



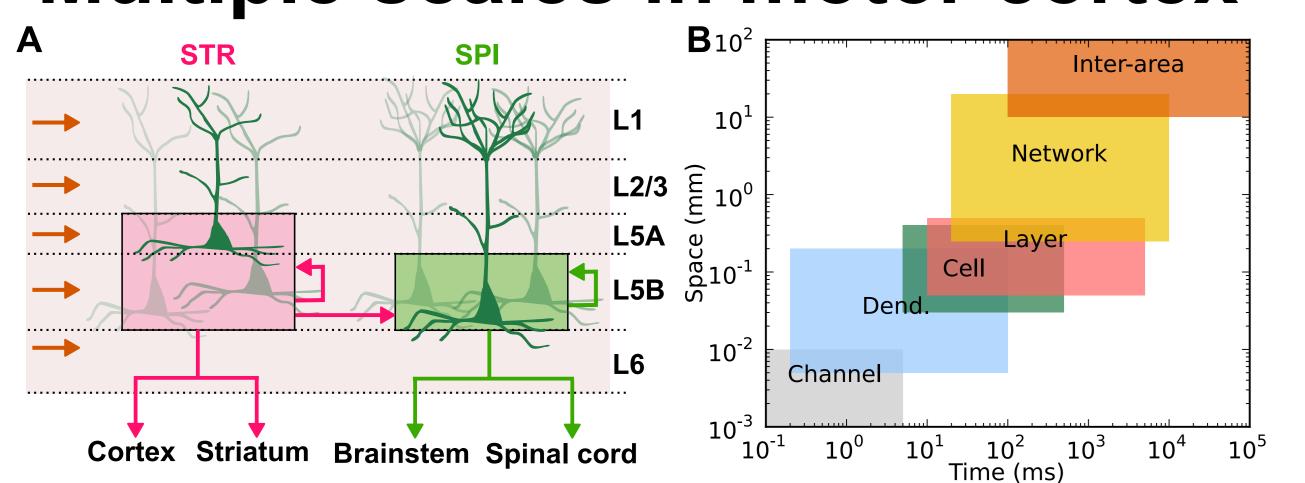
Microconnectomics of primary motor cortex: a multiscale computer model

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Introduction Multiple scales in motor cortex

