What Is The Role of ATP in Molecular Clock Synchronization?

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Abstract

The environment produces repetitive, predictable stimuli. The sun sets routinely each night, and animals adapt automatically by establishing subconscious sleeping patterns. Physiological patterns arise from oscillators known as molecular clocks. These biochemical timekeepers are present in nearly all of an organisms cells. Molecular clock synchrony is crucial to prevent weakening of collective output. Recent investigation of brain cells in mice suggests a synchronizing role of ATP in the mammalian clock. The biochemical mechanism of synchronization via ATP remains unknown. Furthermore, instances in which ATP behaves as a signaling molecule are exceedingly rare. The Scheper Model, a system of two delay differential equations, is used to simulate the interaction of ATP with the mammalian clock. I demonstrate theoretical feasibility of the synchronization process, and offer a method of quantifying synchrony between mammalian clocks. Jointly, these techniques yield predictive power and the potential to intelligently manipulate synchrony among molecular clocks.

1 Introduction

An organism's circadian rhythm is comprised of daily patterns in its physical, mental and behavioral processes. Circadian rhythm literally means "around a day rhythm." It's as though the body sets an hourglass each morning to ensure proper sequencing and timing of its functions throughout the day. In general, biological timekeeping fundamentally arises from oscillatory output within cells. Molecular clocks produce this oscillatory output by organizing biochemical processes into negative feedback patterns.

In the past century, the precise cellular processes responsible for these negative feedback systems have been mapped extensively. Additionally, ways in which biological clocks adjust to environmental signals have been well characterized. Contrarily, mechanisms by which clocks communicate with one another remain poorly understood.

In multicellular organisms like mammalians, billions of intracellular clocks are continually oscillating. To prevent weakening of the overall output, the clocks must be kept in phase, or synchronized. In late 2014, data from a neuroscience experiment suggested that ATP, the universal energy molecule, had a synchronizing role in brain cells from mice. From a biological perspective, this observation proved difficult to explain. Not only is ATP's biological role in the clock unknown, but systems in which ATP serves a non-energetic role are exceedingly rare. In this paper, I demonstrate the mathematical feasibility of ATP's ability to single-handedly synchronize multiple molecular clocks. In section 2, I outline the precise details of the neuroscience experiment that inspired my research, and explain the methods I used to simulate observations made in the lab.

In section 3, I show that these simulations provide mathematical proof of concept for ATP's ability to synchronize. This result allows for several inferences which uncover clues about the underlying biochemistry of synchronization. Furthermore, I offer a potential method of predicting and manipulating molecular clock synchrony. Finally, section 4 discusses the possible implications of this research with a focus on human medicine.

2 Background

Dr. Mark Zoran's lab at Texas A&M University produced data in late 2014 which studied the oscillatory output of astrocytes from mice. The astrocytes were plated in 12 separate colonies. Each plate's levels of extracellular ATP concentrations were measured every 10 minutes for a 72 hour period. ATP concentrations appeared to rise and fall with a period of roughly 24 hours among each colony [Figure 1]. Thus, it was concluded that ATP was a component of the astrocyte molecular clock. In a following experiment, extra exogenous ATP was added to each of 12 new colonies of astrocytes at identical time points. Not only did the rising and falling of extracellular ATP become more exaggerated within each colony, but each of the 12 oscillatory outputs appeared to shift into a common phase [Figure 1]. Clearly, ATP was synchronizing the astrocyte's clock.

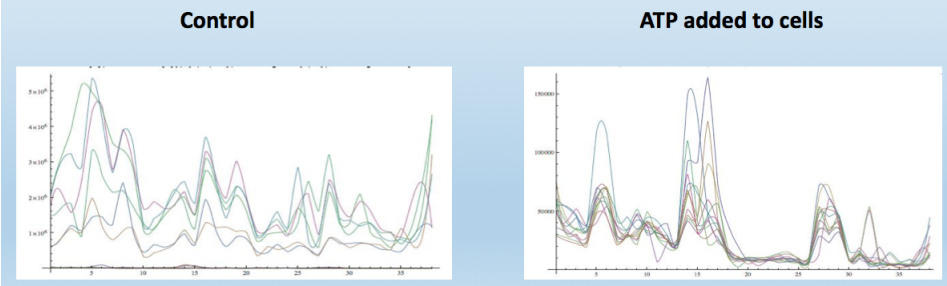

Figure 1: Dr. Zoran's Experiment

Since ATP is a component of the molecular clock, the simplest hypothesis was that an effectively instantaneous, equivalent increase in a component common to multiple clocks could bring their outputs into phase.

