CONSTRUCTING AN ACTION POTENTIAL MODEL: EASY AS ABC?

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Introduction. Brief description of project. Start with motivation "frame research".

IN-SILICO MODELLING OF CARDIAC ELECTROPHYSIOLOGY

Computational modelling important test hypotheses. Homogenous tissue. Ignore cell-level propagation.

TOWARDS A DISCRETE-CELL APPROACH

Microscopic propagation can have an effect. Discrete-cell modelling. Separate interconnected regions. Validation difficult. HL1-6. First step.

MODELLING AN ACTION POTENTIAL

$$I_K = G_K \cdot a \cdot i \cdot (V - E_K)$$

$$\frac{da}{dt} = \frac{a_{ss} - a}{\tau_a}$$

$$a_{ss} = 1/[1 + e^{-(V+22.5)/7.7}]$$

$$\tau_a = 0.493e^{-0.0629V} + 2.058$$

- Parameters fit to experimental patch clamp data.
- Traditional fitting methods do not account for uncertainty in estimates.
- Approximate Bayesian Computation (ABC) produces posterior distribution for each parameter.

Equation gating variables. Hierarchical. Number of parameters. Patch clamp experiments to fit. Traditional vs ABC.

HYPOTHESIS

The ABC approach can be used to construct a validated mathematical model of the action potential of a HL1-6 cell while taking into account uncertainties in parameter estimates arising from insufficient fitting data, biological variability and/or parameter redundancy.

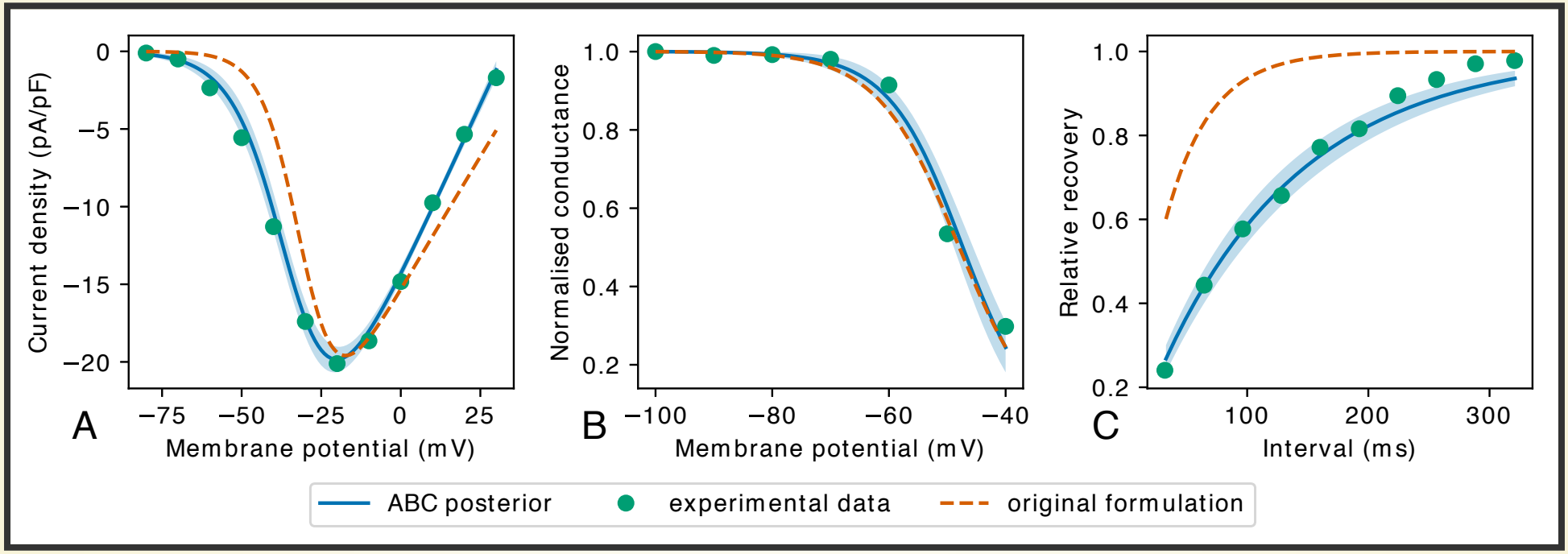
AIMS

1. Develop an ABC implementation to estimate parameter posterior distributions for individual ion currents.
2. Investigate the sources of any uncertainty and unidentifiability in parameter estimates.
3. Construct the full action potential model and validate with action potential recordings from biological experiments.

