Motor cortex neurons: from experiment to model via evolutionary algorithms

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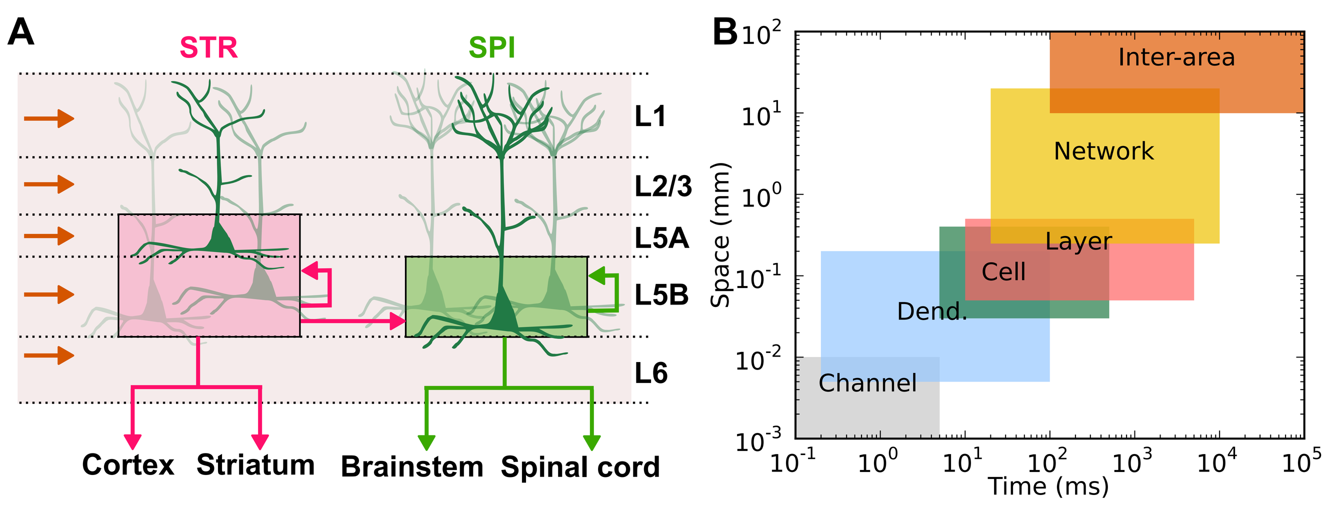
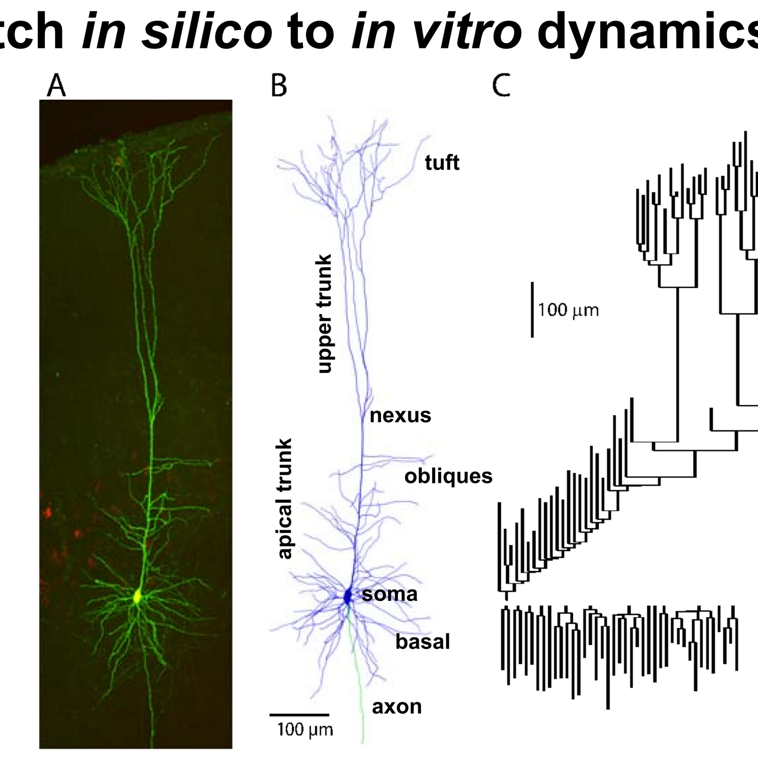
Introduction

The thick tufted corticospinal cells (SPI) in layer 5 of motor cortex gate information flow out of motor cortex, thereby contributing to movement. We have developed computer models of SPI neurons to understand their complex dynamics.



