Using Python and Julia to Model Ion Channel Kinetics.

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1. Introduction

Pacemaker 'HCN' (Hyperpolarization-activated, Cyclic Nucleotide-gated) channels are important for regulating rhythmic activity in the heart and brain.

Mathematical models are used to describe how HCN channels transition between closed and open states.

Here, we show a three-step workflow for modelling ion channel function using tools in Julia/Python:

1. **Global optimization**
2. **Monte Carlo Markov Chain (MCMC) sampling**
3. **Validation**

2. A Mathematical Model for Pacemaker 'HCN' channels.

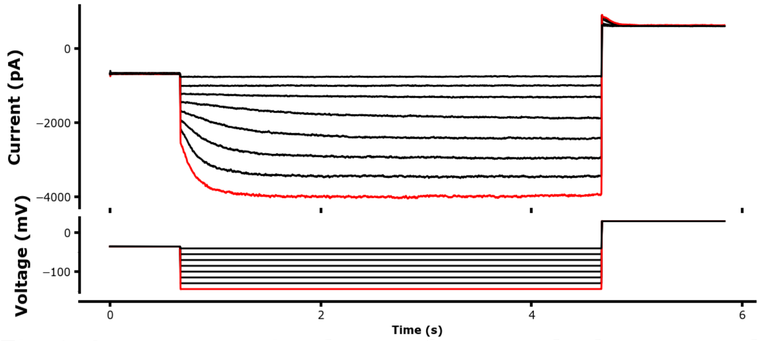


Fig. 1. A representative dataset from patch-clamp recording of HCN channels. Current traces (top) are elicited by voltage steps (bottom) from -55mV to -145mV (red) to open the channels.

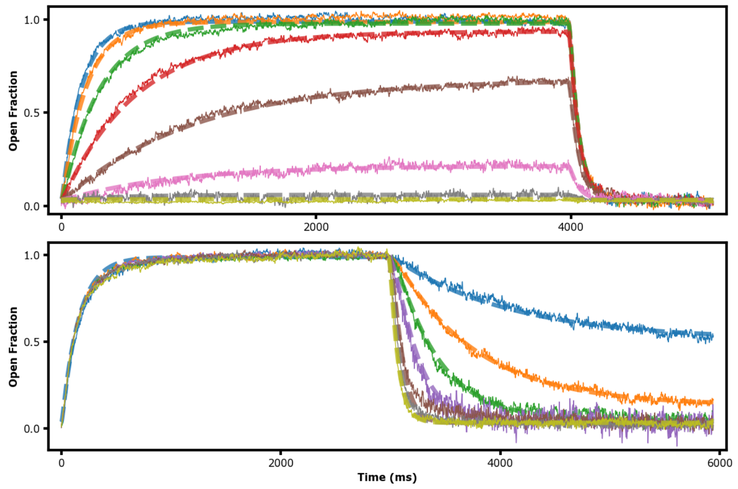
$$
\begin{array}{ccc}
C_R & \leftrightarrow & C_A \\
\updownarrow & & \updownarrow \\
O_R & \leftrightarrow & O_A
\end{array}
\qquad
\begin{aligned}
\frac{dC_R}{dt} &= -(g_2+\alpha_1)C_R + \beta_1 C_A + h_2 O_R \\
\frac{dC_A}{dt} &= -(g_1+\beta_1)C_A + \alpha_1 C_R + h_1 O_A \\
\frac{dO_R}{dt} &= -(h_2+\alpha_2)O_R + g_2 C_R + \beta_2 O_A \\
\frac{dO_A}{dt} &= -(h_1+\beta_2)O_A + g_1 C_A + \alpha_2 O_R
\end{aligned}
$$

Fig. 2. A mathematical model of 'HCN' channel gating. Only open states (O_R, O_A) are observable, since we can only record electrical current when channels are open. Accurate, fast simulations are achieved by using **DifferentialEquations.jl.**

3. Global Optimization.

Fig.3. Best-fit of the model. The direct output of the model in Fig.2. is the sum of open states, which ranges from 0-1. The data was normalized accordingly, and fit using **BlackBoxOptim.jl** and **GCMAES.jl.**

The top and bottom panels represent distinct datasets that were fit simultaneously for model calibration.



4. Approximating the Posterior Distribution.

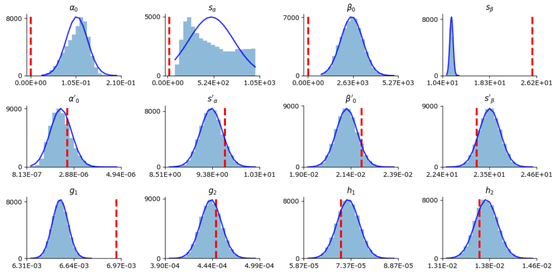


Fig.4. MCMC sampling and prediction. Assuming that experimental noise is independently and normally distributed with zero mean, MCMC (**PyMC3**) was initialized from the global optimum, yielding posterior distributions for each parameter (top left). Samples drawn show close agreement with the data (top right), but do not predict an unseen dataset (bottom right), but neither does a global fit to this data (dashed lines).