CONSTRUCTING AN ACTION POTENTIAL MODEL: EASY AS ABC?

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4 Sep 2017

IN-SILICO MODELLING OF CARDIAC ELECTROPHYSIOLOGY

TOWARDS A DISCRETE-CELL APPROACH

MODELLING AN ACTION POTENTIAL

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

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

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

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

- 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.

HYPOTHESIS

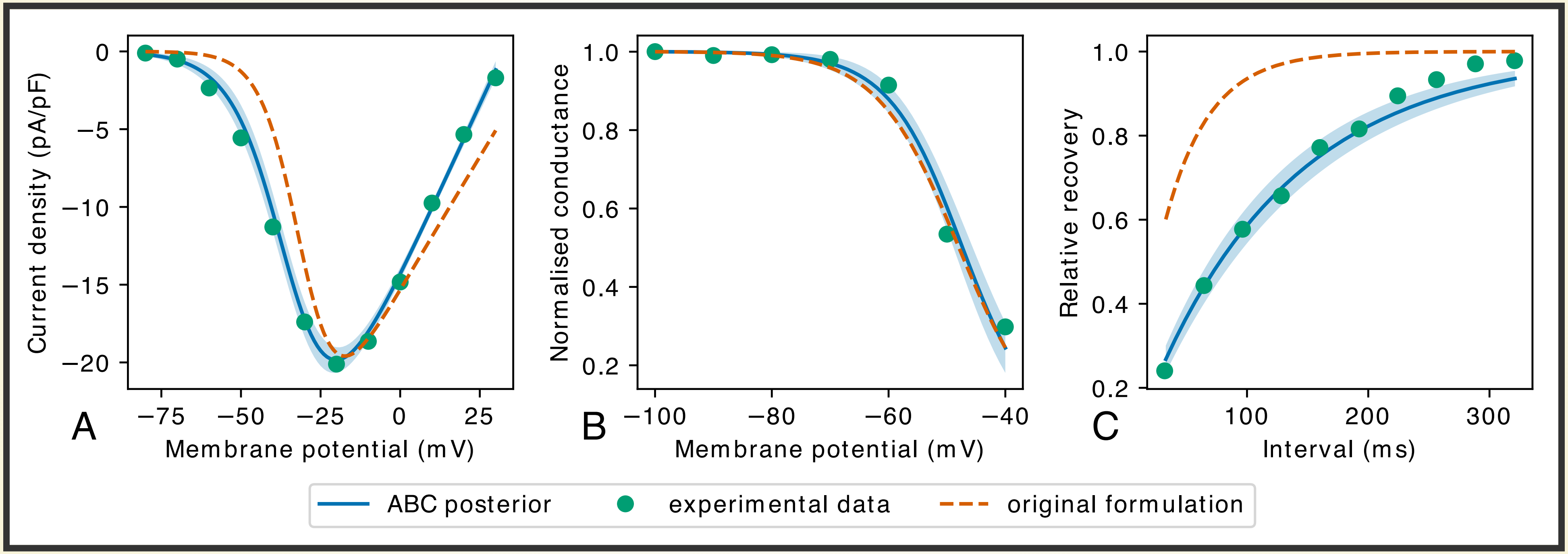
The ABC approach can be used to construct a validated mathematical model of the action potential of a HL1-6 cell while taking into account uncertainties in parameter estimates arising from insufficient fitting data, biological variability and/or parameter redundancy.

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.