Brief description of ABC. Input output.

AIM 1: PARAMETERISING ION CURRENTS USING ABC

- ABC outperformed traditional maximum likelihood estimation, and provides uncertainty in simulation output.

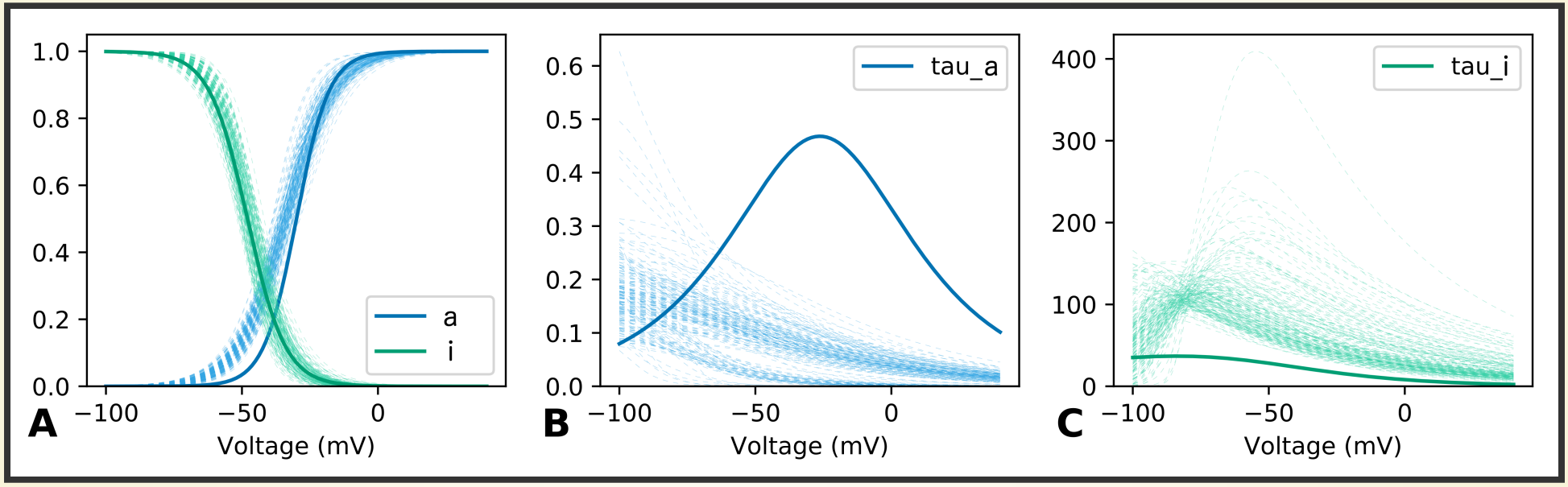


ABC vs Maximum Likelihood fitting of T-type Calcium current: A = activation, B = inactivation, C = recovery.

Three graphs/protocols. Graph description. Improves fit. Distribution narrow. Recovery harder to fit. Appears well constrained but underlying variables.

