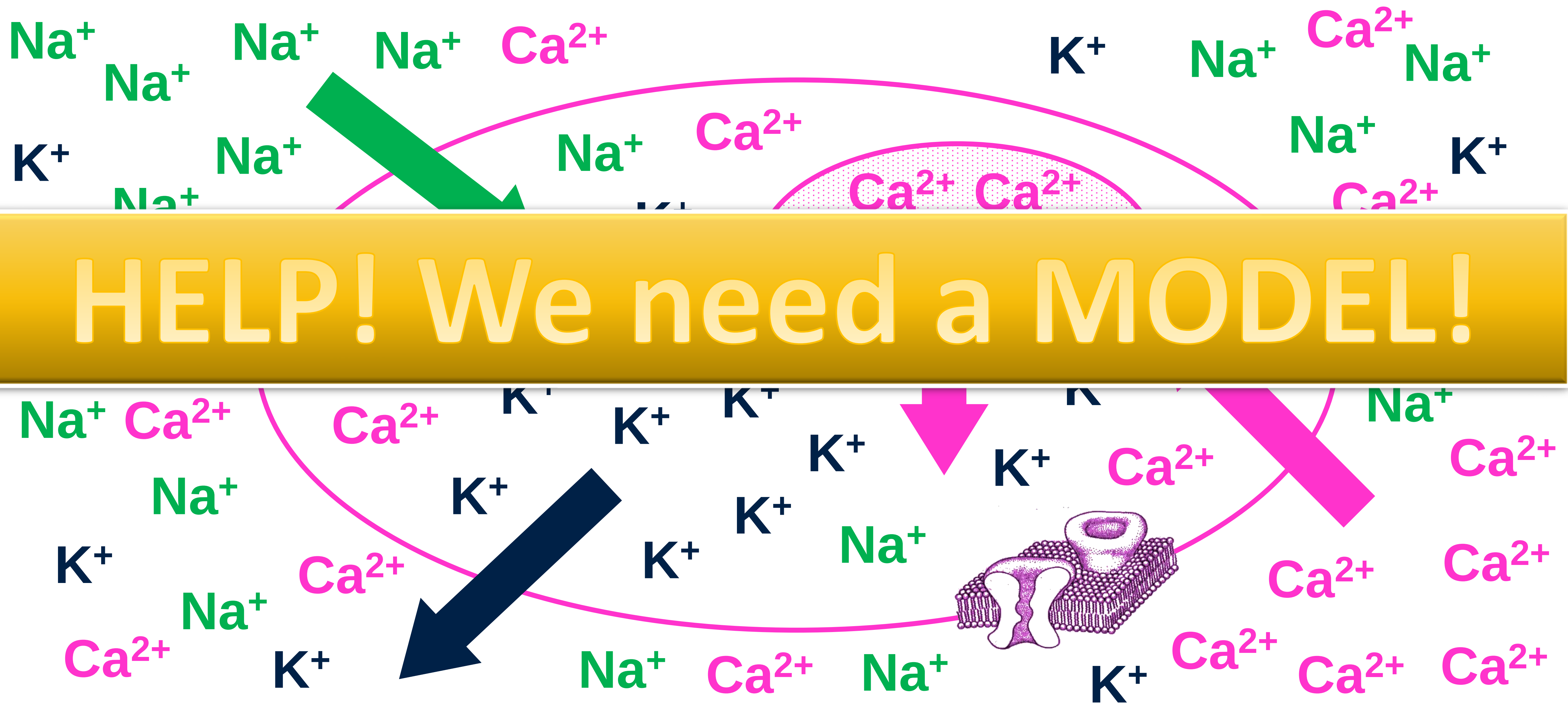
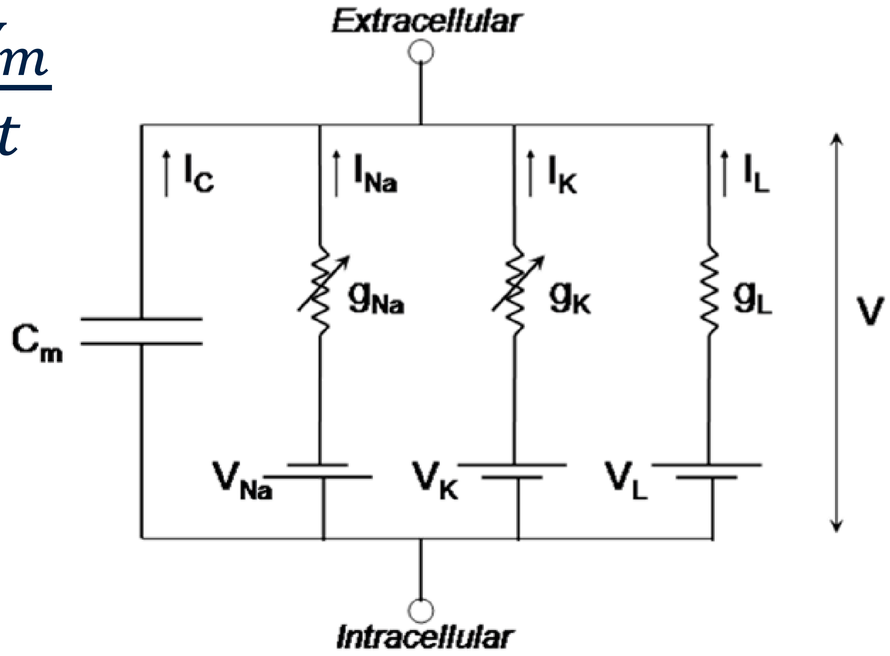


HELP! We need a MODEL!

Back to the Origin: Hodgkin & Huxley

- The approach is the same used by Hodgkin & Huxley:
  - ✓ Model of the squid giant axon
  - ✓ Nobel Prize in 1963

$$I_{tot} = C_m \cdot \frac{dV_m}{dt}$$



The total current is the sum of all the single ionic currents in the cell, each one with its specific formulation

$$I_{Na} = g_{Na} \cdot m^3 \cdot h \cdot (V_m - E_{Na})$$

maximal conductance *driving force*

gating variables

By varying between 0 and 1, the gating variables regulate the opening/closing of che ion channels

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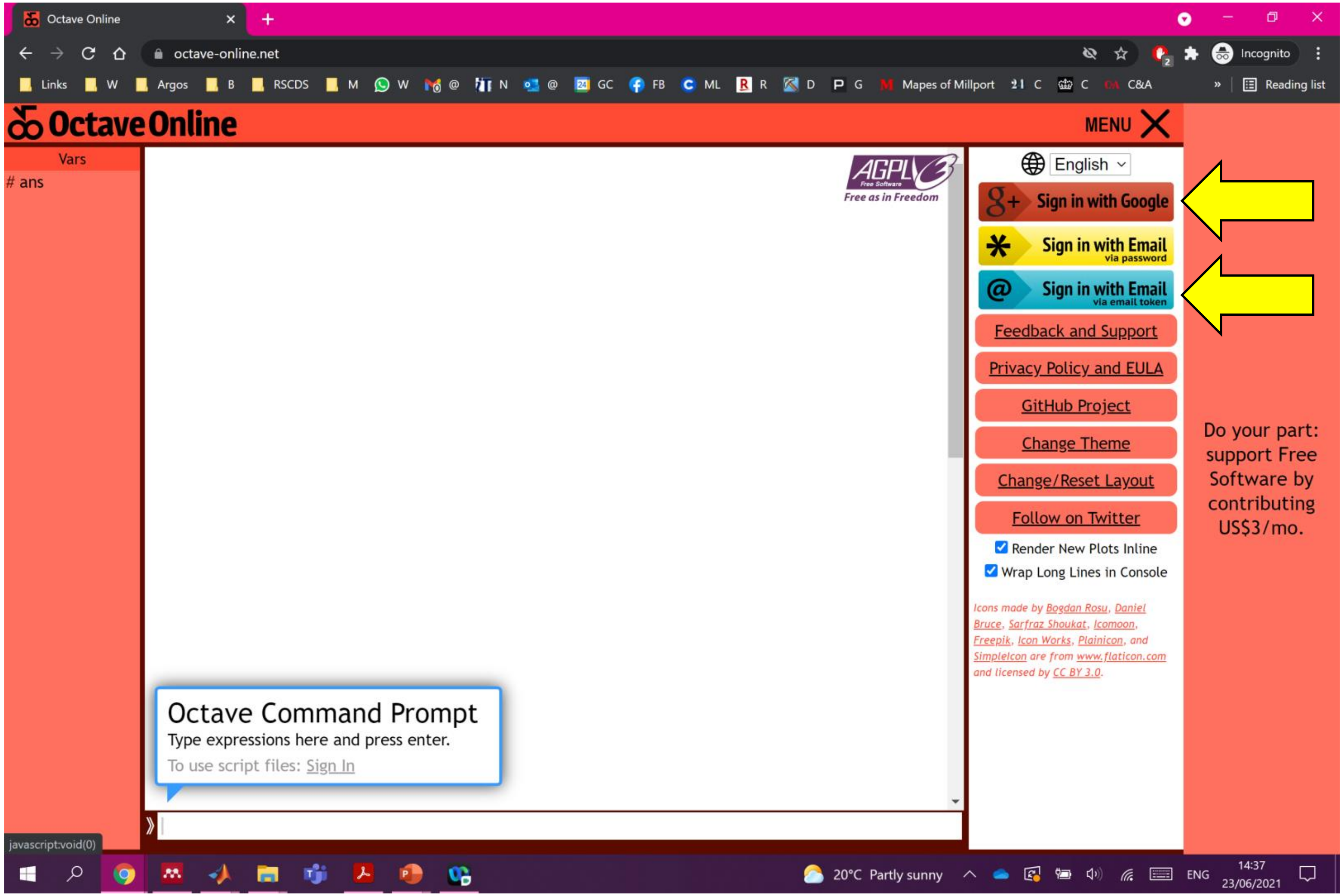
Hands-on Part 1: the Hodgkin & Huxley Model

- Go to: https://octave-online.net/ and sign-in
- Click on the “Bucket” link provided for Exercise 1



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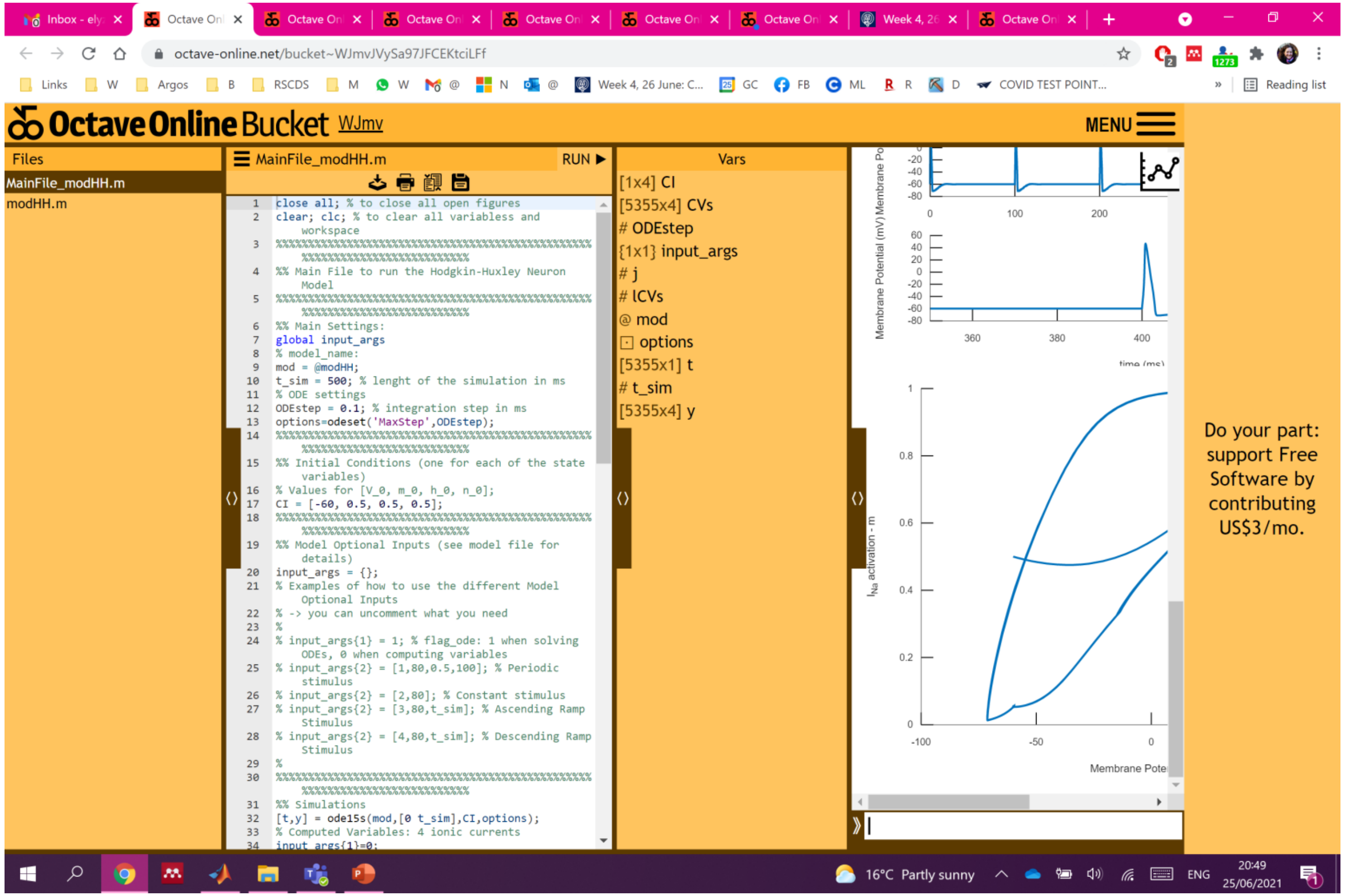

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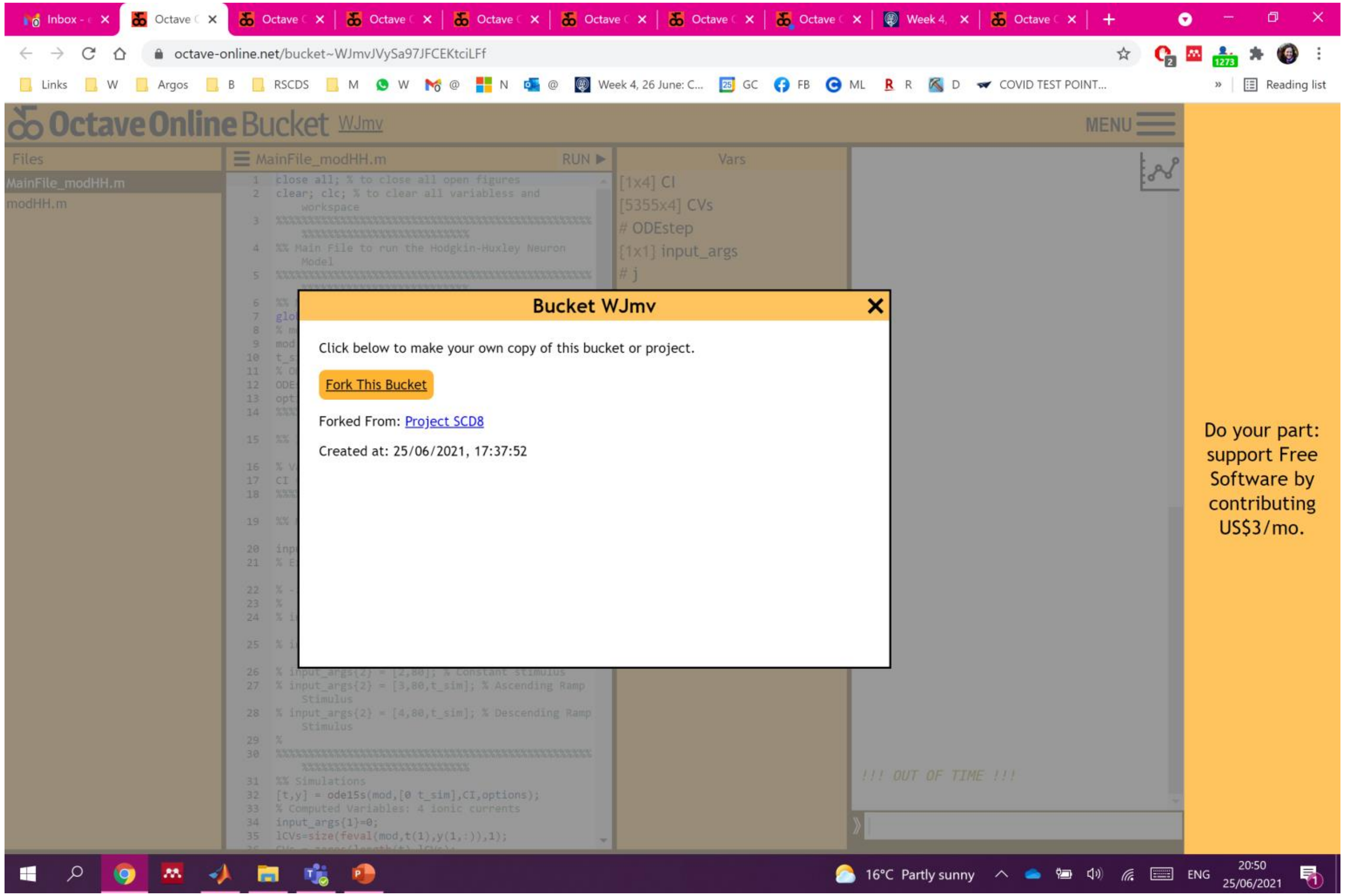
- "Fork" the Bucket by clicking on the name: this will create your own project that you can modify
- From the main page, you can see and access to all your projects
- **If this works, you can go to slide 26**



