# Optimal Granularity in QSP Model Structures

## The Pros and Cons of Model Complexity In Cardiac Simulations

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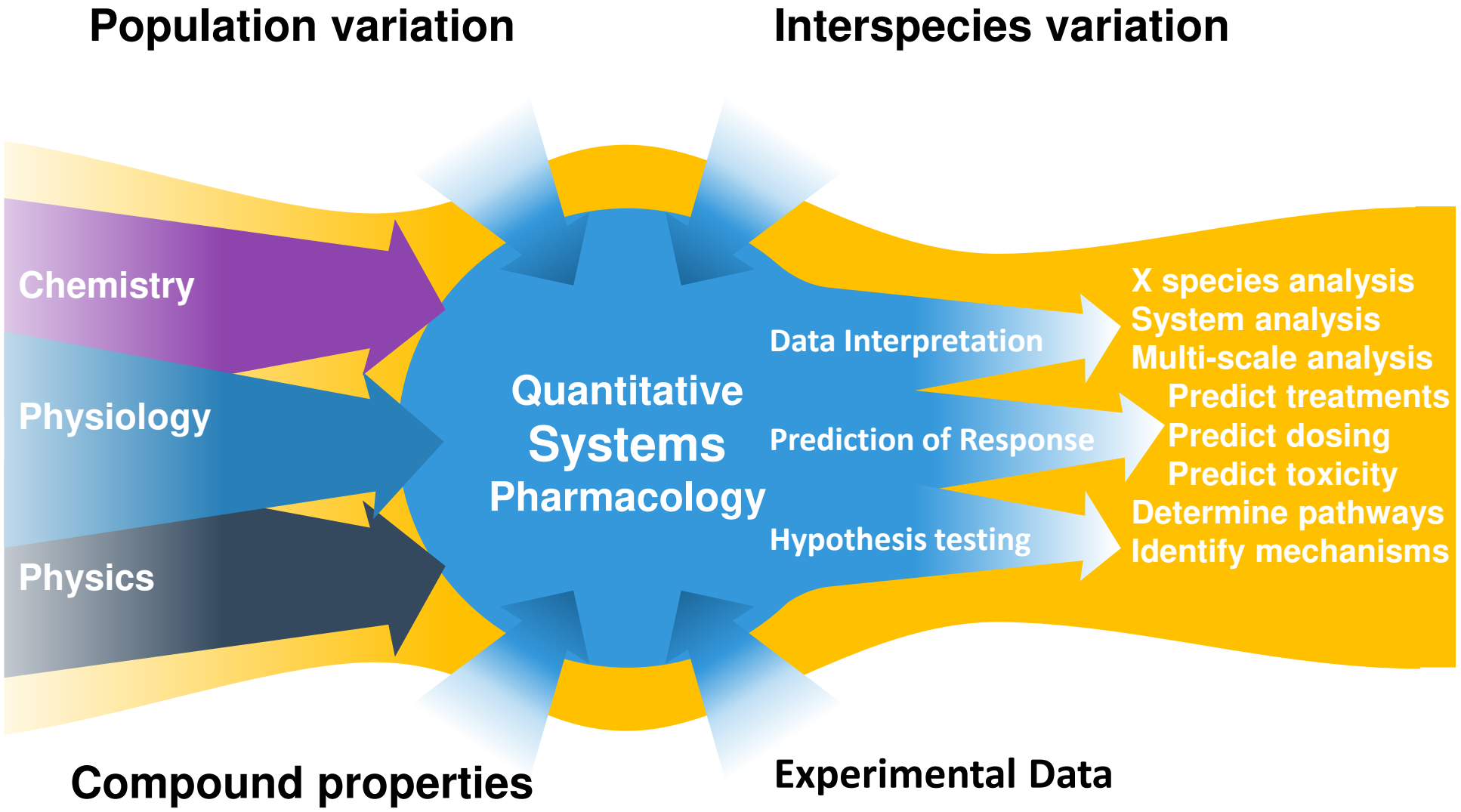
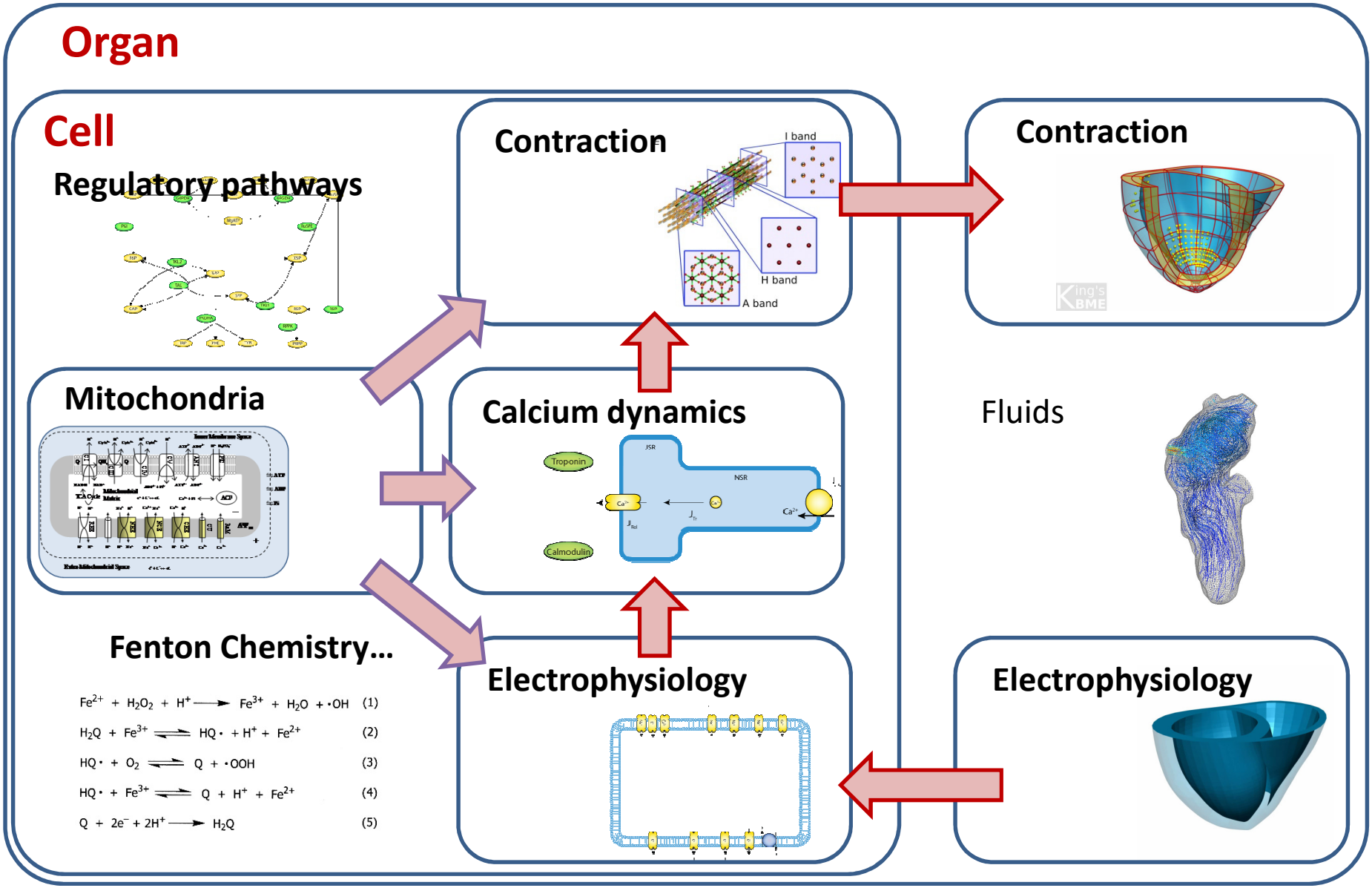
**King's College London**

# Quantitative Systems Pharmacology



# What systems are involved?



# What Level of Granularity is Required in Time?

**Acute Toxicity (<1 minute)**

Arrhythmia, QT prolongation

**Metabolic Time scales (15-30 minutes)**

Acute mitochondria dysfunction

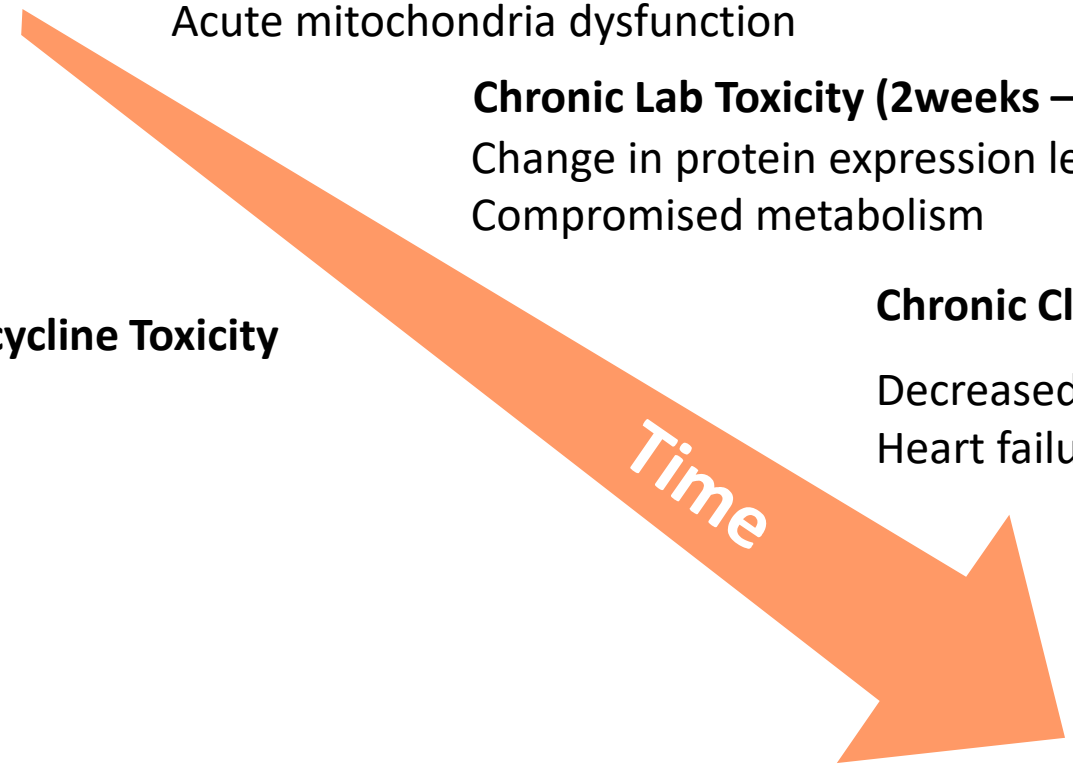
**Chronic Lab Toxicity (2weeks – 6 months animal, in-vitro prep)**

Change in protein expression level
Compromised metabolism

**Chronic Clinical Toxicity (1+ years patients)**

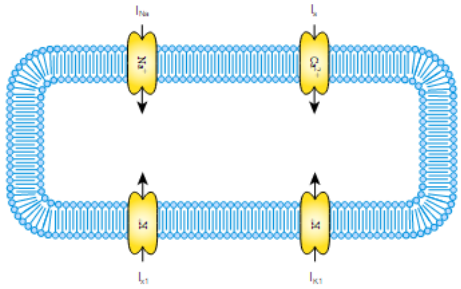
Decreased ejection fraction
Heart failure

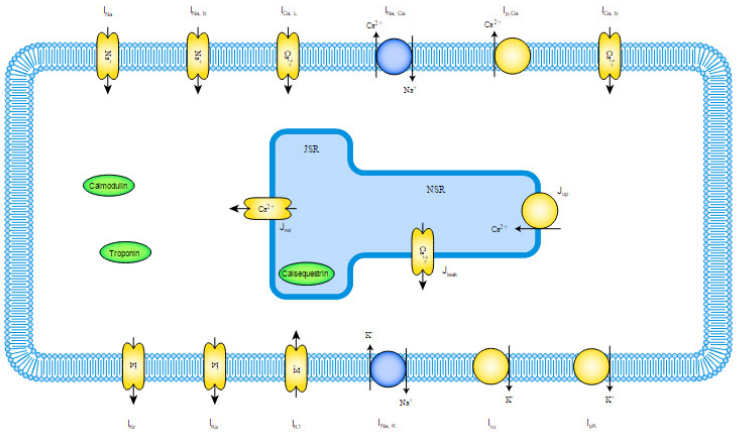
**Anthracycline Toxicity**



# Do we need to model a system representative of the population or do we need to model the population ?

# Is there a cost of complexity?






**Accessing correct implementations of the equations**

CellML

(100+ cardiac cell models)