AIM 2: INVESTIGATING UNIDENTIFIABILITIES

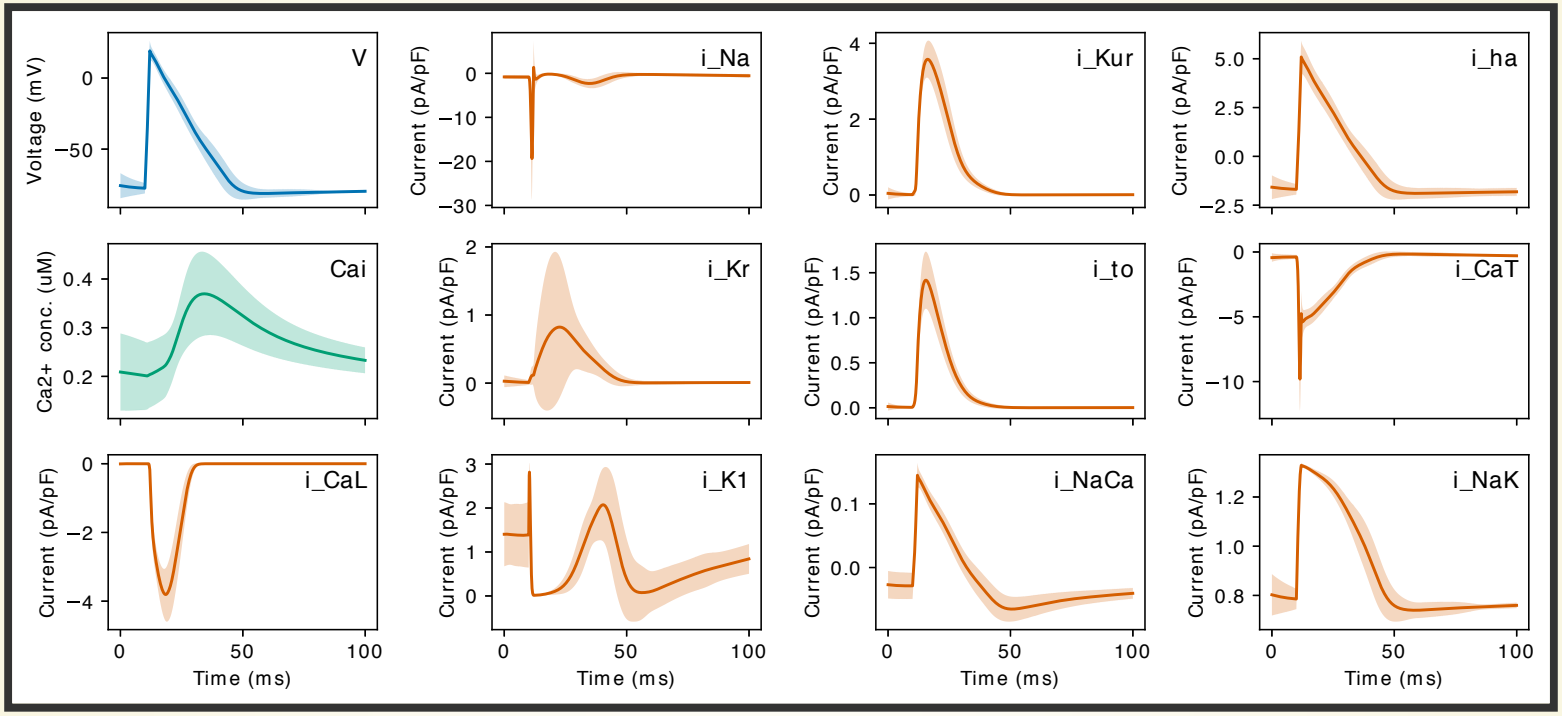
- Time constant curves could not be constrained by standard protocol patch clamp data.



Underlying variables in ion current equations with ABC parameter posteriors: A = steady-state, B = activation time constant, C = inactivation time constant.

Plot description. Steady-state well constrained. Time constants wide variation. Practical unidentifiability. Rerun ABC before full model.

AIM 3: VALIDATING THE FULL CELL MODEL



variable	HL1-6 model	HL1-6 experiment	HL-1 experiment
APD_{90} (ms)	32.4 ± 0.5	42 ± 9	
V_{rp} (mV)	-77.5 ± 0.3	-67 ± 2	-68.8 ± 1.6
AP amplitude (mV)	96.8 ± 0.5	105 ± 2	
$V_{overshoot}$ (mV)	19.3 ± 0.5		15.3 ± 1.9

Advantage propagate uncertainty. Quantitative measurement. Resting potential difference. Sodium channel fitting threshold.