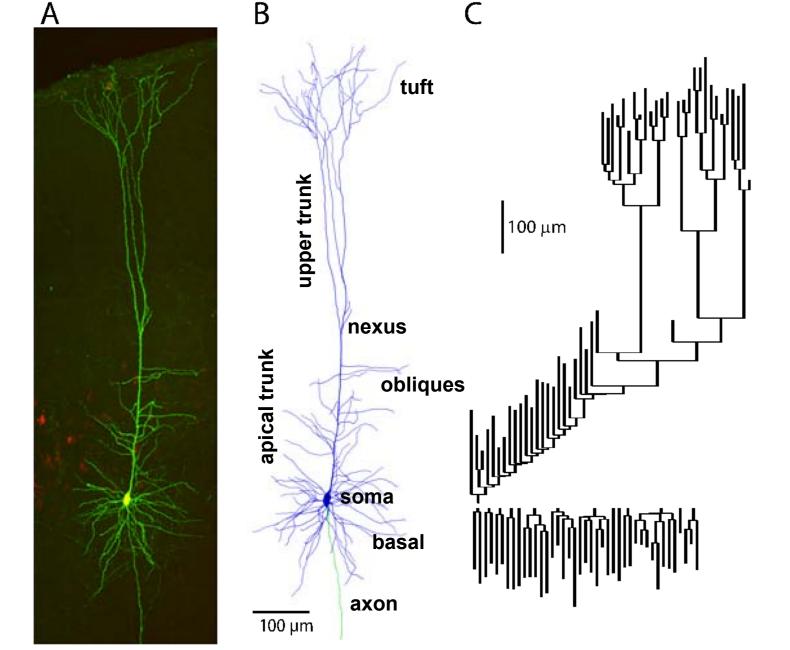


Cell Level

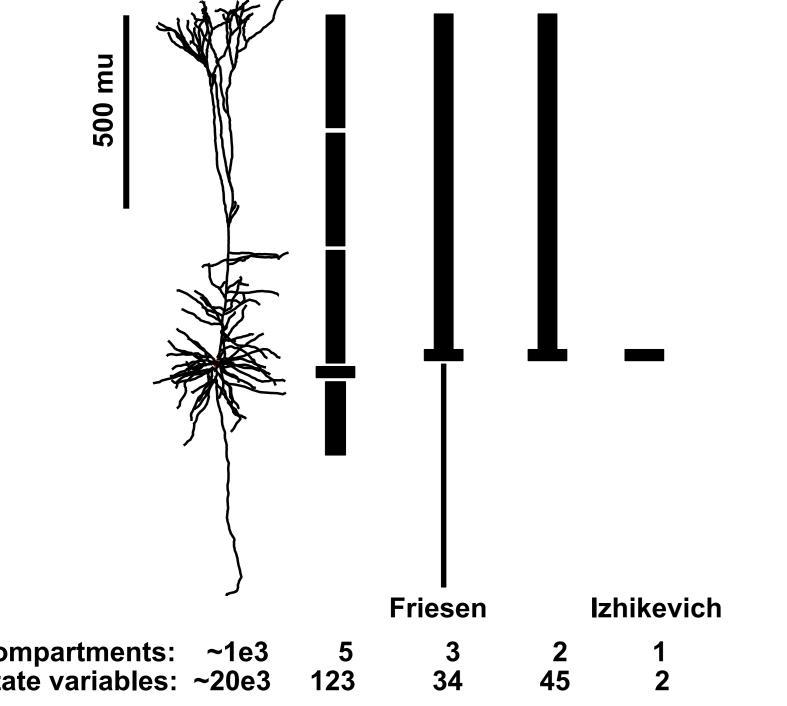
The thick tufted corticospinal cells (SPI) in layer 5 of motor cortex gate information flow out of motor cortex, thereby contributing to movement. We have developed computer models of SPI neurons to understand their complex dynamics.

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.