SBML

(34 cardiac cell models)

**Functional Curation allows automated checking of implementations**

Cooper J, Mirams GR & Niederer SA. (2011). High-throughput functional curation of cellular electrophysiology models. *Prog Biophys Mol Biol* **107,** 11-20. https://travis.cs.ox.ac.uk/FunctionalCuration/

# In physiology studies there is a saying:
# We only learn something when the model breaks

```
An error has occurred:  To continue :

Press ENTER to return to your Model, or

Press CRTL + ALT + DEL to restart you simulation
```

# However, if using the model as a tool we simply learn that the tool does not work

# Complex models are not a single entity

Complex models combine multiple simpler components into a single framework

Complex models (should) rely on more data to constrain parameters and **Comprehensively validate the model**

# Fine Model Granularity

**PROS**

Aspire to be closer representation of biology
Easy access to model equations
Compute time often reasonable

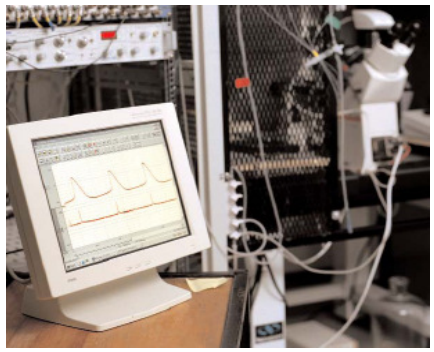
**CONS**

Hard to determine what has gone wrong when they break
Built from distinct components and not comprehensively validated
Validation is often against easily measureable phenotypes

## Finding the ~~limitations~~ opportunities of complex models through the model creation process

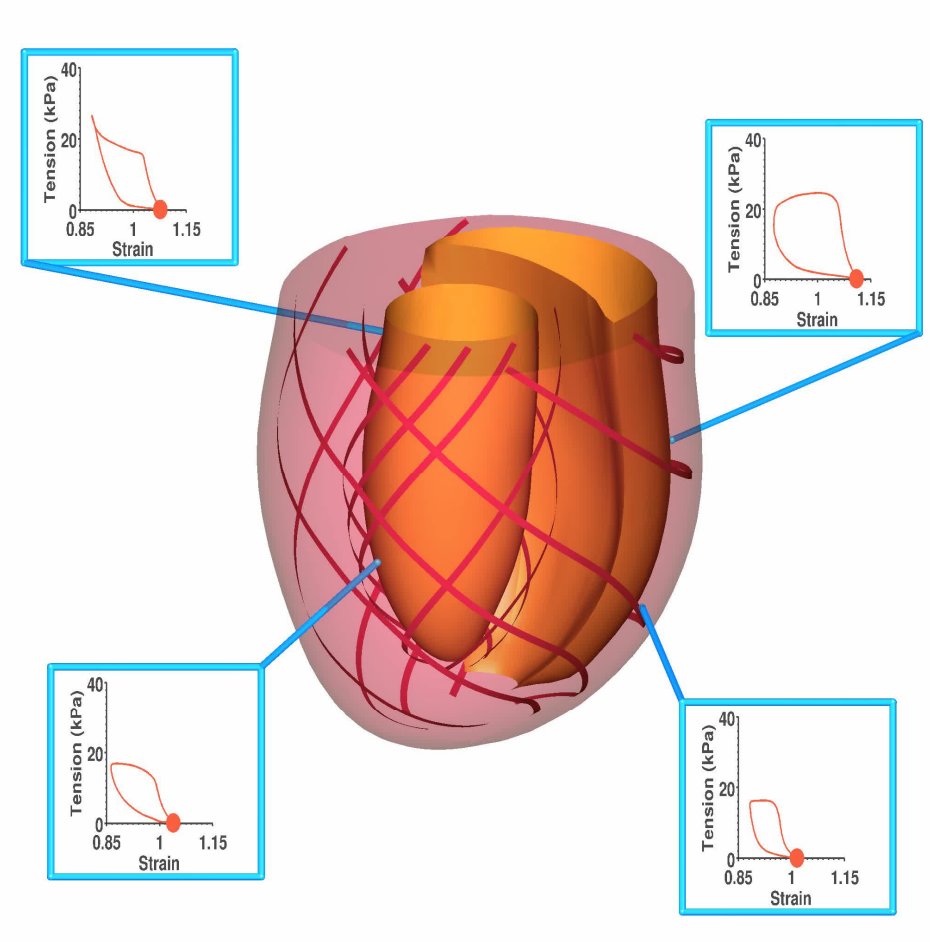
## Case Study:

## Modelling the Rat Ventricular Myocyte



# Wish to model electro-mechanics whole rat heart

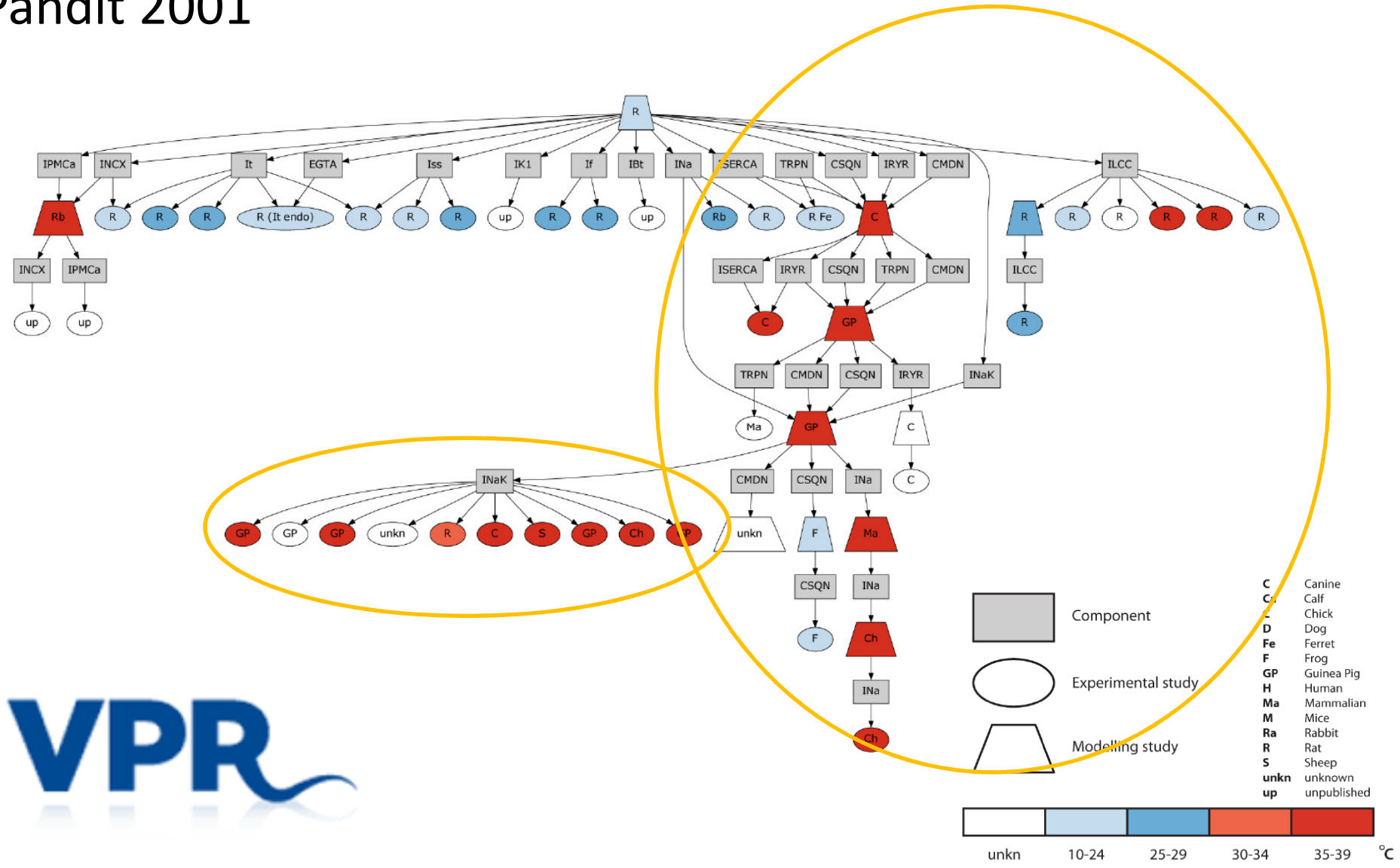
1. Biphasic calcium frequency response
2. Able to operate at physiological (6Hz+) frequency
3. Simulate at physiological temperatures



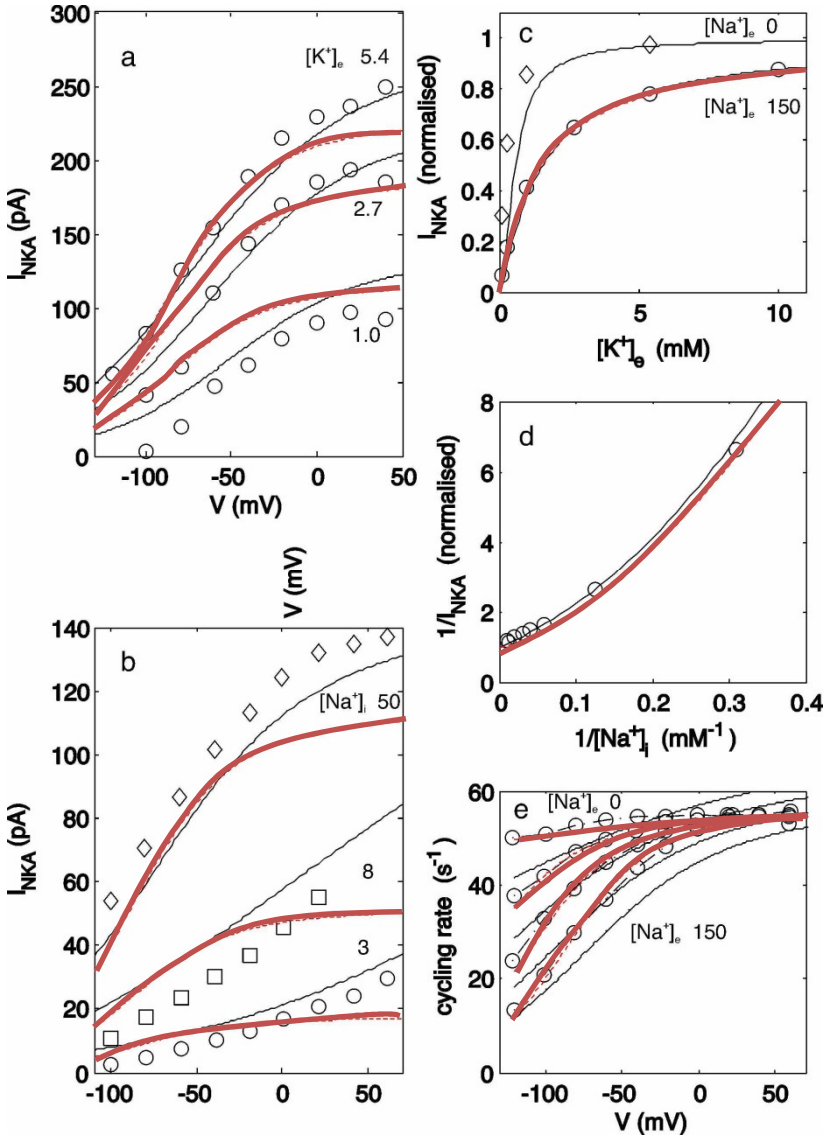
# Using the rat as an example

How are we currently modelling the rat ventricular myocyte?