AIM 1: PARAMETERISING ION CURRENTS USING ABC

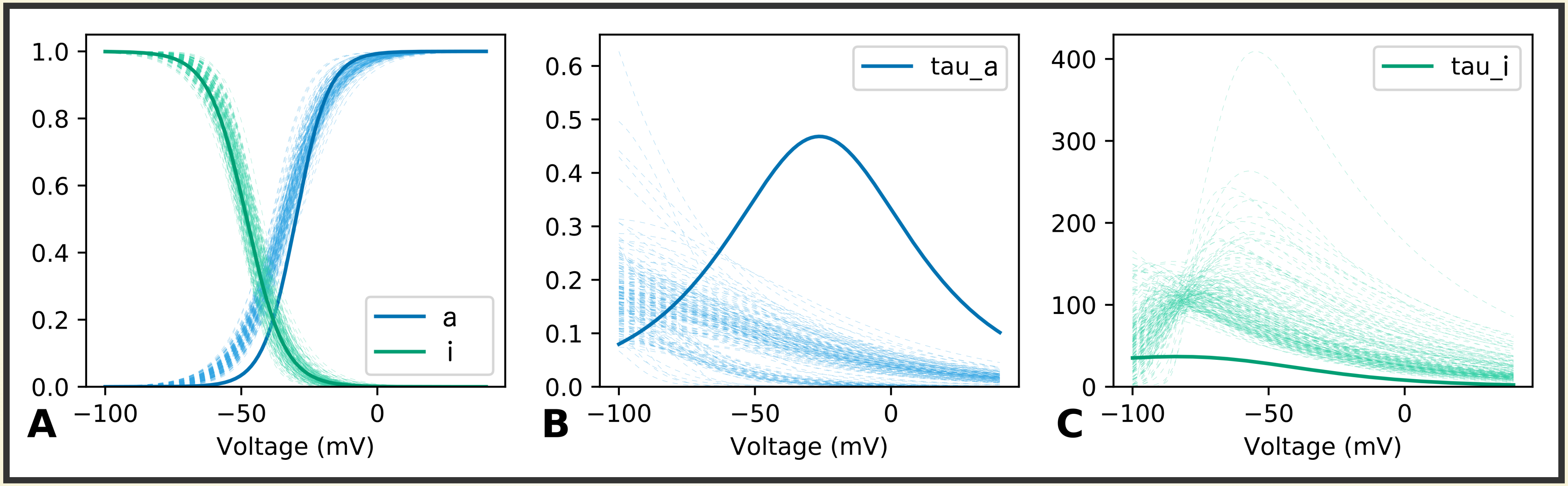
- ABC outperformed traditional maximum likelihood estimation, and provides uncertainty in simulation output.



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

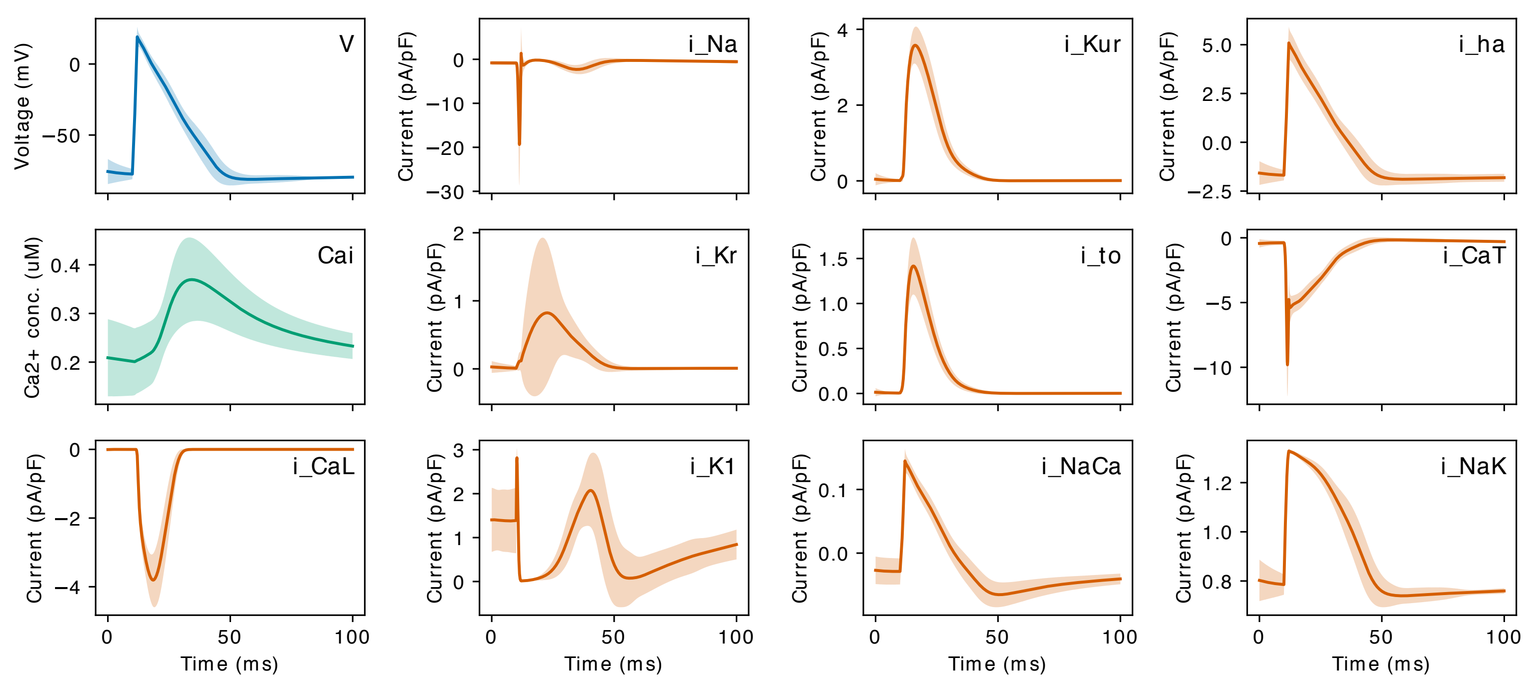
AIM 2: INVESTIGATING UNIDENTIFIABILITIES