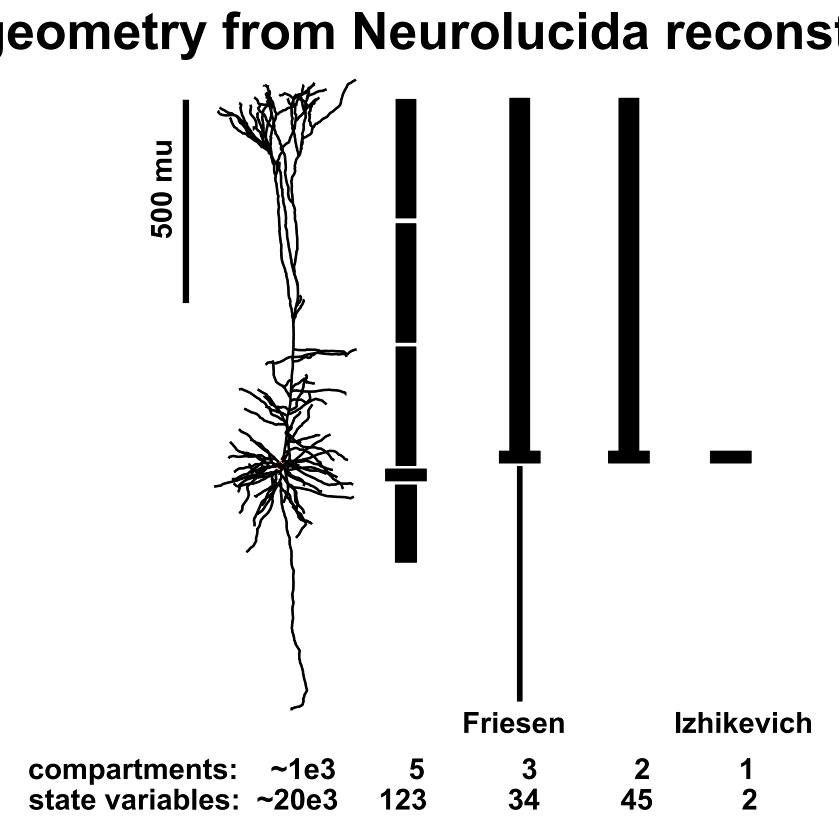
Methods

We used SPI somatic whole-cell recordings to optimize multiple types of neuronal models to match *in silico* to *in vitro* dynamics.



Model Complexity

Our most detailed SPI model had dendritic and axonal geometry from Neurolucida reconstruction.