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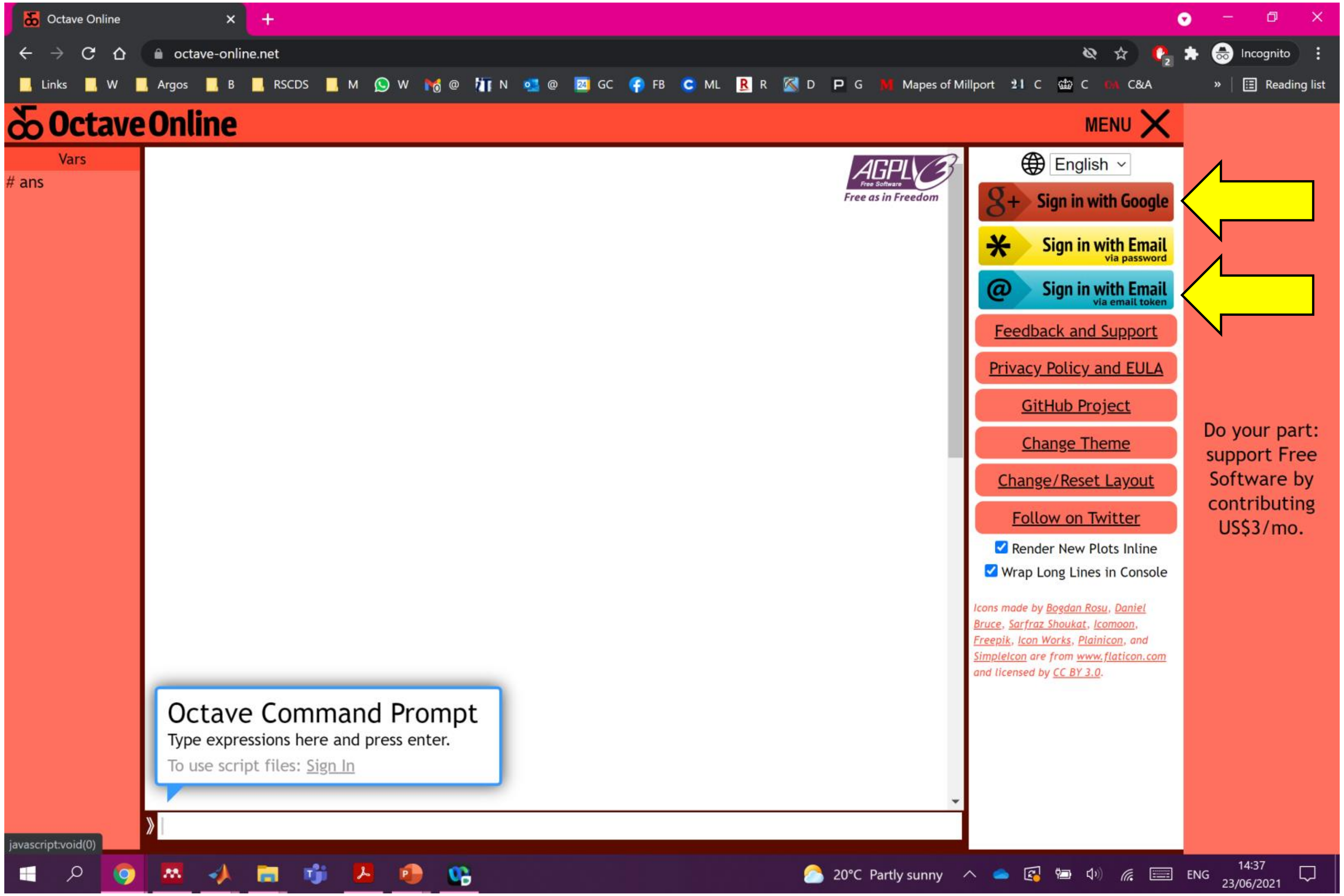

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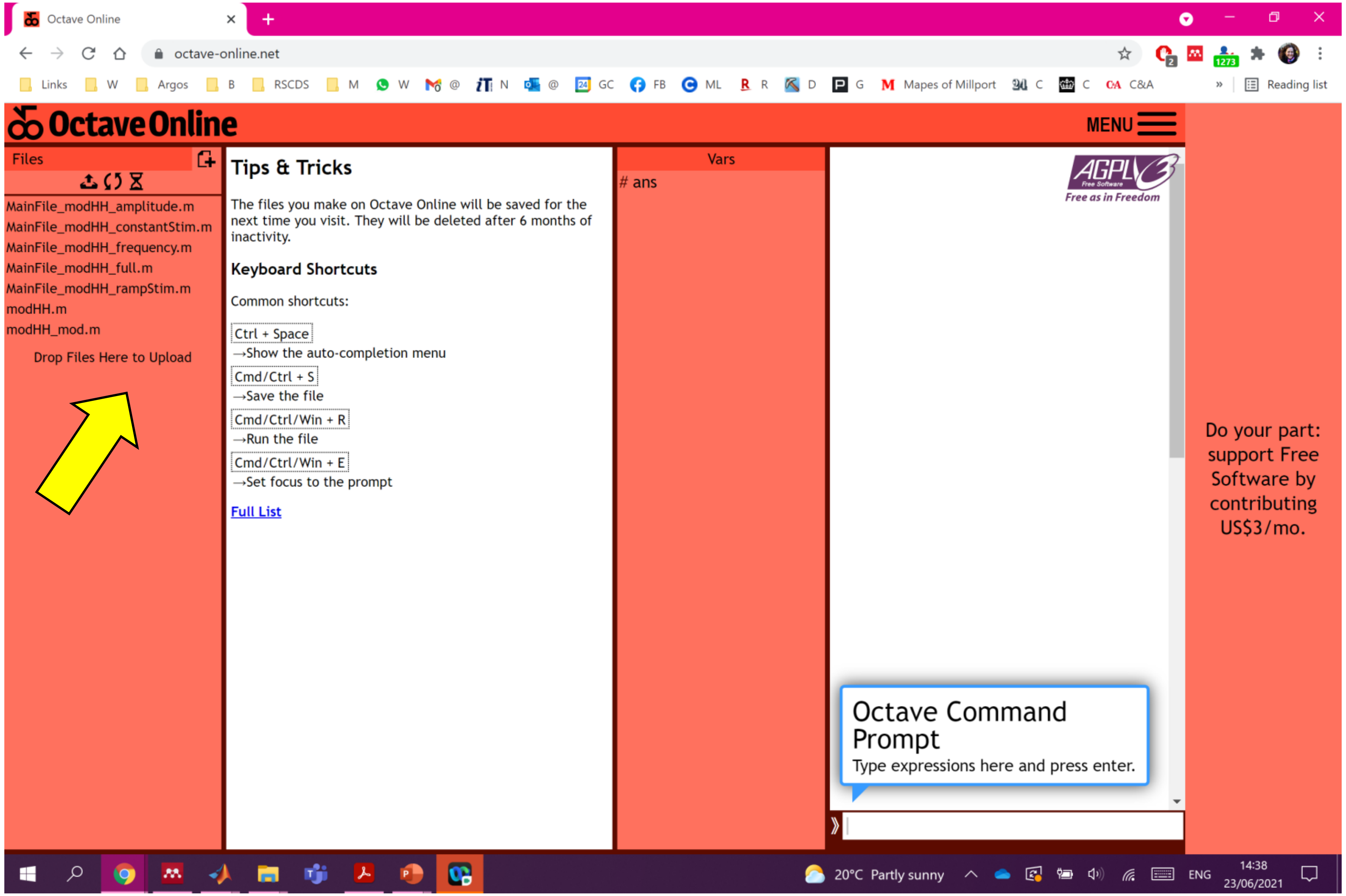

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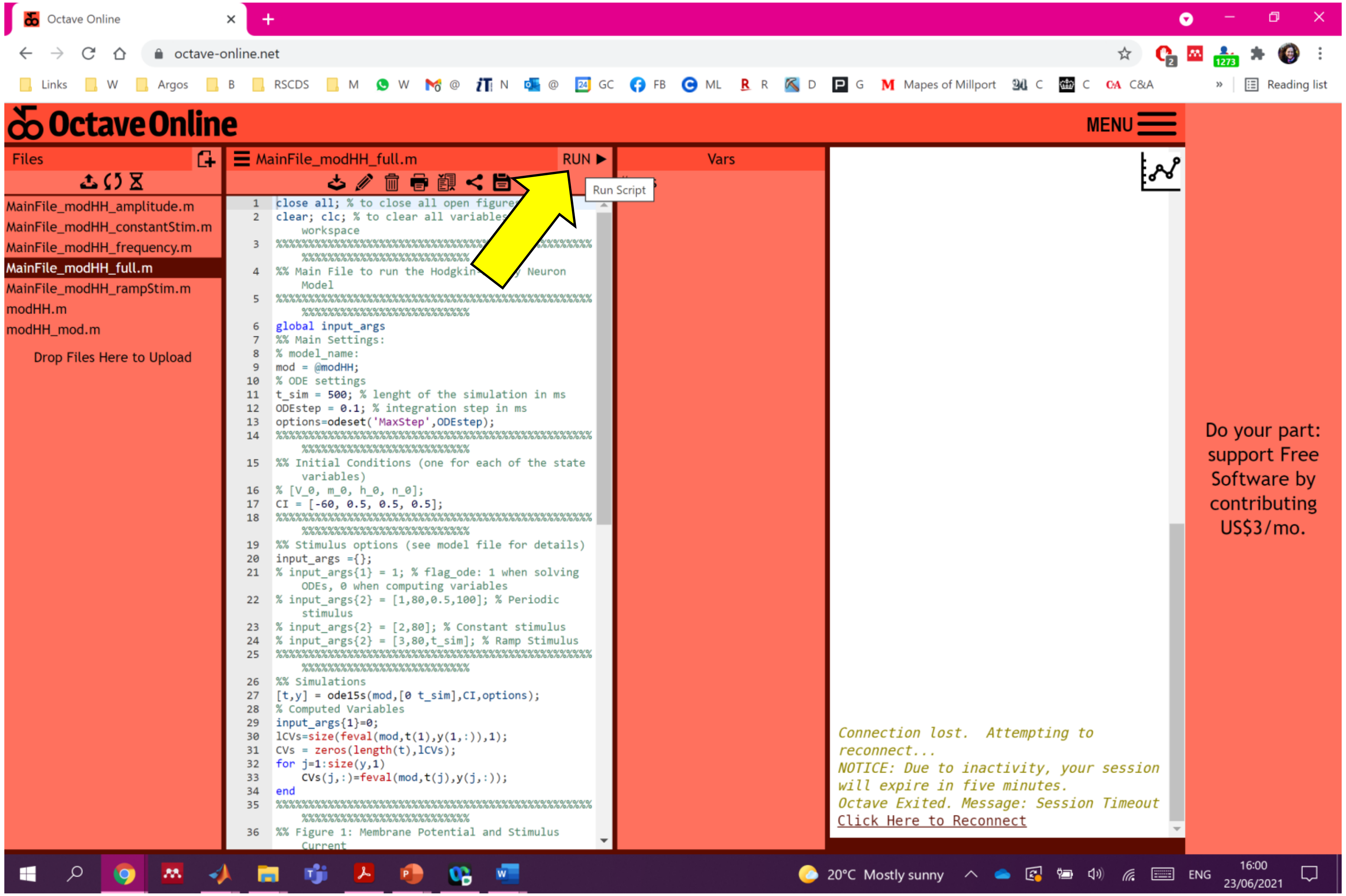
- Open the file MainFile_modHH and Run it



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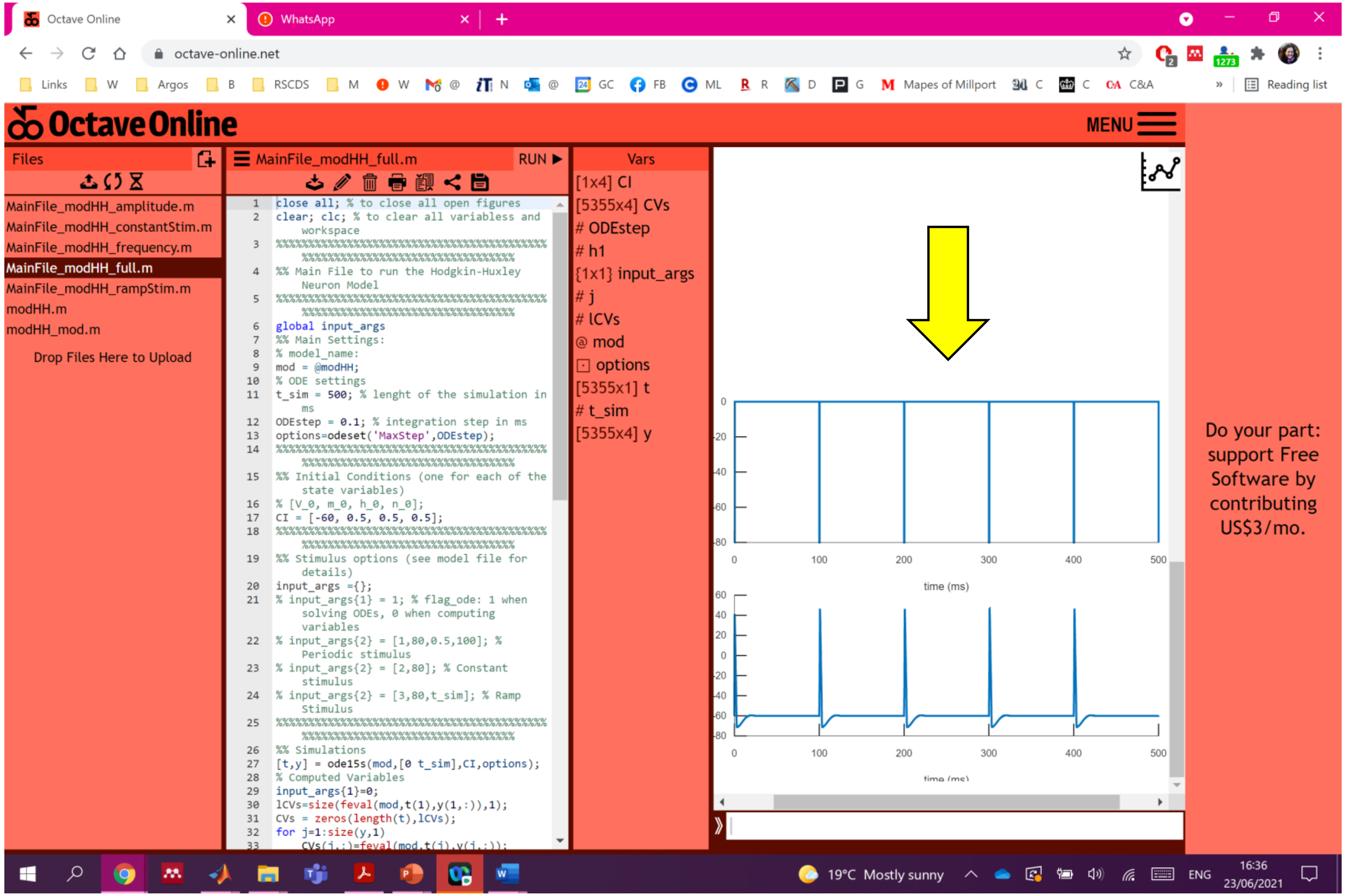
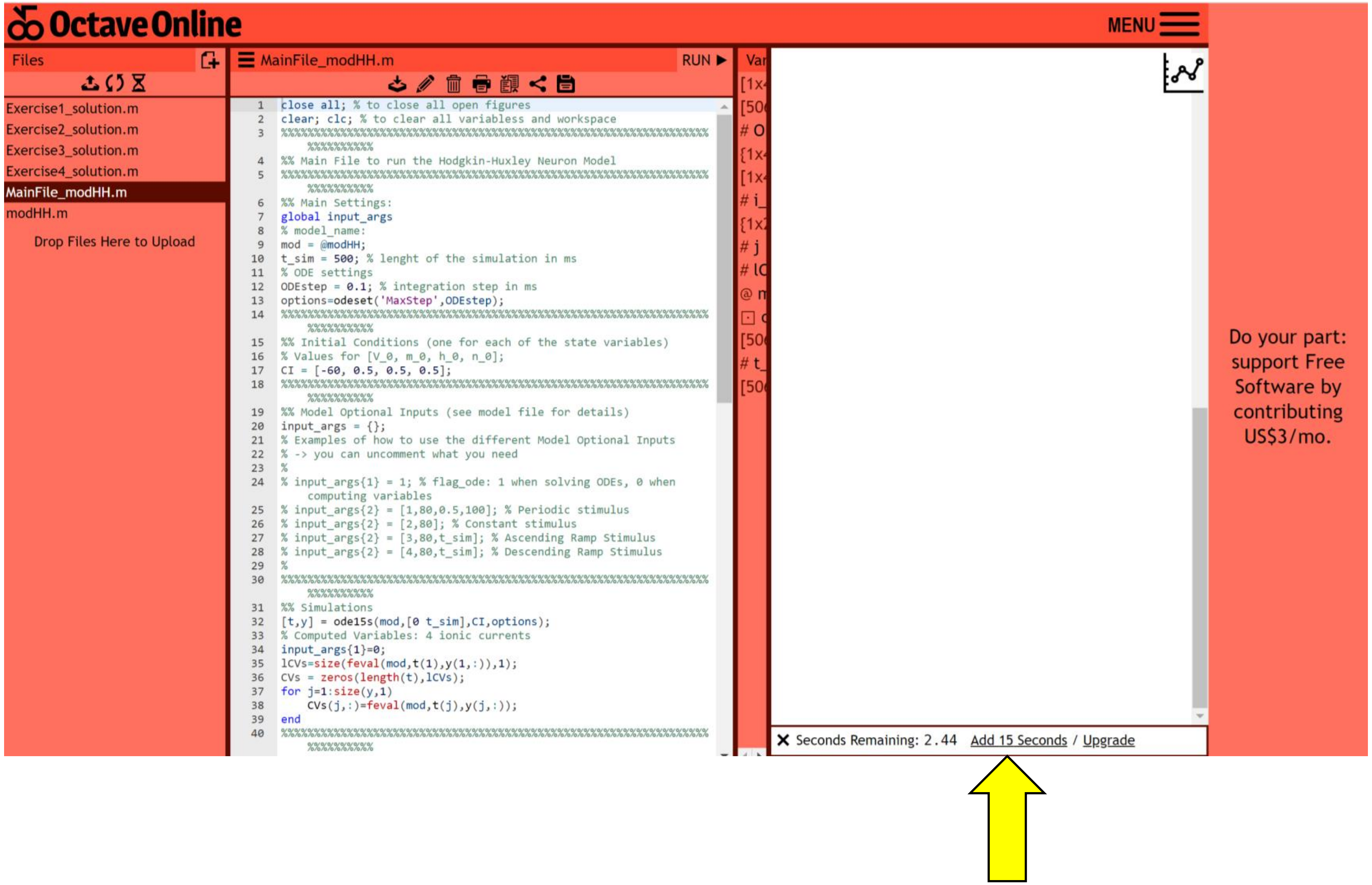
- Open the file MainFile_modHH and Run it: look at the results ☺



