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Modeling of drosophila circadian system based on locomotor activity

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Abstract— **Due to the 24-hour lighting-dark cycle on earth, circadian rhythm regulates the biochemical and physiological processes of almost all living organisms, including plants, insects, and mammals. Maintaining the regular cyclicity of this internal clock, called entrainment, is important to the well being of an organism. For human, circadian disruption can lead to lower productivity, digestive problems, decreased sleep efficiency and other health problems. Various models have been proposed for the circadian rhythm, from empirical oscillator type models to genetic network based biochemical models. These models are used to gain insight into the mechanism governing the circadian rhythm, but may also be used to formulate light-based control strategies for its regulation. As a first step towards our eventual goal of light based circadian rhythm regulation for human, we are conducting experiments with drosophila (fruit fly), measuring the interaction between light intensity and wavelength and its locomotive activity level. Instead of the high order biochemical models proposed in the past, we consider a second order empirical oscillator model, with light intensity as input and activity as the output. By first entraining the flies in a regular rhythm and then observe the effect of light pulses, we are able to identify the model parameters based on the input/output experimental data. The model shows promising predictive capability: Our simulation shows that two blue pulses can shift the phase of drosophila circadian pacemaker by 12 hours, while the experiment result is 13.3 hours.**

I. INTRODUCTION

The Earth has a regular 24-hour pattern of daylight and darkness over most of its surface. Terrestrial species have adapted to this daily pattern by evolving biological rhythms, called circadian rhythm, that repeat at approximately 24-hour intervals. In humans, circadian rhythms manifests itself in the sleep/wake cycle, cyclic hormone production, and levels of daytime/nighttime performance and alertness. Lack of synchrony between the master clock in the brain and the external environment, referred to as circadian misalignment, can lead to circadian disruption, with the detrimental consequences ranging from increased sleepiness during the day, lower productivity, gastrointestinal disorders, to long-term health problems such as increased risk for cancer, diabetes, obesity, and cardiovascular disorders [1], [2]. Rotating-shift work, transcontinental flights, irregular sleep patterns, all of which will lead to irregular light/dark exposures, can all contribute to circadian disruption.

The cyclic nature of the circadian rhythm lends itself naturally to be modeled as a nonlinear oscillator. Such simple empirical models have been used successfully to gain insights into the human circadian rhythm and its interaction with artificially controlled lighting [3]. With the advent of biochemical analytical tools, circadian system models based on genetic network of varying complexity have been also been developed [4], [5]. These models describe the oscillation of circadian related proteins, and provide a physical grounding of the mechanism of circadian system. These models have been used, in simulation, to demonstrate the potential to regulate the circadian rhythm by regulating the light stimuli. Most of the work is open loop in nature, based on the phase response curve, PRC (amount of phase shift due to a specified light pulse input at different circadian phases) [3]. Some closed loop strategy has also been suggested and demonstrated in simulation [6], [7]. Closed loop control is attractive as it could accommodate variations between models and disturbances from the environment. However, there has been no experimental implementation of light control with closed loop circadian rhythm feedback, as the state of the circadian rhythm is not easily measured. For human, circadian rhythm may be determined from the hormone (e.g., melatonin) level in saliva or blood samples. Indirect measurement such as core body temperature (used in [3]) is a good indicator, but is difficult to instrument beyond a laboratory setting. Other indirect observables have been suggested, such as activity, pulse/heart rate, surface body temperature, etc., but their correlations to the circadian rhythm are frequently masked by other factors.

In this paper, we take the first step towards the experimental study of closed loop circadian rhythm control by adjusting the light input. We use drosophila as the model organism, as the experiment protocol is relatively simple, its circadian rhythm has been well studied, and the cost is not prohibitive. Such biological experiment is important for validation and development of the modeling and control methodology. Comparing to human and mouse, drosophila experiments are less costly. Several mutants of drosophila with known circadian rhythm properties are available for controlled experiments. Although clock genes in human are not exactly the same as in drosophila, there are some similarities, such as the shape of the phase response curve and the circadian sensitivity to the blue light. The center manifold analysis and averaging method have been used to show that the empirical oscillator model is a limiting case of the biochemical drosophila circadian model [8], indicating the generality of the empirical modeling approach. The primary focus of the paper on building a empirical limit cycle model for the drosophila circadian system. This model quantifies

