2018 IMAG Futures Meeting –
Moving Forward with the MSM Consortium (March 21-22, 2018)
Pre-Meeting Abstract Submission Form

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Institutions: SUNY Downstate; Northwestern University; Yale

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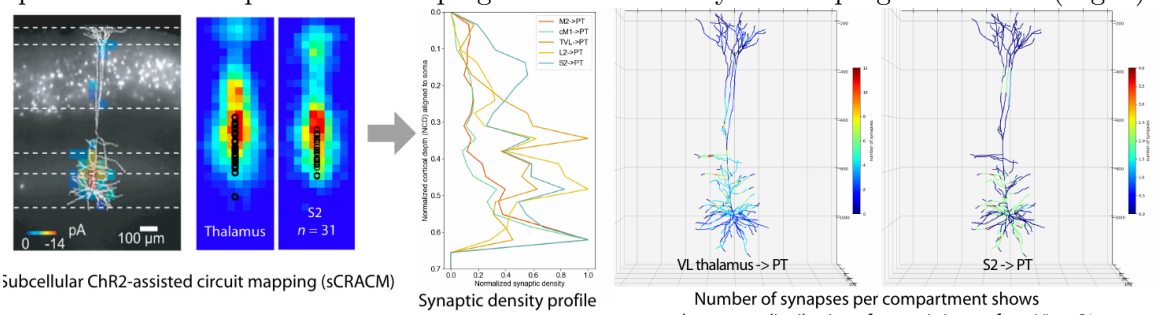
Title of Grant: Microconnectomics of neocortex: a multiscale computer model

Which MSM challenges are you addressing from the IMAG 2009 Report?

#1 Next-generation multiscale models that integrate between different scientific fields We have been developing the tools to bridge the gap between chemophysiology, traditionally handled by computational system biology and electrophysiology, the traditional focus of computational neuroscience.[5]
#3 Novel methods to fuse data-rich and data-poor scales to enable predictive modeling We have fused genetic algorithm (GA) to model dynamics at the cell level[9] with GA for dynamics at the network (tissue) level in order to fill in data-poor dendritic based on somatic and network dynamical measures.
#4 fuse biological and/or behavioral processes and mechanisms to model outcomes as a result of various interventions We have worked at the interface of neural dynamics and behavioral measures by looking at the relation of gamma activity to information transfer and by evaluating the interaction between ion channel and network factors in the context of a memory network.[8]
#5 Reproducible and reusable multiscale models All of our published models are available in the neural model database (modeldb.yale.edu).
#6 Multiscale models coupled with standardized protocols for model-driven data collection We have developed techniques to extract data from optogenetic synapse localization techniques (sCRACM) to build a model with synapses at identified dendritic locations (Fig. 1).
#8 Problem-driven multiscale models that require high performance computing
We have been developing new techniques for providing our mixed ODE/PDE/event-drive simulations on HPCs.[1, 2, 3, 4, 7] Working with the San Diego Supercomputer Center, we received the 2017 HPCwire Reader's Choice Award for "Best Use of AI." (hpcwire.com/2017-hpcwire-awards-readers-editors-choice)
#15 Underlying mechanisms of therapeutic interventions Our dystonia paper provided an example of how multi-drug multi-target pharmacotherapy could be predicted in ways that could never be done in animal trials due to combinatorial explosion.[6] This represented a new collaboration with another clinical neurologist/modeler with expertise in dystonia (Dr. Sanger).

Are you using machine learning and or causal inference methods and how? We use machine learning techniques (Genetic Algorithms) to adjust parameters according to our fitness functions at cell and tissue levels. As noted, we won an HPC AI award for this.

Please briefly describe significant MSM achievements made. We have developed novel techniques for developing network circuitry from optogenetic data (Fig 1):

