**Multi-scale Modeling of Circadian Rhythms: From Metabolism to Regulation and Back**

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**Abstract**. Predictive modeling relies on solving equations in which the necessary equation parameters are either based on first principles, such as Hamiltonian systems, or on empirical data such diffusion constants or rate parameters. This requirement has hampered the predictive modeling of biological systems in that the relevant scales (e.g. those in metabolism) are too large and complex to be modeled by first principles, and the necessary rate constants are not generally available. We are addressing this challenge by implementing a new approach to the law of mass action that does not require rate parameters but instead uses chemical potentials. This new approach is possible because of advances in statistical thermodynamic methods in the last 20 years. Due to the statistical formulation of the theory, the tools are capable of direct integration of metabolomics and proteomics data. We are using these tools to fundamentally understand the relationship between metabolism and molecular circadian clocks with regard to the role of the circadian clock in increasing the metabolic efficiency of the cell.

*Goals***:** The goal of this research is to develop and implement a new computational and theoretical method for modeling biological systems that fills a gap in modeling mass action dynamics. The method bridges data-poor scales (parameters for mass action kinetics) and data-rich scales (chemical potentials of metabolites, and metabolite, protein & transcript data) to enable predictive modeling from enzymatic reactions (10-3 to 100 s-1) to gene and protein regulation (~20 minutes) to circadian rhythms (24 hours). We are:

* Implementing an approach to the law of mass action that uses chemical potentials rather than rate constants. This approach involves a rescaling of the fast degrees of freedom, resulting in a compression of the time-dependence to fewer relative scales. Steady state processes can be ‘telescopically’ modeled to address the scale of interest while collapsing faster scales.
* Using the new method to understand the relationship between central metabolism and circadian rhythms in *Neurospora* *crassa* by using a multi-scale model of metabolism that will include regulation of the circadian clock.

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Timescales that the simulations using statistical thermodynamics will cover. Enzymatic reactions occur on the millisecond to second timescale while gene and protein expression occur on the minute to ~30 minute scale and the circadian rhythm occurs over a period of 24 hours.