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the influence of light pulses on the the locomotor activity, which is easy to measure and can be used for feedback light control. Based on the recent publication on the light pathway to activity, we propose a second order limit cycle model with light as input and activity as output. By taking advantage of the spectral tunability of LED illumination, we present some initial results on model parameter identification. An open loop phase shift experiment shows that the phase shift prediction by the identified model is within 10% of the experimental result. The closed loop feedback control simulation using the identified model shows a 3-day reduction of the 12-hour phase shift compared to the nature light dark pattern.

II. Drosophila circadian system and locomotor activity

In the complete darkness, the clear 24-hour pattern of drosophila locomotor activity shows that the activity is influenced by the circadian pacemaker. Drosophila's circadian pacemaker is very sensitivity to light and can be entrained by even 0.01 lux light. As in human, drosophila's circadian system is most sensitive to the blue light, and almost completely insensitive to the red light [9], [10]. The circadian photoreceptor in drosophila deep brain, CRY (cryptochromes), plays an important role in regulating the impact of light on the circadian system. The mutant drosophila, cry^b inhibits the expression of CRY and therefore its circadian system does not response to the light input. Similarly, over-expression of CRY makes the circadian system hypersensitive to light. CRY belongs to a family of blue light sensitive proteins. When CRY is expressed in the LNvs cells in Drosophila, these cells will be sensitive to light, and the circadian pacemaker transcription loops in the LNvs, PER/TIM and CLK/CYC, are directly affected. The pacemaker in turn regulates the expression and release of neuropeptide PDF, which affects the locomotor activity. The CRY is spectral-selective, red light cannot go through this pathway [11].

Another light-activity pathway is through perception. The compound eye and other eye structure of drosophila can detect light, which directly influences its activity [12]. From experiment, it is clear that the locomotor activity peaks just after the light switch on or off. Even for short red light pulses, which do not influence the circadian pacemaker, the activity amplitude will suddenly increase and then quickly recover. This phenomenon has been observed in cry^b, whose circadian pacemaker does not response to light pulses. A study of gl^{60j}, cry^b double mutants drosophila, which are blind flies without CRY, shows that high intensity light can still influence the locomotive activity [12], indicating other pathways from light to activity, in addition to circadian systems and vision.

III. Limit cycle model of drosophila circadian system

The experiment data shows that the model circadian system and locomotor activity of drosophila is highly nonlinear. For the first step, our goal is to build a model which can predict the activity response and circadian phase shift due to short light pulse. Motivated by the empirical models developed in e.g., [3], we use the following second order model structure for the drosophila circadian system:

$$\dot{z} = f_0(z) + f_1(z)L(I) \quad (1)$$
$$y = c(z) + h(z,I) \quad (2)$$

where I is the irradiance of the light pulse, y is the activity, and the state variable z is a 2×1 vector. While the drosophila is placed in complete darkness, ignoring factors such as aging and food drying out, the locomotor activity oscillates with a constant amplitude and period modeled by the unforced dynamics

$$\dot{z} = f_0(z),\ y = c(z).$$

The free-running (i.e., in complete darkness) oscillation is governed by $f_0(z)$. Light impacts activity through the drosophila circadian system and vision system. The vision system can be considered as the feedthrough from light to activity, $h(z,I)$. The effect of light on the circadian pacemaker is captured by $f_1(z)$. Instead of using a high order biochemical model, we approximate the function $f_0(z)$ and $f_1(z)$ as polynomials with coefficients identified using the experimental data. The overall hypothesized model structure of the following form:

$$\begin{aligned}
z &= \begin{bmatrix} z_1 & z_2 \end{bmatrix}^T \\
f_0(z) &= Az + \begin{bmatrix} D_{11}^T & D_{12}^T \\ D_{21}^T & D_{22}^T \end{bmatrix} \begin{bmatrix} g(z_1) \\ g(z_2) \end{bmatrix} \\
A &= \frac{\pi}{12}\begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix}, B_1^T = \begin{bmatrix} 1 & 0 \end{bmatrix}, B_2^T = \begin{bmatrix} 0 & 1 \end{bmatrix} \\
g(x) &= \begin{bmatrix} x^1 & x^3 & x^5 & x^7 \end{bmatrix}^T \\
f_1(z) &= \begin{bmatrix} J_1^T k(z) & J_2^T k(z) \end{bmatrix}^T \\
k(z) &= \begin{bmatrix} 1 & z_1^1 & z_1^2 & z_1^3 & z_2^1 & z_2^2 & z_2^3 & z_1 z_2 & z_1 z_2^2 & z_1^2 z_2 \end{bmatrix}^T
\end{aligned}$$

where D_{ij} is 4×1 and J_i is 10×1.

IV. Experimental Setup and System Identification

To measure the drosophila activity level, we use the Drosophila Activity Monitor System (DAM5) manufactured by Trikinetics [13]. One activity monitor has 32 channels. In each channel an infrared LED and detector pair is placed across the center of a glass tube in which a drosophila lives. The monitor counts the number of times the 32 drosophilas walk across the center of the tubes between two samplings. The sampling interval is set at 1 min. The activity monitors are placed in light-tight incubators with Philips Rebel LEDs at different wavelengths as light sources and mirrors mounted on the inner surface of the incubators. The positions of LEDs are optimized by the optical simulator, ZEMAX, to ensure the light uniformity on the monitor. Mathwork xPC Target system is used for data acquisition and light control. The LEDs include red at $\lambda = 627$nm and blue at $\lambda = 470nm$. For both colors, we use pulse duration of 5-min. We shall characterize light intensity in terms of irradiance (optical

power per unit area) instead of lux, as lux is for human perception which is very different from drosophila.

The drosophila used in the experiment is a strain of wild type drosophila with the free running period very close to 24 hours. The life span of the adult drosophila is about a month. Several factors may influence the activity, such as age, gender, food freshness and other environmental factors. In the experiment, the drosophila are males emerged in recent 3 days, so they have same gender and similar age. The time frame of one experiment is 8 days and the drosophila's activity level is relatively constant within these days. Furthermore, high pressure air through a humidifier is used for ventilation and keeping the food from drying. In the future, temperature sensors will be mounted on the monitor to detect the variation of the temperature, which may also entrain the drosophila's circadian pacemaker and stimulate the activity. If required, heater or refrigerator may be used to control the temperature.

Fig. 1. ZEMAX simulation and the experimental incubator.

An unforced circadian pacemaker is used as a reference to characterize the phase shift due to pulse light stimulus. As shown in Figure 2, at time t, the unforced circadian pacemaker $z_u(t)$ is the same as the forced pacemaker $z_f(t)$. A short duration light pulse, staring at t and ending at $t+\Delta T$, kicks the forced state $z_f(t)$ off the limit cycle to $z_f(t+\Delta T)$, while the unforced pacemaker continues moving along the limit cycle to $z_u(t+\Delta T)$. This transient process results in an immediate phase shift of $\Delta\phi_a$, which is the phase difference between $z_f(t+\Delta T)$ and $z_u(t+\Delta T)$. The resulting orbit then converges back to the limit cycle, with an additional phase shift of $\Delta\phi_b$.

In the sample experimental run shown in Fig. 3, the drosophila are entrained in a 12hr-12hr white-light/dark cycles for 2 days and then kept in darkness, except for a blue pulse (1.35W/m^2) at 23:00 of day 3. The experiment data shows that drosophila reaches steady phase within one day after the pulse while the amplitude is still decaying back to the steady state (i.e., still in the recovery phase). This suggests that the phase shift in the recovery phase is small, and we shall assume that $\Delta\phi_b$ is zero, and $\Delta\phi_a$ is the total phase shift. We also noticed that the activity amplitude increased slightly after the pulse stimulus and decrease to a constant in 3 days, which shows that the amplitude of circadian pacemaker is increased temporarily by the pulse and the unforced dynamics pulls the pacemaker back to limit cycle at a certain rate.

