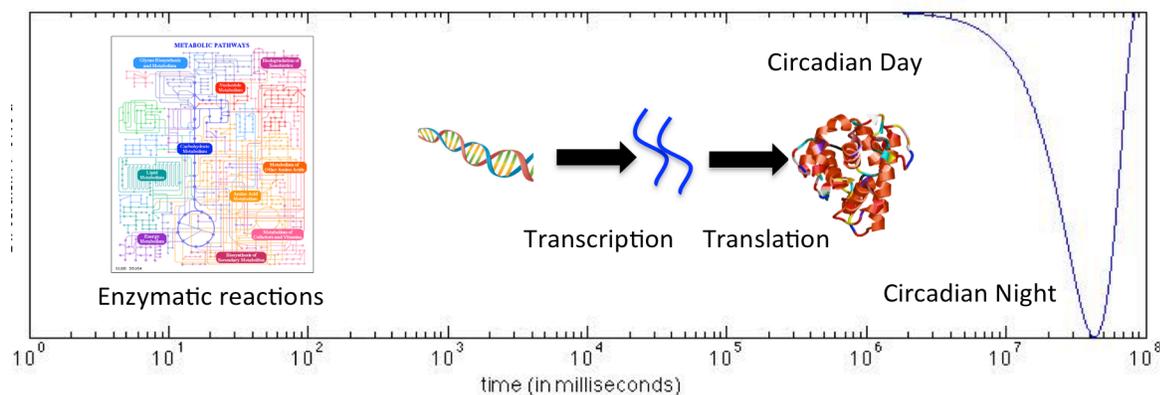


Multi-scale Modeling of Circadian Rhythms: From Metabolism to Regulation and Back

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Project 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. Based on statistical thermodynamics, 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 10^0 s⁻¹) to gene and protein regulation (~20 minutes) to circadian rhythms (24 hours).



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.

To accomplish this, 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.

Abstract: Cell metabolism is modeled using fundamental principles from which necessary kinetic parameters and regulation points can be derived when experimental data is not available [1]. The principle of maximum entropy production, a consequence of the second law of thermodynamics, is used to infer rate parameters for simulating the mass action kinetics of metabolism. Simulation predictions of metabolite levels of central metabolism of *Neurospora crassa* then allows for inference of post-translational enzyme regulation. Subsequent simulations

