Summary

The goal of this project is to conduct a global statistical survey of neuronal cell-types, taking into account morphological, electrical, biophysical, molecular, and computational properties of neurons. Cell-type classification is one of the major challenge areas in the BRAIN initiative. Determining cell-types and their subtypes in the brain is a necessary first step toward a comprehensive connectomics study of the brain, and to narrow the gap between the more abundant structural data relatively scarce functional data. This project will conduct the cell-type survey in the mouse brain. The mouse is one of the most widely studied mammalian species and there is a high availability of gene knockin/knockout variants and molecular probes, thus it is an ideal organism to study neuronal cell types. This project will integrate and build upon the project team's expertise and prior results in morphological, electrical, biophysical, molecular, and computational characterization of neurons to infer their cell types.

This project will investigate the following interrelated objectives: (1) Morphological survey of neuronal types across major cortical and subcortical nuclei in the mouse brain. Using the Knife-Edge Scanning Microscope (KESM) to section and image the entire mouse brain stained in Golgi at 1 micrometer resolution, a dense survey of neuronal morphology will be conducted. 3D reconstruction algorithms and statistical analysis techniques will be used to establish morphology-based cell-types. (2) Measurement of biophysical properties of different morphological classes of neurons. Cell stiffness (or elasticity) will be measured at single-cell resolution using a high-throughput microfluidics platform and the results correlated to neuronal cell types inferred based on other characteristics. Cell-type classification through biophysical properties is a yet unexplored territory. (3) Molecular characterization of different morphological classes of neurons. Transgenic mouse strains expressing GFP in GABAergic neurons will be imaged with fluorescence KESM and validated with conventional methods. Other molecular markers also will be used to further differentiate neuronal cell types based on their molecular identity. (4) Computational characterization of different morphological classes of neurons. Multicompartmental simulation will be conducted on reconstructed neuronal morphology from step (1) above to obtain variability in electophysiological signatures due to morphological variability. Optimized algorithms and parallel algorithms will be developed for massive neuronal simulations (on the order of millions of neurons). (5) Neuroinformatics platform for the exploration and analysis of data from above, (1) through (4). Density maps of cell-type-specific properties will be generated and overlaid on top of a web-based atlas platform called the Knife-Edge Scanning Microscope Brain Atlas that is already in place, and the maps registered to gene-expression atlases (Allen Brain Atlas) and connectivity atlases (Allen Mouse Connectivity Atlas, etc.) to provide genetic/molecular and connectivity-based differentiation of cell types.

The proposed multi-parametric classification of neurons and multi-modal validation of those cell types are expected to enable expanded connectomics research, and span the current knowledge gap between neuronal structure and function.