Pandit 2001



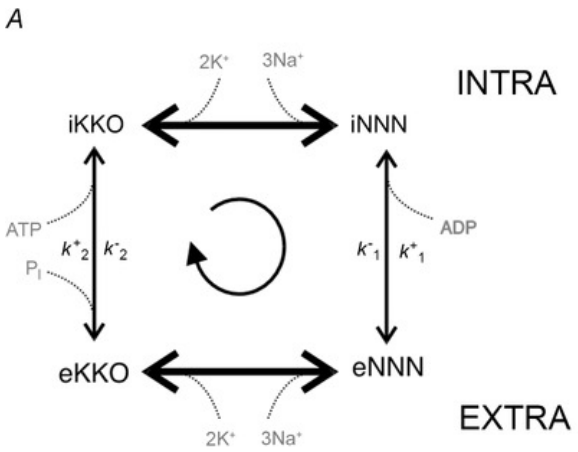
# Modelling the Sodium Potassium pump

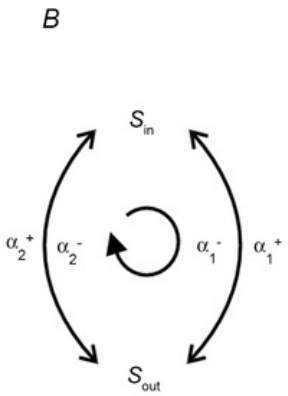



Nakao & Gadsby (1989)
Luo & Rudy (1991)

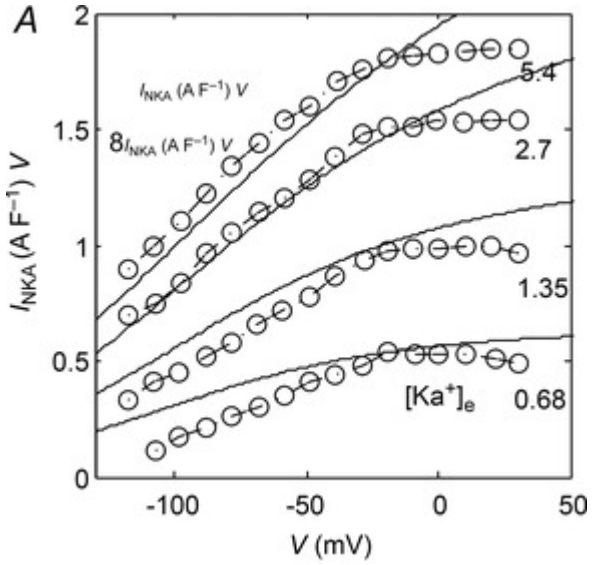
Phenomenological Model
Incompatible with compound binding

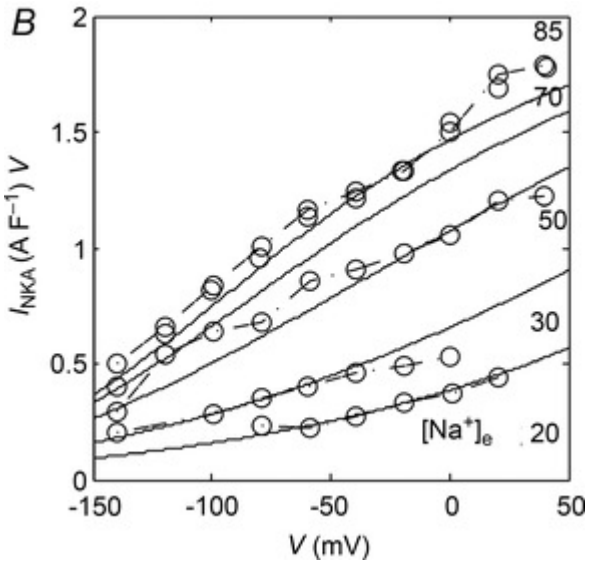
# Modelling **Protein Function**



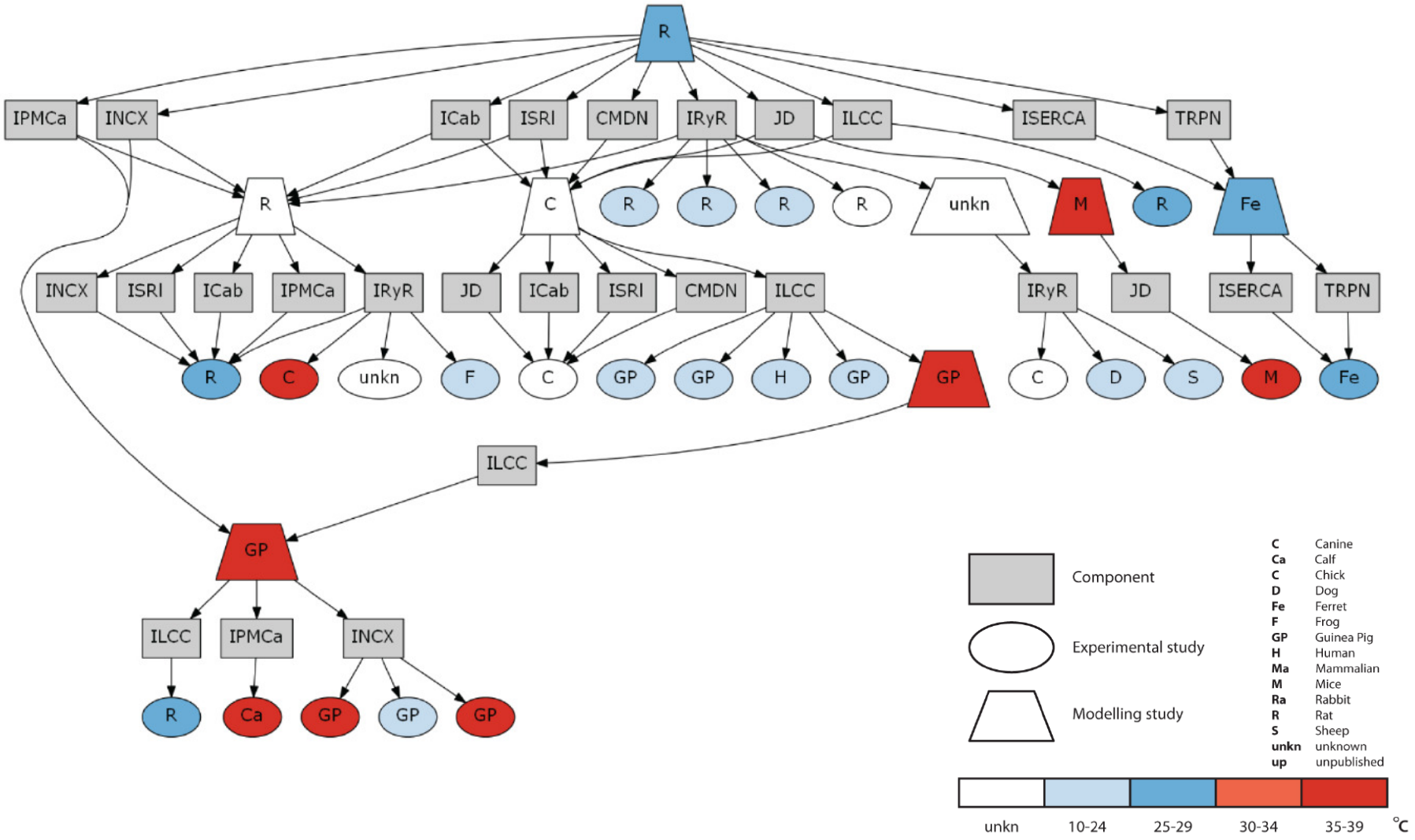

$$\nu^{-1} = \frac{1}{k_1^+}\left[1+\left(\frac{K_{Nai3}}{[Na^+]_i}+\frac{K_{Nai3}K_{Nai2}}{[Na^+]_i^2}+\frac{K_{Nai3}K_{Nai2}K_{Nai1}}{[Na^+]_i^3}\right)e^{-\Delta\frac{eV}{kT}}\right]$$
$$+\frac{1}{k_2^+}\left\{\begin{array}{l}1+\frac{K_{Ke}}{[K^+]_e}\left(1+\frac{[Na^+]_e}{K_{Nae1}}+\frac{[Na^+]_e}{K_{Nae2}}\right)+\left(\frac{K_{Ke}}{[K^+]_e}\right)^2\left(1+\frac{[Na^+]_e}{K_{Nae1}}+\frac{[Na^+]_e^2}{K_{Nae1}K_{Nae2}}\right)\\ +\frac{[Na^+]_e}{K_{Nae3}}\left[1+\frac{K_{Ke}}{[K^+]_e}\left(\frac{[Na^+]_e}{K_{Nae1}}+\frac{[Na^+]_e}{K_{Nae2}}\right)+\left(\frac{K_{Ke}}{[K^+]_e}\right)^2\frac{[Na^+]_e^2}{K_{Nae1}K_{Nae2}}\right]e^{-(1-\Delta)\frac{eV}{kT}}\end{array}\right\}$$



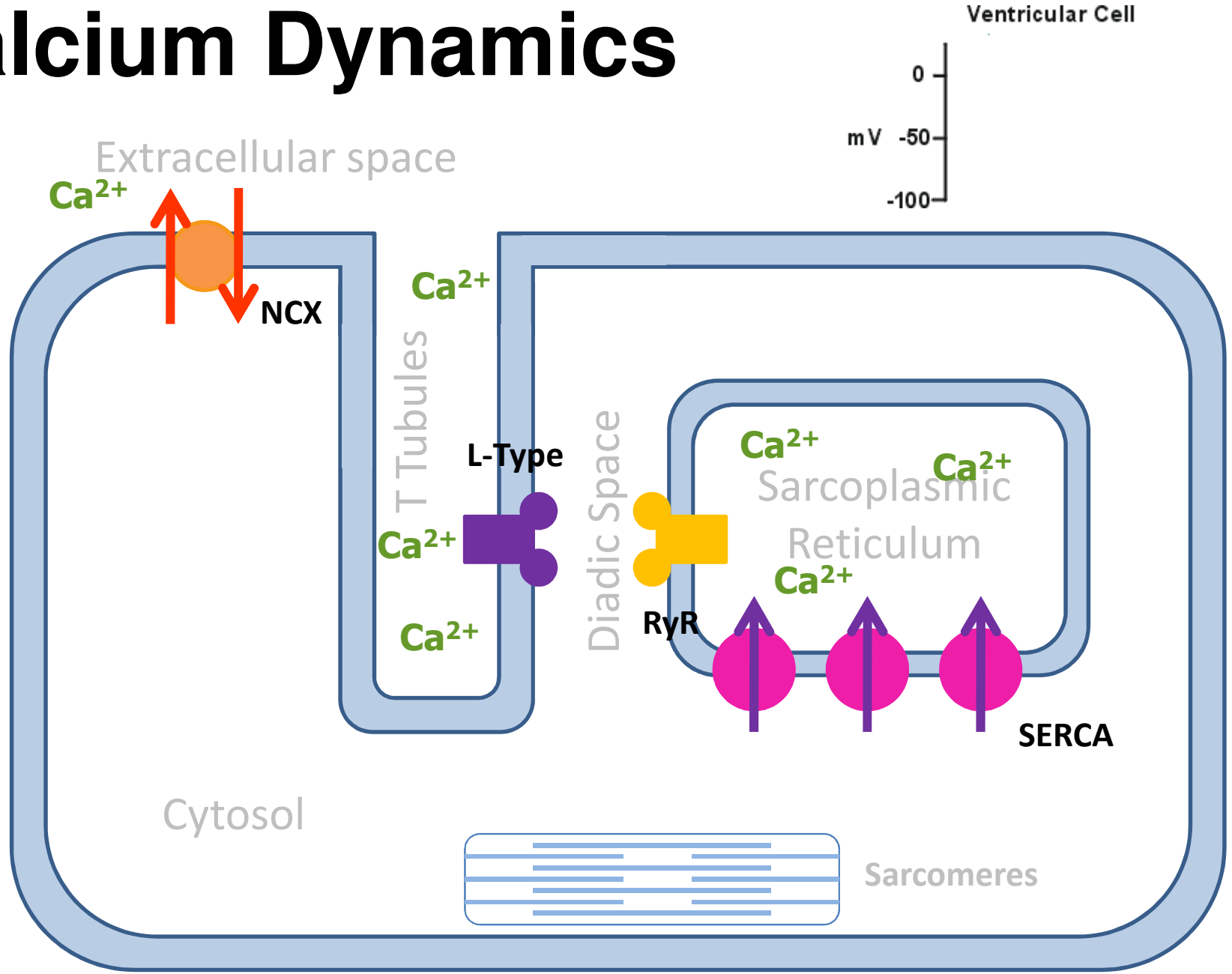




Lewalle A, Niederer SA & Smith NP. (2014). Species-dependent adaptation of the cardiac Na+/K+ pump kinetics to the intracellular Na+ concentration. *The Journal of Physiology* **592,** 5355-5371.