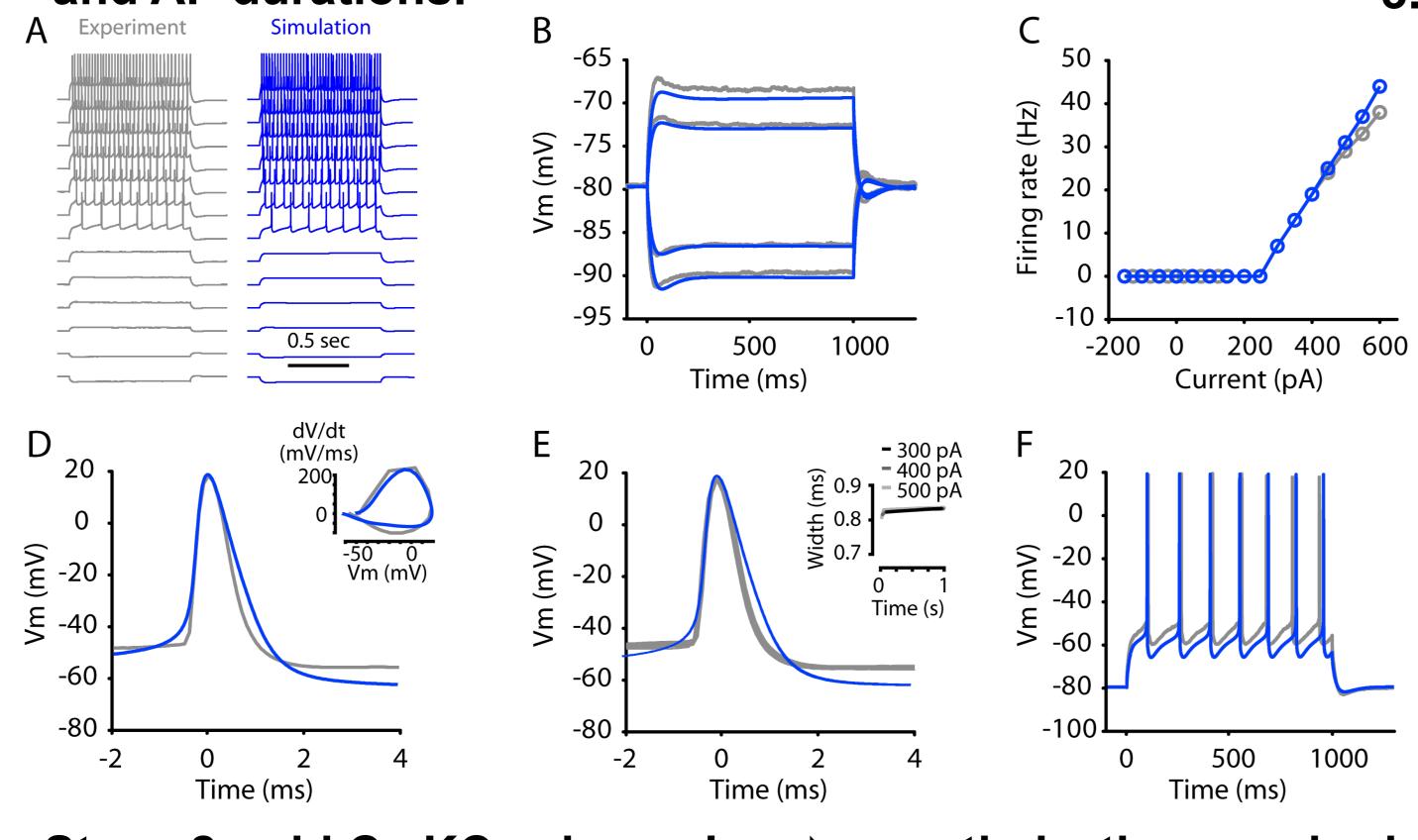


Model neurons included the following ion channels: INa and IKdr for action potentials (AP); IKa for rapid repolarization following APs; IKd for spike-frequency acceleration; Ih for resonance, sag, contribution to resting membrane potential (RMP); calcium (Ca) channels (L, N-type) and calcium-activated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

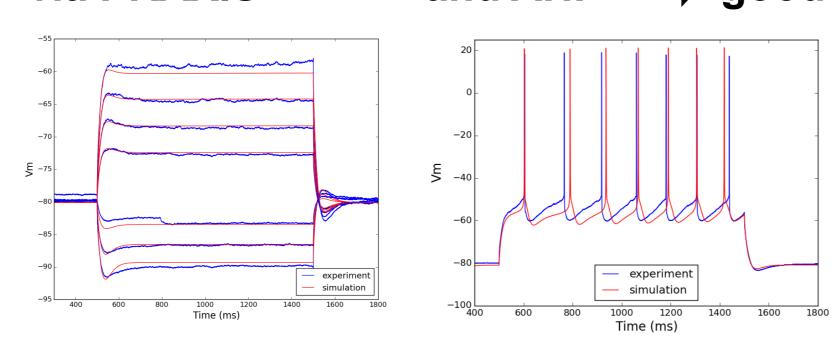
Two optimization methods were used: 1. NEURON's principal axis (PRAXIS) algorithm. 2. evolutionary algorithms.

Single cell modeling Results

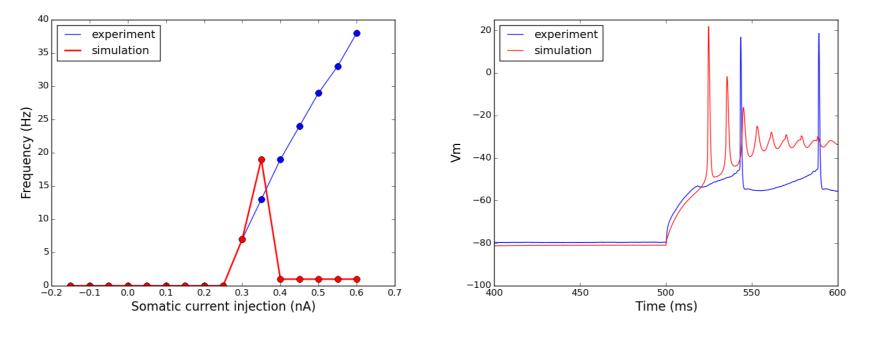
Stage 1: optimize model using PRAXIS for subthreshold fits, then tune manually to get right spike times, AHPs, and AP durations.