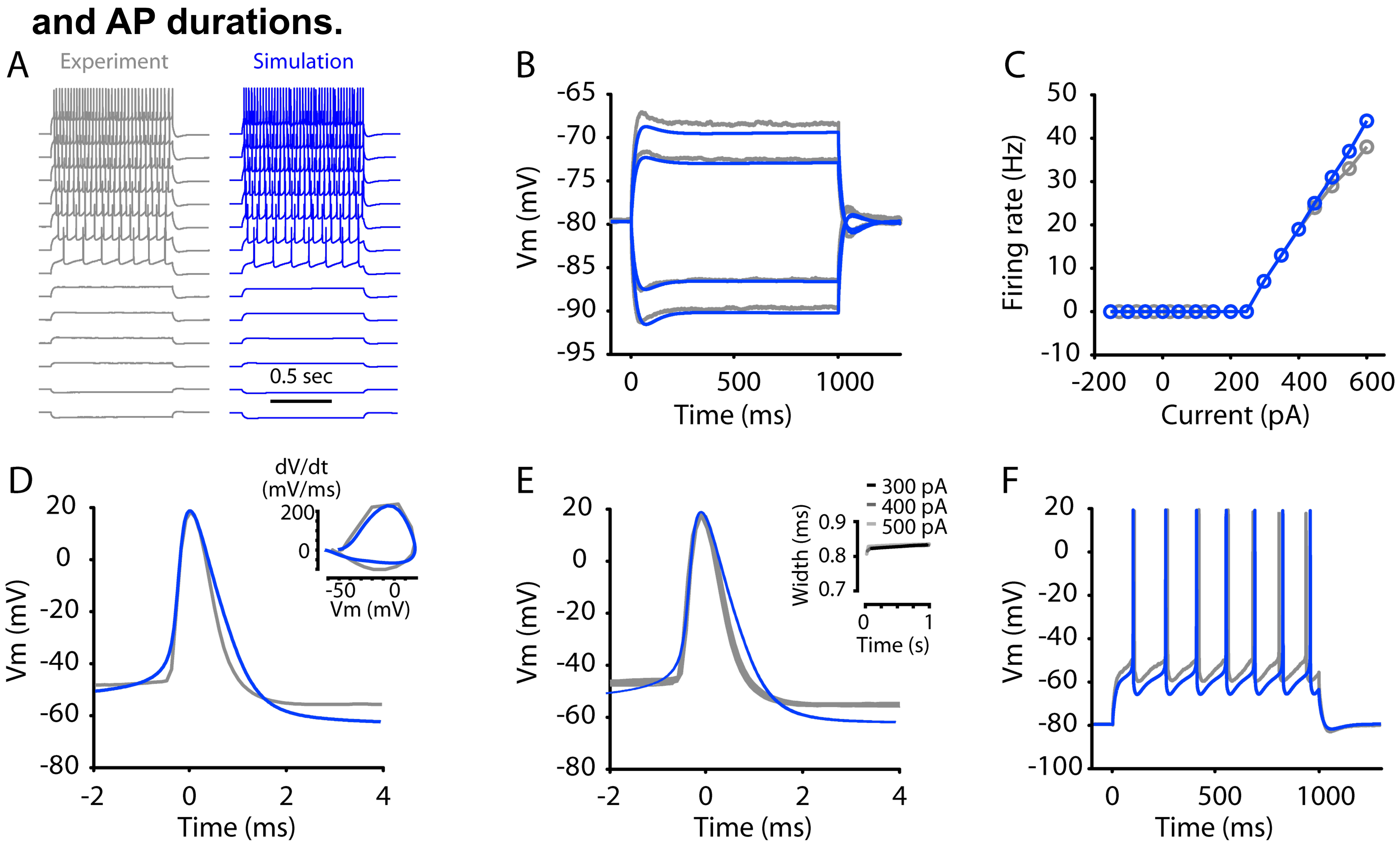


Model neurons included the following ion channels: INa and IKdr for action potentials (AP); IKa for rapid repolarization following APs; IKd for spike-frequency acceleration; Ih for resonance, sag, contribution to resting membrane potential (RMP); calcium (Ca) channels (L, N, T-type) and calcium-activated potassium channels (KCa) for regulating excitability and AP shape. Ion channel distribution was constrained by experimental literature.

Two optimization methods were used: 1. NEURON's principal axis (PRAXIS) algorithm. 2. evolutionary algorithms.

Results

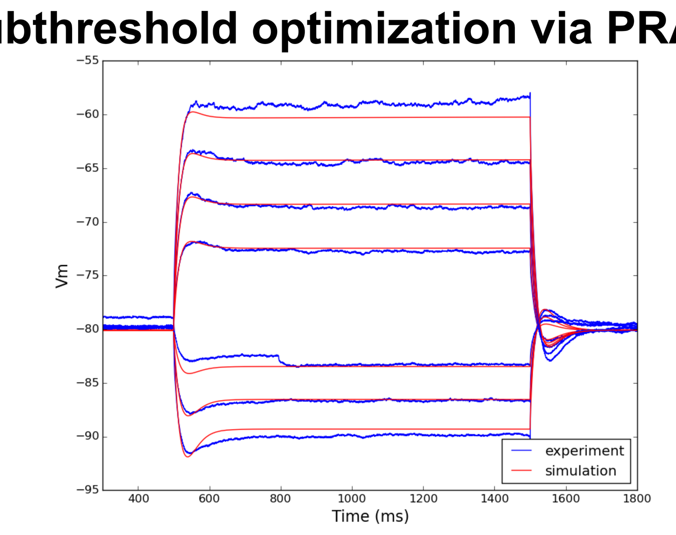
Stage 1: optimize model using PRAXIS for subthreshold fits, then tune manually to get right spike times, AHPs, and AP durations.



