Cellular Circadian Rhythm

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1 Introduction

Circadian rhythms, or the body clock, are (approximately) 24-hour cycles in the biochemical, physiological, and behavioral processes of our bodies. They regulate daily activities, such as sleep, waking, eating, and body temperature regulation.

Jet lag can occur when the body clock is disturbed, for example when people are traveling across time zones or doing shift work. A person may feel drowsy, tired, irritable, lethargic, and slightly disoriented. This phenomenon is related to a disruption in activity and a lack of synchronization in the brain cells of two parts of the brain.

This project will focus on simulating the cellular circadian oscillator and test the oscillator under different circumstances (for example, mismatch the light and cell to simulate jet lag).

There are mainly two central problems we are trying to tackle in the project:

1. Model the circadian oscillator and tune the body clock to 24-hour rhythm
2. Simulate the entrainment of the oscillator by light and molecular noise

2 Cellular Circadian Oscillator Model

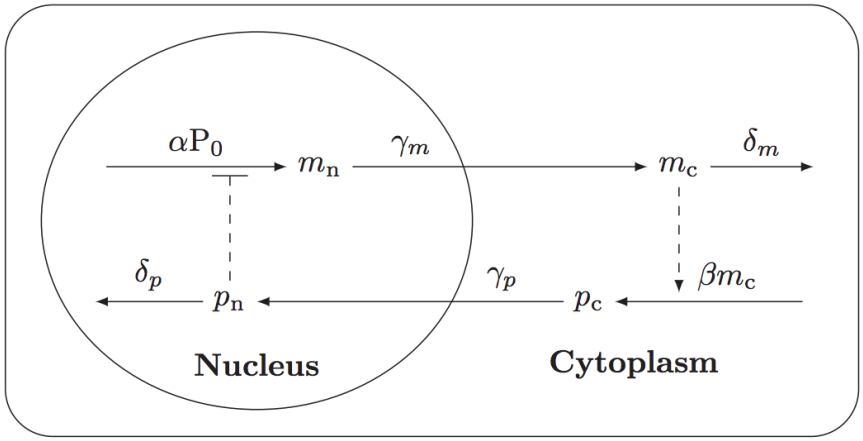

Figure 1: A schematic cellular circadian clock

Above is a four-variable schematic cellular model. The Period (Per) gene is transcribed into Per messenger RNAs (mRNAs) in the nucleus. The Per mRNAs are exported from the nucleus to the cytoplasm to be translated into PER protein and to degrade. The PER proteins then enter the nucleus where they inhibit the transcription of Per gene and degrade in proteasomes in the nucleus.

Parameters:

- m: the number of Per mRNA molecules
- p: the number of PER protein molecules
- subscripts n and c are short for nucleus and cytoplasm respectively
- P_0 : probability that transcription happens
- assume there are r protein-binding sites at which the PER protein inhibits the transcription of the Per gene
- p_n : the total number of PER protein molecules in the nucleus at some particular time
- ξ : the rate that any one protein molecule binds to any one site
- η : the corresponding unbinding rate
- L: the number of occupied sites $L \leq p_n$ and $L \leq r$

- K: the equilibrium constant of the unbinding and binding reactions with units of concentration

Reaction number	Reaction name	Rate (probability per unit time)	Result
1	Transcription of the *Per* gene	αP_0	$m_\mathrm{n} \to m_\mathrm{n} + 1$
2	Export of mRNA from the nucleus	$\gamma_m m_\mathrm{n}$	$m_\mathrm{n} \to m_\mathrm{n} - 1,\ m_\mathrm{c} \to m_\mathrm{c} + 1$
3	Degradation of mRNA (in the cytoplasm)	$\delta_m m_\mathrm{c}$	$m_\mathrm{c} \to m_\mathrm{c} - 1$
4	Translation of *Per* mRNA	βm_c	$p_\mathrm{c} \to p_\mathrm{c} + 1$
5	Import of protein to the nucleus	$\gamma_p p_\mathrm{c}$	$p_\mathrm{c} \to p_\mathrm{c} - 1,\ p_\mathrm{n} \to p_\mathrm{n} + 1$
6	Degradation of protein (in the nucleus)	$\delta_p p_\mathrm{n}$	$p_\mathrm{n} \to p_\mathrm{n} - 1$

