MSM Consortium Plan

Dr. Sanger has been a member of the MSM Consortium for the past 6 years, and he has previously been funded by the consortium for a project on high-speed computational modeling of childhood developmental disorders of spinal and cortical function. He has participated in three of the working groups: "Theoretical and Computational Models", "Clinical and Translational Issues", and "Computational Neuroscience". In the past, he has been co-leader of the Clinical and Translational working group, and he is currently a member of the MSM steering committee.

MSM Consortium Participation Timeline

PI	Year 1	Year 2	Year 3	Year 4
Sanger	Steering Committee	Steering Committee	Computational Neuroscience WG	Computational Neuroscience WG
Giszter		Multi-scale Electrophysiology Create and Lead	Multi-scale Electrophysiology Lead	Multi-scale Electrophysiology Lead

Through the consortium, the investigators plan to share their results and methods, and work with other consortium members to refine the theoretical methods and their practical application. In particular, it is our belief that the stochastic dynamic operator theory may be of great interest for other applications in Theoretical Neuroscience, and we will encourage our colleagues in the MSM working group to explore this possibility. The SDO theory was presented at the 2016 and 2017 MSM consortium meetings, and productive discussions and potential collaborations have been established.

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: **[in progress]** 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: **[in progress]** 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: **[Completed; publication in preparation.]** 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: **[Recent availability of a large-scale human dataset provides the opportunity to apply the SDO theory to connectivity analysis of basal ganglia and thalamus regions. This work is ongoing.]** 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: **[in progress]** 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: **[planned for final year of the grant]** 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: **[in progress; cross validation is used for all analyses]** 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.

Model Credibility and Validation Timeline

	Year 1 **[complete]**	Year 2 **[in progress]**	Year 3	Year 4
Aim 1 Theory	Validation of theory by internal consistency of mathematics and prediction of known parameters from simulated neural population data.			
Aim 2 Kinematics		Validation of kinematic predictions by comparison with perturbed and unperturbed reflex and voluntary movement.		
Aim 3 Pharmacology			Validation of neurotransmitter and ISMS modulation of reflex and voluntary movement.	
Aim 4 Maps				Comparison of predicted maps to known spinal anatomy