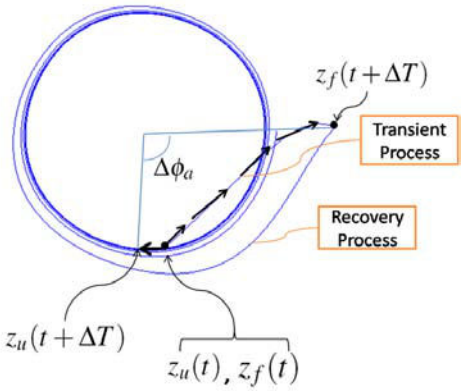

Fig. 2. Effect of light pulse on phase

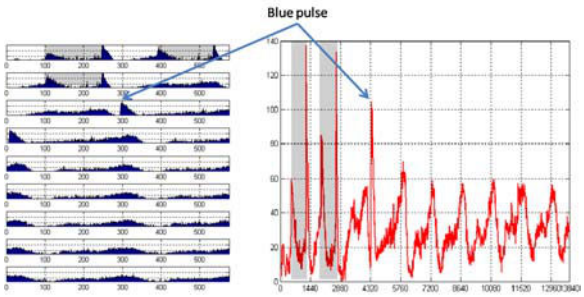

Fig. 3. Drosophila activity data of phase shift experiment. The left panel is the double plotted actogram of activity data. The shaded time is white light entrainment. Double plotted actogram is a graphical display of activity along two time axes to visualize the free running period and phase shift. The activity of two cycles are plotted each line, and the second cycle on a line is the same as the first cycle on the following line. The right panel is the activity data versus time. The data after 7200 minutes show the free running activity pattern.

A. Identification of Forcing Function, f_1

As described in the previous section, we can obtain from the actogram the steady state phase shift due to the application of a (blue) light pulse (which enables us to obtain the PRC). This information may be used to approximately calibrate $f_1(z)$. Since the phase shift has been observed experimentally to be independent of the oscillation amplitude away from the limit cycle, we assume that the phase shift in the recovery process $\Delta\phi_b$ is approximately 0 and the measured phase shift is due entirely to the phase shift in the transient phase, $\Delta\phi_a$. From Figure 2, for a short light pulse with duration Δt, $\Delta\phi_a$ may be computed as

$$\Delta\phi_a = \cos^{-1}\left(\frac{r_a^2+r_b^2-r_c^2}{2r_ar_b}\right) \tag{3}$$

where

$$r_a = \|z_u(t+\Delta T)\|,\ r_b = \|z_f(t+\Delta T)\|$$
$$r_c = \|z_f(t+\Delta T) - z_u(t+\Delta T)\|.$$

Since we do not have $f_0(z)$ at this point, we approximately the unforced dynamics by its describing function, $\dot{z}_u = A_{DF}Z_u$ [7]. By observing the phase of the unforced activity oscillation, we may ascertain $z_u(t)$ and the time t at which the light

pulse is applied. From the describing function based unforced oscillation and the pulse width, we obtain $z_f(t+\Delta t)$, and hence r_b. The forced response is obtained by simulating the following dynamics:

$$z_f(t+\Delta t) = z_u(t) + \int_t^{t+\Delta t} (A_{DF} z_u(\tau) + f_1(z_f(\tau))L(I))d\tau. \tag{4}$$

Therefore, r_a and r_c are function of f_1. We can now find the parameters in f_1, J_1 and J_2, to minimize the difference between the predicted $\Delta\phi_a$ in (3) and the experimentally measured phase shift (which is just the PRC). The comparison between the PRC from the identified model and the experimental PRC from the literature [4] is shown in Figure 4, indicating reasonable agreement. Note that the PRC from [4] is measured using a 1-min white light pulse, not the blue light that we are interested in. We are currently working on the blue pulse experiments to improve the blue pulse based model.

The drosophila circadian system response is not linear to the light irradiance, because arbitrarily high irradiance pulse cannot cause arbitrarily large phase shift. This nonlinear behavior is captured in $L(I)$ converting the light intensity to the drive force which shift the phase of circadian pacemaker. Phase shift measurement based on varying irradiance blue pulse will reveal the relationship between I and $L(I)$. This is also currently under development.