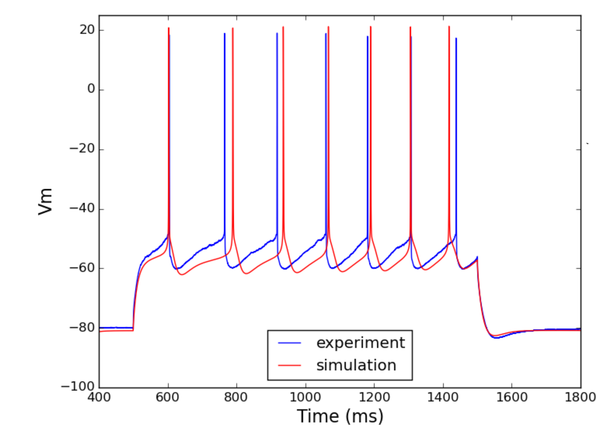
Results

Stage 2: add Ca,KCa channels ⟶ re-optimization required

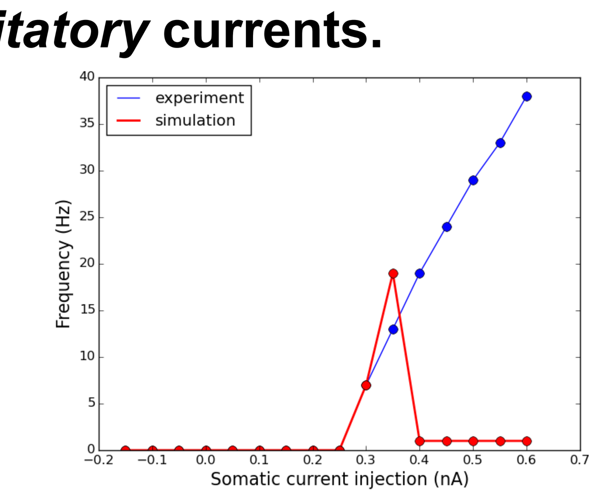
Subthreshold optimization via PRAXIS



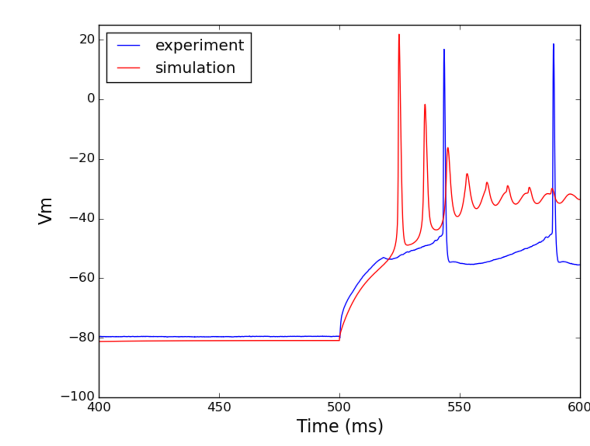
Hand-tuning for spike-timing and AHP ⟶ good fit...



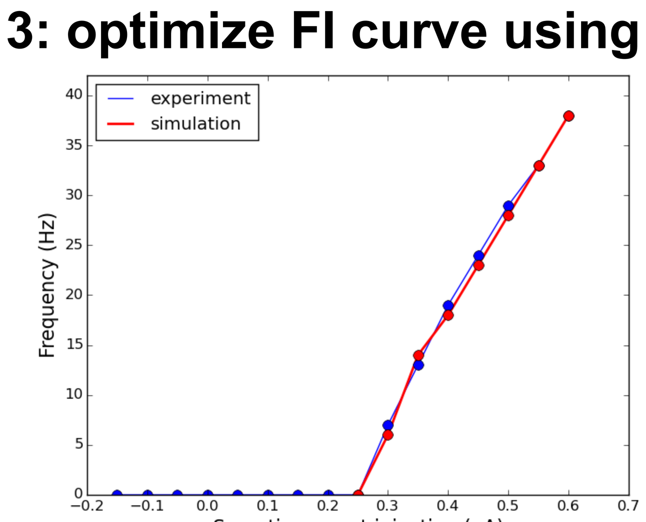
...but difficulty arises since neurons are highly sensitive to the balance of *inhibitory* and *excitatory* currents.



