Model Credibility Plan

The model makes predictions at multiple scales, and accordingly validation needs to be performed at each. It is our intent that datasets not developed by the PIs could be used for model validation, and therefore the software will be designed so that it can be applied flexibly to neurophysiological datasets from a variety of domains by third-party investigators.

(1) Validation of predictions of neural behavior from dynamic variables: Datasets that consist of recordings from single or multiple neurons combined with recording of external dynamic variables such as position, velocity, force, EMG, joint angle, etc. can be used. SDOs and tuning curves can be extracted from a "model construction" portion of the dataset, and the SDOs can then be used to predict neural dynamic behavior on the remaining "test" portion of the dataset. The outcome measure is the error in prediction of dynamic behavior (from use of estimated SDOs) on the test set. When recordings are available for a different animal behavior, the SDOs predict changes in the tuning curves needed to achieve the different behavior. The outcome measure is the error in prediction of tuning curves of a "test" behavior based on SDOs extracted from a different behavior used for SDO model construction.

(2) Validation of predictions of neural population behavior from single neuron behavior: SDOs for inter-neuron connectivity will be extracted for all pairs of neurons recorded simultaneously from a population. Each neuron's firing will be predicted from the recorded firing of all other neurons in a leave-one-out statistical paradigm. The outcome measure is the average error in firing rate prediction over the population. When datasets with pharmacological or electrophysiological interventions are available, the SDO-derived connectivity can be used to predict the population response to modulation of firing rates of subsets.

(3) Validation of neural connectivity: When neurophysiological recordings are available from populations with known connectivity, the connectivity predictions based on inter-neuron SDOs can be compared with the known connectivity. Because of the rarity of such datasets, the method will also be applied to simulated data generated from computational network models. We have obtained permission to use the Hodgkin-Huxley population network spinal models of Drexel colleagues Drs. Markin and Rybak (letter attached) to develop 'ground truth' network spiking data. Spike train sets will be generated from models with known connectivity directly motivated by state of the art models of spinal cord. The capacity of SDO techniques to identify and estimate network dynamics and connection patterns in fictive and non fictive preparation models will be tested. A natural outcome of these validations may be new ways to test such network models using neural population data in addition to current methods in use in the spinal cord research community.

(4) Validation of predictions of inter-population behavior: When neurophysiological recordings are available from two distinct but inter-dependent neural populations (such as different regions of hippocampus, different motor or sensory areas, or different regions of spinal cord) SDOs relating firing of neurons in a source population to firing patterns of neurons in the target population can be derived from a "model construction" set and used to predict the firing pattern on a "test" set. The outcome measure is the error in prediction of the target population firing rates.

(5) Validation of predictions of dynamic variables from neural population behavior: The tuning curves and SDOs for all neurons in a simultaneously-recorded population will be extracted from a "model construction" set for prediction of one or more external dynamic variables (position, velocity, force, emg, etc.) and will be used to predict the dynamic variables on a "test" set by combination of all SDOs and tuning curves over the population of neurons. The outcome measure is error in prediction of the dynamic variables on the test set.

Uncertainty quantification: SDOs provide automatic quantification of uncertainty, because all predictions are stochastic and include specific predictions of the full probability density. Uncertainty can be quantified either as the variance or the entropy of the estimated distribution.

Sensitivity analysis: The relevant measure of sensitivity would be to variations in the dataset. Accordingly, performance will be compared when SDOs are estimated based on randomly-selected subsets of the data. As a control, SDOs will also be estimated based on scrambled data (recording bins randomly permuted) since in this case we would expect no meaningful predictions.

For preliminary validation, we have identified colleagues with specific expertise in this area but who have not been involved with the development of the SDO theory. These colleagues will perform preliminary validation following each specific aim. Software will be simultaneously released for validation by external members of the MSM consortium, or other relevant researchers as identified by the PIs or by NIH staff. The timeline for validation will match the timeline for the aims as proposed. When datasets are available, effort is expected to require approximately 2 person-months for each of the 5 validation levels proposed.