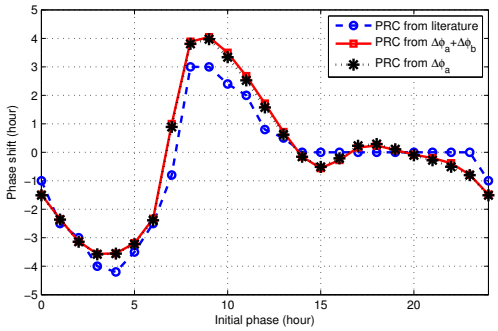

Fig. 4. The phase response curve generated by $\Delta\phi_a$ and $\Delta\phi_a + \Delta\phi_b$.

B. Identification of Unforced Dynamics, f_0

To identify f_0, we also use the response of the circadian system after a short light pulse, but instead of the steady state phase shift in the previous section, we use the trajectory in the recovery process. As mentioned, from the analysis of experiment data in Figure 3, it is reasonable to assume that $\Delta\phi_b \approx 0$, which means the angular velocity is almost constant $(2\pi/24)$ when the oscillator is not on the limit cycle. We also assume that the rate of change of the radius of the oscillation is the same as the rate of decrease of the activity amplitude. We now apply the averaging method to analyze how the parameters in $f_0(z)$, D_{ij}, affects these attributes: angular velocity and amplitude decay during the recovery process. Using amplitude-phase transformation [14], it may be shown that

$$\dot{r}_{averaged}(R) = \frac{\iint \nabla \cdot \vec{F} d\sigma}{2\pi R}$$

$$\omega_{averaged}(R) = \frac{\iint \nabla \times \vec{F} d\vec{\sigma}}{2\pi R^2}$$

where

$$\vec{F}_0 \equiv \begin{pmatrix} f_{01}(z) \\ f_{02}(z) \\ 0 \end{pmatrix}.$$

The integration region is the circle with center at origin and radius R. The amplitude change during the recovery process is governed by $\dot{r}_{averaged}$. The experiment activity plot shows a large increase of activity just after the pulse. The increased activity includes the amplitude change of the circadian pacemaker and direct light feedthrough. The feedthrough disappear quickly, while the amplitude of the circadian pacemaker recovers in three days. Since we cannot isolate the amplitude change of circadian pacemaker from the increased activity, we use the same simulation as in the previous section (describing function with identified forcing term, f_1) to estimate the amplitude of the circadian pacemaker. For our experiment, this is 1.6 at the beginning of the recovery process. The (normalized) experimentally measured activity amplitude drops to 1.2 at day 2, and to 1 at day 3. These data are then used to identify parameters D_{11} and D_{22} in $\nabla\vec{F}$ (and $\dot{r}_{averaged}(R)$). Constraints are also imposed during parameter fitting to maintain certain limit cycle radius and period. By requiring '$\dot{r}_{averaged}(1) = 0$' and '$\ddot{r}_{averaged}(1) < 0$', the limit cycle radius will remain stable and close to 1.

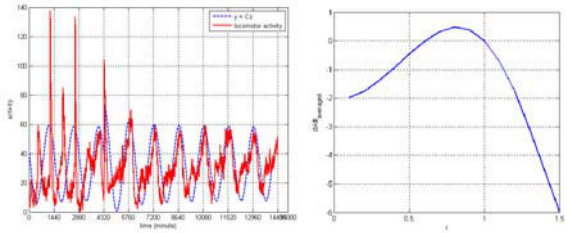

Fig. 5. Left panel: the recovery process fitting result. Since the model is for short pulse stimulus at the point, in all the simulations the first two days in white light entrainment are replaced by free running with same phase. Right panel: The averaged radius changing rate.

The closest fit to the experiment is shown in the Figure 5. However, this set of parameters will generate negative $\dot{r}_{averaged}$ when radius is smaller than 0.6, which means that the origin is a stable focus, and any state close enough to the origin will be attracted. To ensure that the circadian oscillation is sustained, as observed in experiments, we apply an added constraint $\dot{r}_{averaged}(r) > 0, \forall x \in (0,1)$. The improved result is shown in Figure 6 where the origin is now unstable. The form and parameters of $f_0(z)$ will be modified and improved based on more experiments, including the cry^b drosophila experiments which can help us to separate the

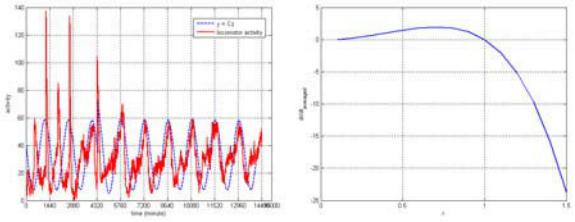

Fig. 6. Left panel: the recovery process fitting result with additional constraints of D_{11} and D_{22}. Right panel: The averaged radius changing rate.

feedthrough from the activity sudden increase due to light pulse and get a clear initial condition of recovery process.