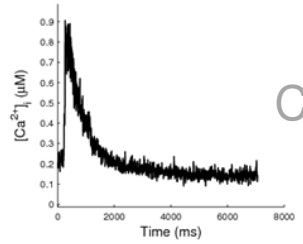
# Hinch Model of rat calcium regulation with graded calcium release



# Calcium Dynamics

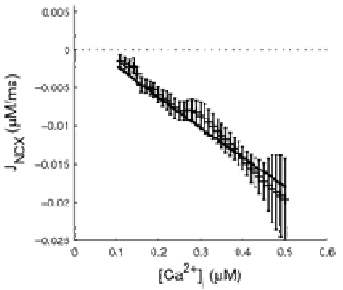


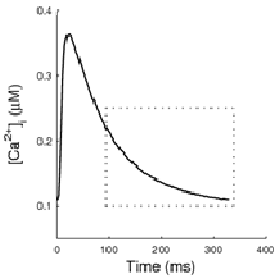
# Modelling **Data Driven**




Ca Flux during Caffeine Ca transient

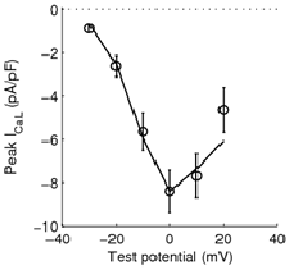
**Fit NCX Model**

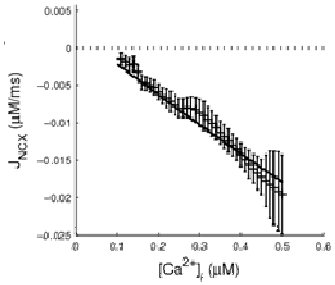



Ca Flux during tail of Field Stimulation Ca Transient. Less Ca Flux through NCX (calculated)

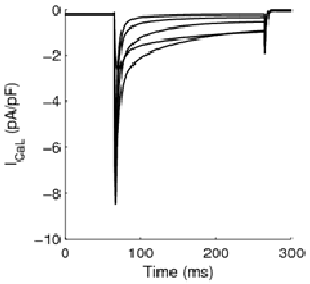
$I_{CaL}$ Voltage clamp traces

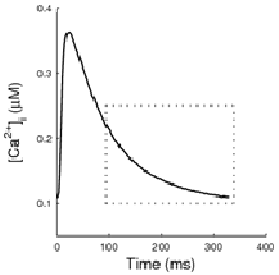



**Fit SERCA Model**

**Fit $I_{CaL}$ Model**

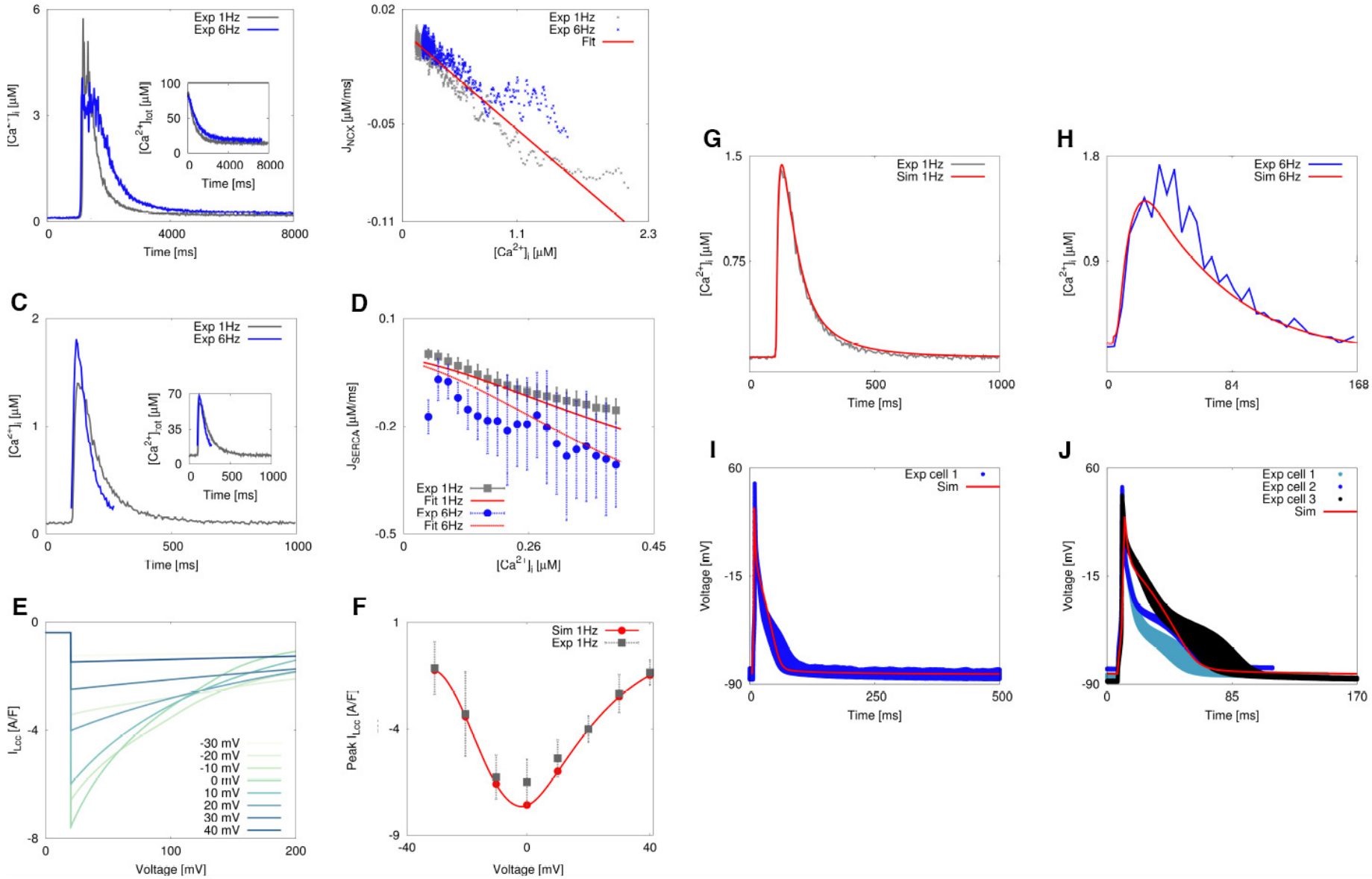


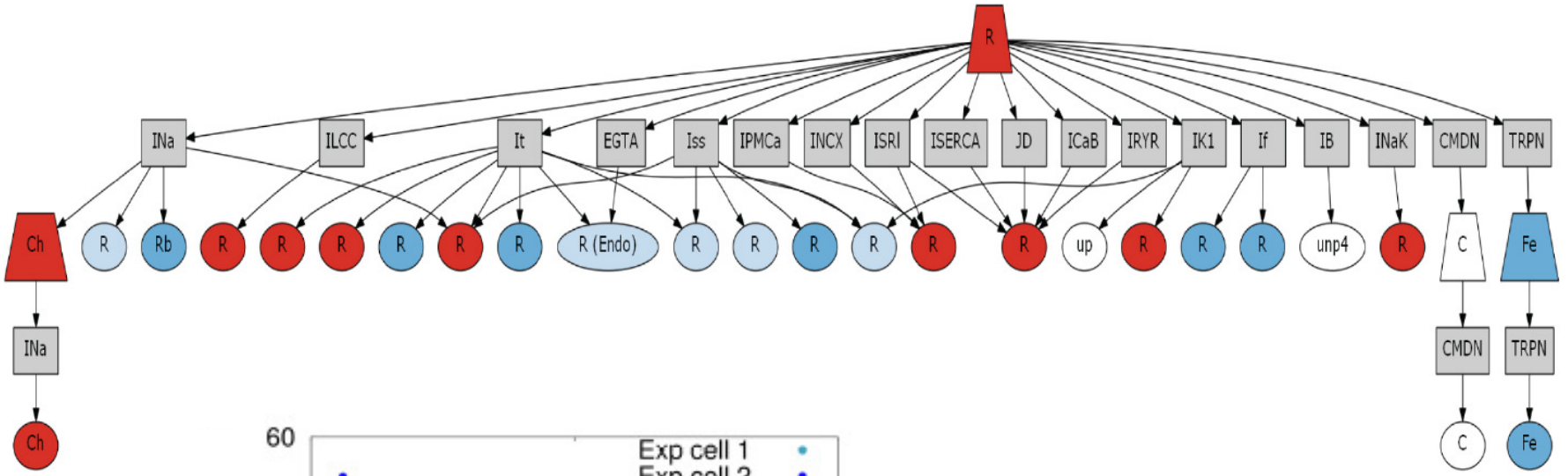

Ca flux during start of Field Stimulation Ca Transient. Less Ca Flux through NCX, SERCA and $I_{CaL}$ (calculated)

