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A computationally efficient algorithm for fitting ion channel parameters

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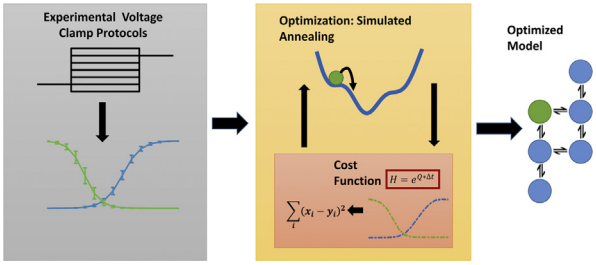
GRAPHICAL ABSTRACT



ABSTRACT

Continuous time Markov models have been widely used to describe ion channel kinetics, providing explicit representation of channel states and transitions. Fitting models to experimental data remains a computationally demanding task largely due to the high cost of model evaluation. Here, we propose a method to efficiently optimize model parameters and structure. Voltage clamp channel protocols can be decomposed into a series of fixed steps of constant voltage resulting in a set of linear systems of differential equations. Given the linear systems, ODE integration can be swapped for the faster matrix exponential routine. With our parallelized implementation, optimized models are able to reproduce a wide range of experimentally collected data within one minute, a 50 times speedup over ODE integration.

- The cost of the objective function is reduced by employing the matrix exponential
- The likelihood of convergence is improved by applying synchronous start simulated annealing
- The approach was tested by optimizing parameters for a model of the cardiac voltage-gated Na^+ channel, $Na_V1.5$, and the KCNQ1 K^+ channel.

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Method

Following the seminal work of Hodgkin and Huxley in 1952 [1], mechanistic ordinary differential equation (ODE) models have been used to simulate dynamics of excitable systems including neurons, myocytes and pancreatic beta cells [2,3]. A persistent challenge in creating these models is the identification of optimal parameters. This difficulty arises from the multi-dimensionality of the search, the exponential form of the rate equations, and the existence of many local minima. Global search methods such as simulated annealing and genetic algorithms have been applied to identify optimal sets of parameters [4–6]. However, these approaches require significant computational resources.

The primary bottleneck for optimization is the numerical solution of ODEs needed to simulate experimentally observed dynamics. When evaluating a large set of models with global searches, this step becomes rate-limiting, and is particularly difficult when the equations become stiff, requiring very small time-steps or complicated implicit schemes [7].

We propose to overcome the ODE barrier by solving these differential equations with the matrix exponential, an approach that has been used to analyze channel kinetics and improve the efficiency of action potential simulations [8,9]. We tested this approach on experimental voltage pulse protocols, optimizing a two discrete-state Markov models of the cardiac Na^+ channel and the KCNQ1 K^+ channel. Optimization was performed using multiple chain simulated annealing [10]. Code has been made publically available at, where demos and https://github.com/silvalab/MMOptimizer instructions on model fitting can be found. Example model graphs and fits to Na^+ experimental data are shown in Fig. 1; K^+ fits are shown in Fig. 2.

We used the following voltage pulse protocols for Na^+ model fitting:

Voltage Dependent Activation (Fig. 1B)*:* A series of depolarizing pulses were applied from −120 mV to 20 mV in 10 mV increments from a resting potential of −100 mV. The voltage-dependence of channel conductance was found from this protocol by finding the peak current during the pulse and dividing by the driving force ($V_m - E_{Na}$), where V_m is the membrane potential and E_{Na} is the reversal potential for Na^+.

Steady State Inactivation (Fig. 1B)*:* Cells were held at −120 mV before being exposed to conditioning pulses ranging from −120 mV to 20 mV in 10 mV increments for 200 ms. Voltage was then stepped to −20 mV and peak current was recorded and normalized by dividing by the maximum current.

Recovery from Inactivation (Fig. 1C)*:* Cells were held at −120 mV before being exposed to a −20 mV depolarizing pulse for 200 ms. Cells were then allowed to recover at −120 mV for durations ranging from 1 ms to 1000 ms before a final depolarizing pulse at −20 mV where peak current was recorded and normalized across samples.

Rise/Fall Time (Fig. 1D)*:* This protocol replicated *Voltage Dependent Activation*. Rise (10%-90%) measured the amount of time it took for current to rise from 10% to 90% of the maximum recorded current. Fall (90%-20%) characterized fast inactivation kinetics by measuring the time it took for current to fall from 90% to 20% peak current.

Conductance Trace (Fig. 1E): In the final protocol we exposed the cell to a single depolarizing pulse and recorded normalized conductance over 5 ms.

Similarly, we used the following voltage pulse protocols for K^+ model fitting:

Voltage dependent activation (Fig. 2B): A series of depolarizing pulses were applied from −100 mV to 60 mV in 20 mV increments from a resting potential of −100 mV. The voltage-dependent channel