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Circadian System Modeling and Phase Control

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***Abstract*— Circadian rhythms are biological processes found in all living organisms, from plants to insects to mammals that repeat with a period close to, but not exactly, 24 hours. In the absence of environmental cues, circadian rhythms oscillate with a period slightly longer or shorter than 24 hours. The 24-hour patterns of light and dark are the strongest synchronizer of circadian rhythms to the solar day. Circadian disruption resulting from lack of synchrony between the solar day and the internal master clock that regulates and generates circadian rhythms had been linked to a variety of maladies. Circadian disruption, as experienced by night shift workers or by those traveling multiple time zones can lead to lower productivity, digestive problems and decreased sleep efficiency. Long-term circadian disruption has been linked to serious health problems, such as increased risk of cancer, cardiovascular disease, diabetes and obesity. Biochemical and empirical mathematical models describing the circadian clock and its response to light input have been developed by various research groups. Biochemical models describe the kinetics of the interaction between different proteins and may be of high order depending on the complexity of the model. Empirical models are based on nonlinear oscillators, such as the van der Pol oscillator, and are, therefore, much simpler. Though empirical models do not have a biochemical basis, it has been shown that they do represent the averaged asymptotic behavior of the biochemical models. In this paper, we analyze a simple empirical model proposed by Kronauer and colleagues and discuss how light control may be used to promote circadian entrainment. In contrast to most of the existing approaches, which are based on phase response curves, we propose a feedback-based system. Through simulation, we show that the recovery of a 12-hour jet lag can be shortened from 7 days to 2.5 days.**

I. Introduction

The Earth rotates on its axis with a regular and predictable 24-hour pattern of daylight and darkness. Terrestrial species have adapted to this daily pattern by evolving biological rhythms that repeat at approximately 24-hour intervals. These are called circadian rhythms (circa=approximately; die=day). For humans, circadian rhythms are regulated and generated by a master clock located in the suprachiasmatic nuclei (SCN) in the hypothalamus in the brain. The SCN governs a wide range of biological cycles, from cell division, to hormone production, to behavior (e.g., sleep-wake) that, when synchronized with the natural light/dark cycle, enables the organism to entrain these cycles to its particular photic niche (diurnal or nocturnal) and to its location on Earth. In humans, examples of circadian rhythms include the sleep/wake cycle, 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 attendant detriments 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 SCN exhibit sustained oscillations *in vivo* and *in vitro*. Numerous mathematical models have been proposed to describe the oscillations of the master clock. For example, based on studies in Drosophila Melanogaster (commonly known as fruit fly), a 10-state model of the kinetics of the circadian clock gene network has been proposed [3] and has been used for circadian system control [4], [5]. It is important to note, however, that although applicable across species, clock genes in mammals are not exactly the same as in fruit flies.

An alternative approach is to use a nonlinear oscillator, such as the van der Pol oscillator, as an empirical model for the circadian rhythm. Such approach has long been proposed [6], and more recently it was used by Richard Kronauer et al. [7]. The Kronauer model describes the relationship between light stimulus and the oscillation of human core body temperature, which is an acceptable phase marker of the circadian system. In the Kronauer model, the circadian system is represented by a modified Van der Pol oscillator with a 24-hour period. Light stimulus is first converted into a drive $\hat{B}$ through a light stimulus dynamic processor, process L. This is analogous to the bleaching of photopigments in retinal photoreceptor by photons, which remain unusable for further photon response until they are regenerated. The drive $\hat{B}$ feeds into the process P which represents the circadian pacemaker. The drive $\hat{B}$ is first modulated to B which is the input of the modified van der Pol oscillator. The oscillator output is related to the oscillation of core body temperature which is used as a phase marker of the circadian system. As argued in [8], the empirical model may be considered as the asymptotic case of the biochemical model in an averaged sense. A reduced order modeling approach for the biochemical model has also been proposed in [9].

The effect of light stimulus is commonly characterized by the *phase response curve* (PRC), which plots the *steady state* phase shift as a function of the time of the day at which a light pulse with a given amplitude and duration is applied. The PRC may be generated experimentally using test subjects or numerically with a chosen simulation model. An open-loop circadian entrainment method has been proposed

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based on the PRC constructed from the Kronauer model [10] to design a light-dark pattern for jet lag treatment. However, open-loop control does not address the difference between individuals and the uncertain ambient light disturbance. In [5], the 10-state circadian oscillation model of Drosophila is used to construct the PRC. A closed-loop phase shifting control based on the model predictive control method is developed based on this PRC. With only the timing of the light pulse adjustable (intensity and duration are constant), the simulation result shows that a 12-hour phase shift is achieved within 3.5 days.