- 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.

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

CONCLUSIONS

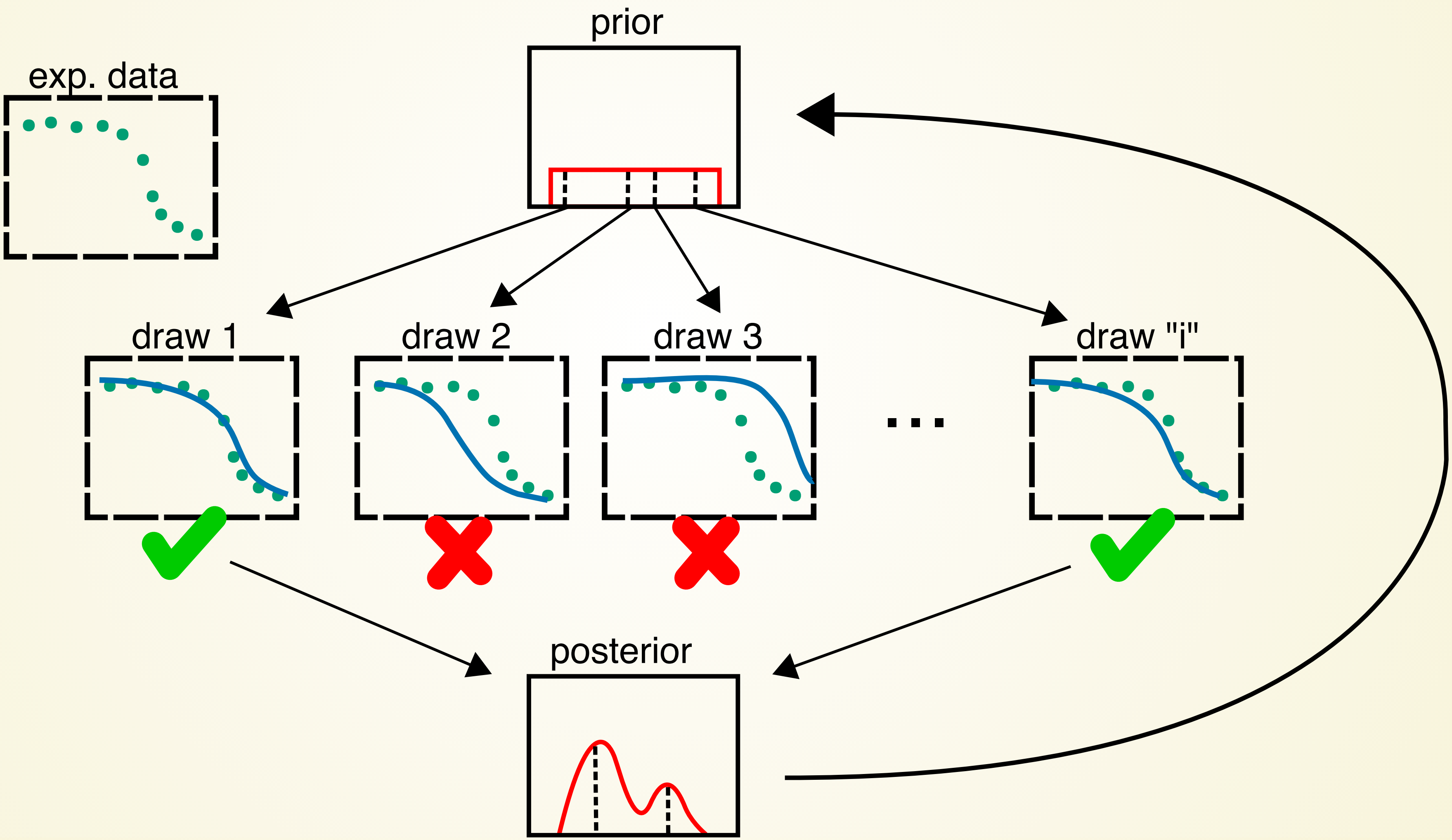
1. ABC is an effective approach to infer model parameters while accounting for uncertainties and/or unidentifiabilities.
2. Standard protocol voltage patch clamp data is not sufficient to completely constrain time constant parameters.
3. The full action potential model reproduces qualitative and quantitative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