Hands-on Part 1: IMPORTANT

- When a file takes more than 10 seconds to run, you need to add computing time, by clicking on “Add 15 seconds”
- This might be needed a few times if the simulation is long



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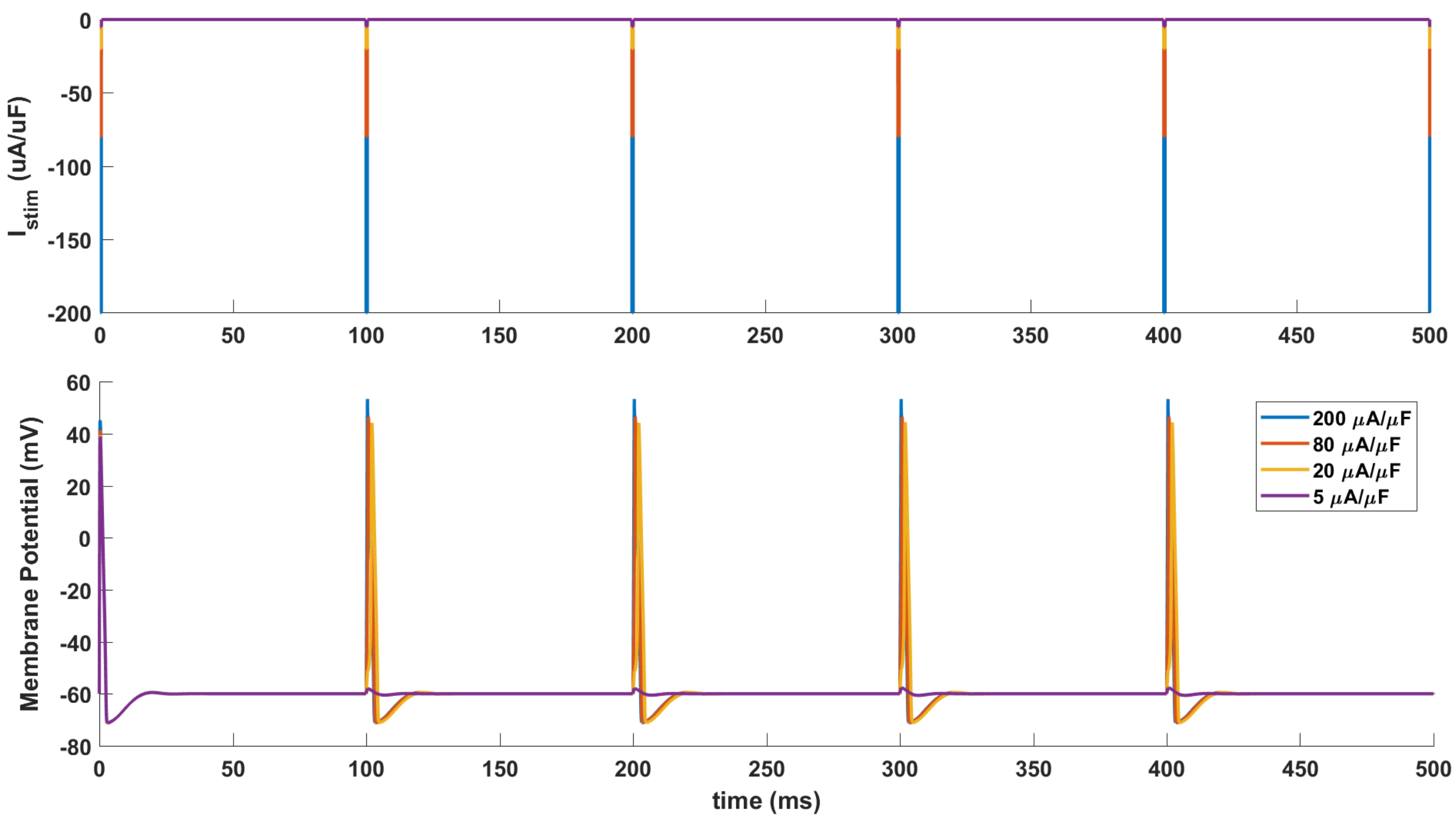
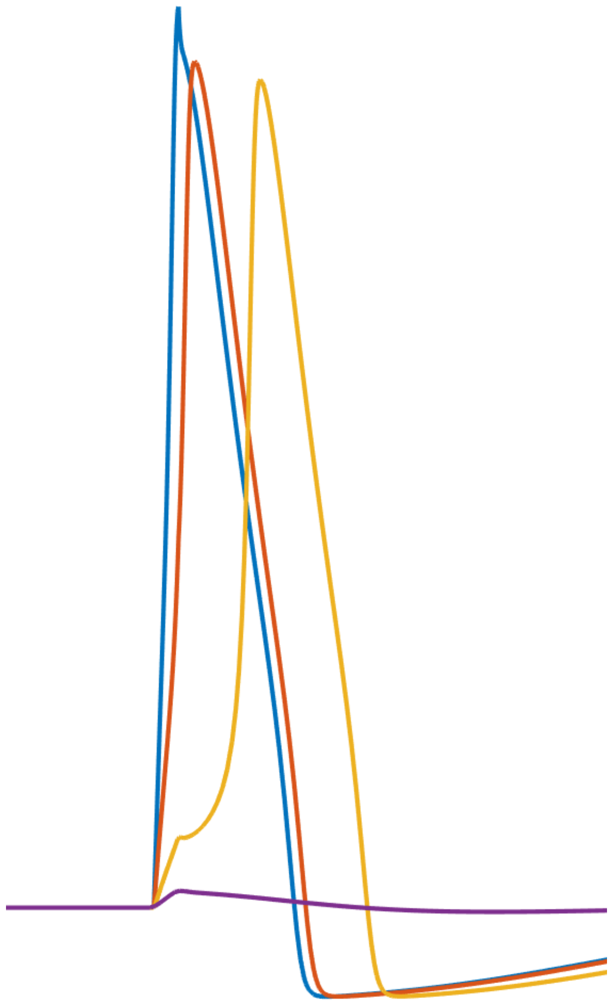
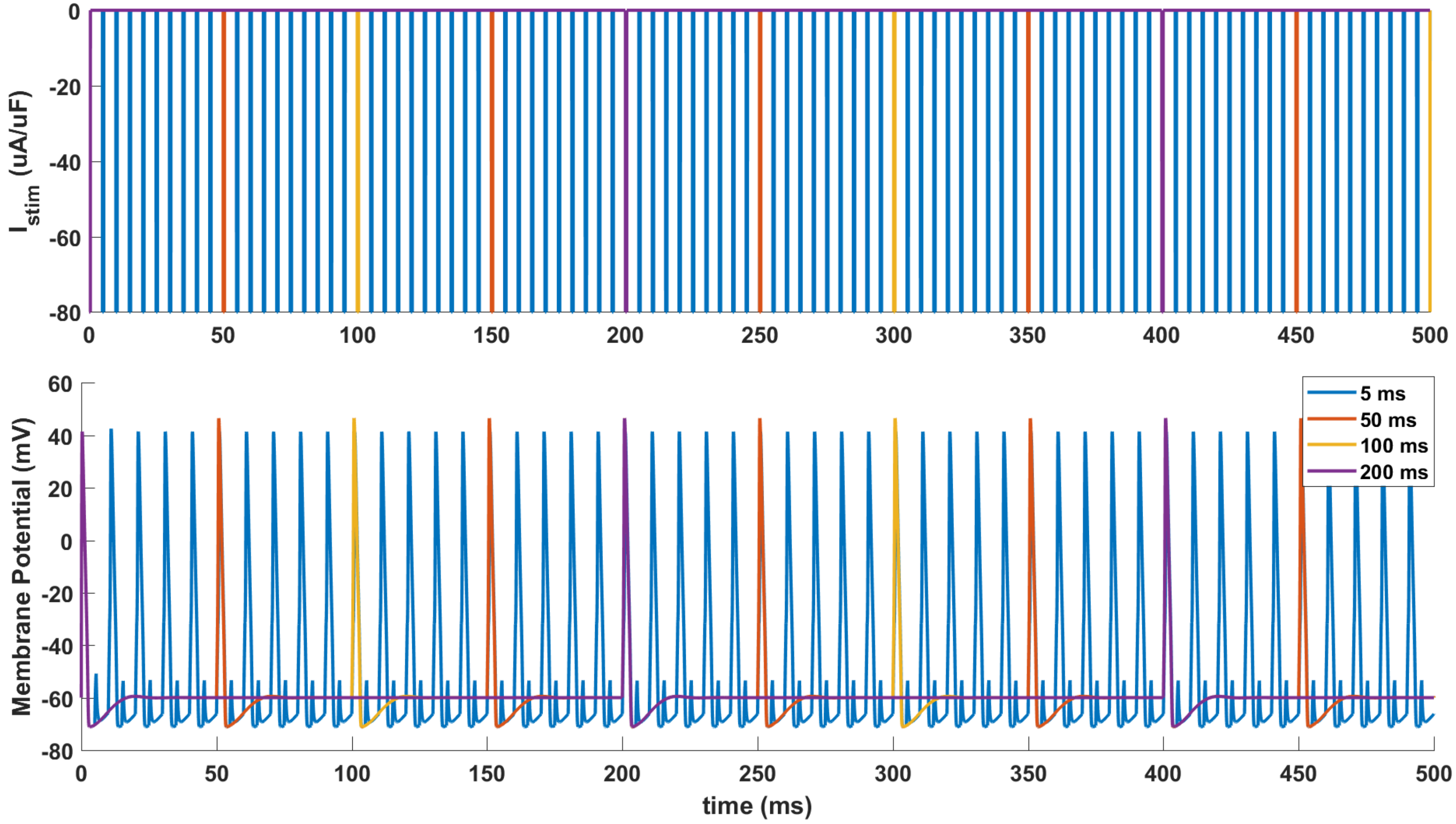
Summary and Conclusions