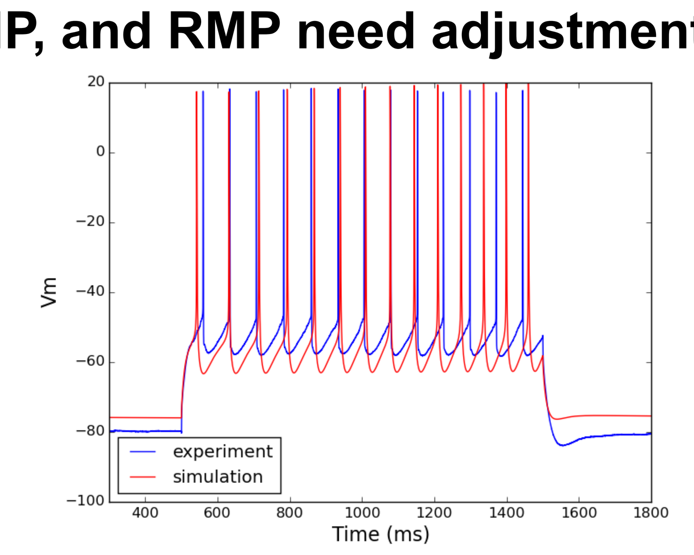
The additional Ca excitability may produce depolarization blockade.



Stage 3: optimize FI curve using PRAXIS



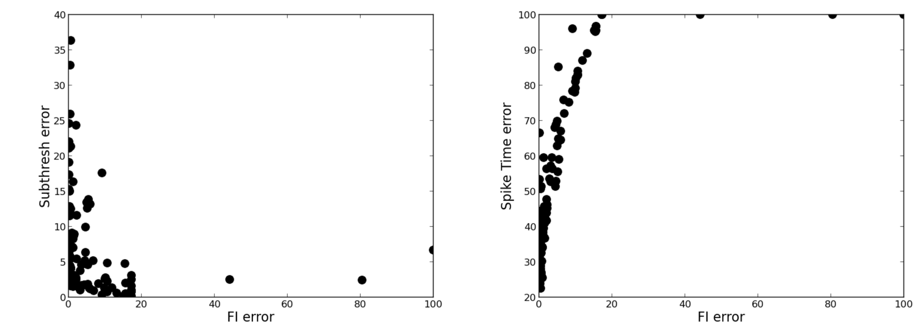
Most current injections produce accurate spike times. However, sag, AHP, and RMP need adjustment.



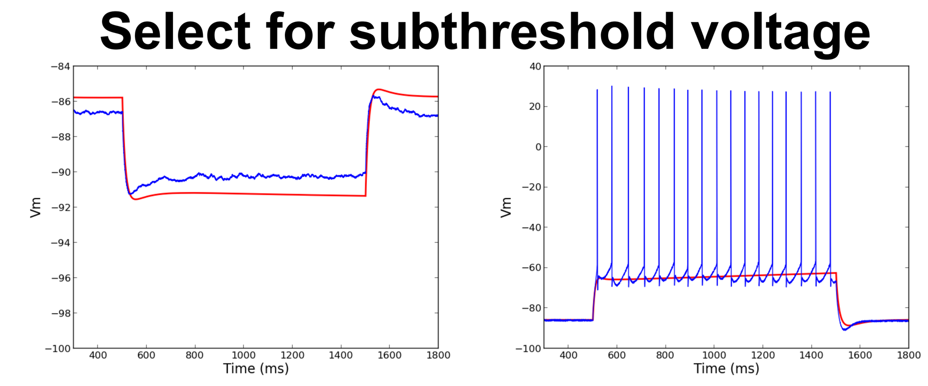
Evolving Models

Strategy: use evolutionary multiobjective optimization to optimize multiple fitness functions, and then interactively select models with desired dynamical features.