CONCLUSIONS

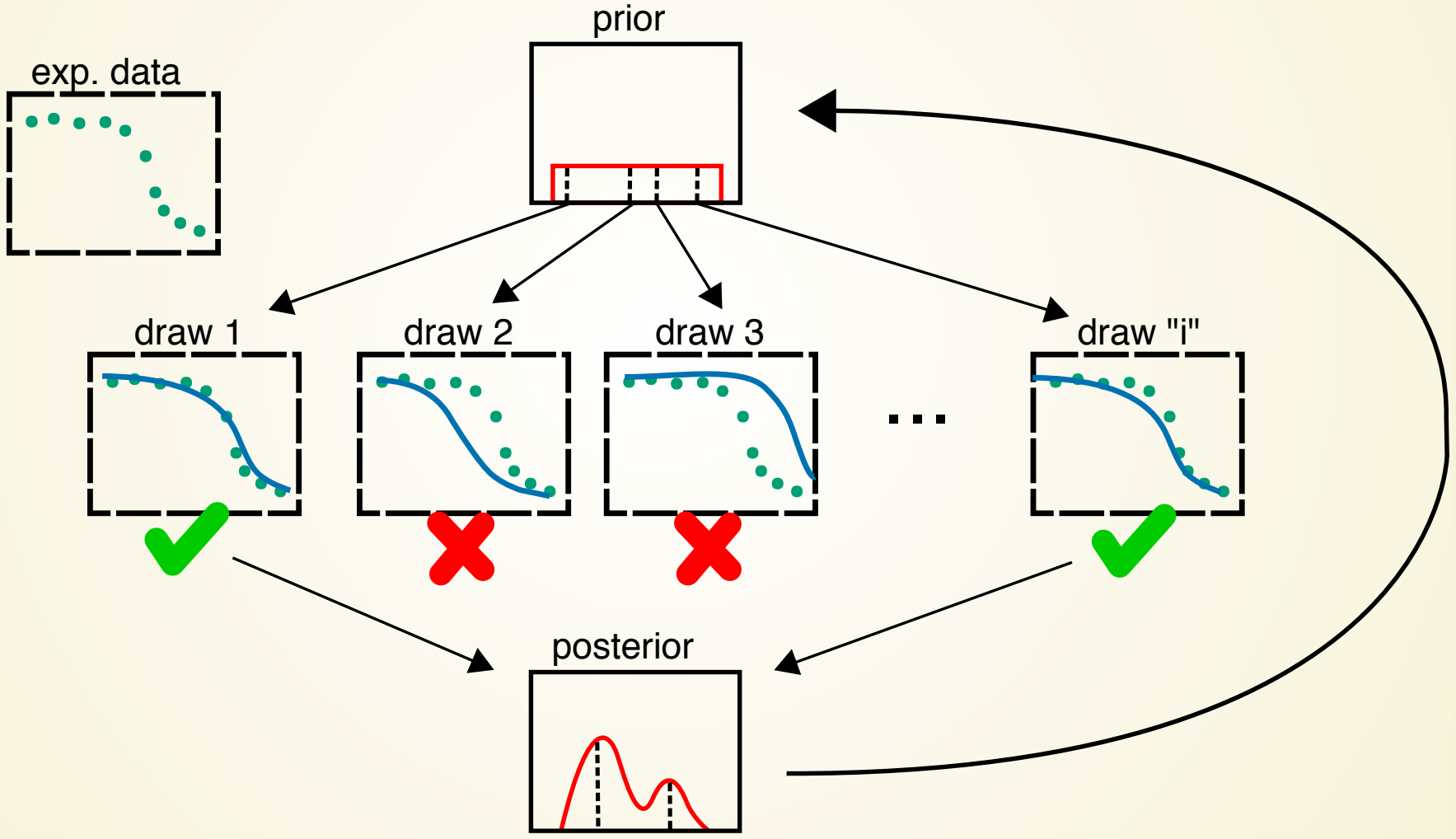
1. ABC is an effective approach to infer model parameters while accounting for uncertainties and/or unidentifiabilities.
2. Standard protocol voltage patch clamp data is not sufficient to completely constrain time constant parameters.
3. The full action potential model reproduces qualitative and quantitative characteristics of the HL1-6 myocyte.

Hypothesis partially accepted. Aim 1 complete. Time constants not constrained. Part validation. Further work.