EXERCISE 1: Changes of Amplitude

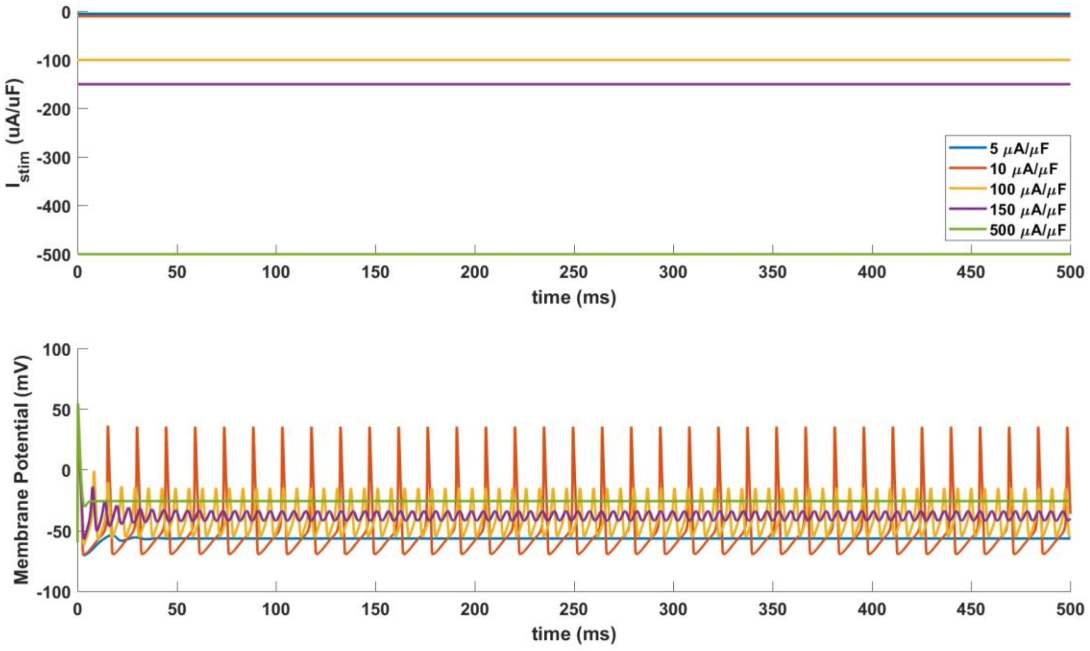


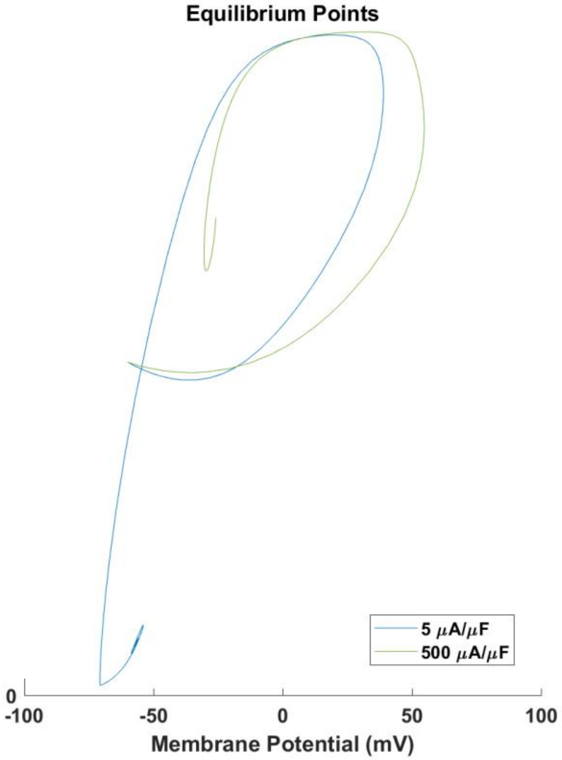


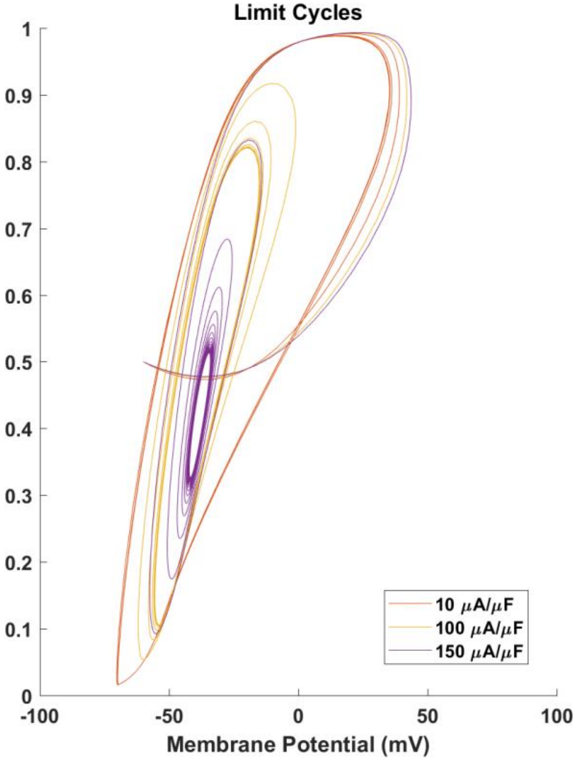
EXERCISE 2: Changes of Frequency



EXERCISE 3: Constant Stimulus

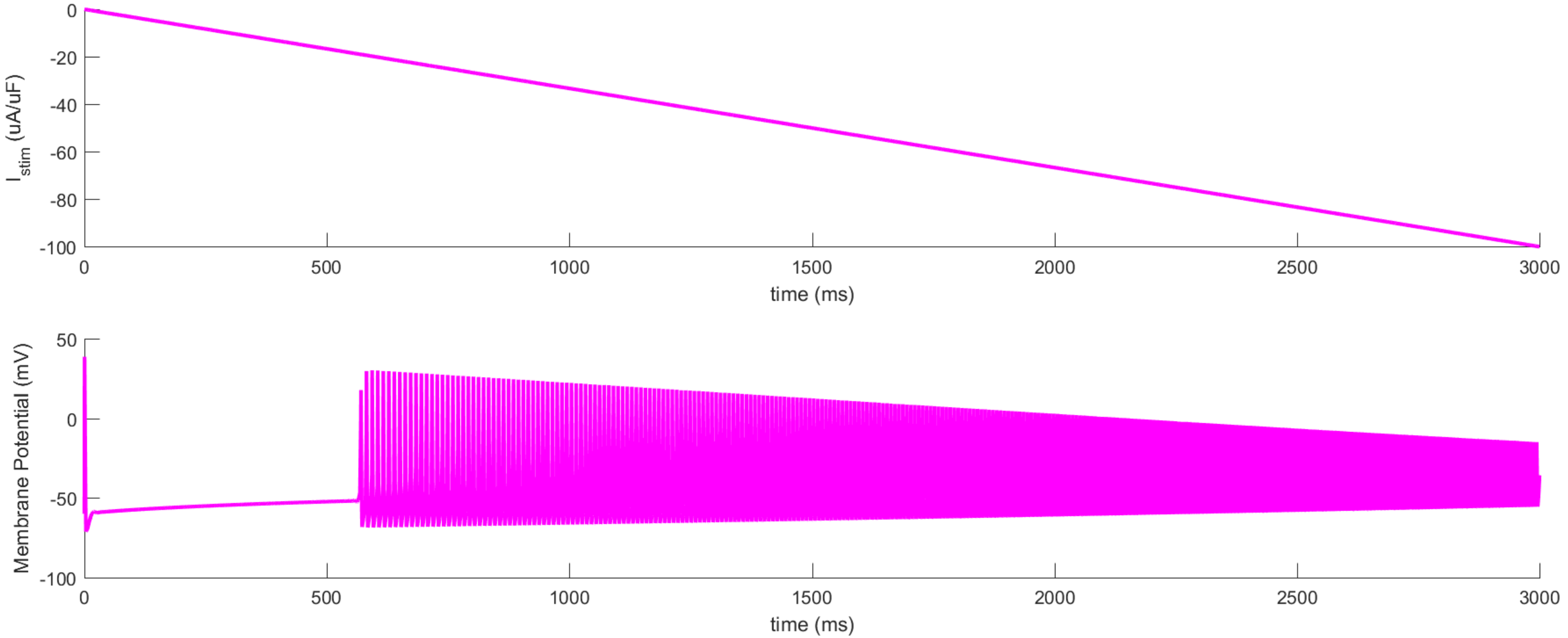




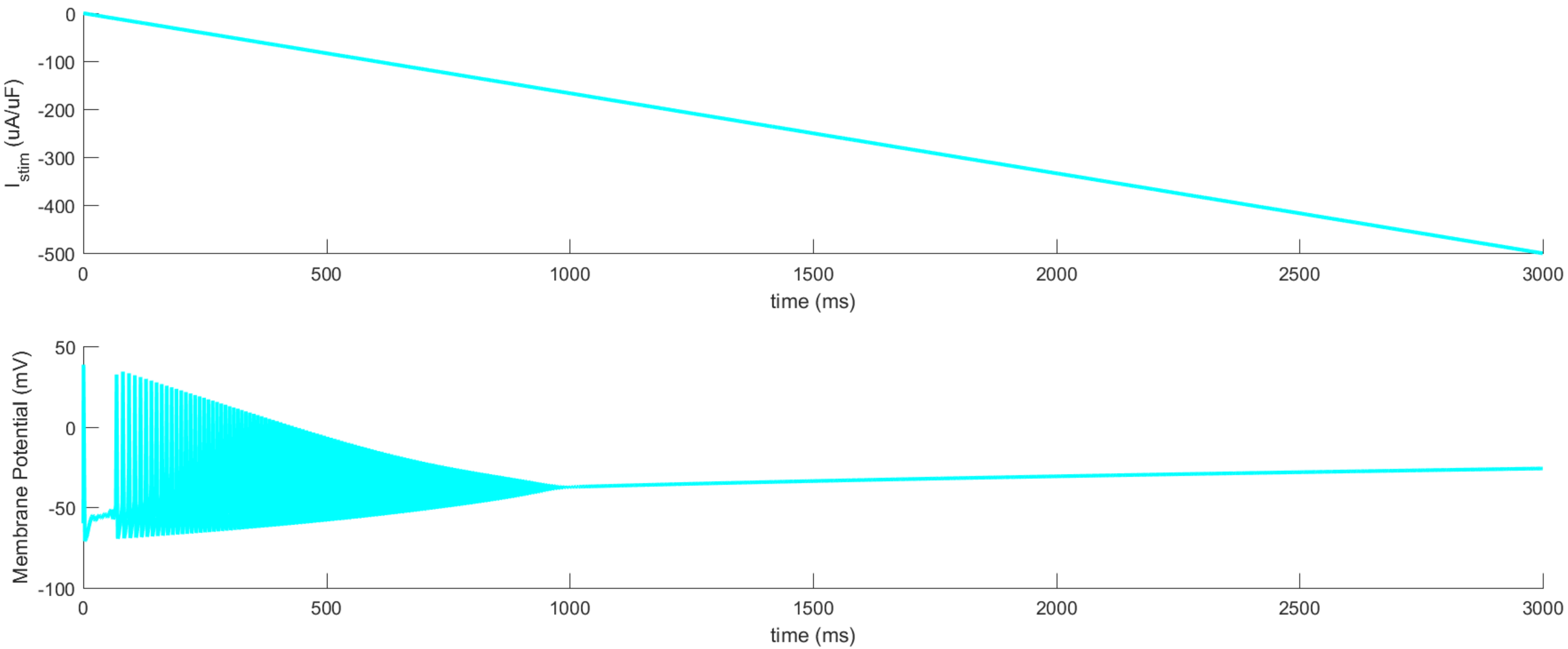


- OFF/ON Threshold: I_1: **approx. 7 μA/μF**
- ON/SAT Threshold: I_3: **approx. 162 μA/μF**

EXERCISE 4: Bifurcation (1)



EXERCISE 4: Bifurcation (2)



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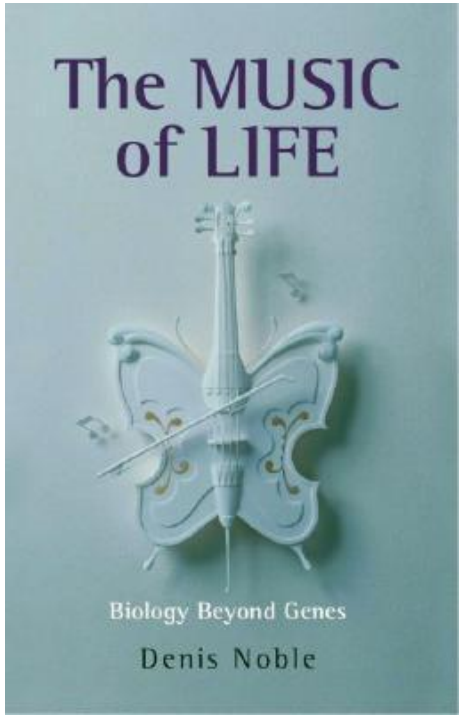
Summary and Conclusions

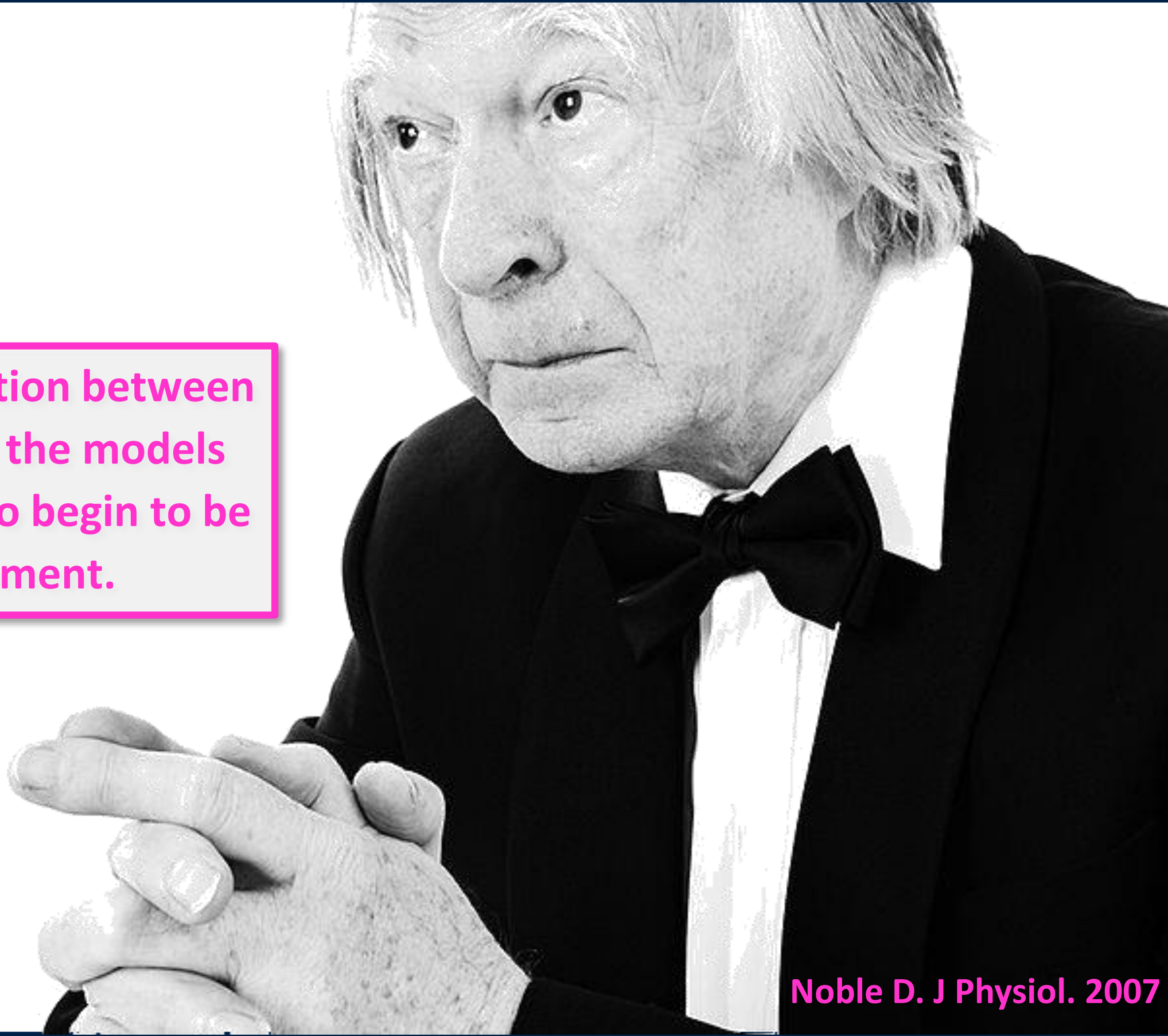
From H&H to the first Models of Cardiac Cells

- **Denis Noble** (Nature, 1960)
  - ✓ First Cardiac Action Potential model, based on the Hodgkin-Huxley equations
  - ✓ It was a Rabbit Purkinje model



With over 50 years of interaction between simulation and experiment, the models are now sufficiently refined to begin to be of use in drug development.

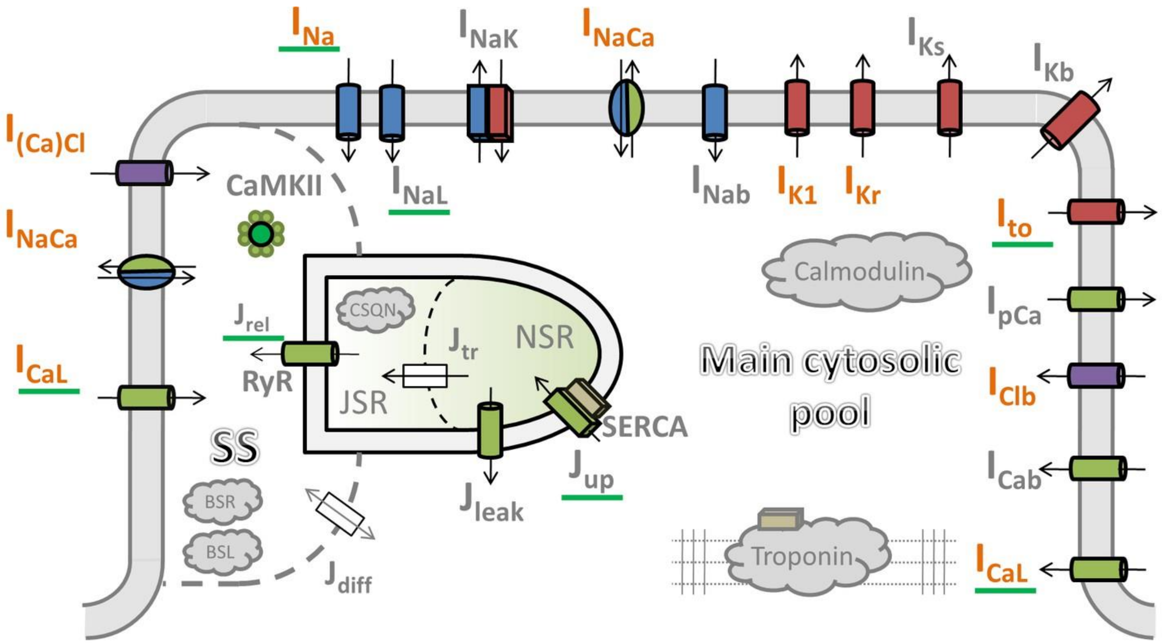
The first human cardiac models have been developed in the late '90s

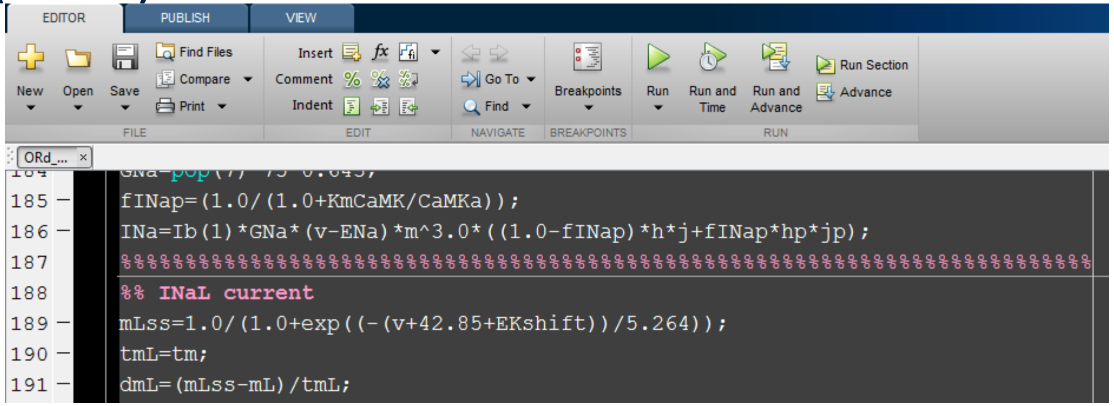


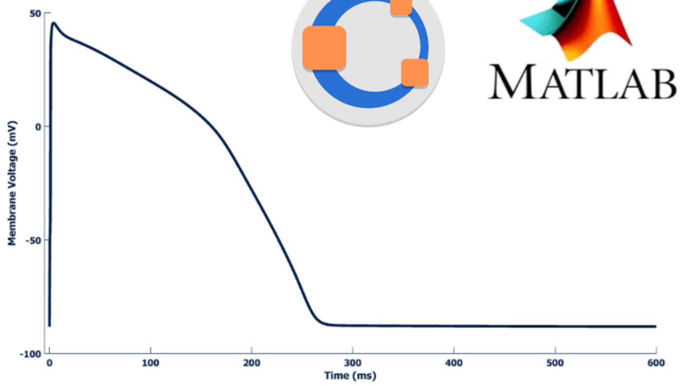
Noble D. J Physiol. 2007

A Human Ventricular Action Potential Model

- **Tomek et al. Human Ventricular Action Potential Model (2019)**
  - ✓ Based on the gold standard by O'Hara et al. (2011)







