**Multiscale Modeling of the Mammalian Circadian Clock: The Role of GABA Signaling (U01EB21956)**

The goal of this project is to combine modeling, experiment and computation to unravel the effects of environmental conditions on the network topology, synchronization behavior and entrainment properties of the mammalian circadian clock. The project leverages our expertise in experimental determination of functional connectivity across circadian neuron populations, multicellular modeling of the circadian clock with heterogeneous networks of coupled neural oscillators and new computational tools for efficiently simulating large populations of networked heterogeneous cells. Additional project information is provided here: https://simtk.org/projects/circadian-gaba

**Model Credibility Plan**

1. **List of Planned Actions**

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

Year 2: The MATLAB codes developed in Year 1 will be converted to SBML and evaluated. MATLAB codes for the multicellular model and network reduction method will be evaluated.

Year 3: The MATLAB codes developed in Year 2 will be converted to SBML and evaluated. MATLAB codes for the benzodiazepine administration model and network simulation method will be evaluated. MATLAB algorithms will start being ported to high performance clusters and translated to Gnu FORTRAN or C++.

Year 4: The MATLAB codes developed in Year 3 will be converted to SBML and be evaluated. MATLAB codes for the benzodiazepine simulation and optimization methods will be evaluated. The MATLAB codes will be converted to SBML and evaluated.

1. **Information Gained by Each Credibility Action**

Model simulation code evaluation: This action ensures that different versions of the models generate the same results, remain consistent with available data, provide reasonable ease-of-use and allow user modification.

Network reduction and simulation code evaluation: This action ensures that reduced-order models capture the dominant behaviors of the full-order models, provide reasonable ease-of-use and allow user modification.

1. **Actions and Activities Classified within the CPMS TSR Framework**

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| Number | Rules | Actions/Activities |
| 1 | Define context clearly | The context of the multiscale model has been defined as for simulation of coupled neurons in the mammalian suprachiasmatic nucleus (SCN) to predict network synchronization and entrainment to external cues such as light. |
| 2 | Use appropriate data | Most of the data used for model development and validation is being generated by one of the co-PIs as part of this project or was generated in other funded projects. Other data has been obtained from the open literature. |
| 3 | Evaluate within context | The model is being evaluated for its ability to produce phase and amplitude coherence metrics in agreement with data. Model evaluation also is being performed with ensemble average and distribution data for key circadian metrics such as period and sustained rhythmicity.  |
| 4 | List limitations explicitly | We explicitly list the simplifying assumptions and their associated limitations, such as the lack of action potential modeling and the inability to predict network dynamics on short-time scales. |
| 5 | User version control | We have not yet made any of the models developed in this project public, but we do use internal version control. |
| 6 | Document adequately | When provided for MSM evaluation or made publicly available, the model simulation codes will be fully documented to facilitate use. |
| 7 | Disseminate broadly | When provided for MSM evaluation or made publicly available, we will provide model codes, simulation scenarios, representative results and experimental datasets against which the model was tested. |
| 8 | Get independent reviews | All our model simulation and network reduction codes are being evaluator by a third-party evaluator with expertise in circadian systems. |
| 9 | Test competing implementations | We intend to develop and evaluate MATLAB, C++ and Python versions of our codes to test consistency across different implementation and to provide code options for end users. |
| 10 | Conform to standards | We have adopted generally accepted standards for neural network modeling. |

How Planned Activities Will Lead to a Credible Model: By generating experimental data specifically designed for model development and evaluation as a funded part of the project, we expect the models to reproduce key aspects of circadian behavior such as neurotransmitter mediated synchronization and desynchronization, network entrainment to varying light schedules, and the altered behavior of mutant neurons. By providing thoroughly tested and fully documented models to third-party evaluators, we expect the credibility of our models to be demonstrated. This work will facilitate wide use and modification by end users.

Progress To-Date and Plans for Next Reporting Cycle: Our third-party evaluator has assessed MATLAB and Python codes for the single neuron model including aspects of intercellular signaling. The evaluator has verified that the base code had been correctly converted from MATLAB to Python. For several new features, the evaluator verified the assumptions stated matched the mathematics, which then matched the code. During the next six months, the evaluator will test our MATLAB and Python codes for network generation/reduction, network data mining, and networked neurons and astrocytes.

Issues/Concerns Identified: The only problem identified has been the proposed conversion of MATLAB codes to SBML codes. We have found that many end users simply convert SBML codes into MATLAB, so we do not intend to produce SBML implementations at this time.

Other Factors: None at this time.