A Low Dimensional Model for Mouse Circadian Rhythms

University of Michigan Summer Mathematics REU - Final Report

Supervisor: Victoria Booth
Collaborator: Kevin Hannay
Written by Carolyn Fulton

Abstract

Circadian rhythms are the environmentally driven daily cycles of physical and cellular activity exhibited by most all organisms. Disruption of said cycles in humans has been found to negatively impact overall health. The utilization of model organisms, such as mice (*Mus musculus*), are essential to providing behavioral, physiological and cellular scale analyses that may never be available for humans. This report will discuss the work done thus far to develop a low-dimensional limit cycle oscillator model for mouse circadian rhythms, which has been fit and validated against a large library of light phase response curve data for mice. The intention is to enable a cross-species comparison to improve integration of multiscale data sets between model organisms and human studies.

Background

Circadian rhythms are the endogenous oscillations of cellular activity found in all living organisms. Throughout the day, maximum and minimum physiological behaviors exhibited by an organism can be monitored to reflect the nature of the internal system. Circadian rhythms are often referred to as a biological clock due to this behavior, as the system entrains to the surrounding environmental factors. The most powerful influence on circadian rhythms in mammals is light, which aids in the functionality of timing an organism's macroscopic behavior in comparison to the time of day. Not only is the system coupled between the internal and external environments in this fashion, but also between the central and peripheral communities of neurons in the suprachiasmatic nucleus (SCN). As seen in Figure 1, light is optically perceived and then processed within the SCN. The central community of neurons is first to process the light input, which is then signaled to the peripheral community and then further to the cellular oscillators found throughout the rest of the organism. The cellular oscillators each exhibit an individualized behavior which collectively reflects a macroscopic behavior which can be measured. For example, each cell may initiate the necessary means for melatonin secretion at unique times and their tendency surrounding a specific time will indicate the overall behavior. Measurement of this behavior for every single cell is currently unrealistic as well as unreasonable to consider. Thus, being able to evaluate the macroscopic behavior and how it reflects upon the internal behavior is key to studying circadian rhythms.

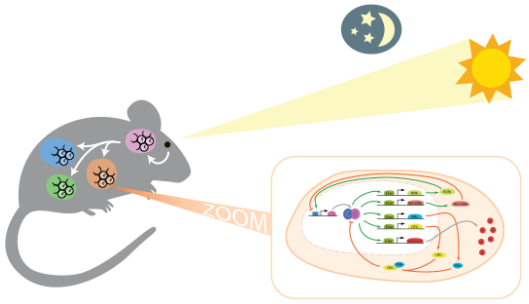

Figure 1: An illustration of the circadian light processing system at a cellular level of a mouse [6].

The dual coupling found in this system is very complex and has the capacity to become desynchronized. In humans, abrupt changes to light schedules such as when an individual experiences jet lag or is involved in shift work can leave the internal biological clock out of synchrony with its environment. Prolonged exposure to desynchrony leaves individuals susceptible to pathological, physiological, and psychological maladies such as cancer, depression, and sleep disorders. The study of circadian rhythms attempts to understand and alleviate rhythm desynchrony. Experimental protocols studying circadian rhythms will intentionally perturb factors of a controlled environment, generate desynchrony, in order to evaluate the initiated responses and patterns of entrainment of the subjected organism. Behavioral outputs related to the internal circadian systems are the primary markers by which the responses are measured. Time measurements of the macroscopic behavior before the stimulus may then be compared to the behavior afterwards to derive the change in circadian phase by the stimulus per circadian time. These measurements of the change in phase at a given circadian time can be evaluated for the duration of the proper period (typically 24 hours) to produce a phase response curve. Phase response curves are one of the many ways circadian rhythms are analyzed in the field.

Some macroscopic behaviors can be extremely invasive to measure due to the depth of extraction needed for proper measurement. Human circadian rhythm studies are very isolated due to the invasiveness of some of the means necessary for proper analysis and the resources necessary to produce both proper compensation and moral consideration. This is where model organisms, such as *Mus musculus*, play a vital role in circadian rhythm study. Model organisms provide a way by which scientists can extrapolate more data to develop a better understanding of circadian rhythms at the cellular level, the extent of which may never be plausible in human studies. Thus, by utilizing readily available light phase response data in *Mus musculus*, this research worked to develop a working mathematical model of circadian phase responses in mice with intentions of cross-species comparison as well as providing a pathway for other multiscale model organism data sets to be integrated.

