Optimizing computer models of layer 5 motor cortex pyramidal neurons using somatic whole cell recordings

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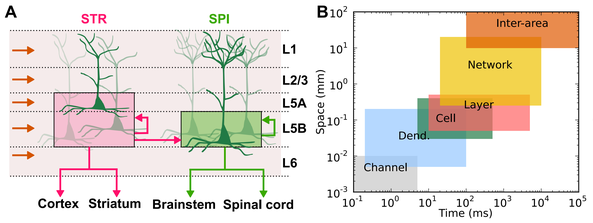
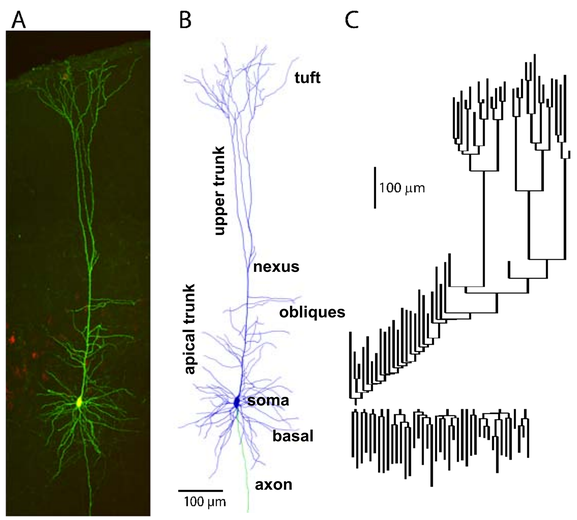
Multiple scales in motor cortex



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.

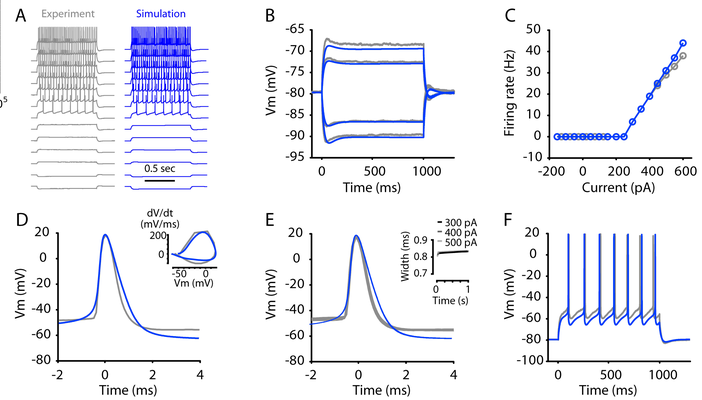


Our most detailed SPI model had dendritic and axonal geometry from Neurolucida reconstruction.

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-type) and calcium-activated potassium channels (KCa) for regulating excitability and AP shape. Ion channel distribution was constrained by experimental literature.

Results

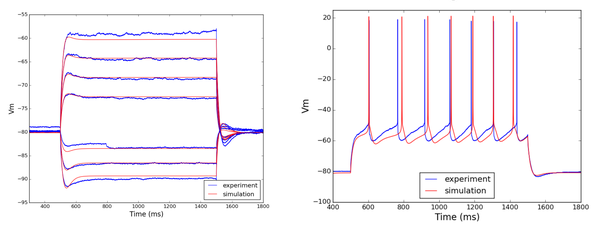
Initial approach: optimize model using principal axis (PRAXIS) algorithm for subthreshold fits, then manually optimize for spike times, AHPs, AP durations.



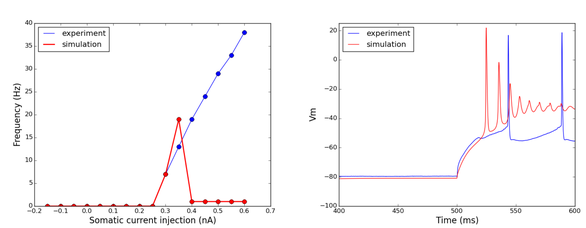
Next: add Ca,KCa channels ⟶ re-optimization required

Subthreshold opt. via PRAXIS

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



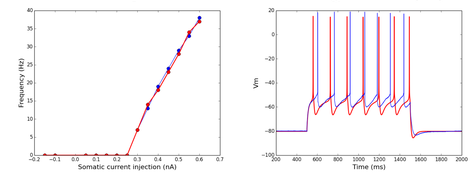
...difficulty arises since neurons are sensitive to the balance of *inhibitory* and *excitatory* currents, sometimes leading to depolarization blockade.