MATLAB

Human *In Silico* Drug Trials

Image Credit: Shutterstock

Possible drug identified → Animal testing → Clinical trials → Drug approved for sale

Drug approved for sale → Drug withdrawn from the market

Prospective Validation ↑ (Possible drug identified → Animal testing)

Retrospective Validation ↗ Drug approved for sale; → Drug withdrawn from the market

Human *In Silico* Drug Trials

Image Credit: Shutterstock

Possible drug identified → Animal testing → Clinical trials → Drug approved for sale → Drug withdrawn from the market

Prospective Validation

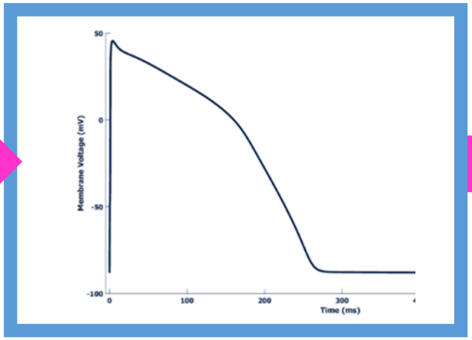
To build credibility in the models

Retrospective Validation

In Silico Drug Trials: Design

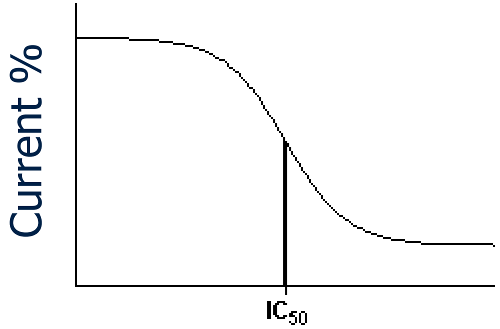
INPUTs

Drug effects on ion channels

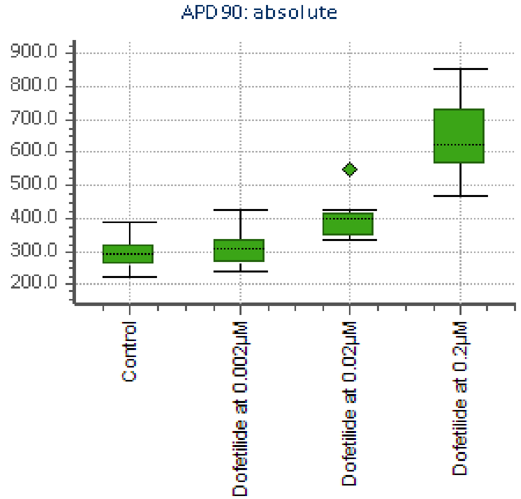


OUTPUTs

Drug-induced changes in AP

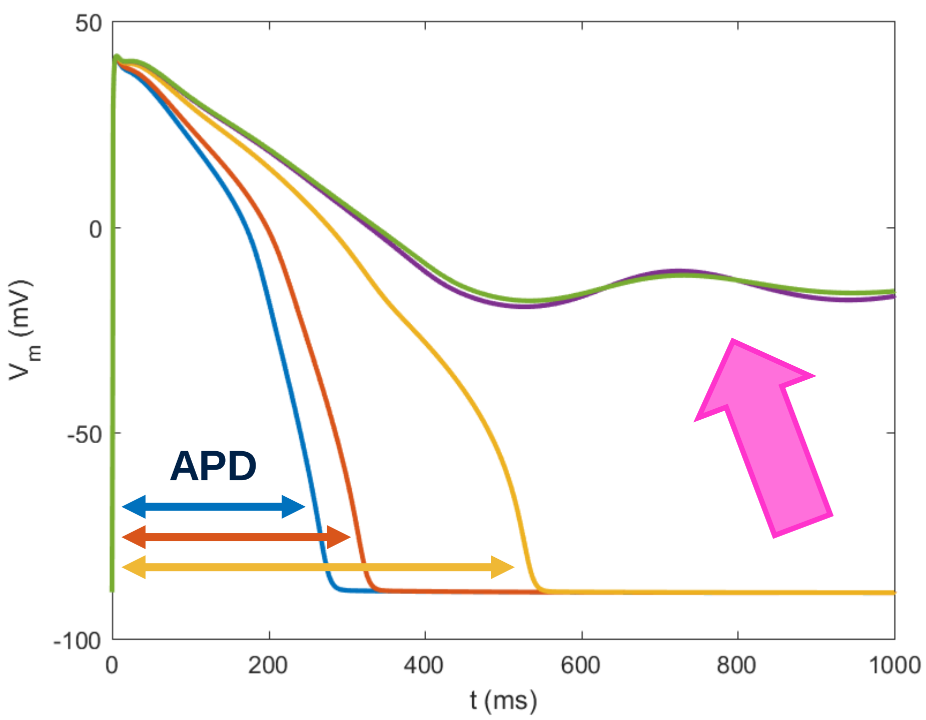


$$Current\ \% = \frac{1}{1+(\frac{x}{IC50})^h}$$

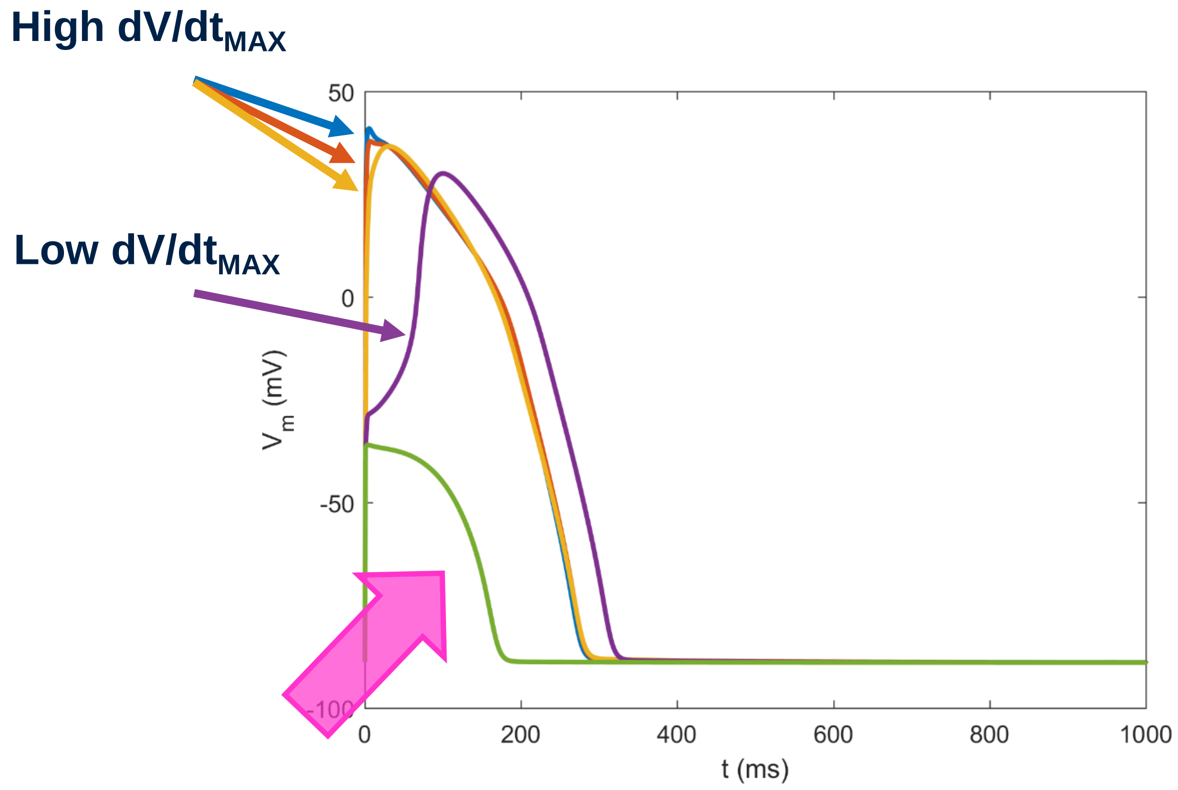


Biomarkers and Drug-induced Abnormalities

- Action Potential Duration (APD)
  - ✓ When the APD is too prolonged, **Repolarisation Abnormalities** are observed

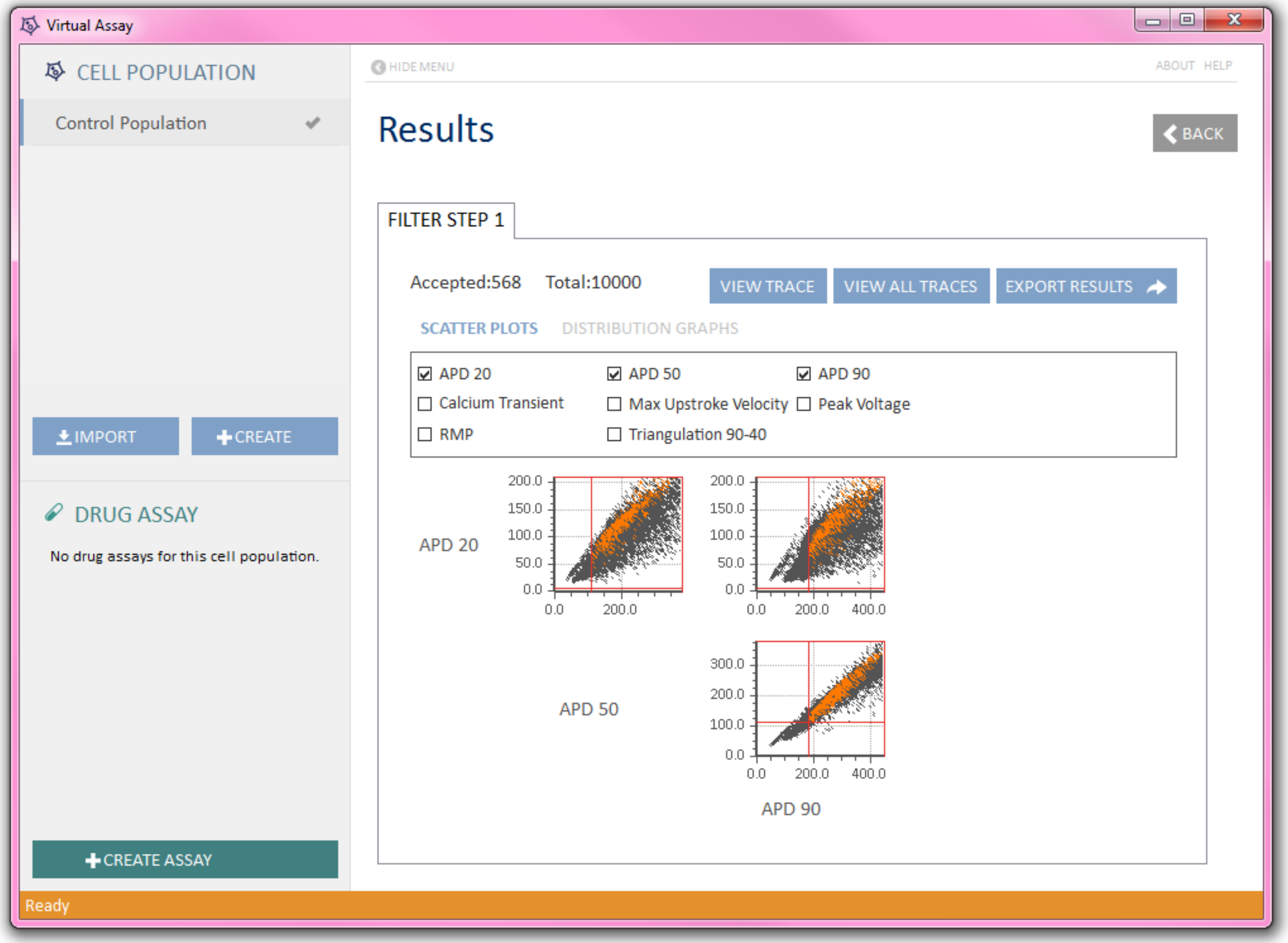


- Max Upstroke Velocity (dV/dt_{MAX})
  - ✓ When the dV/dt_{MAX} is decreased too much, **Depolarisation Abnormalities** are observed



Virtual Assay Software

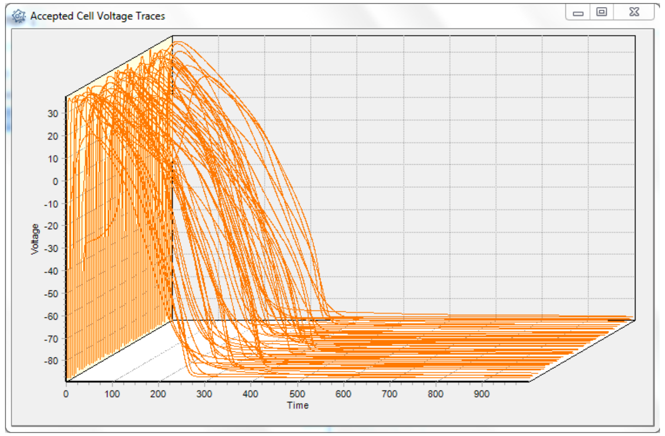
- *In Silico* predictions of inter-subject variability in drug response