ACKNOWLEDGEMENTS

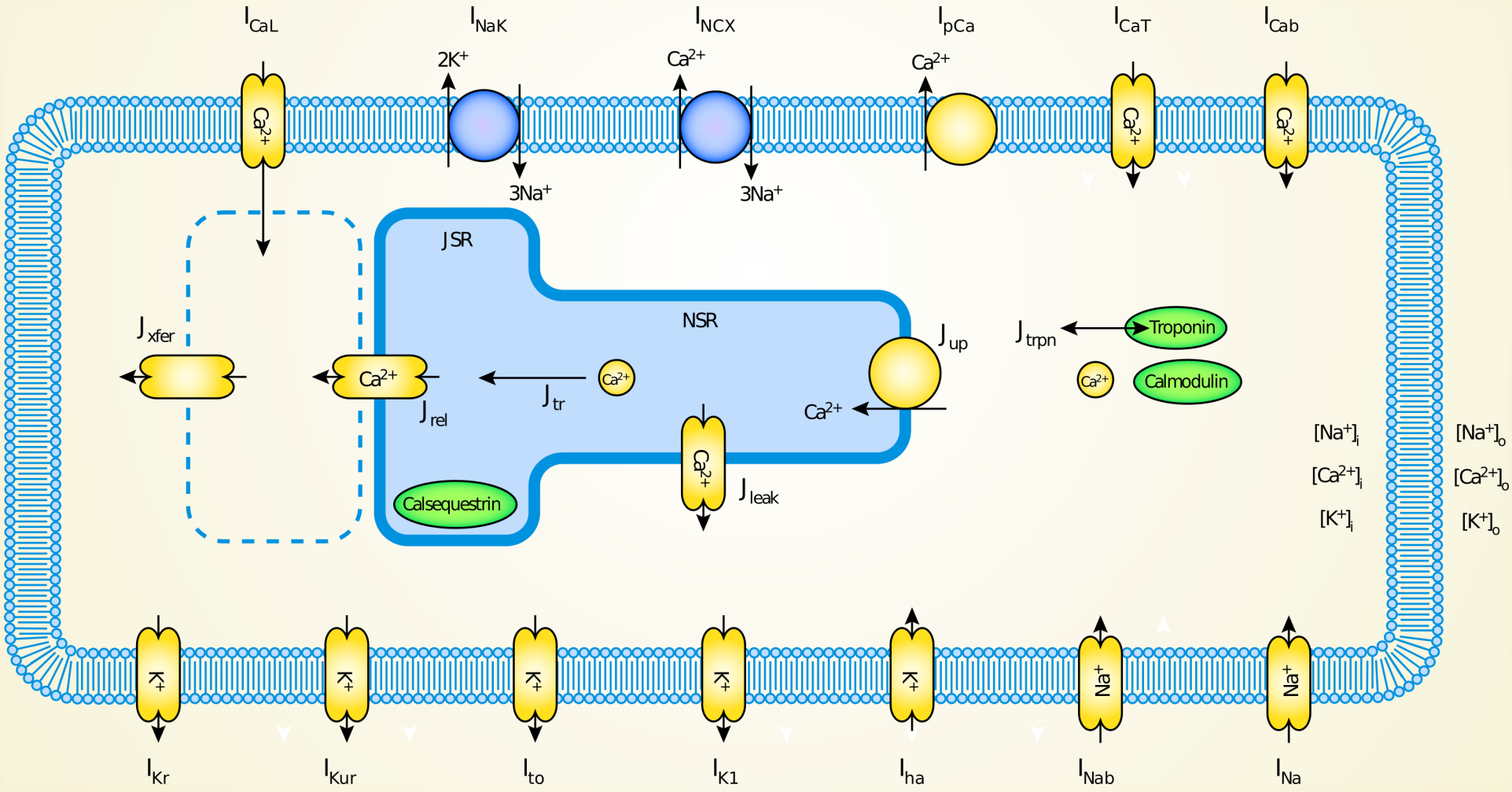
- Dr Chris Cantwell
- All members of ElectroCardioMaths Programme
- British Heart Foundation

APPROXIMATE BAYESIAN COMPUTATION (ABC)



