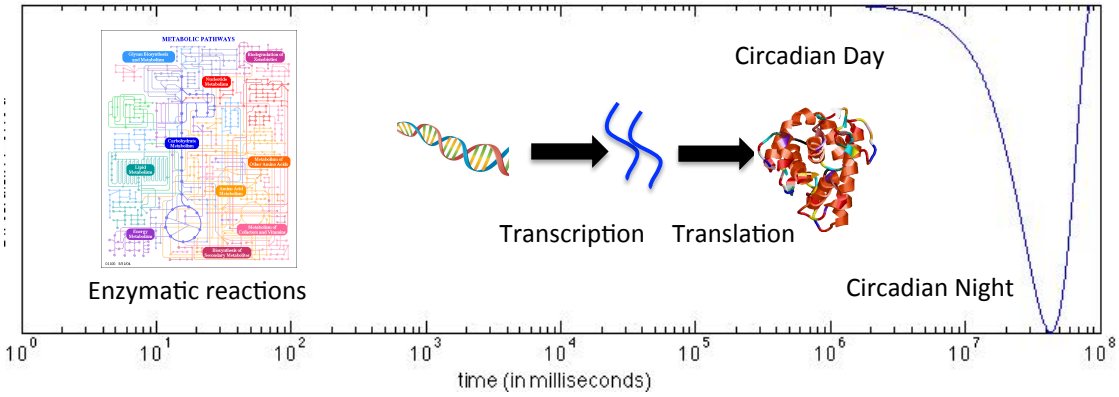
Multiscale Modeling of Circadian Rhythms

The purpose of the model is to model and simulate a cell, especially metabolism, by bringing in more physics than was previously possible and to couple reactions on the millisecond time scale (enzyme kinetics) with the circadian clock that operates on the 24 hour time scale.



What is new inside? A new mathematical approach was developed that combines optimal processes in physics (maximum caliber) with reinforcement learning to infer all necessary rate parameters needed to model metabolism rigorously. After inference of an optimal model, a population of diverse, sub-thermodynamically optimal models, with rate constants, can be easily generated. The circadian clock is modeled on the 24 hour time scale using ODEs, while metabolism can be solved tens of thousands of times during the circadian cycle using optimization methods.

How will this change current practice? Currently, thermodynamics and kinetics are usually ignored when using traditional constraint-based flux modeling such as flux balance analysis. The new method rigorously models thermodynamics and kinetics, and is scalable beyond metabolism to look at protein production as well. The new optimization methods ensures that these methods will be fast and scalable.

End Users The methods can be applied to any system, for instance to study differentiation in stem cells. The platform is open source, coded in python, and metabolomics and proteomics data are useful but not required.

William Cannon, Pacific NW Nat. Lab
Jay Dunlap, Dartmouth
NIBIB, U01EB022546