OXFORD UNIVERSITY INNOVATION

Oxford Computer Consultants

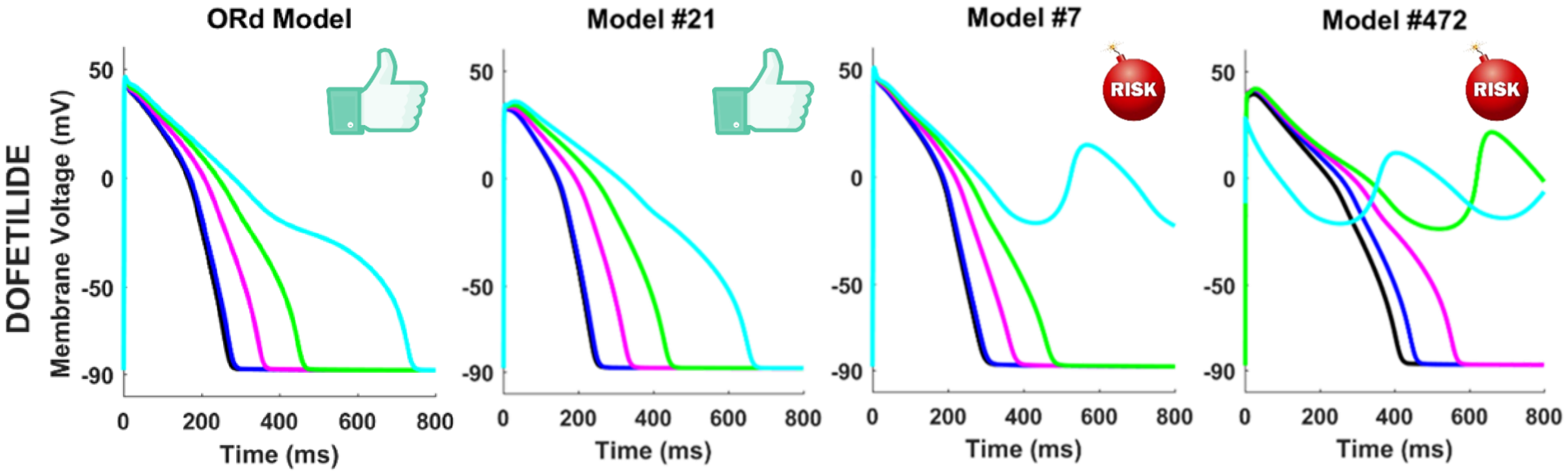
EPSRC



Human

Virtual Assay

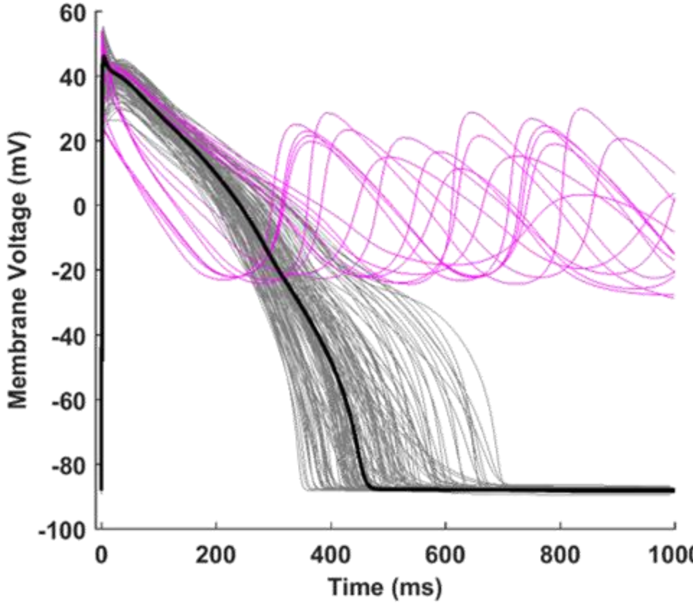
In Silico Drug Trials: RESULTS

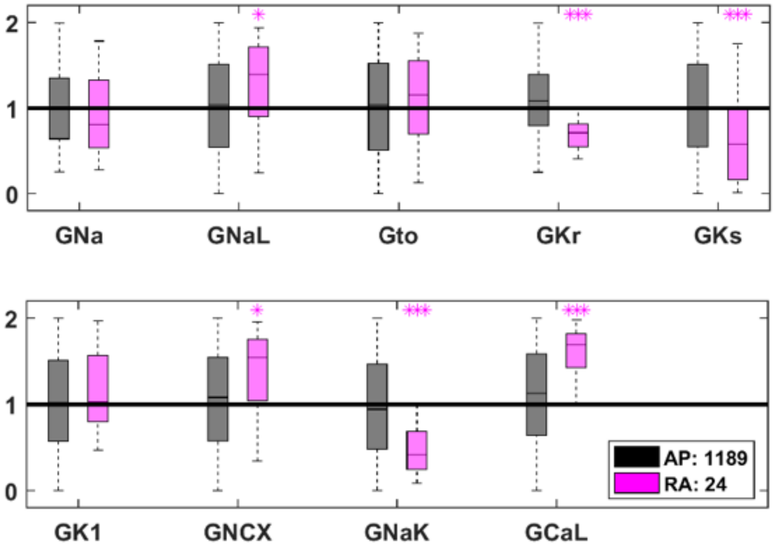


TRUE +	TRUE –
26	23
FALSE +	**FALSE –**
0	6

Computer models

Accuracy: 89 %





	Patients	Models
TRUE +	RISK	RISK
TRUE -		
FALSE +		RISK
FALSE -	RISK	

Passini et al. Front Physiol. 2017

Towards Replacement of Animal Experiments

frontiers in Physiology

ORIGINAL RESEARCH
published: 12 September 2017
doi: 10.3389/fphys.2017.00668

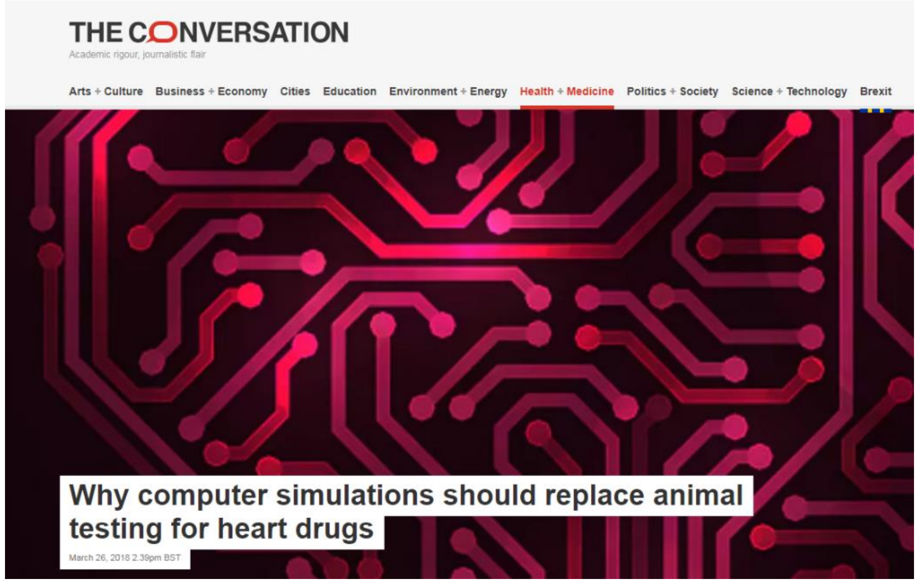
Human *In Silico* Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity

Elisa Passini[1], Oliver J. Britton[1], Hua Rong Lu[2], Jutta Rohrbacher[2], An N. Hermans[2], David J. Gallacher[2], Robert J. H. Greig[3], Alfonso Bueno-Orovio[1] and Blanca Rodriguez[1]*

[1] Computational Cardiovascular Science Group, Department of Computer Science, University of Oxford, Oxford, United Kingdom, [2] Global Safety, Pharmacology, Discovery Sciences, Janssen Research and Development, Janssen Pharmaceutica NV, Beerse, Belgium, [3] Oxford Computer Consultants Ltd., Oxford, United Kingdom

TRUE +	TRUE –
26	23
FALSE +	**FALSE –**
0	6

Computer models
Accuracy: 89 %



Animal experiments
Accuracy: 75-85 %

Passini et al. Front Physiol. 2017

Outline

Royal Institution Masterclasses in Computer Science: Year 10, 2021

Computational Biology

Part I

1) **9.30-9.45: Introduction**

   Computational Biology and Computer Models of the Action Potential

1) **9.45-10.45: Hands-on**

   The Hodgkin & Huxley model

Break (15 mins)

Part II

1) **11:00-11:15: Introduction**

   Computer Models of the Heart and Drug Safety Testing

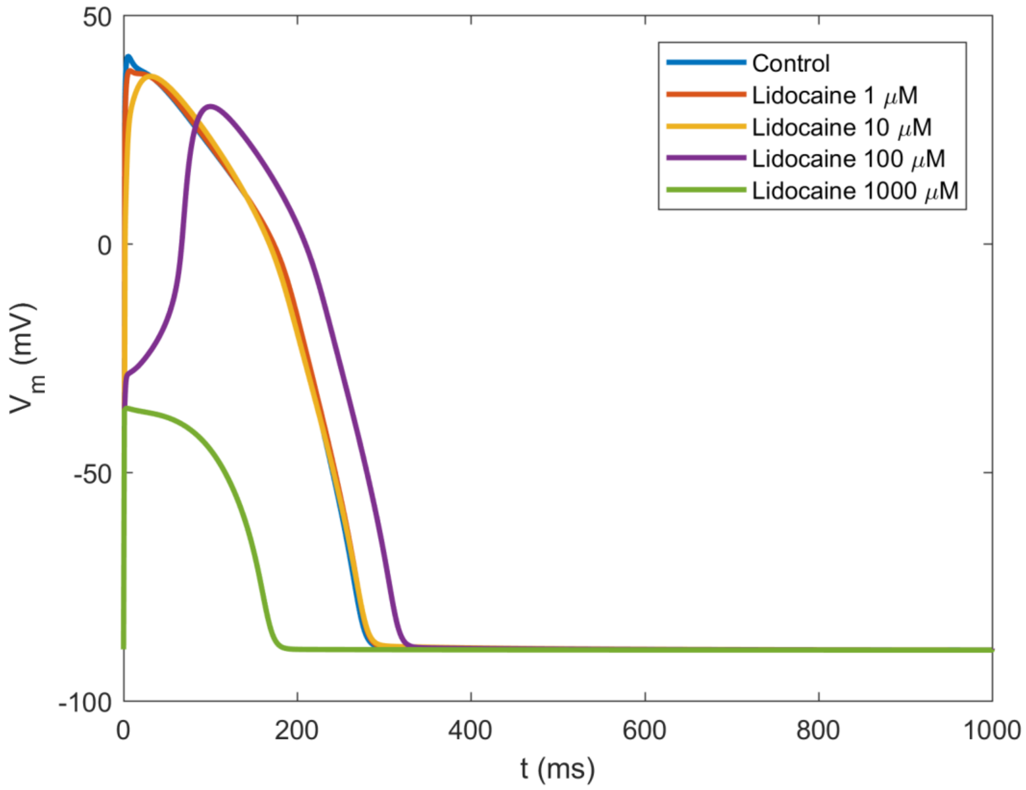
1) **11.15-11:45: Hands-on**

   Human in Silico Drug Trials

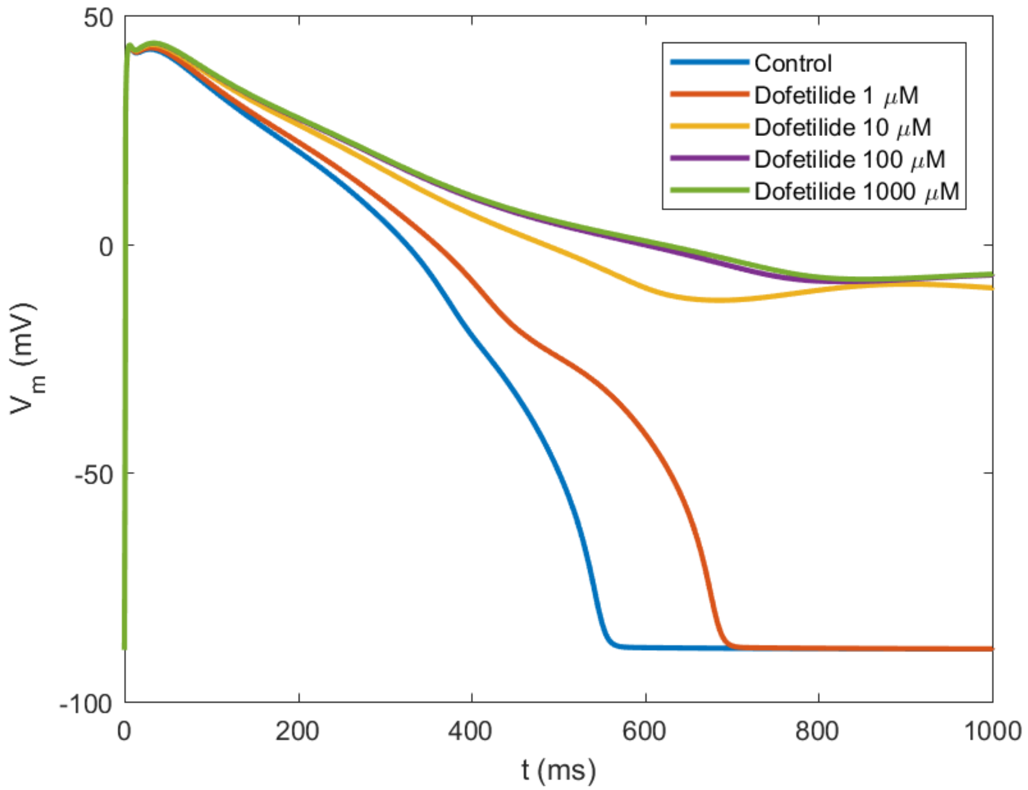
Summary and Conclusions

EXERCISE 1: Lidocaine and Dofetilide

- Lidocaine
  - ✓ Decreased dV/dt_{MAX}
  - ✓ Depolarisation Abnormalities at high concentrations

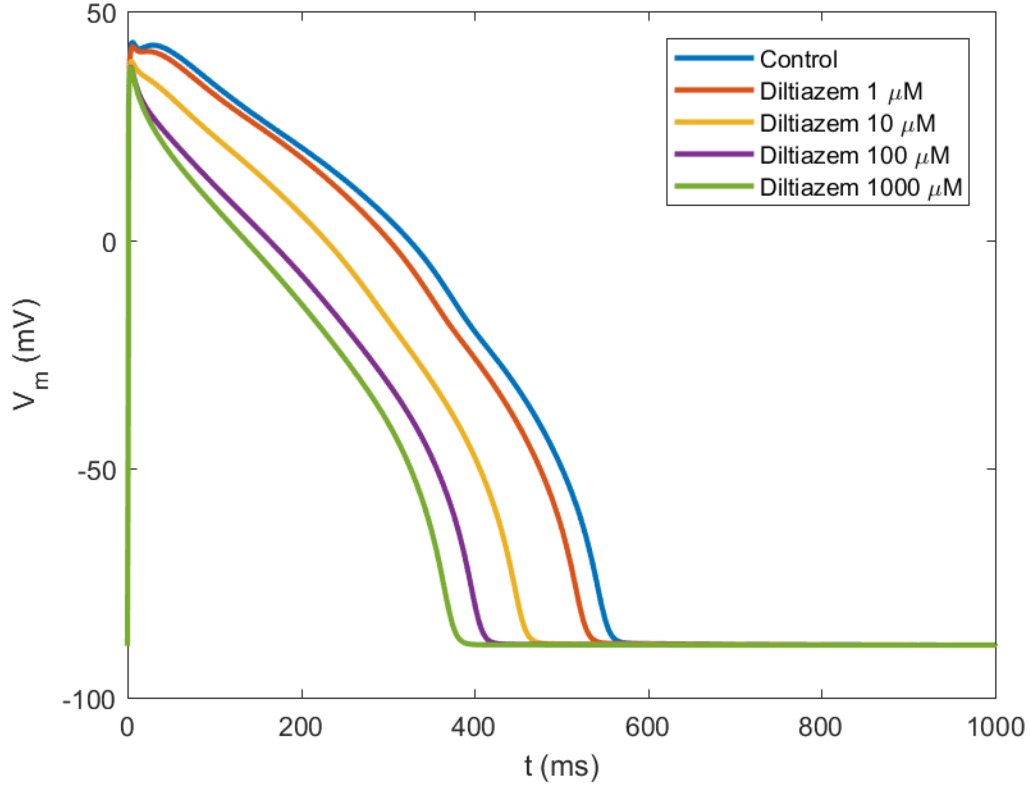


- Dofetilide
  - ✓ Increased APD_{90}
  - ✓ Repolarisation Abnormalities at high concentrations

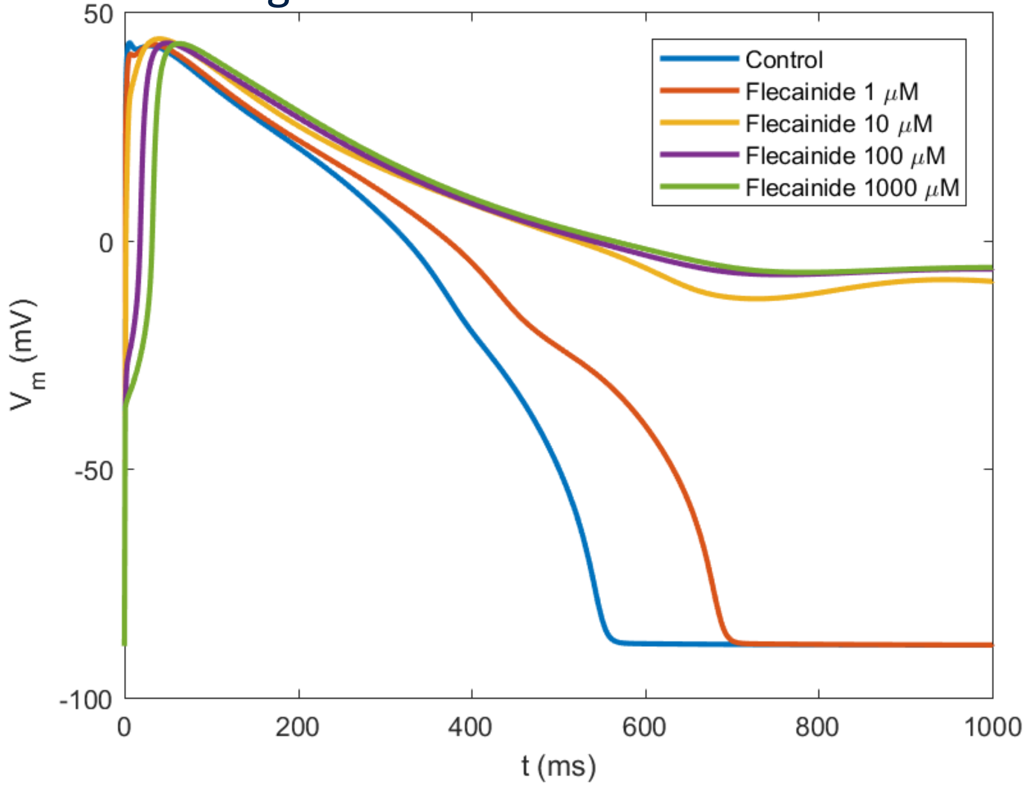


EXERCISE 1: Diltiazem and Flecainide

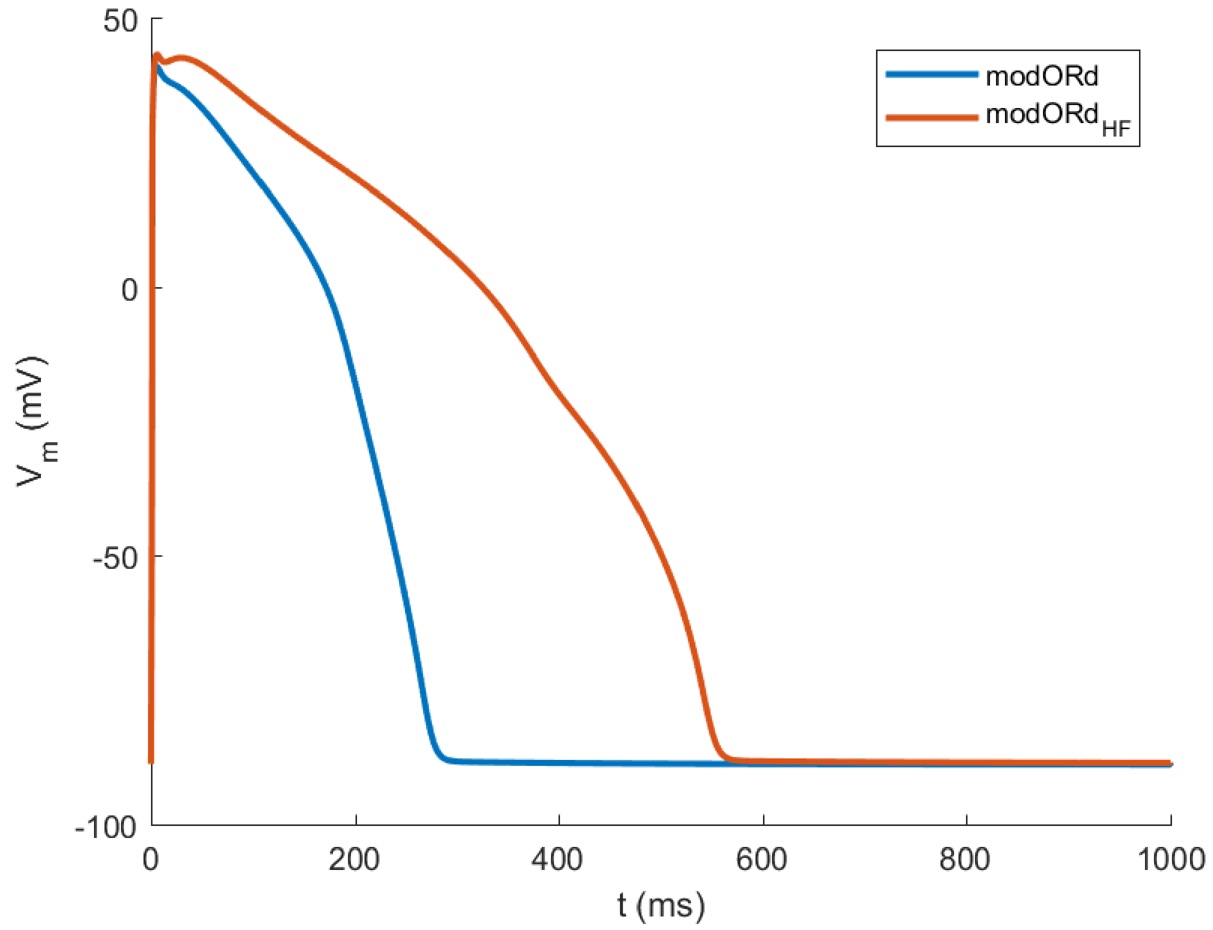
- Diltiazem
  - ✓ Decreased APD_{90}
  - ✓ No abnormalities observed