Stage 2: add Ca,KCa channels — re-optimization required Subthreshold opt. Hand-tuning for spike-timing and AHP \longrightarrow good fit... via PRAXIS

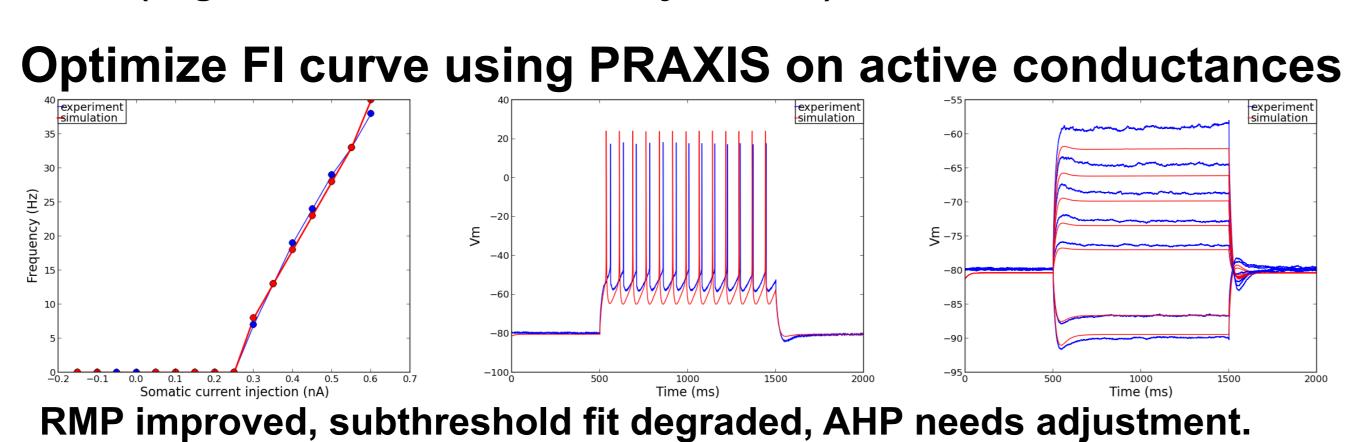


...difficulty arises since neurons are sensitive to the balance of inhibitory and excitatory currents, sometimes leading to depolarization blockade.

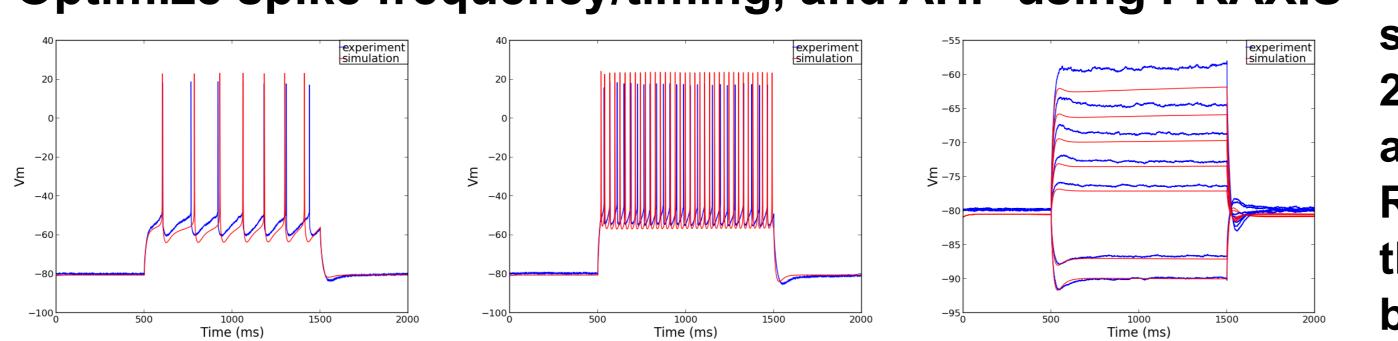


Optimize FI curve using PRAXIS on ALL params

Most current injections produce accurate spike times (sag, AHP, and RMP need adjustment)