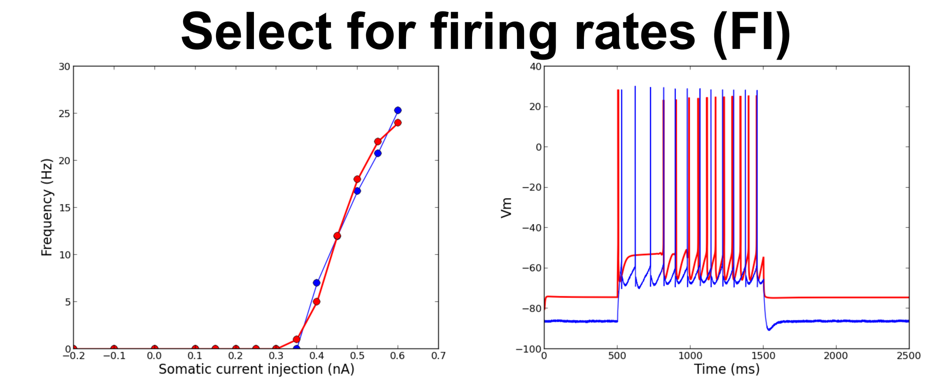
Tradeoffs in fitness measures



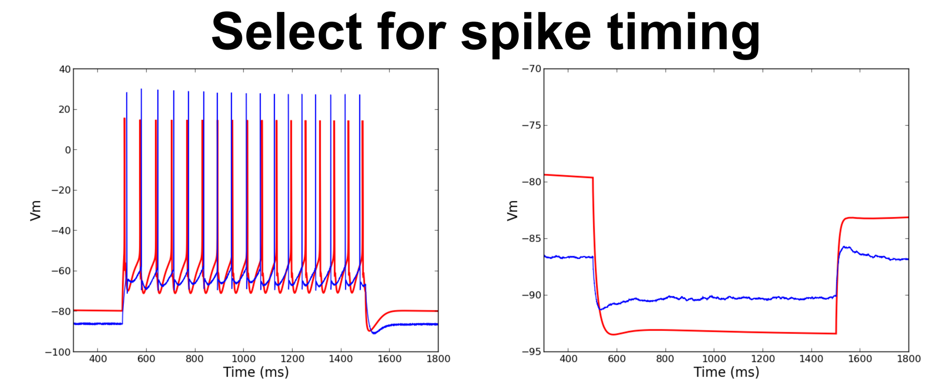
Select for subthreshold voltage



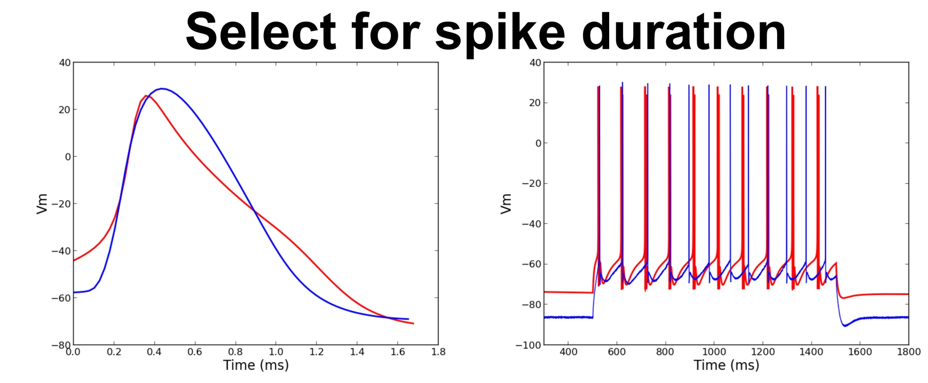
Select for firing rates (FI)