- Flecainide
  - ✓ Decreased dV/dt_{MAX} and increased APD_{90}
  - ✓ Repolarisation Abnormalities at high concentrations

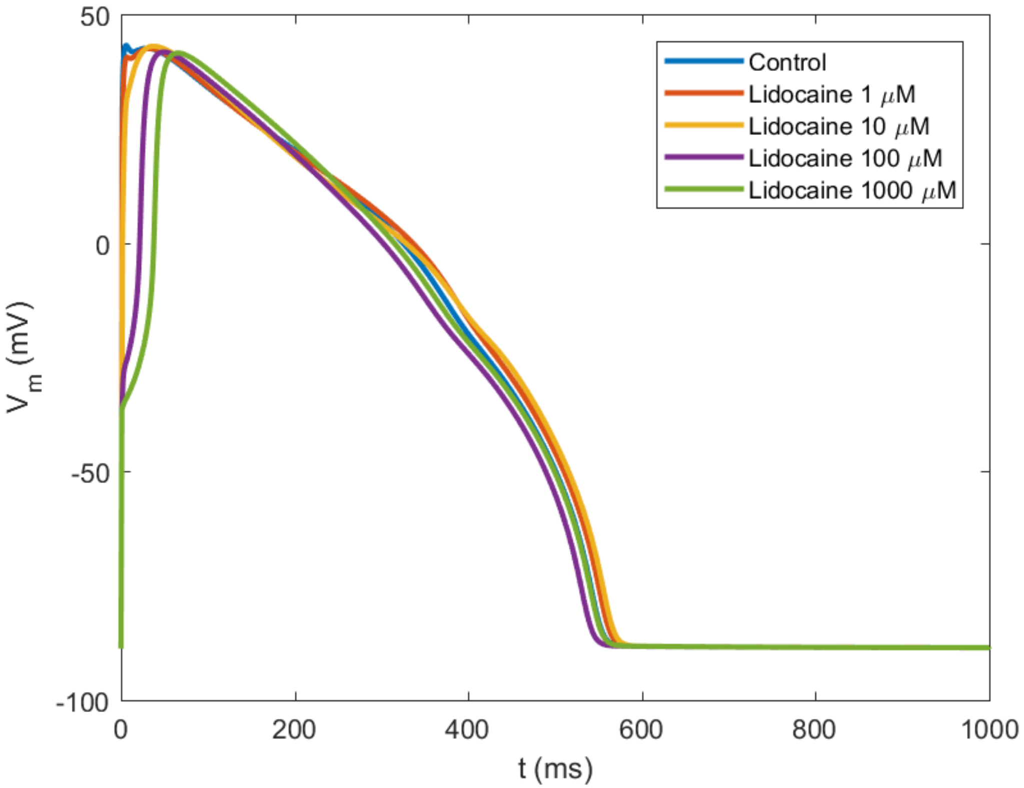


EXERCISE 2: Control vs Heart Failure

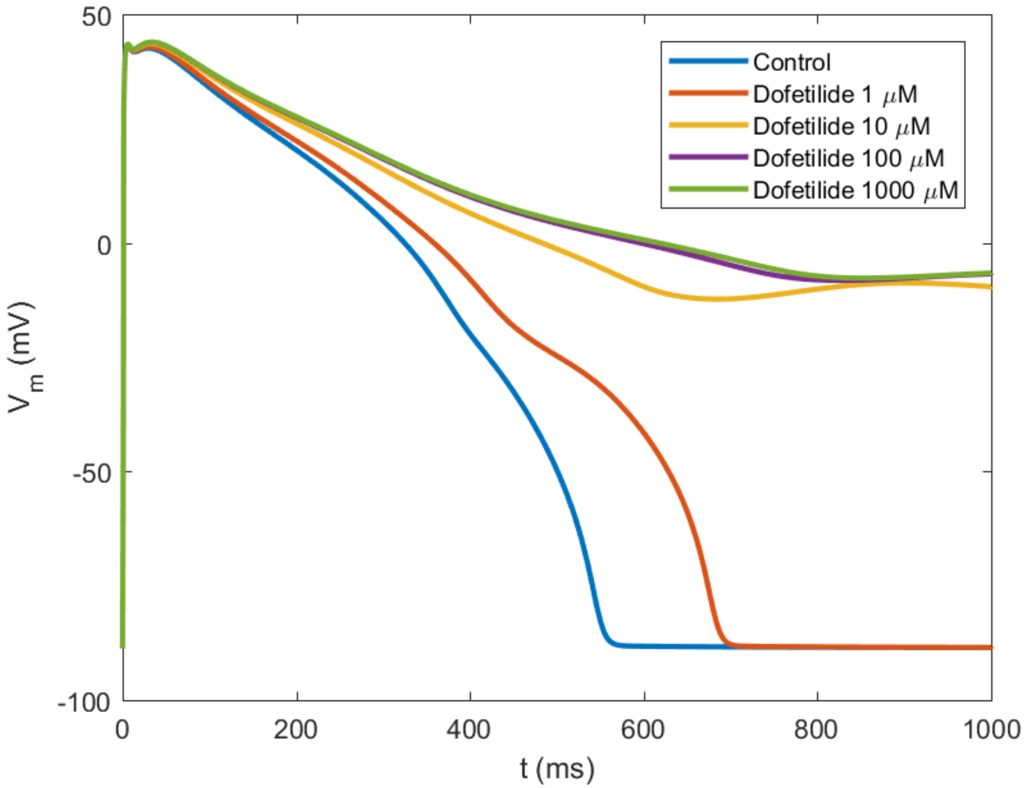


EXERCISE 2: Drug Effects with HF

- Lidocaine
  - ✓ No abnormalities observed

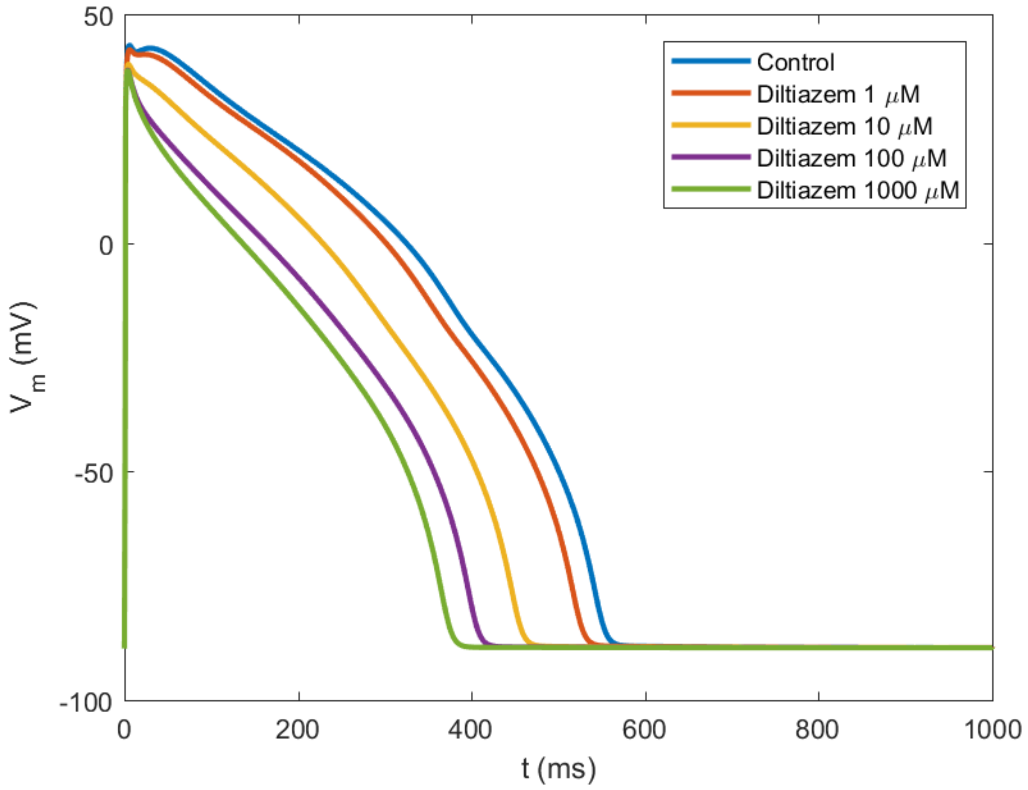


- Dofetilide
  - ✓ More repolarisation Abnormalities

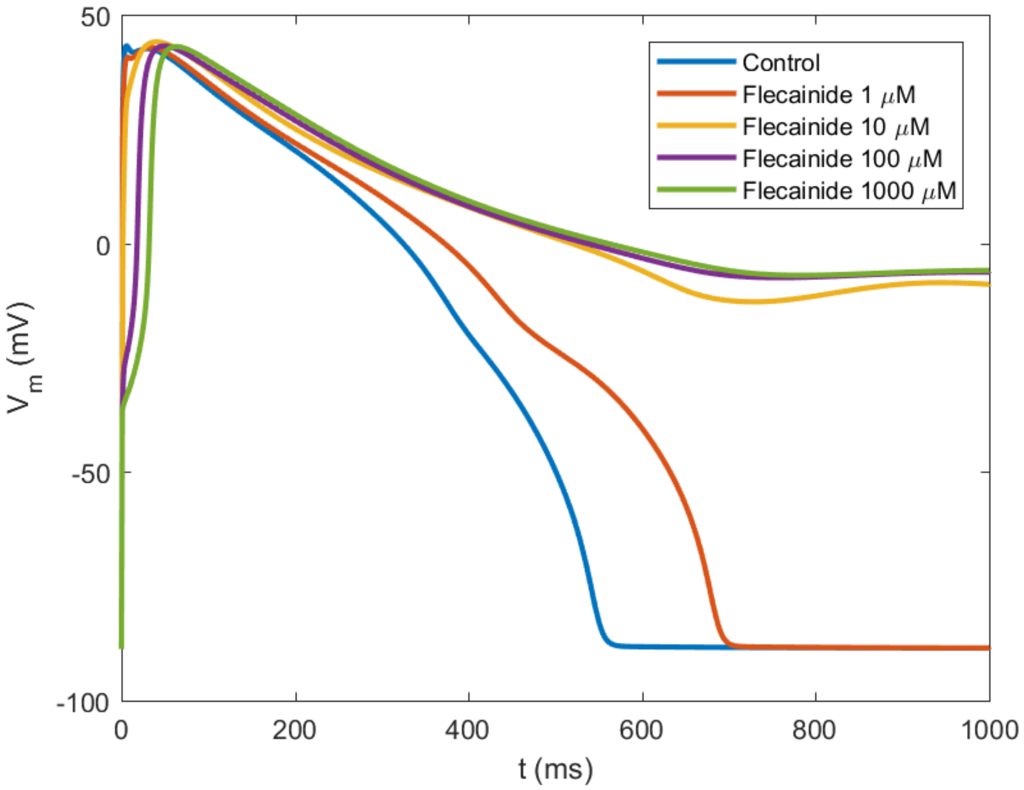


EXERCISE 2: Drug Effects with HF

- Diltiazem
  - ✓ No major differences observed



- Flecainide
  - ✓ More repolarisation Abnormalities



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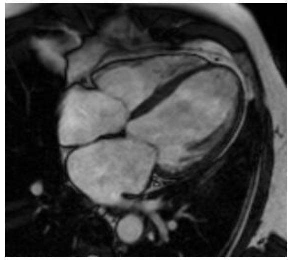
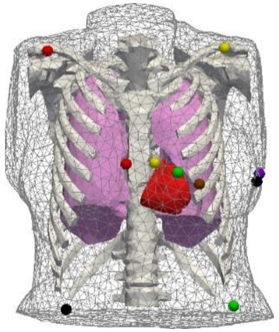
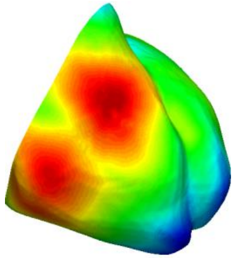
Summary and Conclusions

From the Ion Channel to the ECG

Tissue/Organ

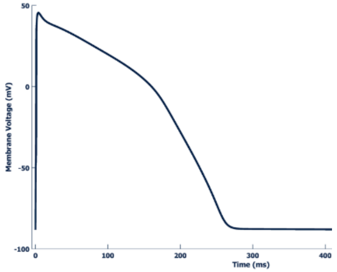


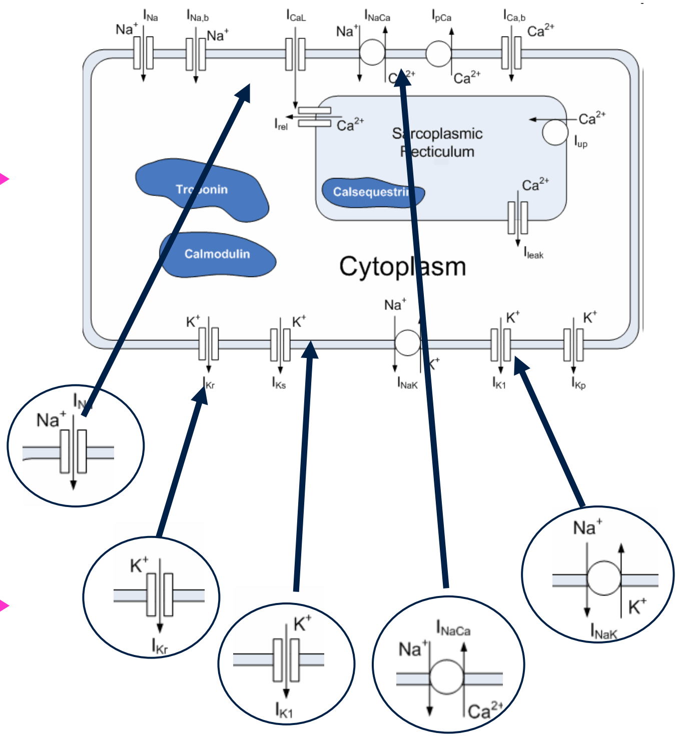




Whole-Organ models

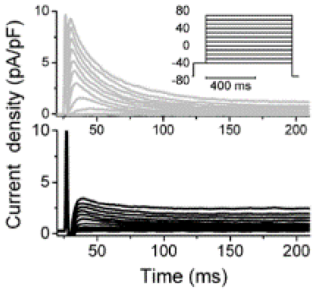
Single Cell





Action potential models

Ion Channel

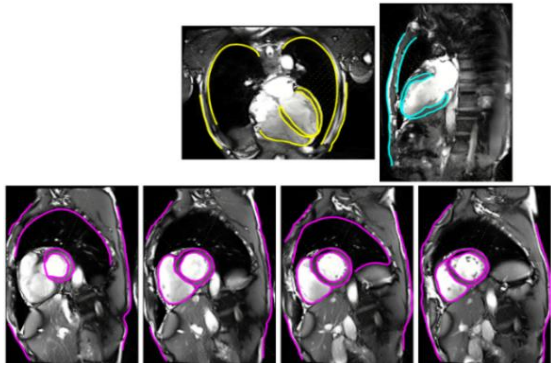


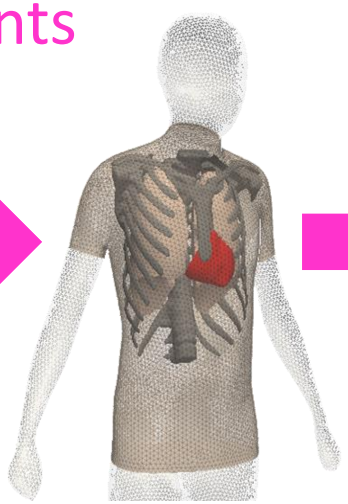
Ionic current models

Image credits: Doregan (cardiac MRI), Coppini et al. Circ Res. 2013 , Carusi et al. AJP 2012