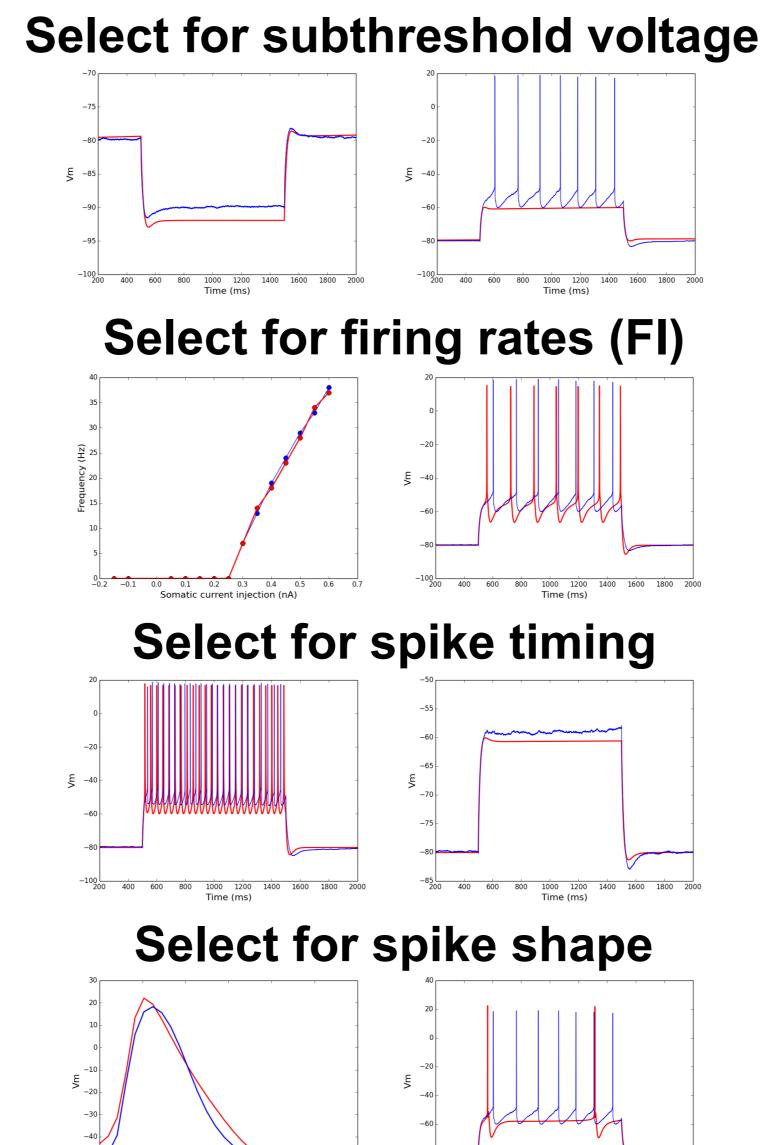
Optimize spike frequency/timing, and AHP using PRAXIS



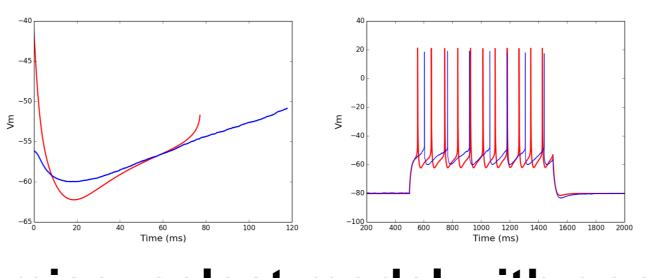
Tradeoffs between fitness functions: spike timing and AHP improved but subthreshold fit is degraded at higher current injections.

