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

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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.

References:

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 IKd 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.

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

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

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