Strategy: Evolving Models

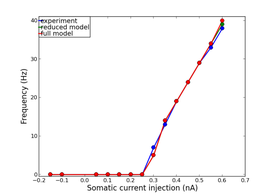
1. **PRAXIS to fit subthreshold steps**
2. **evolutionary multiobjective optimization**
3. **select models with desired features**

Example: select for firing rates (FI)

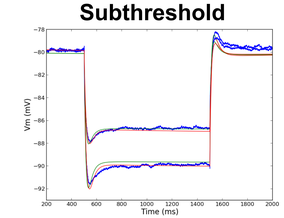


Strategy effective for finding good fits to experimental data for the reduced 5-compartment model and the most detailed (full) model.

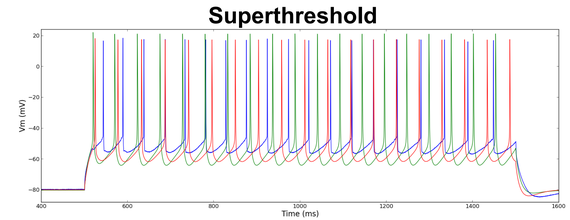
FI



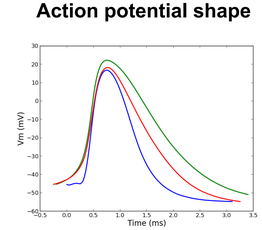
Subthreshold



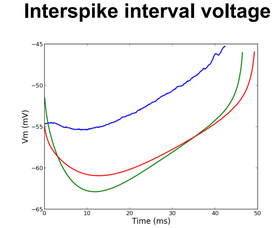
Superthreshold



Action potential shape



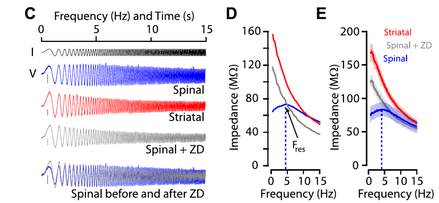
Interspike interval voltage



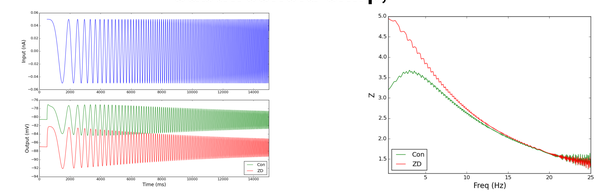
SPI Input/Output (I/O)

Experiment: SPI neurons display Ih-dependent resonance

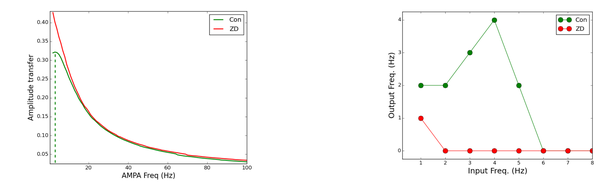
Chirp subthreshold current clamp (Sheets 2011)



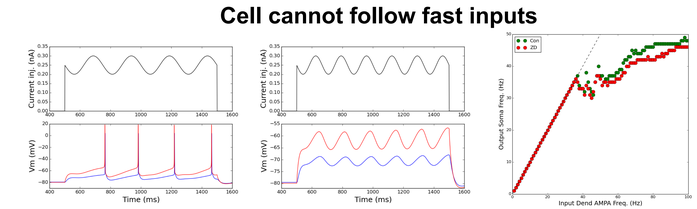
Model: similar Ih-dependent resonance profile under: subthreshold chirp,



subth. AMPA stim at dend, near-threshold clamp at dend



Cell cannot follow fast inputs



Conclusions

1. **Our SPI neuron models replicate important dynamical features of SPI neurons observed *in vitro,* including subthreshold voltage, firing rate, spike timing, interspike-interval voltage, and Ih-dependent I/O and resonance profiles.**
2. **Sequential optimization produced *better* models:**
   a. **optimize passive parameters (capacitance, leak, Ra) and density of channels contributing to subthreshold responses (HCN, Kd).**
   b. **optimize density of channels contributing to superthreshold responses (Na, Kdr, Ka, Ca, KCa).**
3. **Evolution created a set of models optimized in high-D fitness space; searching allowed selecting quality-of-fit of specific fitness functions.**

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References: [1] Corticospinal-specific HCN expression in mouse motor cortex: Ih-dependent synaptic integration as a candidate microcircuit mechanism involved in motor control. PL Sheets, BA Suter, T Kiritani, CS Chan, DJ Surmeier, GMG Shepherd. J Neurophysiology 106:2216-2231, 2011.
[2] Intrinsic electrophysiology of mouse corticospinal neurons: a class-specific triad of spike-related properties Suter BA, Migliore M, Shepherd GMG. Cerebral Cortex 23(8):1965--1977, 2013.