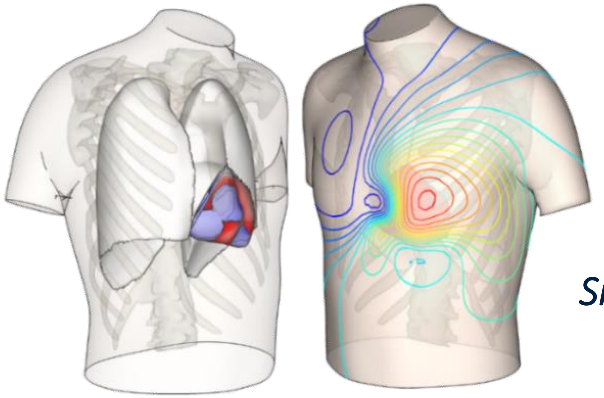
Towards Personalised Heart Models

Clinical Images from Patients



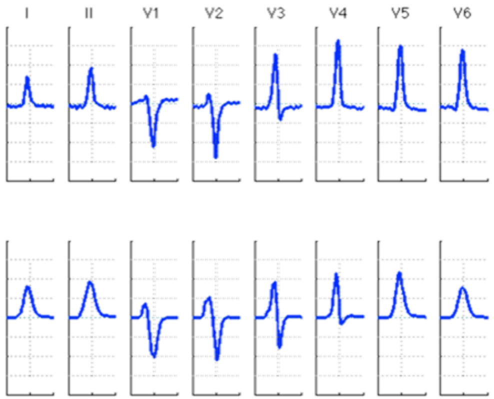


High Performance Computing Simulations

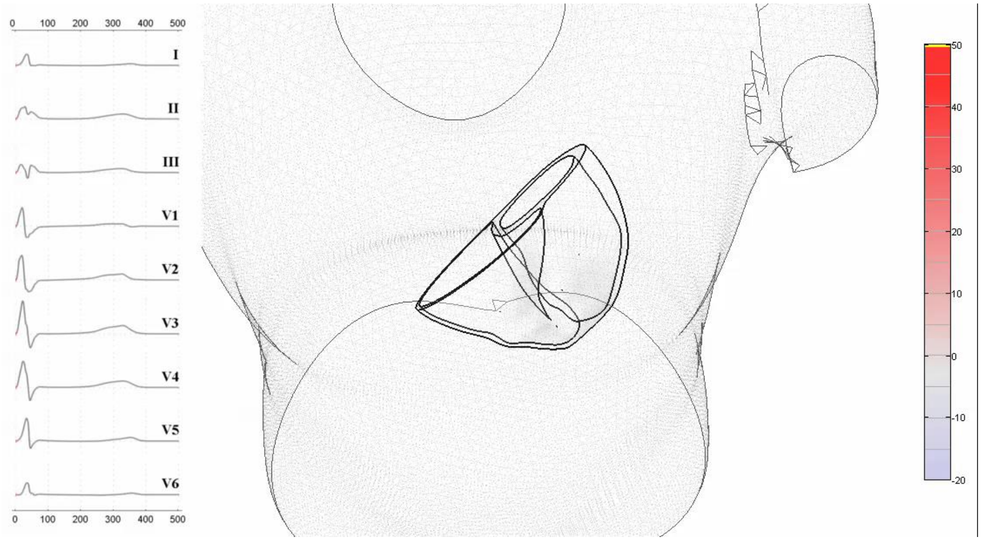


Patient ECG

Simulated ECG

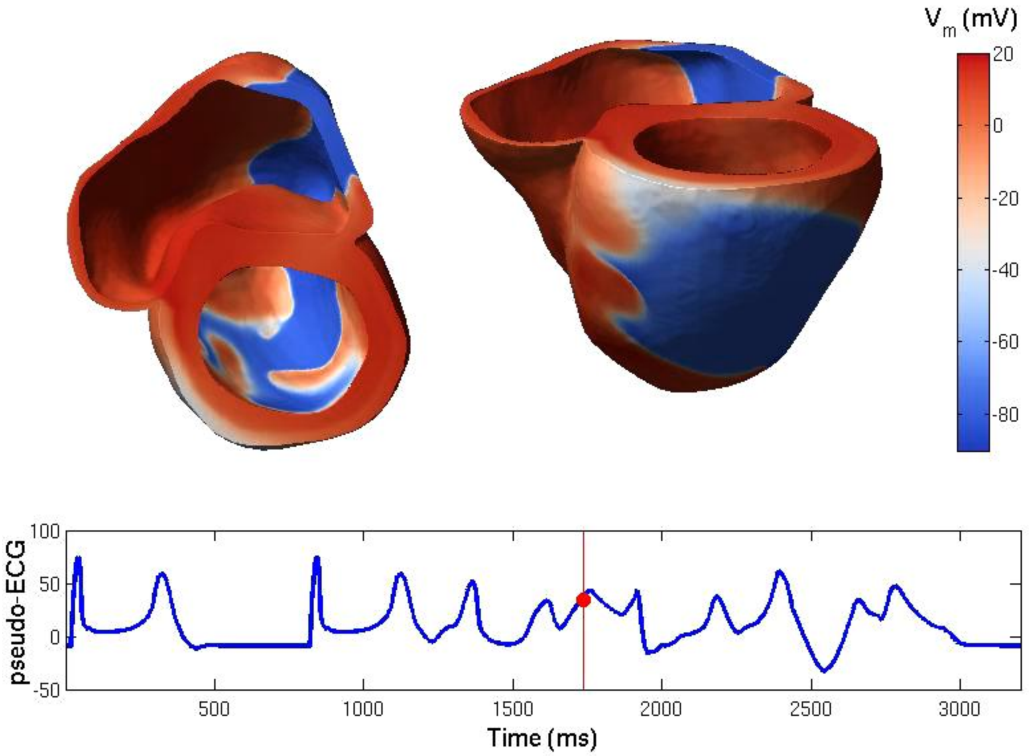


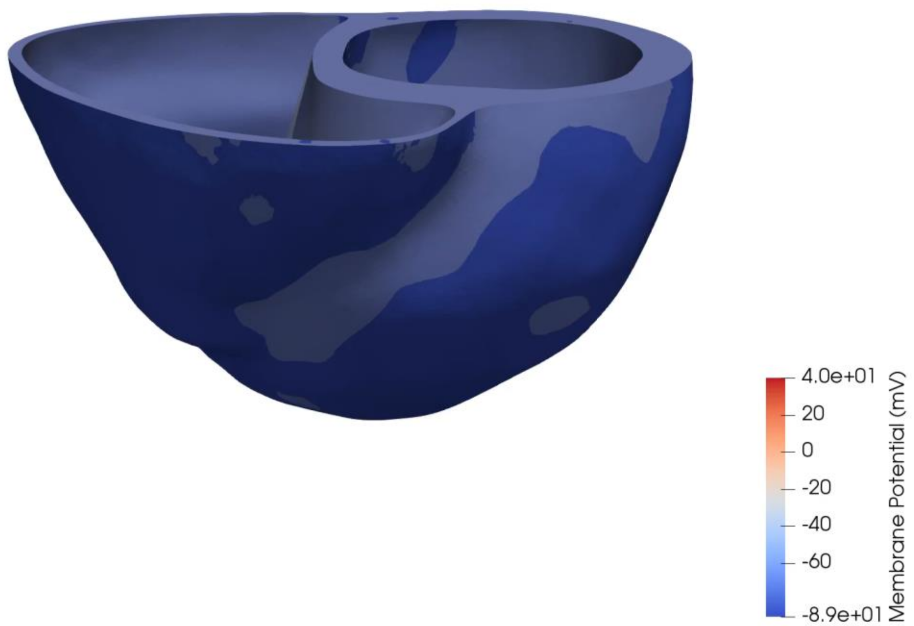
Different Anatomical models



Mincholé and Zacur et al. Front. Physiol. 2019

Examples of 3D Simulations





archer

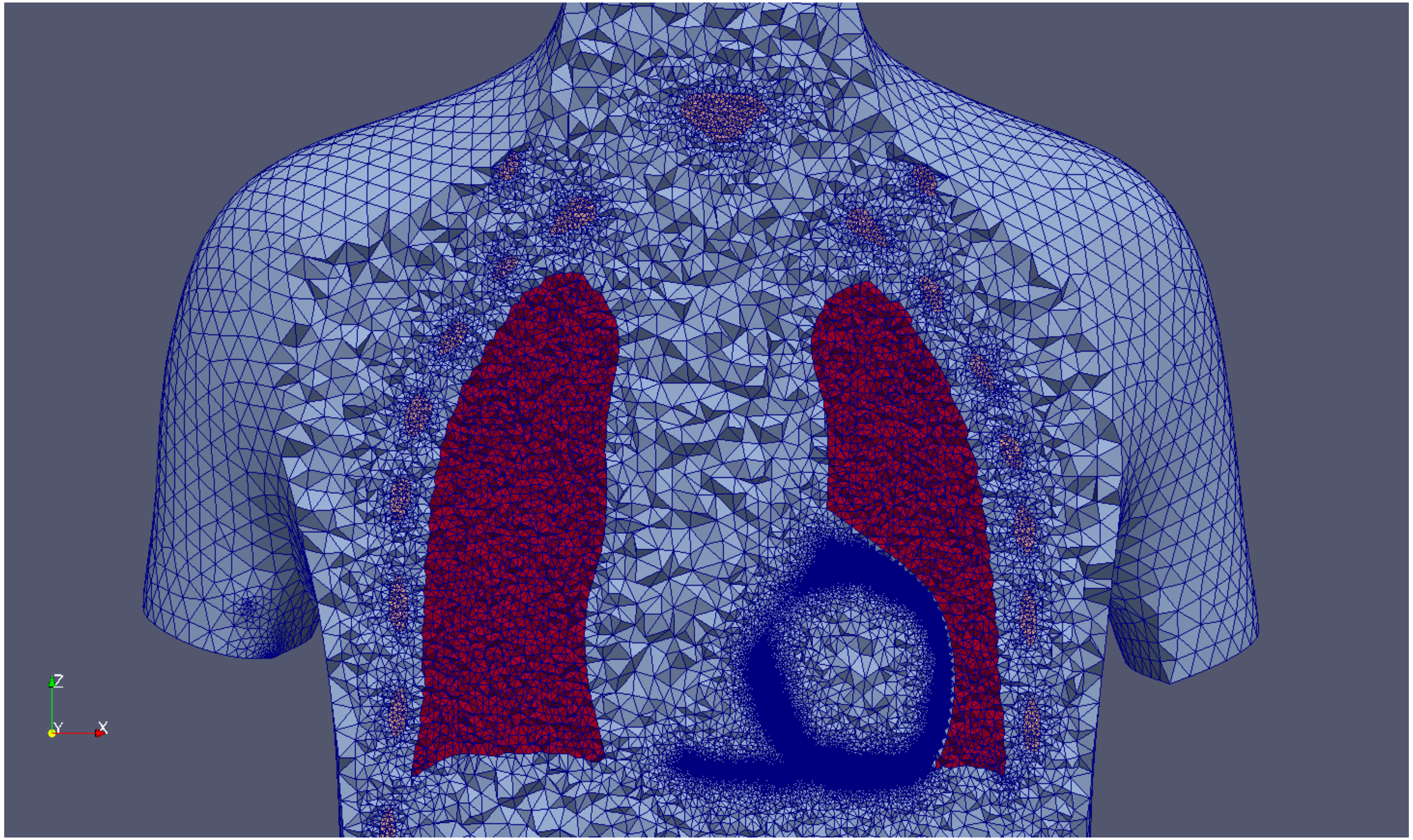
BSC Barcelona Supercomputing Center

1 heart beat:
60 minutes
600 cores

PRACE

Ana Mincholé, Ernesto Zacur, Jenny Wang

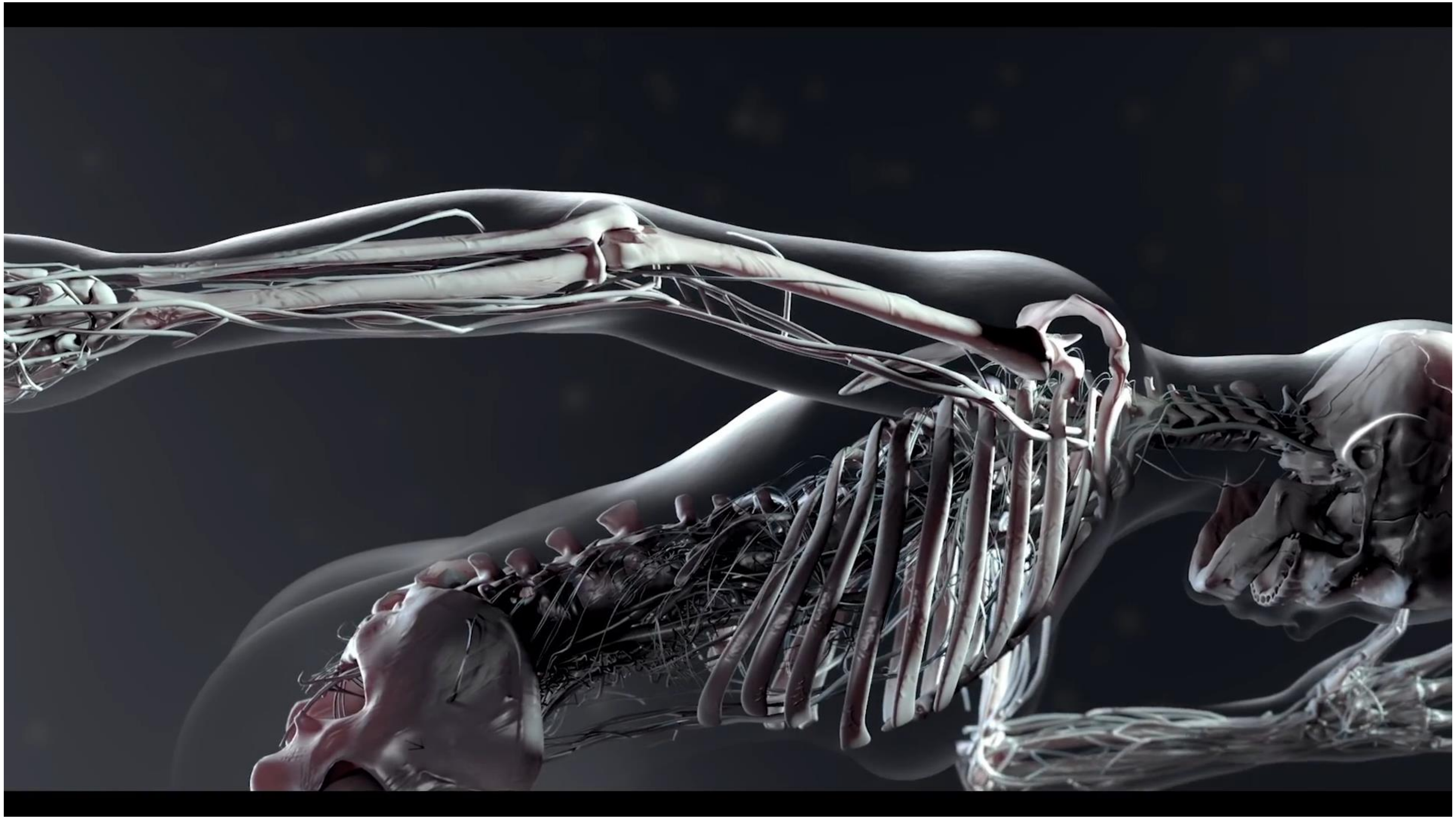
Why? Millions of elements and nodes…



- Each element in the 3D structure represents one cell, with its model
- All elements are interconnected
  - ✓ more equations for the propagation of the signal
- Small size elements to capture fast phenomena

Mincholé and Zacur et al. Front. Physiol. 2019

Virtual Humans



YouTube

CompBioMed

Acknowledgements

Questions?

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http://www.cs.ox.ac.uk/ccs

- **Blanca Rodriguez**
- **Alfonso Bueno-Orovio**
- **Oliver Britton**
- Xin Zhou
- Cristian Trovato
- Jenny Wang

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Oxford Computer Consultants
University of Oxford
Department of Computer Science
wellcome trust
CompBioMed
British Heart Foundation
transQST
NC3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research
Janssen Pharmaceutical Companies of Johnson & Johnson
ucb
AnaBios Redefining first in human
MSD Inventing for Life
AMGEN
FDA
InSilicoTrials
Servier
gsk
AstraZeneca
Sanofi
abbvie
Lilly

Thank You!