(Scheper et al. 1999) outlines the Scheper model, a set of two delay differential equations which describe the circadian clock. Operating via one promoting parameter, x, and one inhibitory parameter, y, the system generates a negative feedback loop.

$$\dot{x}(t) = \frac{r_x}{(1+y(t)^2)} - q_x * x(t)$$

$$\dot{y}(t) = r_y * x^3(t-\tau) - q_y * y(t)$$

When the production and degradation rates of each parameter are adjusted properly (Leise et al. 2006), the model produces oscillations with a period of approximately 24 hours. Thus, its ability to simulate molecular clock output is realistically descriptive. Although antiquated, the mRNA-Protein interaction is a valuable method for visualizing the production of oscillations. [Figure 2] depicts the transcription of mRNA which is translated into a protein that serves to prevent further transcription of the gene it is encoded by. Thus, a negative feedback loop arises and the result is oscillatory output. The pink curve reflects the protein parameter, which is the inhibitory y parameter. Conversely, the small blue curve represents the mRNA parameter, which is the promoting x parameter.

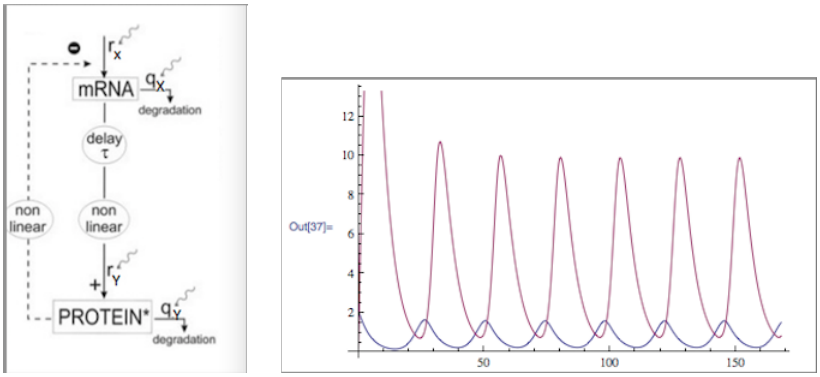

Figure 2: The Scheper Model with Mathematica Output

3 Main results

The original hypothesis was substantiated via simple trial and error simulations. Two oscillators, initially set out of phase with a period of roughly 24 hours, were effectively synchronized when a common value, Δ (7 times greater than initial parameter value), was added to their x values at the common time t=50 hours. Interestingly, changes in the y parameter did not lead to synchronization, and had minimal effect in general on the output. Thus, it could be concluded that ATP would be best represented by the x, or promoting parameter.

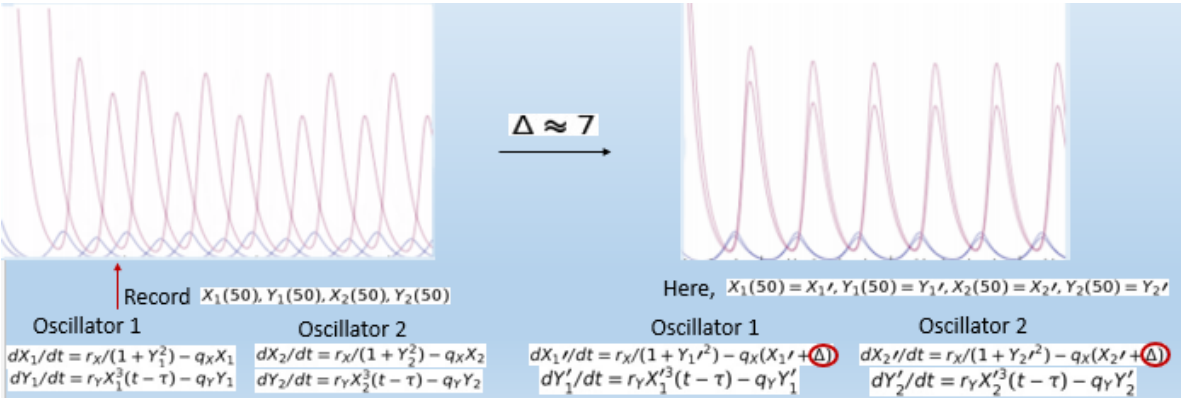

Figure 3: Initial simulation of Δ

While this result demonstrated feasibility of the data, it was limited in predictive power. Many questions were left unanswered. How much ATP is optimal for synchronization? Do the oscillators' parameters affect ATP's synchronization ability? In order to answer questions of this caliber, I developed a method of quantifying synchronization.