Strategy: Evolving Models

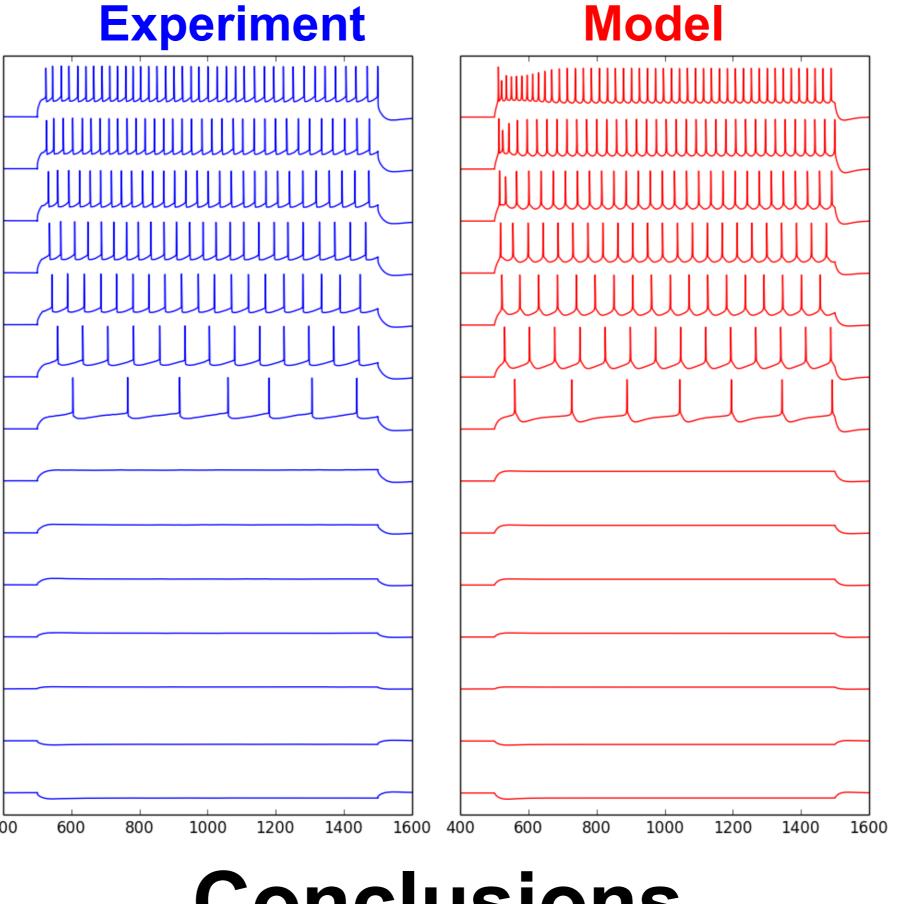
- 1. PRAXIS to fit subthreshold steps 2. evolutionary multiobjective optimization
- 3. select models with desired features







Compromise: select model with good fits for subthreshold voltage, FI, and interspikeinterval voltage



Conclusions

- 1. Our SPI neuron models replicated 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 subthreshold responses (HCN, Kd).
- b. optimize density of channels contributing to super-threshold responses (Na, Kdr, Ka, Ca, KCa).
- 3. Evolution created a set of models optimized in multidimensional fitness space; searching allowed selecting the quality-of-fit of specific fitness functions.

Network modeling

♦ Framework for multiscale modeling of neuronal circuits with the following key features:

- Simulator-independent full specifications of network (including subcellular).
- Simulator-independent instantiation of network (all cells, connections, ...).

Simulation

Results

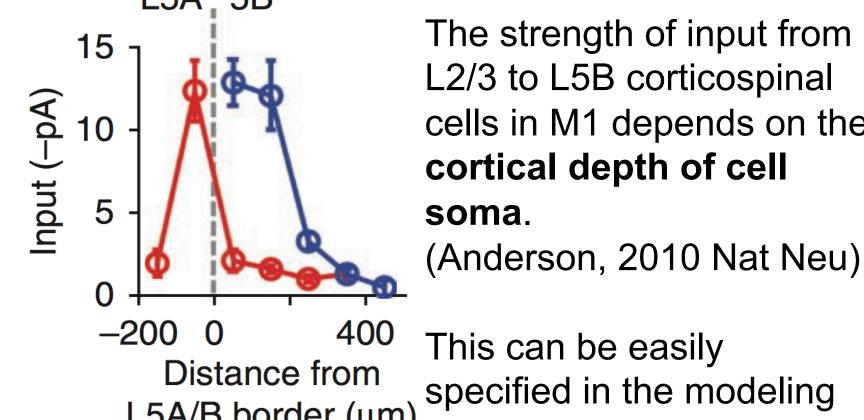
(spikes, traces)