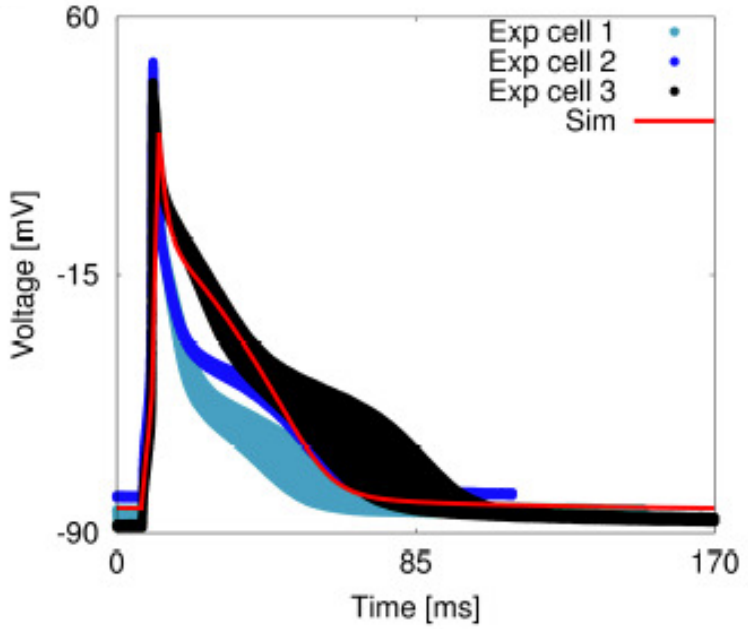
**Fit RyR Model**

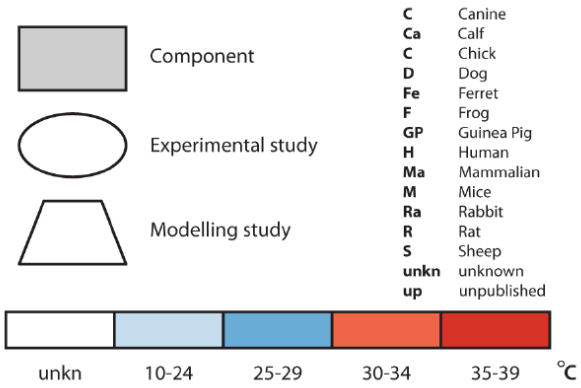
# Modelling Data Driven



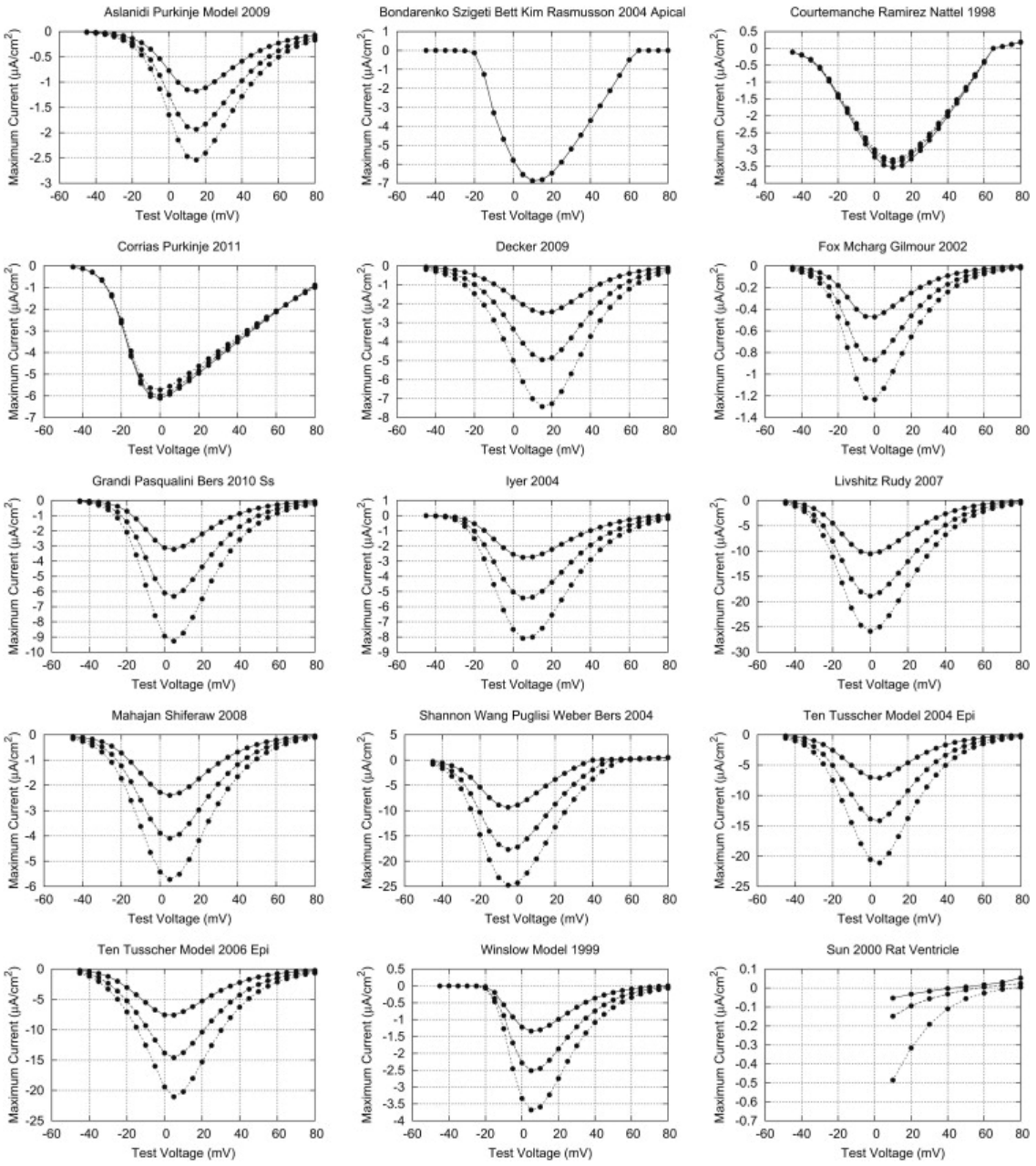
# Modelling **Data Driven**



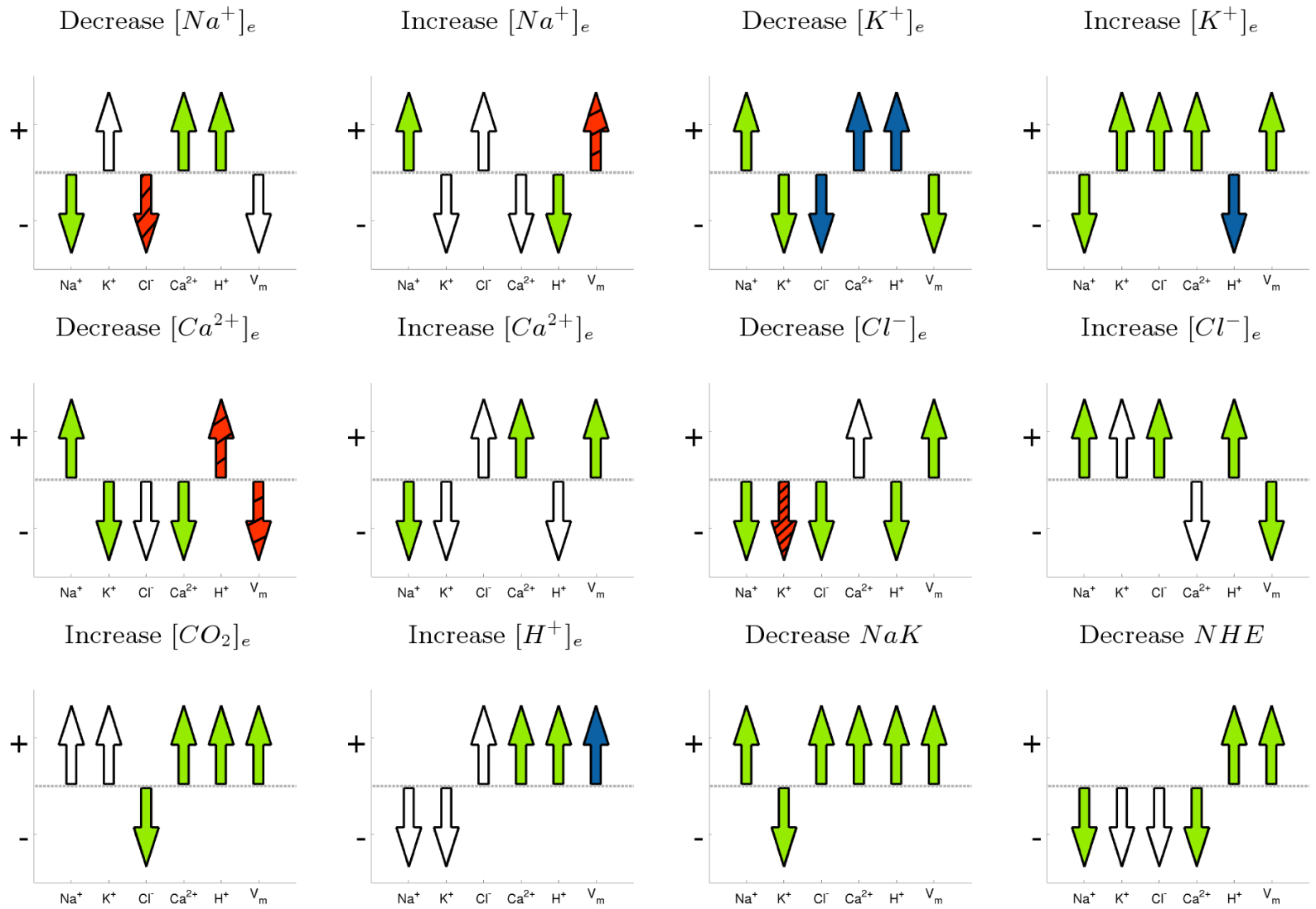
# High through put functional curation of models and components




No ability yet to link to experimental data

Cooper J, Mirams GR & Niederer SA. (2011). High-throughput functional curation of cellular ep models. *Prog Biophys Mol Biol* **107,** 11-20.

# Defining simple agreed upon quality control tests




Niederer S. (2013). Regulation of Ion Gradients across Myocardial Ischemic Border Zones: A Biophysical Modelling Analysis. *PLoS One* **8,** e60323.

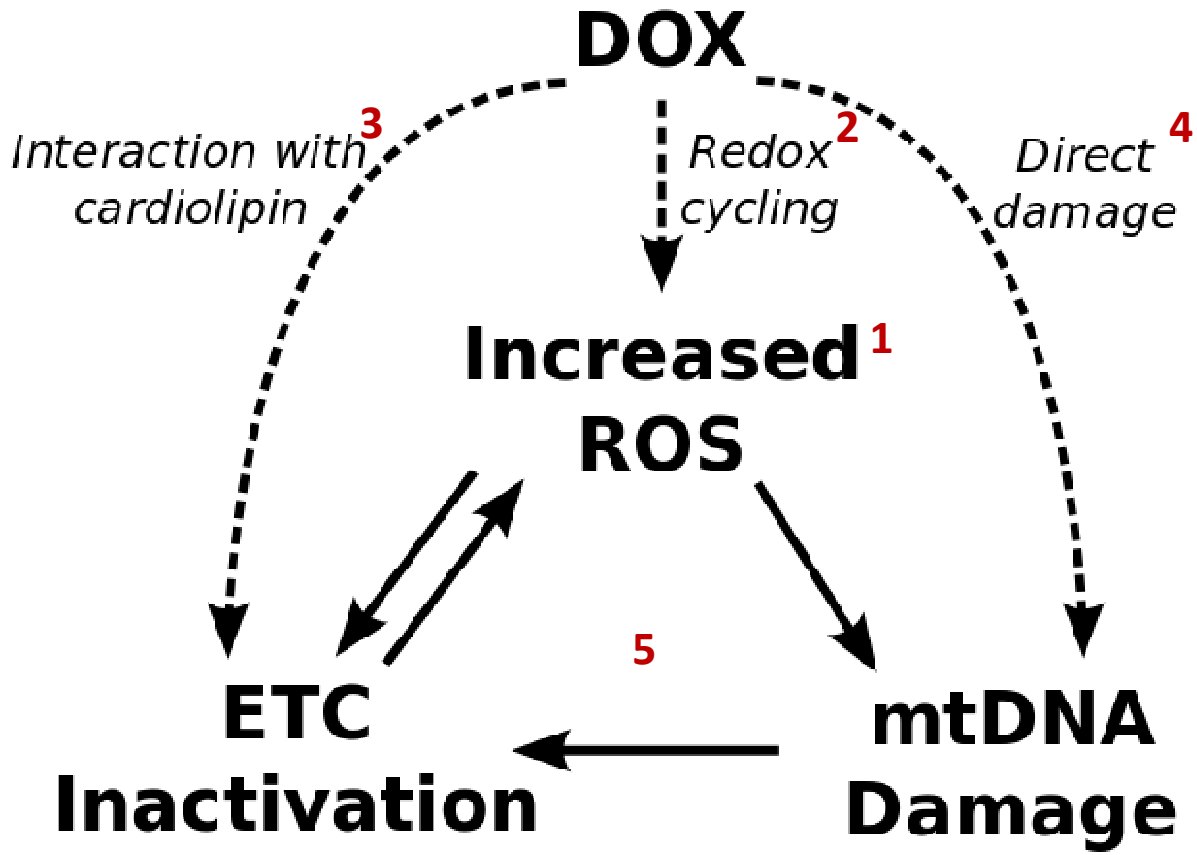
# Doxorubicin is an effective anticancer drug

- ✓ Potent and broad-spectrum
- ✓ Widely used in the treatment of leukemias and solid tumors
- ✓ Stops DNA replication and triggers apoptosis

- ✘ Severe Cardiotoxicity that leads to CHF
- ✘ Cumulative, dose-dependent and irreversible
- ✘ 50–60% contractile dysfunction with 430–600 mg/m2 doses
- ✘ Symptoms can progress years or even decades after chemotherapy

