**Michael Henson: Multiscale Modeling of the Mammalian Circadian Clock: The Role of GABA Signaling**

To promote validation with experimental data and modification by other researchers, our computational modeling and analysis tools will have a modular architecture. The project will produce five separate software modules for the single neuron model, the cell-to-cell coupling tool, the multicellular model, the network reduction tool, and the network simulation tool. MATLAB will be used for initial development efforts to enable rapid prototyping of the computational modules. Following third-party evaluation, the MATLAB modules will be converted into systems biology markup language (SBML) compliant codes to facilities wide usage across the research community. These SBML modules also will be evaluated by a third party to ensure their effectiveness and ease of use. Funds have been requested to support the third party evaluation efforts of Dr. Stephanie Taylor (Colby College Computer Science Department), a noted researcher in circadian systems modeling and computational methods. She will receive MATLAB and SBML codes from Henson and Kevrekidis and perform independent evaluations of code performance, robustness and ease of use. The multiscale modeling codes developed by Henson will be evaluated with respect their predictive capability using published data augmented with data generated in this project. Model assessment metrics will include synchronization rates, entrainment dynamics to different light-dark-cycles, and effects of pharmacological agents such as TTX on network rhythmicity and synchronization. The models also will be subjected to parameter sensitivity analysis to determine points of fragility and to identify possible model limitations. Successful completion of these tests will provide confidence that the models are capable of producing semi-quantitatively accurate predictions sufficient to explore network design principles. The cellular network reduction and simulation tools developed by Kevrekidis will be evaluated with respect to their flexibility, speed, and integration with the multiscale modeling codes.

We will work with the MSM Working Groups on Computational Neuroscience and Theoretical and Computational Methods to identify additional individuals who can perform independent evaluations of the modeling and computational methods. Our long term goals are to develop a multiscale model of the SCN that can be used by other researchers to investigate circadian system behavior and to develop general cellular network modeling and simulation tools so that researchers can apply our methods to other systems than the mammalian circadian clock. The following timeline will be followed for third party evaluation of the computational modeling and analysis tools. Dr. Taylor will allocate two weeks during each summer of the project to perform this work.

**Year 1:** MATLAB codes for the single neuron model and network generation method will be evaluated by Taylor.

**Year 2:** The MATLAB codes developed in Year 1 will be converted to SBML and evaluated by Taylor and selected members of the relevant MSM working groups. MATLAB codes for the multicellular model and network reduction method will be evaluated by Taylor.

**Year 3:** The MATLAB codes developed in Year 2 will be converted to SBML and evaluated by Taylor and selected members of the relevant MSM working groups. MATLAB codes for the benzodiazepine administration model and network simulation method will be evaluated by Taylor. MATLAB algorithms will start being ported to high performance clusters at PICSciE and translated to Gnu FORTRAN or C++.

**Year 4:** The MATLAB codes developed in Year 3 will be converted to SBML and be evaluated by Taylor and selected members of the relevant MSM working groups. MATLAB codes for the benzodiazepine simulation and optimization methods will be evaluated by Taylor.

**Year 5 (previously year 4):** The MATLAB codes developed in Year 4 will be converted to SBML and evaluated by Taylor and selected members of the relevant MSM working groups.