**A model for circadian oscillations in the Drosophila period protein (PER)**

**Project Team:**

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**Problem statement:**

Circadian rhythms are set and extremely important metabolic processes that cyclically regulate biological outcomes on a 24-hour cycle. This response to 24-hour light cycles is evolutionarily conserved and observed in all domains of life. The circadian rhythm is a stable oscillatory response under steady state conditions. In this study, we seek to recreate the results published by Goldbeter, 1995 [1]. We also seek to further investigate circadian rhythms upon exposure to environmental toxins. Environmental toxins can affect gene transcription rates, mRNA synthesis rates, mRNA degradation rates, translation rates, and protein degradation rates. We also seek to determine numerical stability of a mathematical model of gene regulation upon sudden changes in light exposure (i.e. 24-hour day to 4-hour day) by applying a forcing function on the PER expression rate [3]. To reproduce the inherent randomness in biological systems, we would like to have a stretch goal of creating a stochastic algorithm in order to realistically mimic *Drosophila* system stability.

**Expected outcomes:**

To validate the paper and our subsequent models of *Drosophila* circadian cycles, we will first recreate Goldbeter’s paper, specifically Figures 1 and 2 which depict PER protein formation over time and PER mRNA concentration vs total PER protein. Once we have modified code to produce the accurate results, we will parametrically vary vs to simulate *Drosophila* exposure to an environmental toxin that causes transcriptional inhibition. We expect that low values of vs will cause dampening of the oscillations into a stable solution. We can also increase transcriptional rates by varying vs to determine the point at which oscillations become unstable. Lastly, upon forcing *Drosophila* to adapt to a 4hr light cycle from a 24hr light cycle, we expect to see fluctuations as the system moves toward a new steady state.

**Methods and Approach**

Stability analysis will start with constructing the overall Initial Value problem vector and find solutions to the homogeneous problem. From these solutions, we will probe 2nd order dynamics using the Jacobian and categorize each solution’s stability via Jacobian eigenvalue analysis and determination of the results of the eigenvalue analysis as related to the temporal behavior of the oscillatory amplitude of the mRNA and nuclear PER proteins. We will also construct a Bifurcation diagram based on the system’s parametric dependence on phospine’s putative transcription inhibition. Kinetic Monte Carlo simulations (Tau leaping algorithm) will probe ways in which the system crosses from one stable solution to another within a stable subspace.To probe phasic entrainment effects, the v PER expression rate parameter (vₛ) will be turned into a sinusoidal forcing function that will run at various-length cycles (10 - 40 hours) between 0 (total darkness) and the originally stated vₛ value.

**New Additions to the Original Paper**

Dactinomycin is a drug which is one the most popular inhibitors of transcription in cells . It is made from Streptomyces bacteria and its structure consists of two cyclic peptides linked together through a phenoxazine derivative. It has been shown to inhibit transcription in all three eukaryotic polymerases. The drug accomplishes this by preferentially intercalating into GC rich sequences and stabilizing topoisomerase complexes, this prevents RNA progression. For this project, we plan to model the effects of a similar drug which will act as a toxin that inhibits transcription of the mRNA. This inhibitor would reduce the value of the constant vₛ in the reaction 1a.

**References –A short list of cited works:**

[1] Goldbeter, A. (1995). A model for circadian oscillations in the Drosophila period protein (PER). *Proceedings of the Royal Society of London. Series B: Biological Sciences*, *261*(1362), 319-324.

[2] Bensaude O. (2011). Inhibiting eukaryotic transcription: Which compound to choose? How to evaluate its activity?. *Transcription*, *2*(3), 103–108. https://doi.org/10.4161/trns.2.3.16172

[3]Leloup, J.-C., & Goldbeter, A. (2003). Toward a detailed computational model for the mammalian circadian clock. *Proceedings of the National Academy of Sciences*, *100*(12), 7051–7056.<https://doi.org/10.1073/pnas.1132112100>