This function effectively describes the distance between two sets of oscillatory curves from the Scheper Model. Thus, the larger the function value, the less synchronized two clocks may be assumed to be.

$$F(\Delta) = \int_a^b [(x_1(t) - x_2(t))^2 + (y_1(t) - y_2(t))^2]dt$$

a=initial time point, b=final time point

Oscillator 1: $(x_1(t), y_1(t))$

Oscillator 2: $(x_2(t), y_2(t))$

Δ = Amount of ATP added

It is important to note that the initial time point must be well chosen to avoid irrelevant initial output, depicted below.

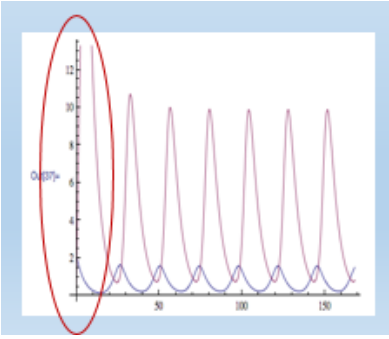

Figure 4: Output excluded from integral

The following computations were necessary to obtain the derivative of the function:

$$F(\Delta) = \int_a^b [(x_1(t) - x_2(t))^2 + (y_1(t) - y_2(t))^2]dt$$

$$\frac{\partial \dot{x}(t)}{\partial \Delta} = -[\frac{\partial x(t)}{\partial \Delta} q_x] - [\frac{\partial y(t)}{\partial \Delta} * \frac{2y(t)r_x}{(1+y(t)^2)^2}]$$

$$\frac{\partial \dot{y}(t)}{\partial \Delta} = 3[\frac{\partial x(t)}{\partial \Delta} x^2(t-\tau)] - [\frac{\partial y(t)}{\partial \Delta} * q_y]$$

$$F'(\Delta) = \int_a^b 2(\frac{\partial x_1(t)}{\partial \Delta} - \frac{\partial x_2(t)}{\partial \Delta})((x_1(t) - x_2(t))dt + \int_a^b 2(\frac{\partial y_1(t)}{\partial \Delta} - \frac{\partial y_2(t)}{\partial \Delta})((y_1(t) - y_2(t))dt$$

Based on preliminary testing in Mathematica, I was able to make several inferences, The majority of function output thus far suggests that in any case, ATP addition has a logarithmic effect on synchrony. In other words, diminishing returns are evident, albeit more ATP is always better for synchrony. When oscillator parameters are adjusted such that the initial phase difference is smaller, simulations predict less ATP is necessary for effective synchronization.

Furthermore, ATP does not seem to have a desynchronizing effect in any case. Specifically, instances in which two identical oscillators have generated a nonzero function value, F, for any value of Δ have not been observed. Future research is necessary to understand the general behavior of this function. Optimization techniques and functions of additional parameters would almost certainly offer utility.

4 Discussion

Gene transcription, which is catalyzed by enzymes, is the fundamental promoting process in the mammalian molecular clock. As my initial findings suggest ATP's effects are in magnifying promoting processes in the clock, its biochemical role as a promotor is likely. ATP allosterically activates many enzymes, which offers one plausible explanation for the data.

As with most biological simulations, my research has several limitations. Firstly, I assume the Scheper Model adequately describes the negative feedback system in the mammalian clock. Moreover, the model itself groups all promoting and inhibiting processes together, respectively. I also assume instantaneous addition and uniform mixing of ATP. Also present are limitations with respect to my predictive methods. The function must be supplied with two reference oscillators. This means that the function could only provide a Δ value for specific oscillators. Thus, the optimal value of Δ would not be general. Furthermore, the function may misinterpret differences in peak amplitude as phase differences.

The implications of this investigation are thrillingly far-reaching. The knowledge I aim to capture could theoretically lead to the development of a drug that could regulate and strengthen ones circadian rhythm. As a result, annoyances such as jet lag could be eliminated entirely. Ultimately, molecular clock intercommunication remains poorly understood, and further research is essential.

5 Acknowledgements

This research would have been impossible without the guidance of my research mentors.

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6 References

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