ACKNOWLEDGEMENTS

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

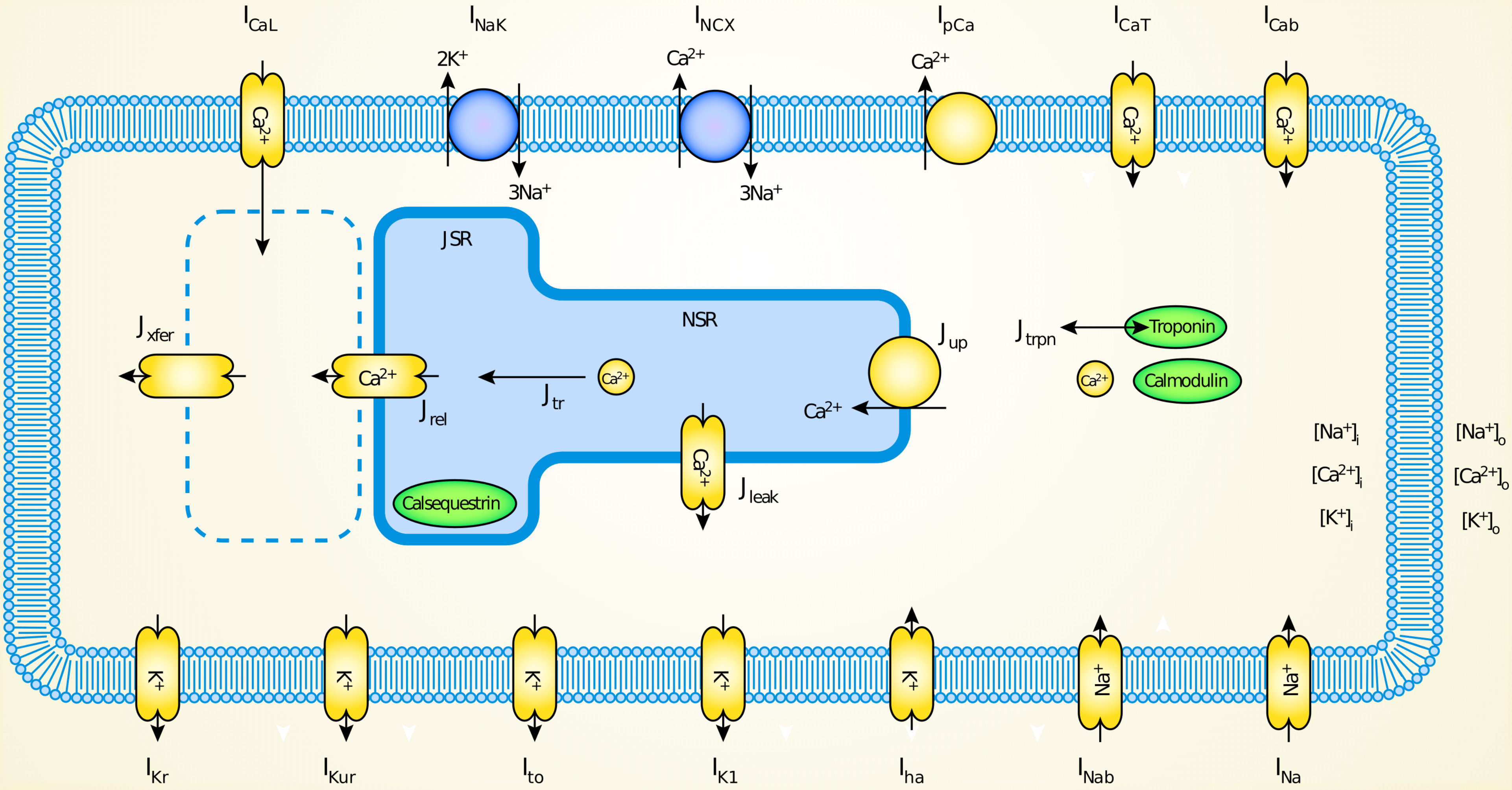
Presentation created using reveal.js. Source for ABC implementation and slides available on Github.

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.