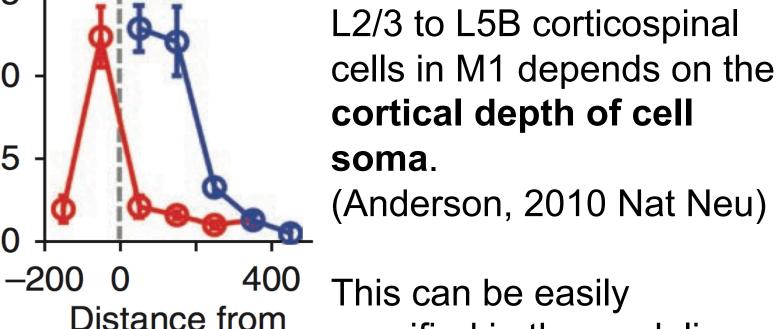
Visualization,

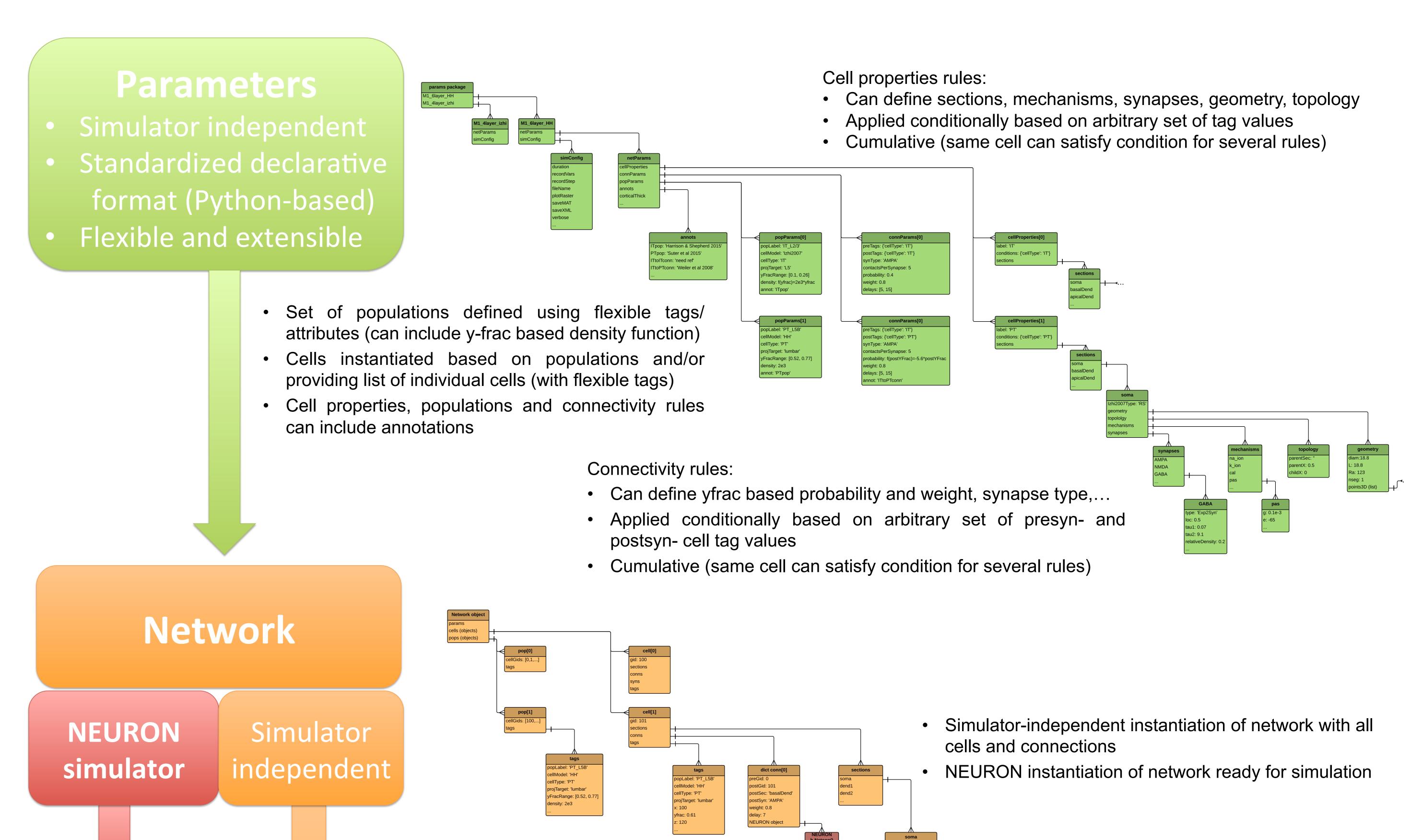
Analysis and

data sharing

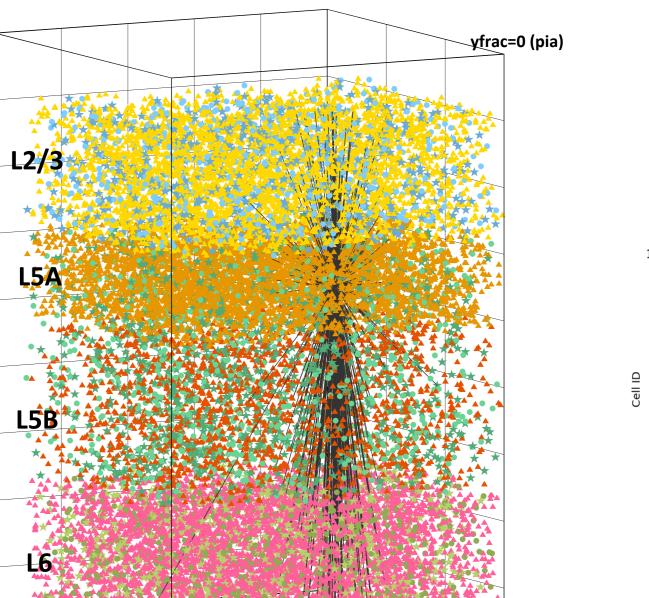
- NEURON specific instantiation of network for simulation and generation of outputs (spikes,...).
- Standardized but flexible and extensible format to define cell properties, populations and connectivity rules.
- Provides support for normalized cortical depth (yfrac) dependence of cell density and connectivity.