Methods

In this research, *Mus musculus* was selected as the model organism of focus. Mice are often used in studies requiring model organisms due to genetic and physiological similarities to humans as well as their expression of behavioral endophenotypes. Mice were useful for this model due their circadian period of approximately 23.8 hours being relatively close to the human circadian period of 24.2 hours as well as their circadian measurement data being much more accessible than that of humans as previously described. The key difference noted between mice and humans when modeling their circadian rhythms is that mice are nocturnal. The organism and the use of only unaltered light applied with accessible phase response curve data were factors for consideration when filtering possible datasets for fitting the model. The two datasets used to fit the model up to this point both came from the same lab, keeping the strain and circadian timing methods constant. The primary dataset [3] applied a variety of light pulse durations to ninety-six male wild-type C57BL/6JOlaHsd mice after fourteen days of light-dark (12:12) entrainment followed by pulses and dark freerun to produce seven phase response curves, one for each pulse duration. This paper was selected for the variety and extent of the available data. The secondary dataset [4] provided the freerun range of mice, as initially the freerun was estimated using the human freerun period range.

The previously developed human mathematical model [1] is a derivation of a high dimensional neuronal phase oscillator system. The derivation process reflects that of the Kuramoto and Ott Antenson methodology. The nature of deriving the high dimensional oscillator system into a low dimensional model, a parallel between the microscopic and the macroscopic biological relationship of the system itself, enables physiological interpretations of the model's parameters. Such is particularly useful when computing models for model organisms as the differences between parameters may be interpreted as the differences between the processing systems when compared to the human model parameters. As seen in Figure 2, the model is a single population evaluation of amplitude, mean phase and corresponding light components with thirteen total parameters. The model parameters include circadian representations and light processing components, both of which were fit using a least-squares cost function, shown in Figure 3.

$$\dot{R} = -(D+\gamma)R + \frac{K}{2}\cos(\beta)R(1-R^4) + L_R(R,\psi)$$
$$\dot{\psi} = \omega_0 + \frac{K}{2}\sin(\beta)(1+R^4) + L_\psi(R,\psi)$$
$$L_R(R,\psi) = \frac{A_1}{2}B(t)(1-R^4)\cos(\psi+\beta_{L1}) + \frac{A_2}{2}B(t)R(1-R^8)\cos(2\psi+\beta_{L2})$$
$$L_\psi(R,\psi) = \sigma B(t) - \frac{A_1}{2}B(t)\left(\frac{1}{R}+R^3\right)\sin(\psi+\beta_{L1}) - \frac{A_2}{2}B(t)(1+R^8)\sin(2\psi+\beta_{L2})$$

Figure 2: The single population model representing amplitude, phase and corresponding light components respectively [1]. All thirteen parameters of this model have appropriate physiological interpretation.

$$C(\vec{\theta}) = \frac{1}{2}\sum_{k=1}^{4}\sum_{j=1}^{N_k}\left(\frac{M_{kj}(\vec{\theta}) - D_{kj}}{\sigma_k}\right)^2$$

Figure 3: The least-squares cost function utilized in fitting the parameters for the single population model. $M_{kj}(\vec{\theta})$ represents the model output and D_{kj} represents the experimental measurements under the assumption of normally distributed errors of standard deviation σ_k. [1]

When analyzing the data for mice, circadian model parameters were always allowed to vary in order to properly fit the data. The light processing components were both kept constant with the human model as well as allowed to vary. This was done to evaluate the influence of each type of parameters. A primary focus in this research is understanding how light processing in mice may be vastly different than in humans and how adjustments to account for that may go deeper than the parameters. These ideas will be further evaluated in the Results and Discussion sections.

Data extraction was performed using Engauge Digitizer software. Computational processing was performed using Julia based programming systems.