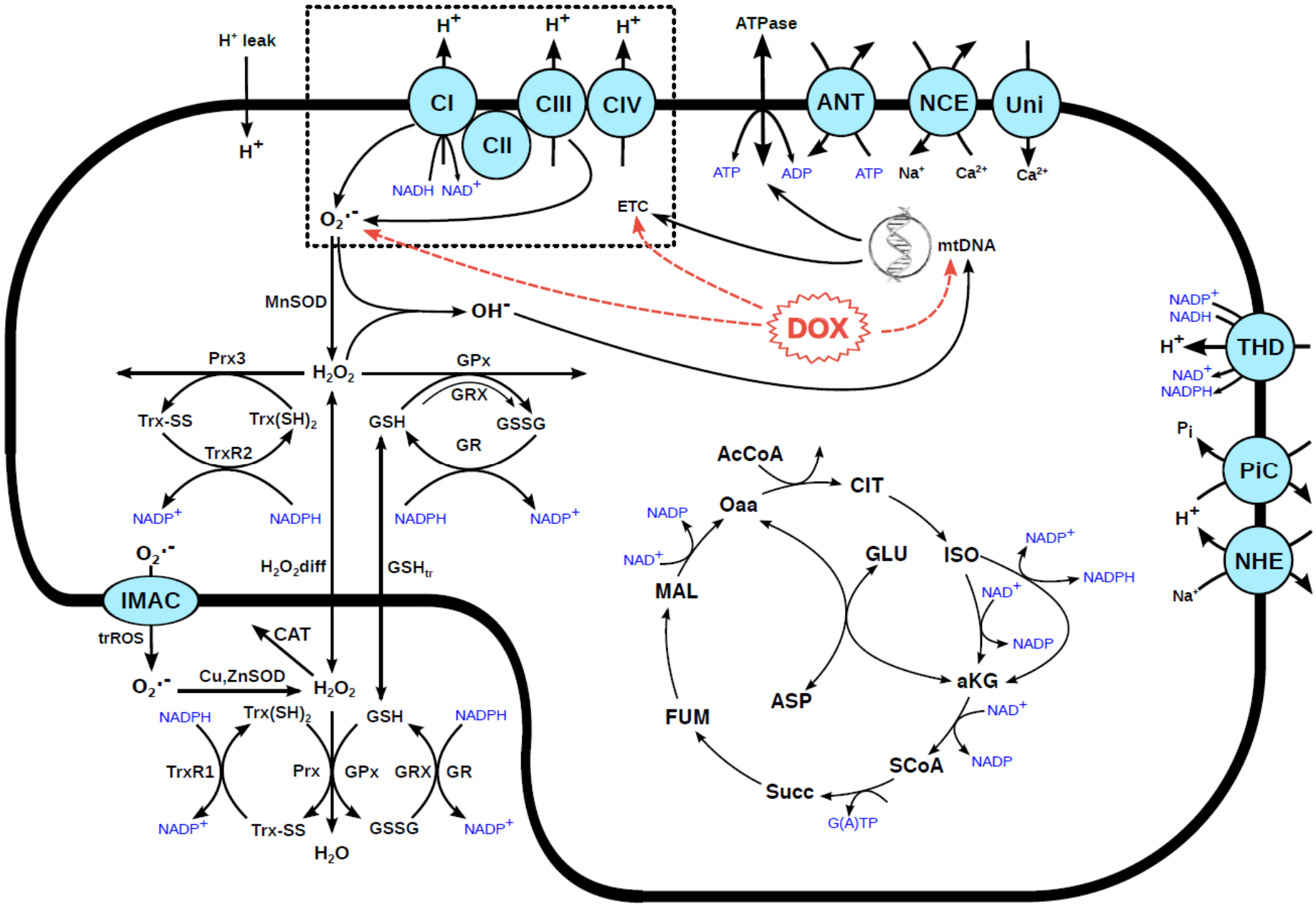
HECATOS

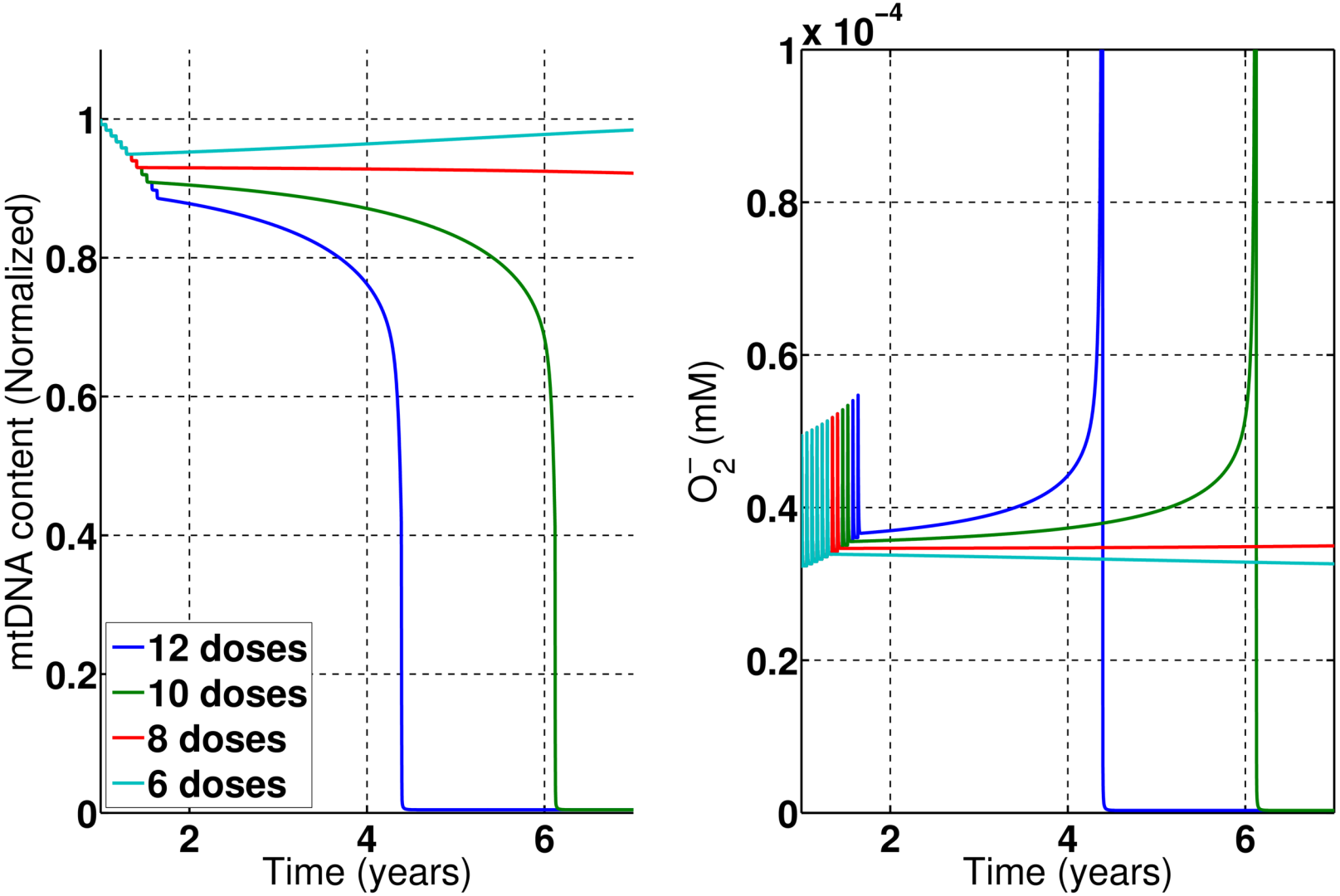
# The mechanism of DOX cardiotoxicity is controversial



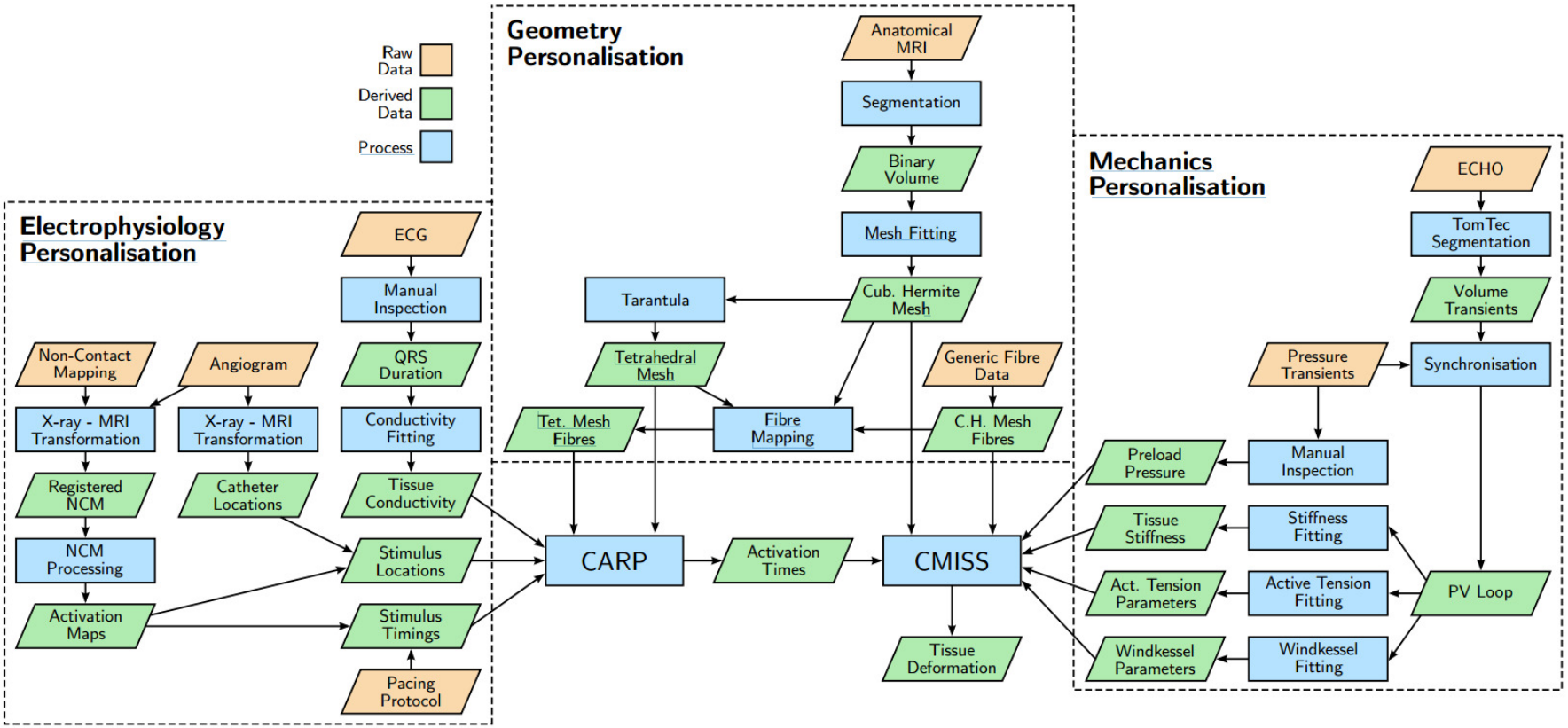


1) G. Minotti, P. Menna, E. Salvatorelli, G. Cairo, and L. Gianni. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacolog-ical Reviews, 56(2):185{229, Jun 2004.
2) Kelvin J. A. Davies and James H. Doroshow. Redox cycling of anthracyclines by cardiac mitochondriai. anthracycline radical formation by nadh dehydrogenase. The Journal of Biological Chemestry, 261(7):3060{7, Mar 1986.
3) O. Marcillat, Y. Zhang, and K. J. Davies. Oxidative and non-oxidative mechanisms in the inactivation of cardiac mitochondrial electron transport chain components by doxorubicin. Biochemical Journal, 259(1):181{189, Apr 1989.
4) J. M. Berthiaume and K. B. Wallace. Persistent alterations to the gene expression prole of the heart subsequent to chronic doxorubicin treatment. Cardiovascular Toxicology, 7:178{191, 2007.
5) Dirk Lebrecht, Bernhard Setzer, Uwe-Peter Ketelsen, J org Haberstroh, and Ulrich A. Walker. Time-dependent and tissue-specic accumulation of mtdna and respiratory chain defects in chronic doxorubicin cardiomyopathy. Circulation, 108(19):2423{9, Nov 2003.