- Provides support for hybrid networks combining point neurons and detailed multicompartment neurons.
- Analysis, visualization and data sharing (mat, pickle, txt, xml, neuroml) of parameters and simulation results.
- Designed by experimentalists and modelers to faciliate collaboration between them.



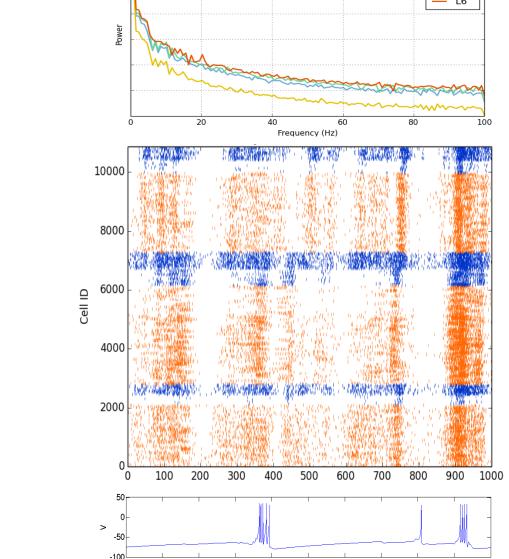




OpenSourceBrain (OSB) Geppetto visualization and analysis tools



Matlab network representation



Python analysis of simulation

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