Results

A new parameter set, found in Table 1, for the model was computed based upon the fits to both datasets [3, 4]. From this comparison, possible physiological interpretations can be made. The parameters include representations coupling, form of the phase response curve of each clock neuron, noise strength, sensitivity to low level light, and frequency dispersion. The most prominent difference between the parameter sets can be found in both the β_L components as well as the A_1 component. Both parameters are categorized as parameters influencing the form of the phase response curve for each clock neuron. The last four parameters were noticeably left constant when deriving the mouse model parameters. This was done for simplicity and may be redone to evaluate the influence those parameters have as they are primarily light processing

components, which we presume may have a great influence on the adjustment of this model due to the biological differences between human and mice light processing.

Parameters	Mouse Model	Human Model
ω_0	0.27200222	0.263524
K	0.069999647	0.0635842
γ	0.023959989	0.024
β_1	0.001066727	-0.09318
A_1	0.994455721	0.3855
A_2	0.151071646	0.195123
β_{L1}	2.324876829	0.0026
β_{L2}	2.914025151	-0.957756
σ	-0.109700035	0.0400692
$\alpha_{constant}$	0.05	0.05
p	1.5	1.5
I_0	9325	9325
D	0.0075	0.0075

Table 1: Comparison of the computed mouse model parameters to the human model parameters for each of the thirteen model parameters listed in the left-hand column.

The mouse model parameters were then utilized in producing phase response curve models to experimental protocols reflecting mice exposed to various hour long durations of 100 lux light followed by dark freerun [3].The outputs for each pulse duration can be found in Figure 4. There is notable similarity to some of the curves to typical human phase response curves, though the growing tendency for delays as the pulse duration increases is not often seen for humans. This may be due to mice being nocturnal and having a different biological relationship with light than humans. Understandably, the model fit is significantly better with the mouse model parameters than with the human model parameters. There is room to improve these fits with further parameter optimization to allow the light processing parameters ($\alpha_{constant}$, p, I_0, D) to vary, incorporating the consideration of the light processing being vastly different between humans and mice.

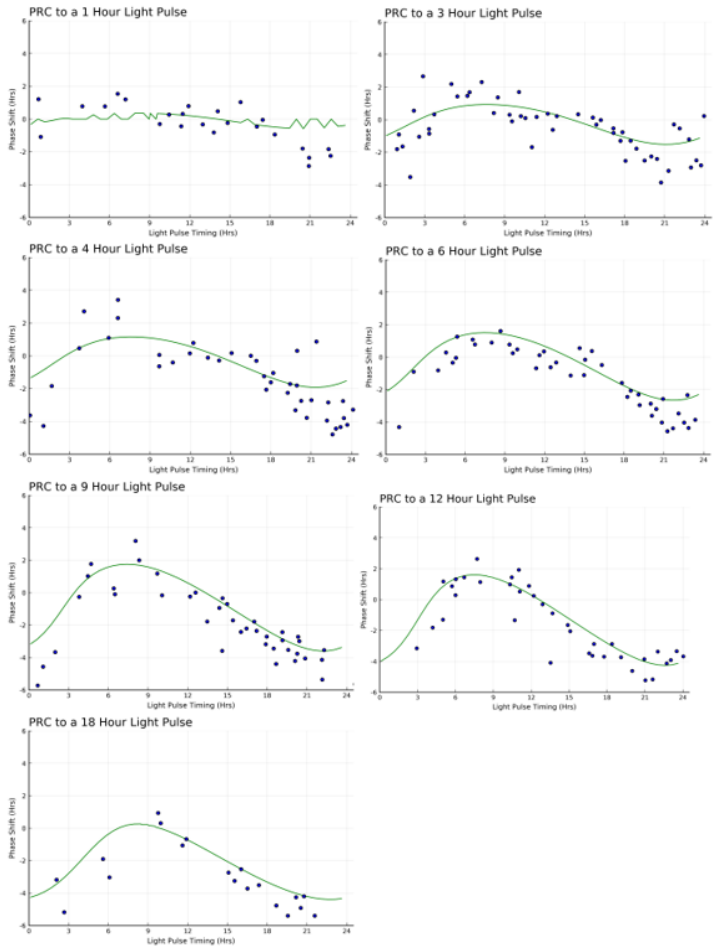

Figure 4: Plots of the Comas 2006 data of varying pulse durations for shift in phase (hours) per administered circadian time (hours). The data of the phase response curve is shown in blue with the model fit to the data using the mouse model parameters shown in green.