Figure 2: Reaction table

In the limit of large numbers of molecules, the system would become deterministic. The dynamics of the model are approximately described by the following systems of equations.

$$
\begin{aligned}
\frac{dM_\mathrm{n}}{dt} &= \frac{\alpha}{V_\mathrm{n}}\left(\frac{K}{K+P_\mathrm{n}}\right)^r - \gamma_m M_\mathrm{n}, \\
\frac{dM_\mathrm{c}}{dt} &= \gamma_m\left(\frac{V_\mathrm{n}}{V_\mathrm{c}}\right)M_\mathrm{n} - \delta_m M_\mathrm{c}, \\
\frac{dP_\mathrm{c}}{dt} &= \beta M_\mathrm{c} - \gamma_p P_\mathrm{c}, \\
\frac{dP_\mathrm{n}}{dt} &= \gamma_p\left(\frac{V_\mathrm{c}}{V_\mathrm{n}}\right)P_\mathrm{c} - \delta_p P_\mathrm{n},
\end{aligned}
$$

Figure 3: kinetic equations

V_n is the volume of the nucleus, and V_c is the cytoplasmic volume. The capitalized variables are concentrations of molecules.

3 Methodology

There are mainly two kinds of model we are proposing to use here - Physical Modeling Methods and Numerical Methods.

3.1 Physical Modeling Methods

To model the oscillator, I am planning to use the model discussed in the paper by Guanyu Wang and Charles S.Peskin:

- **Entrainment under 12:12 light-black cycles**: I plan to solve the system of equations both under constant light conditions and under 12:12 light-dark (LD) cycles (12 hours of light followed by 12 hours of darkness each day). I am looking for both deterministic and stochastic solution. Then compare the stochastic simulation result with the numerical solution of the differential equations for the deterministic case. Then make graphs showing the changes in the model.

- **Scaling to vary the amount of noise**: If we want to make the relative noise level of the systems smaller, we can increase the volume of the cell because of Law of Large Numbers. Then, we can make $\frac{\alpha}{V_n}$, $\frac{V_n}{V_c}$, and all the initial concentrations constant. Adding noise may help simulate jet lag. Performing various experiments to test in what level noise would be more helpful.

3.2 Numerical Methods

To model this oscillator, I am planning to use Forward Euler Method, Backward Euler Method, and Newton's Method, and others when the situation requires:

- Euler Methods:
  When testing the oscillator in the condition of constant light and light-dark cycles, I would solve the systems of ODEs by using forward Euler methods. If an accurate approximation is needed, I would change to backward Euler methods.

- Newton's Method:
  When using backward Euler methods, chances are that I also need Newton's methods to solve state of the molecule in a particular time.

4 Case study

With the methods and models proposed above, I am planning to study two topics, both of them are concerning about the performance of the cellular circadian oscillator:

- Light-dark cycles
  After tuning the oscillator to the 24-hour rhythm, I will model the oscillator under different scales of time. First test the oscillator under constant light. Then test under light-dark cycle with 12 hours of light followed by 12 hours of darkness. Then the more interesting part would be model jet lag, by changing the light-dark cycle suddenly.

- Scale the system
  Make the volume of the cell larger would have two major effects. The first one is when the volume is larger, the system would be deterministic and can be used to compare with the stochastic case. The second one is the scale of the system would help vary the amount of noise.

The two cases can be combined to have more experiments and results. For example, adding noise in the system can help observe how the jet lag effect would act differently.

References

[1] Wang, Guanyu and Peskin, Charles S (2018). The minimum energy of bending as a possible explanation of the biconcave shape of the human red blood cell. *Physical Review E,* 97(6).