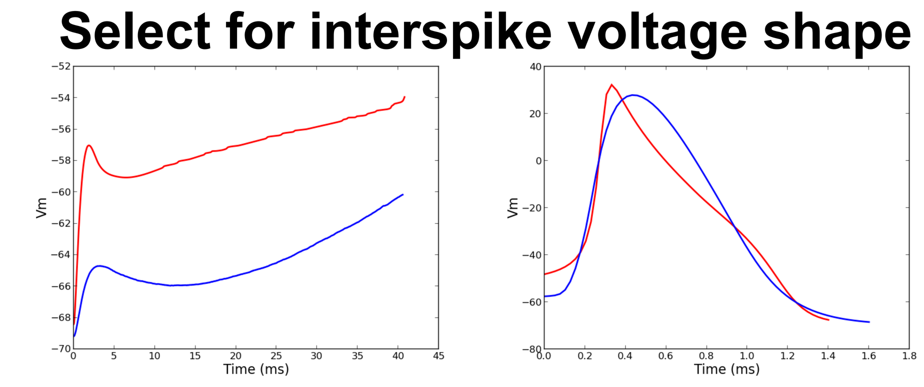
Select for spike timing



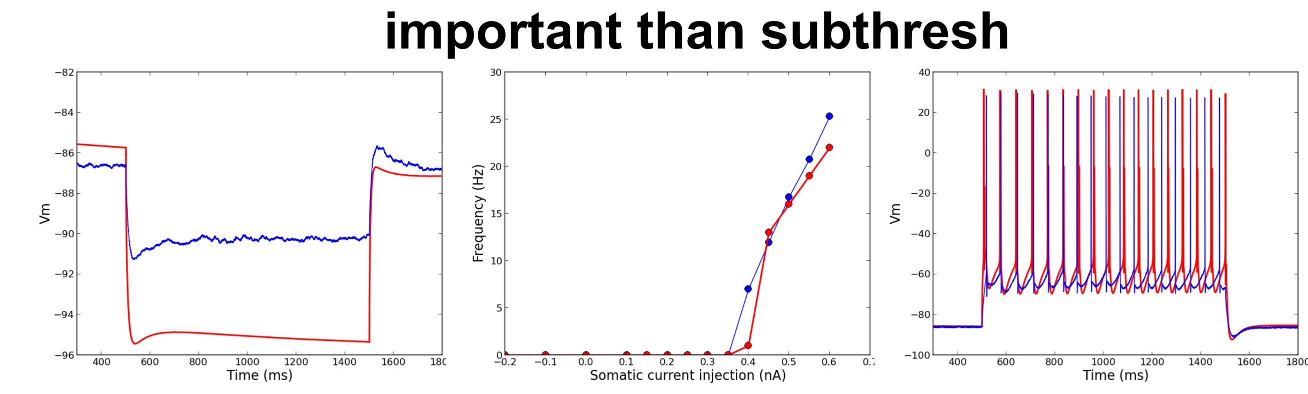
Select for spike duration



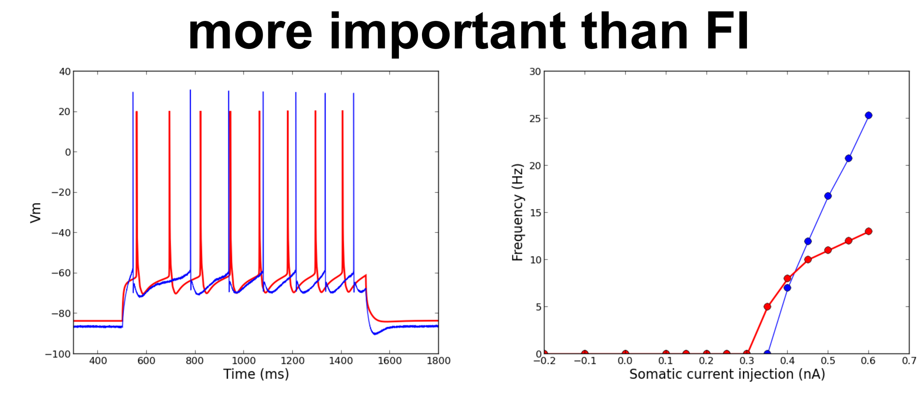
Select for interspike voltage shape



Compromise: FI more important than subthresh



Compromise: subthresh more important than FI



Conclusions

1. Multiple classes of our SPI neuron models were able to replicate important dynamical features of SPI neurons observed *in vitro*, including subthreshold voltage, firing rate, spike timing, and interspike-interval voltage.

2. Sequential optimization produced *better* models:
a. optimize passive parameters (capacitance, leak, Ra) and density of channels contributing to sub-threshold responses (HCN, Kd).
b. optimize density of channels contributing to super-threshold responses (Na, Kdr, Ka, Ca, KCa).

3. Evolutionary multiobjective optimization created a set of models optimized in a multidimensional fitness space. Interactive searching of this space allowed selecting constraints on the quality-of-fit of specific fitness functions.

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