To confirm the validity of the parameter set and model's ability to predict experimental protocols of mice exposed to unaltered light, the model was applied to a validation set reflecting mice exposed to 150 lux of light for fifteen minutes followed by dark freerun [5]. The model doesn't fit the curve as well as the data in Figure 4, however this may be due to the entrainment of the model to uncommonly large light pulses. Such will be discussed further in the discussion section.

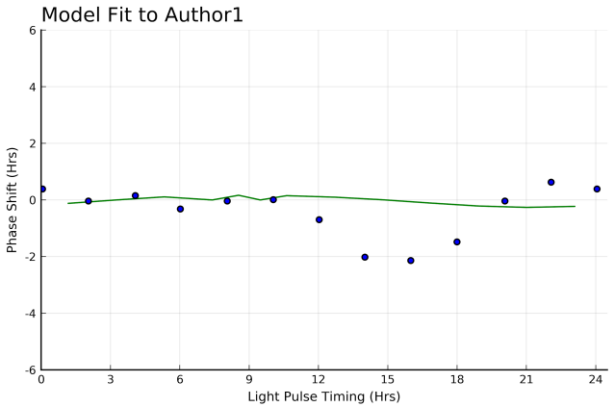

Figure 5: Plot of the Pendergast 2011 data of phase shift (hours) per administered circadian time (hours). The data of the phase response curve is shown in blue with the mathematical model fit in green.

Discussion

With the further work of this research, flexibility of the last four parameters is the initial step to be made to better fit the data as well as understand the biological implications of the relationship between mice and light. Another approach to this would be removing all constraints on the parameters, as some residue of the human model constraints may be restricting the accuracy and capacity for proper interpretations within reason.

One of the first considerations made with the results of the model was the 1-hour pulse, seen in Figure 4, that even with the best-fit parameters of the model, the trend of the data does not provide a legible phase response curve. Such in addition to the fit to the validation datasets (only one shown, Figure 5) with smaller pulse durations brings the consideration that the model is fit appropriately to large scale pulses which causes it to struggle with relatively smaller pulses. Furthermore, integration of a small pulse response like the validation set may provide the adjustment necessary for this model to appropriately predict the behavior of that scale.

Another direction this research could take in response to these results is development of a two-population model to better evaluate the coupling strengths and light processing of the system as well as improve performance of the model. Timing to complete this within the window of the REU was not attained, but still would be a valuable step to take in the development of a low dimensional model of mouse circadian rhythms.

Conclusion

In conclusion, the circadian responses of mice to light have the capacity to be mathematically modeled in this fashion. The fits of the current model reflect similar patterns to human phase response tendencies with some contrast which can be linked to biological differences that may further influence and be considered within the model. The model is not currently working to full capacity, but such implies a capability for further development through

biological evaluation translated to mathematical adjustment to incorporate the proper modeling needs appropriate for the data. Furthermore, a single population model may not be evaluating enough of the coupling responses to accurately reflect mice circadian rhythms and thus may need to be converted to a two-population model.

Acknowledgments

This research was supported by the National Science Foundation DMS-1853506 grant in supplement to the University of Michigan Mathematics Research Experience for Undergraduates.

References

1. K. Hannay V. Booth and D.Forger. “Macroscopic Models for Human Circadian Rhythms”. In: *Journal of Biological Rhythms* (2019).
2. K. Hannay D. Forger and V. Booth. “Macroscopic models for networks of coupled biological oscillators”. In: *Science Advances* (Aug. 2018).
3. M. Comas D.G.M Beersma K. Spoelstra and S. Daan. “Phase and Period Response of the Circadian System of Mice Mus musculus to Light Stimuli of Different Duration”. In: *Journal of Biological Rhythms* 21 (Oct. 2006).
4. M. Comas D.G.M Beersma R.A. Hut and S. Daan. “Circadian Phase Resetting in Response to Light-Dark and Dark-Light Transitions”. In: *Journal of Biological Rhythms* 21 (Oct. 2008).
5. J. Pendergast R. Friday and S. Yamazaki. “Photic Entrainment of *Period* Mutant Mice is Predicted from Their Phase Response Curves”. In: *The Journal of Neuroscience* (Sept. 2010).
6. Unknown. *Illustrated Science*: *The mice circadian clock*. URL: http://www.illustratedscience.net/2011/11/circadian-clock.html. (accessed: 02.27.2020).