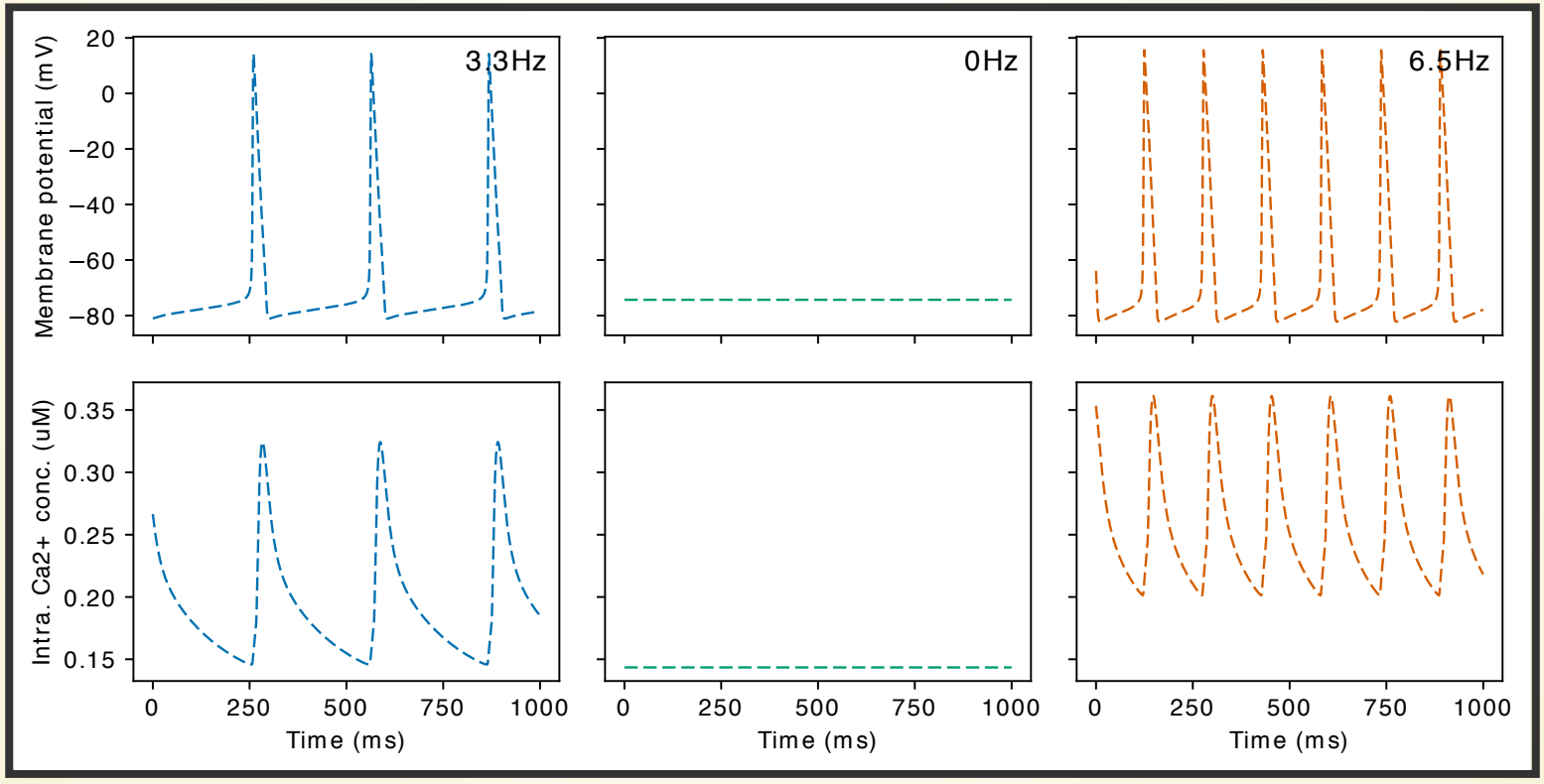
MODEL OVERVIEW

Simulate by solving 35 ODEs at each time step.



AIM 3: SIMULATIONS WITHOUT PACING

- Automaticity in 56% of runs with mean firing rate 4.9±2.0 Hz.
- Comparable qualitative action potential and Calcium transients between simulations and experiments.



Random draw parameters different output. 200 sims 1 second. Automaticity. Qualitatively similar.