To make the phase shift during the recovery process almost zero, we restrict the averaged angular velocity of the oscillator to be always $2\pi/24$ (rad/hr). Only D_{21} and D_{12} are involved in calculating $\nabla \times \vec{F}$. So if we set D_{21} and D_{12} to be zero, then $\omega_{averaged}(r)$ will be $2\pi/24$ at any radius. As shown in Figure 4, the shape of PRC from $\Delta\phi_a + \Delta\phi_b$ is almost the same as the PRC generated by $\Delta\phi_a$ alone since the recovery process introduced little phase shift.

C. Identification of $c(z)$

From figure 3, we see that the free running activity pattern in darkness is periodic with a 24-hour period. It can be approximated reasonably well with the DC term and the first two harmonics. Since the state variables, z_1 and z_2 are approximately sinusoidal with 24-hour period, we choose the following polynomial expansion:

$$\begin{aligned} c(z) &= \phi_c^T \theta_c \\ \phi_c^T &= \begin{bmatrix} 1 & z_1 & z_2 & 2z_1z_2 & z_1^2 - z_2^2 \end{bmatrix} \end{aligned} \quad (5)$$

where θ_c is a 5×1 parameter vector. We have observed that c varies in different experiments, due to the age of flies, survival rate of flies after anesthesia, and even the walking distance in the tube. During a feedback control experiment, these parameters may be updated from the activity data of the first free running day.

D. Identification of Feedthrough, h

As a first step, we try to identify the feedthrough for light pulses with short duration. We are interested in feedthrough corresponding to the blue light because it will be used to shift the circadian phase. One problem is that the blue pulse will also kick the circadian pacemaker off the limit cycle which also cause activity amplitude change, so it is difficult to isolate the feedthrough part from the total activity amplitude change. The best way to solve this problem is to conduct experiments on cry^b mutant flies, whose circadian pacemaker does not response to blue pulses. We are in the process of obtaining such mutants, but in the interim, we demonstrate the identification method by using red light. As red pulses will bypass the circadian pacemaker and stimulate only the activity, the effect from circadian and vision system may be separated. The experimental protocol consists of entrainment in white light for two days, then applying red pulses every two hours, while decreasing the intensity of the pulse day by day. This protocol allows us to find out the relationship between the feedthrough and the pulse irradiance, timing by using only one activity monitor and running the experiment only once.

To first identify the impact of light on activity through the non-circadian path, we apply red light irradiance for seven days: $\{1.62, 1.35, 0.675, 0.337, 0.168, 0.083\}\text{W/m}^2$. As shown in Figure 7, the spikes in activity curve correspond to the light pulses. A median filter is applied to the activity data to remove the spikes. The smoothed activity data is the portion driven by the circadian pacemaker (i.e., $c(z)$). The original activity data with the smoothed portion removed is then the feedthrough term. Using the max-filter we can find the envelop of the feedthough, which oscillates with 24-hour period as shown in Figure 8. Note that the feedthrough is asymmetric – higher at circadian night and lower during circadian day. Also, the feedthrough appears not to be influenced by the light intensity, possibly due to saturation.

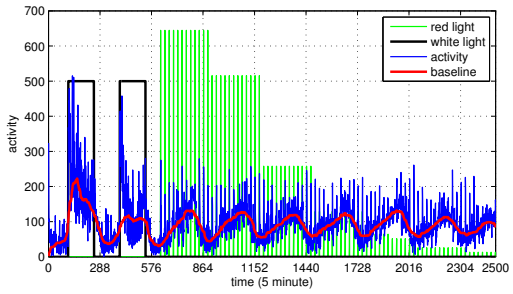

Fig. 7. The red light stimulus, drosophila activity and baseline of activity.