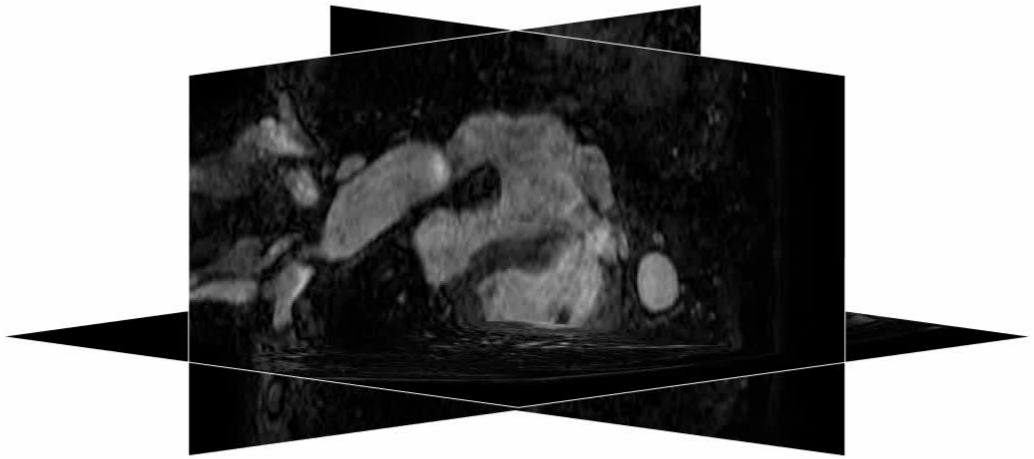

H+ leak
H+
H+
H+
H+
CI
CII
CIII
CIV
ATPase
ANT
NCE
Uni
ATP
ADP
ATP
Na+
Ca2+
Ca2+
NADH
NAD+
O2·-
ETC
mtDNA
DOX
MnSOD
OH-
Prx3
H2O2
GPx
GRX
Trx-SS
Trx(SH)2
GSH
GSSG
TrxR2
GR
NADP+
NADPH
NADPH
NADP+
NADP+
NADH
H+
NAD+
NADPH
THD
Pi
PiC
H+
NHE
Na+
O2·-
IMAC
H2O2diff
GSHtr
trROS
CAT
O2·-
Cu,ZnSOD
H2O2
NADPH
Trx(SH)2
GSH
NADPH
TrxR1
Prx
GPx
GRX
GR
NADP+
Trx-SS
GSSG
NADP+
H2O
AcCoA
CIT
NADP
Oaa
NAD+
GLU
ISO
NADP+
NADPH
MAL
NAD+
NADP
ASP
aKG
NAD+
FUM
SCoA
NADP
Succ
G(A)TP


mtDNA content (Normalized)
1
0.8
0.6
0.4
0.2
0
2
4
6
Time (years)
12 doses
10 doses
8 doses
6 doses
x 10^-4
1
0.8
0.6
0.4
0.2
0
O2- (mM)
2
4
6
Time (years)

# Virtual Patient Toxicity

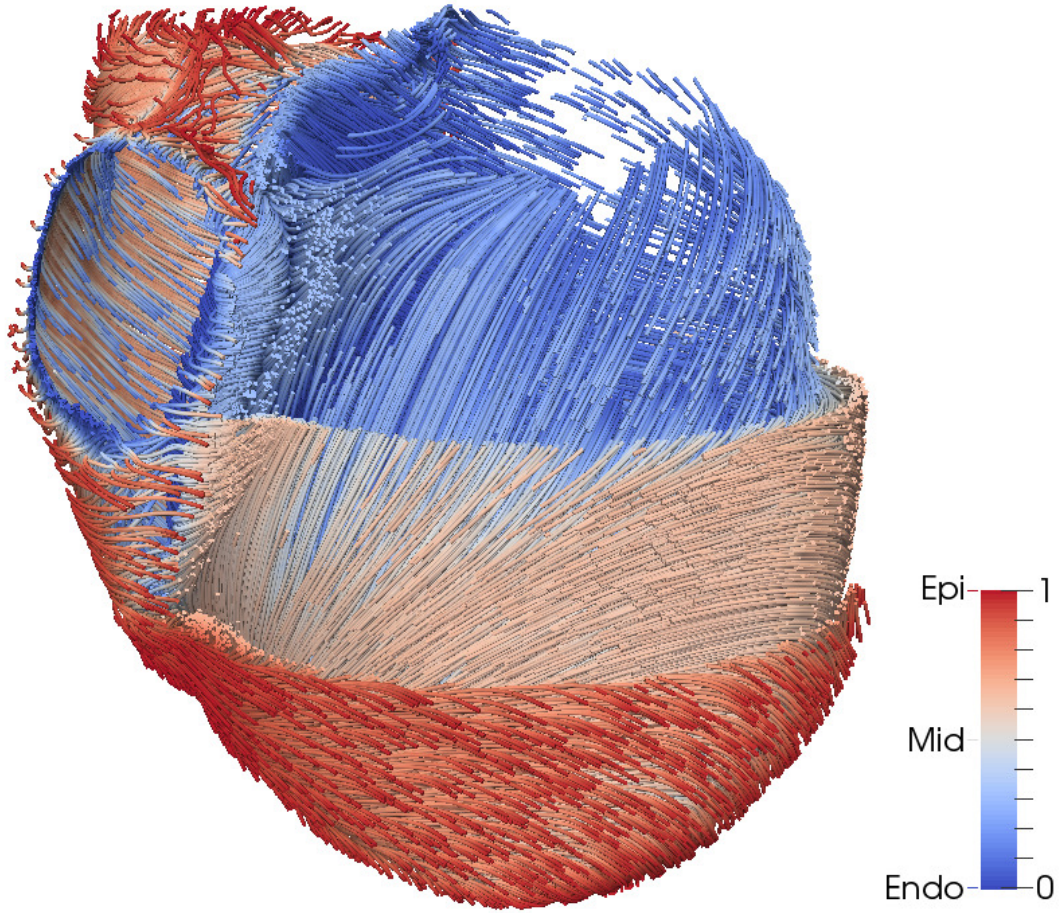


# Modelling **Anatomy**

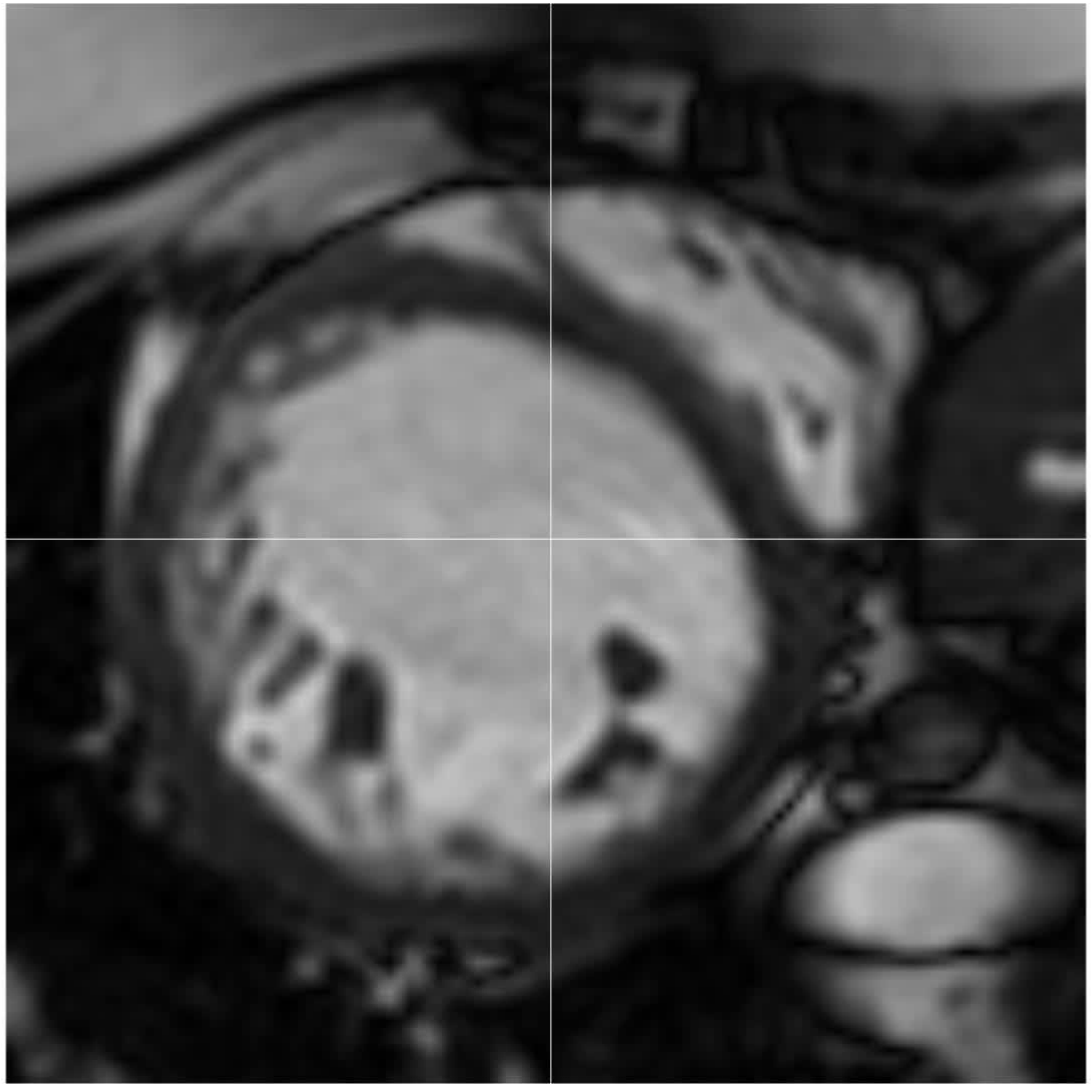


Lamata P, Niederer S, Barber D, Norsletten D, Lee J, Hose R*, et al.* *Personalization of Cubic Hermite Meshes for Efficient Biomechanical Simulations. Medical Image Computing and Computer-Assisted Intervention – MICCAI 2010: Springer Berlin / Heidelberg:380-387.*