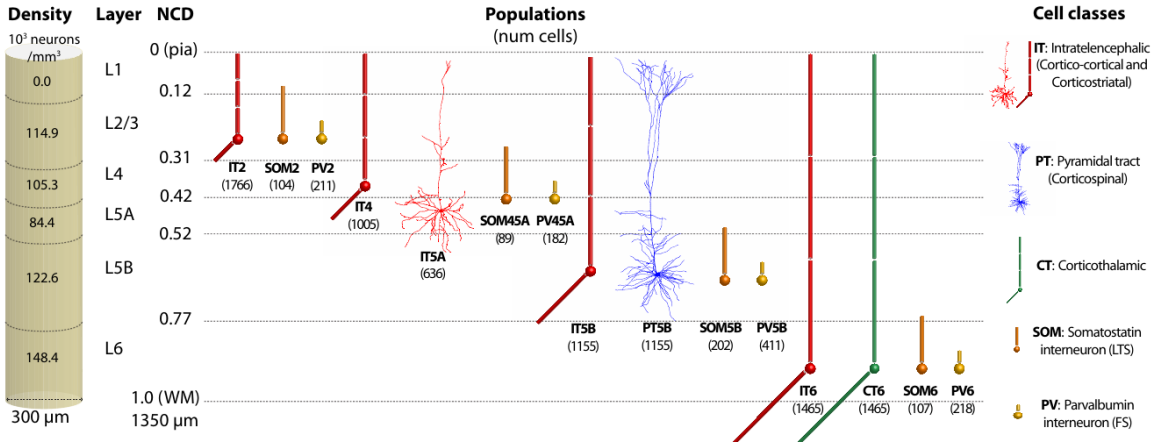


Subcellular ChR2-assisted circuit mapping (sCRACM)

Synaptic density profile (dendritic density corrected)

Number of synapses per compartment shows complementary distribution of synaptic inputs from VL vs S2

We have developed one of the few neocortical network models based as far as possible on a set of coherent datasets – data from one species, one strain, one age group, one cortical area; (however, some parameters are being set from prior estimates or measurements; Fig 2).



Please suggest new MSM challenges moving forward:
Providing interfaces/meshing between high-level top-down phenomenological models of behavior with low-level bottom-up models of basic physiology.

What expertise are on your team?
Clinical/Simulation – William Lytton, bill.lytton@downstate.edu
Machine Learning/Simulation – Salvador Dura-Bernal, salvadordura@gmail.com
Neurophysiology/Neuroanatomy – Gordon MG Shepherd, gmgshepherd@gmail.com

[1] Salvador Dura-Bernal, Amit Majumdar, Samuel A Neymotin, Subhashini Sivagnanam, Joseph T Francis, and William W Lytton. A dynamic data-driven approach to closed-loop neuroprosthetics based on multiscale biomimetic brain models. In IEEE, editor, *IEEE Interanationl Conference on High Performance Computing 2015 Workshop: InfoSymbiotics/Dynamic Data Driven Applications Systems (DDDAS) for Smarter Systems, Bangalore, India*, 2015.

[2] Z Lin, C Tropper, Y Yao, RA Mcdougal, MN Patoary, WW Lytton, and ML Hines. Load balancing for multi-threaded pdes of stochastic reaction-diffusion in neurons. *J Simulation*, 11:267, 2017.

[3] Zhongwei Lin, Carl Tropper, Robert A McDougal, Mohammand Nazrul Ishlam Patoary, William W Lytton, Yiping Yao, and Michael L Hines. Multithreaded stochastic pdes for reactions and diffusions in neurons. *ACM Transactions on Modeling and Computer Simulation (TOMACS)*, 27(2):7, 2017.

[4] WW Lytton, AH Seidenstein, S Dura-Bernal, RA McDougal, F Schürmann, and ML Hines. Simulation neurotechnologies for advancing brain research: parallelizing large networks in NEURON. *Neural Comput*, 28:2063–2090, 2016.

[5] RA McDougal, ML Hines, and WW Lytton. Reaction-diffusion in the NEURON simulator. *Front Neuroinform*, 7:28, 2013.

[6] SA Neymotin, S Dura-Bernal, P Lakatos, TD Sanger, and WW Lytton. Multitarget multiscale simulation for pharmacological treatment of dystonia in motor cortex. *Front Pharmacol*, 7:157, 2016.

[7] S.A. Neymotin, A.M. Mathew, C. Kerr, and W.W. Lytton. *Computational Neuroscience of Neuronal Networks*. Springer Verlag, New York, 2012.

[8] SA Neymotin, RA McDougal, AS Bulanova, M Zeki, P Lakatos, D Terman, ML Hines, and WW Lytton. Calcium regulation of HCN channels supports persistent activity in a multiscale model of neocortex. *Neurosci*, 316(1):344–366, 2016.

[9] SA Neymotin, BA Suter, S Dura-Bernal, GM Shepherd, M Migliore, and WW Lytton. Optimizing computer models of corticospinal neurons to replicate in vitro dynamics. *J Neurophysiol*, 117:148–162, 2017.