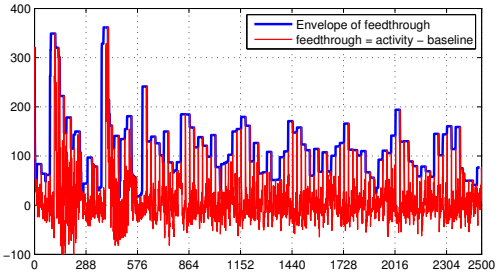

Fig. 8. The intensity of feedthrough.

E. Identified Model Parameters

The parameters in $f_0(z)$ and $f_1(z)$ are summarized in Table I. From the identified limit cycle model, we can estimate the states of the circadian pacemaker. The estimated state trajectory is then used to fit the parameters in $c(z)$ and $h(z,I)$

$$\theta_c = \begin{bmatrix} 27.37 & -7.41 & 8.71 & -1.42 & -9.73 \end{bmatrix}^T \quad (6)$$

$$h(z,I) = \left(\begin{pmatrix} -22.8 & -35.1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} + 112 \right) sign(I). \quad (7)$$

Parameters fitting result	
J_1	[5.18 0.92 1.95 0 -7.55 -0.01 -0.02 0 -0.01 -3.30]^T
J_2	[1.69 -8.93 16.00 -11.15 0.02 -0.02 -0.01 -0.01 0 0]^T
D_{11}	[-0.03 0.17 -0.19 0.04]^T
D_{12}	[0 0 0 0]^T
D_{21}	[0 0 0 0]^T
D_{22}	[-0.03 0.17 -0.19 0.04]^T

TABLE I

IDENTIFIED PARAMETER VALUES THE CIRCADIAN MODEL

V. PRELIMINARY OPENLOOP CIRCADIAN CONTROL EXPERIMENT

The model described in this paper can be used to predict the circadian system's response to pulse light stimulus, and an experiment has been carried out to test the model. The result is shown in Figure 9. In the simulation, two blue pulses positioned at 23:00 in the first day of free running and 6:36 in the third day can shift the circadian phase for 12 hours. In the experiment, the phase is shifted for 13.3 hours, which is about 10% larger than the prediction.

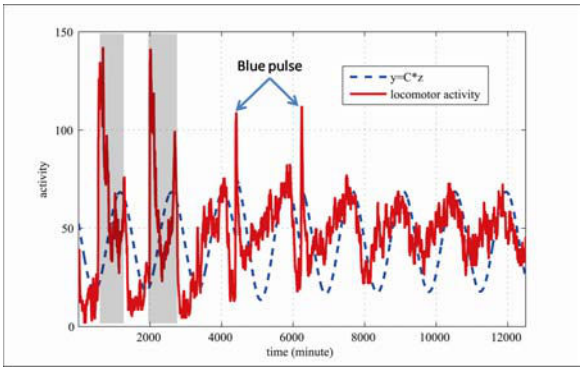

Fig. 9. Model prediction and experiment data of open loop circadian phase shift.

VI. CONCLUSIONS AND FUTURE WORKS

This paper presents the ongoing work on developing an empirical drosophila circadian system model with light pulse as input and locomotor activity as output. An empirical nonlinear oscillator is used for modeling the pacemaker, and the activity output is modeled as a feedthrough combining the effect of both circadian and vision systems. Initial parametric identification results indicate that the model can predict the phase shift of circadian pacemaker to certain blue light pulses, and the activity variation due to red pulses. The 12-hour phase shift experiment result can be predicted by the model within 10%. The close loop circadian phase control based on reference tracking is demonstrated in simulation, which reduces the time required for 12-hour phase shift by 3 hours compared to the natural 12-hour light/dark cycle entrainment. The work reported here is only preliminary as only limited experimental data are currently used: short duration light pulse inputs and no direct measurement of the feedthrough of blue light. More light-tight incubators with activity monitors will be built up and more experiments, including ones involving mutant drosophila and light pulses with varying duration and intensity, need to be carried out to identify the system thoroughly. The longer term goal is to develop a human circadian model and light-based control system by using primarily the activity measurement.

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