# Personalised **Fibres**

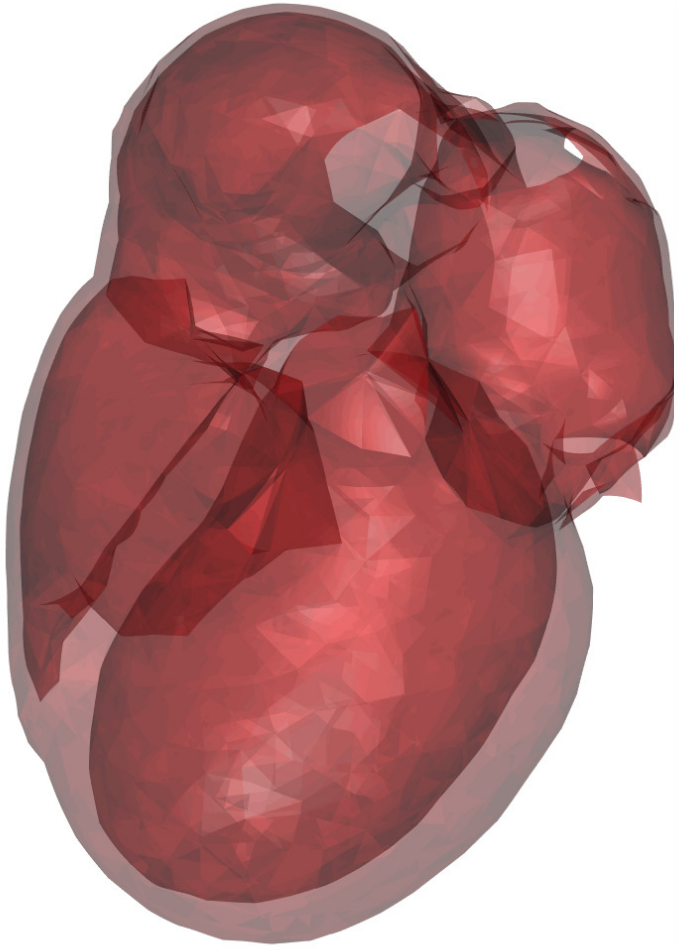


# Personalised Mechanics

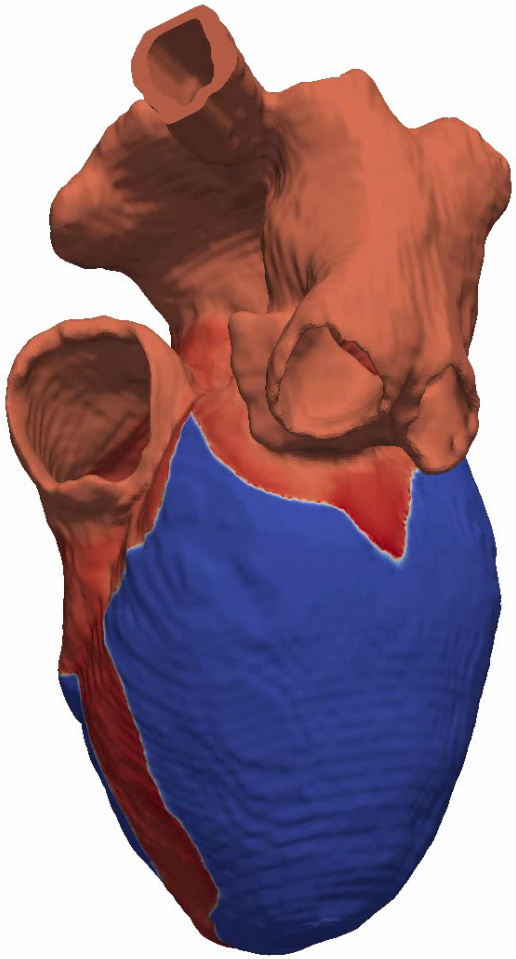


King's BME

# High resolution **Personalised Models**

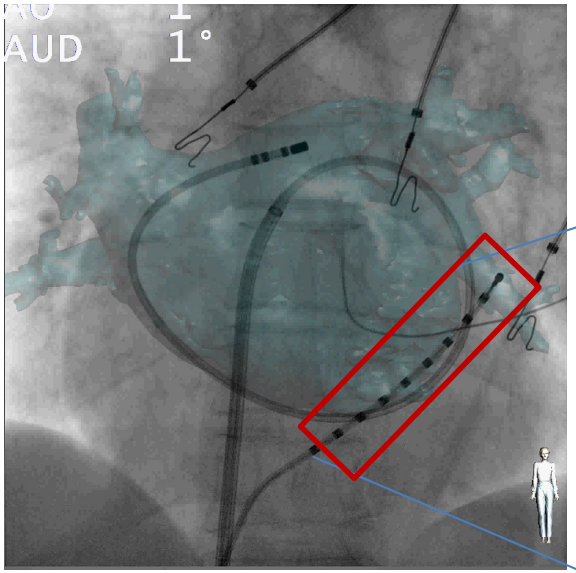


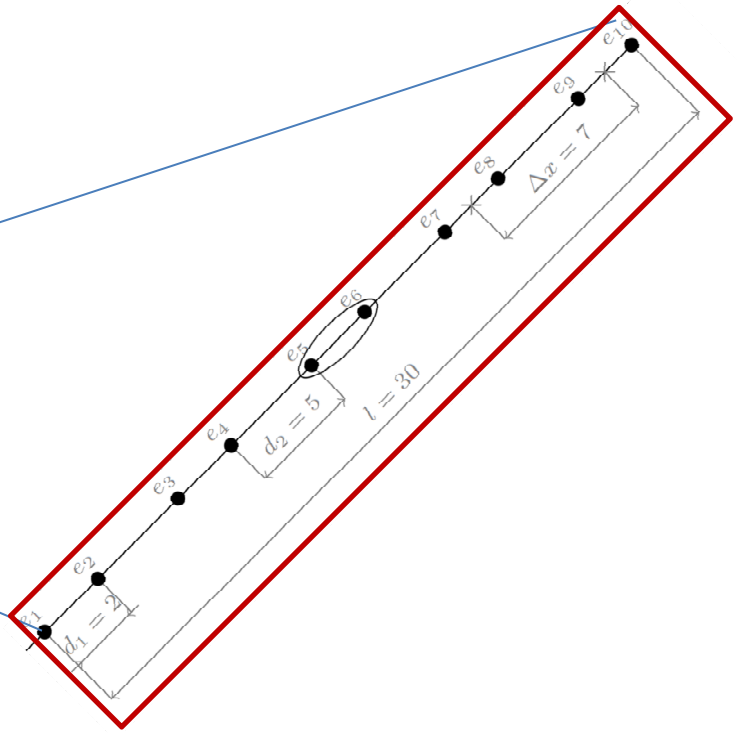
In collaboration with Sander Land

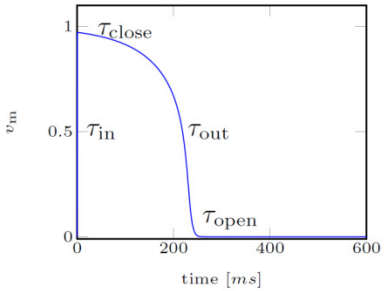


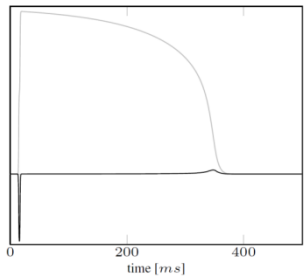
In collaboration with Gernot Plank

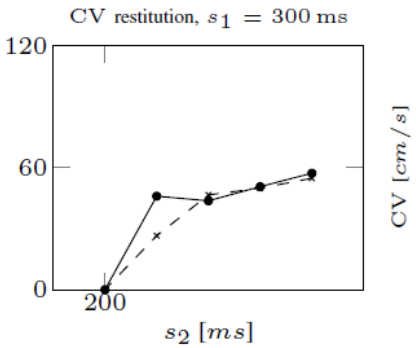
# Data Interpretation: Substrate mapping

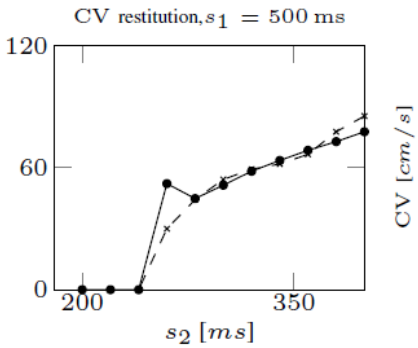


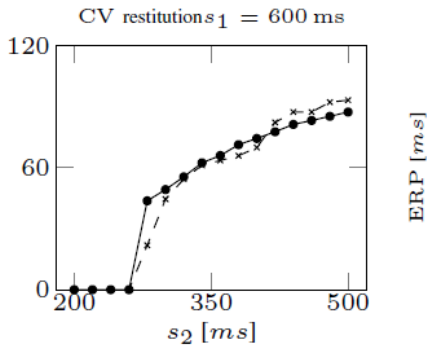



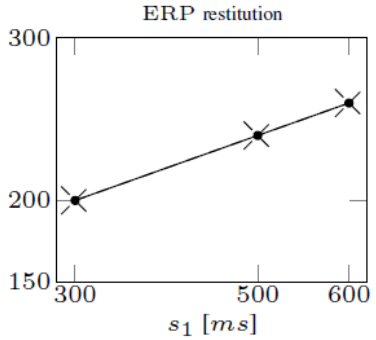

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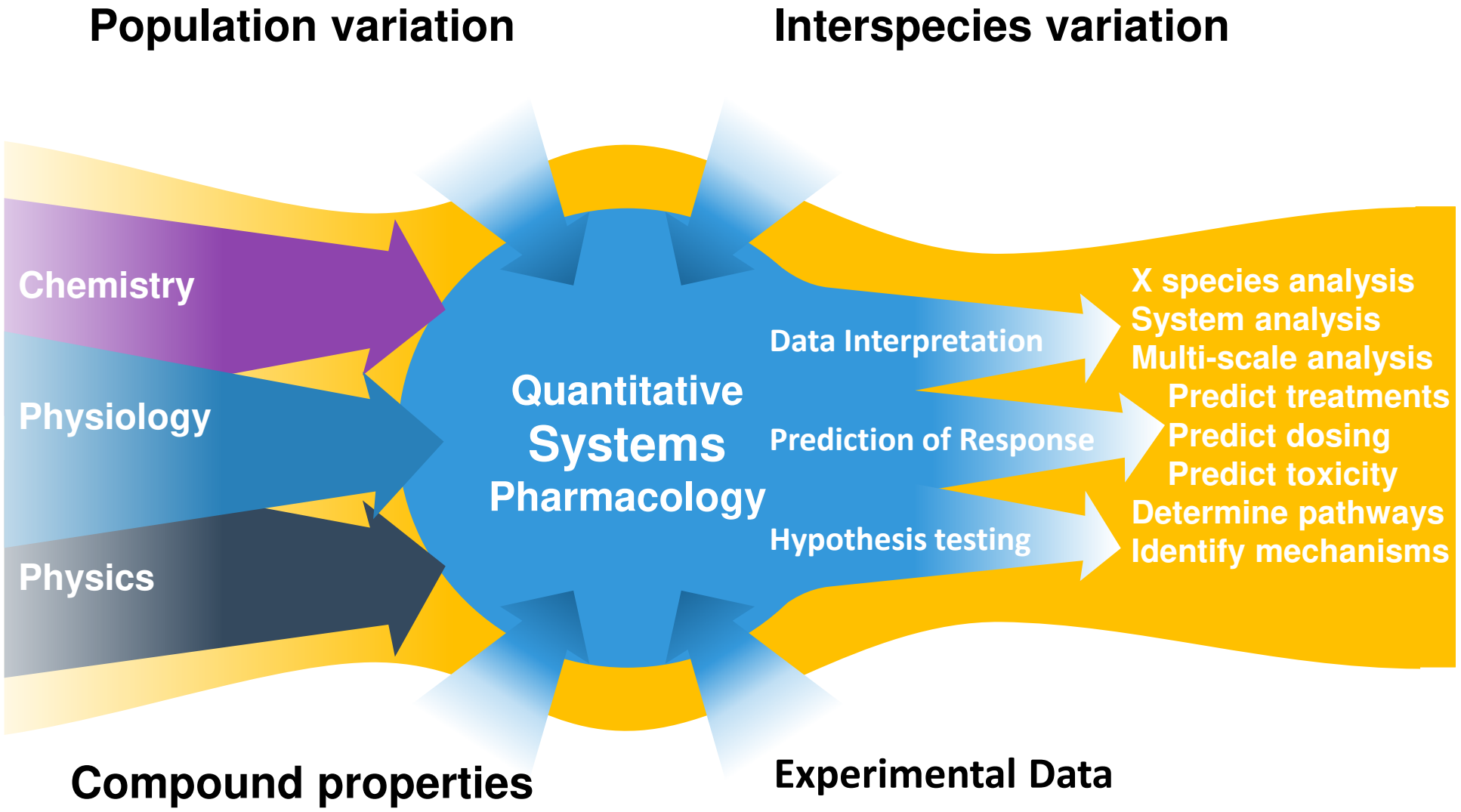
# Quantitative Systems Pharmacology



# Practical Guide for Choosing granularity

How much effort goes into evaluating a novel experimental assay?

1. Choose if re-using existing models (assume yes)
2. Create list of candidate models that meet or exceed desired complexity/ granularity
3. Define a set of functional tests
4. Acquire or define ground truth data

    Consistent data sets will continue to be a challenge

4. Evaluate candidate models against tests
5. Select optimal candidate
6. Evaluate data dependencies
7. Improve model as required

8. Test interpretation assumptions:
   e.g. Is a single cell action potential directly related to the QT interval?