In this paper, we focus on the Kronauer model. We first present an analysis of its behavior and properties, and then propose a feedback control strategy for the light input to regulate the oscillation. By taking advantage of the higher phase shifting efficiency at lower circadian oscillation amplitude, we further modify the controller to a two-step design for faster circadian entrainment. Though the stability analysis is only heuristic at the present, we show through simulation that our proposed method can shorten 12-hour jet lag recovery from 7 days to 2.5 days with 10,000lux (equivalent to full day light but not direct sun) controlled light input.

II. Modeling of Circadian Rhythm

A variety of models have been proposed. Based on the study of Drosophila, a model based on Per and Tim protein dynamics was proposed in [3]. Under some simplifying assumptions, a 10-state affine model is obtained. This model can exhibit a rich set of behaviors from limit cycles to chaotic orbits. The model has been used in some lighting control research to regulate the phase of the oscillation [4], [5]. It is recognized that from the phase control perspective, the model may be reduced. In [9], a 3-state reduced order model was obtained based on proper orthogonal decomposition. More complex model involving the interaction of multiple proteins and gene expressions have been proposed [11], [12], but such complex model has not been used in control analysis.

An alternate approach was proposed by Kronauer for an empirical model relating light input to core body temperature output [7]. This model couples a first order lighting stage, L-process, followed by a second order van der Pol type of oscillator, called the P-process. The overall model is given by

$$\dot{n} = 60\left[\alpha(1-n) - \beta n\right], \; \alpha = \alpha_0 (I/I_0)^p \qquad (1)$$

$$\dot{z} = f_0(z) + f_1(z)u \qquad (2)$$

where

$$z = \begin{bmatrix} x & x_c \end{bmatrix}^T, \; u = G\alpha(1-n), \; f_0(z) = Az + Bg(B^T z)$$

$$A = \frac{\pi}{12}\begin{bmatrix} \mu/3 & 1 \\ -(24/(.99729\tau_x))^2 & 0 \end{bmatrix}, B^T = \begin{bmatrix} 1 & 0 \end{bmatrix}$$

$$g(x) = \frac{\pi}{12}\mu\left((4/3)x^3 - (256/105)x^7\right)$$

$$f_1(z) = \frac{\pi}{12}\begin{bmatrix} 1 & qx_c + kx \end{bmatrix}^T (1-0.4x)(1-0.4x_c)$$

and I is the intensity of the light input. The numerical parameter values given in [7], [13] are:

$$\mu = 0.13, \; \tau_x = 24.2, \; q = 0.33, \; k = 0.55$$

$$\alpha_0 = 0.05, \; \beta = 0.0075, \; I_0 = 9500, \; G = 33.75, \; p = 0.5.$$

Note that this model represents the average circadian rhythm behavior. For a particular organism, τ_x, which determines the period, would deviate from this averaged value.

The Kronauer model is attractive as the oscillator portion is second order and lends itself to more intuitive phase plane analysis. The model of course does not exhibit the same rich range of behaviors as the 10-state model, for example, chaos cannot occur. However, it does capture the essential feature of the circadian rhythm, and we shall use it as a baseline for the development of the phase control algorithms.

III. Analysis of Kronauer Model

For a fixed intensity light input I, $n \to \alpha/(\alpha+\beta)$ with rate $60(\alpha+\beta)$. In this paper, we shall assume that the L process is sufficiently fast (i.e., β is sufficiently large) so that we can just focus on the dynamics of the P process. As n converges to a steady state, the corresponding $u \to G\alpha\beta/(\alpha+\beta)$, which is a monotonically increasing function in α. Therefore, we will consider u as the effective non-negative input variable with maximum value $G\beta$ (corresponding to infinite light intensity).

When there is no light input, i.e., $u = 0$, there is only one equilibrium at the origin, $z = 0$. The linearized dynamics is governed by A which has two unstable complex eigenvalues. This means that the origin is an unstable center, and trajectories near the origin will spiral outward. When x is large, $g'(x)$ becomes negative. It may be shown that vector field points inward. By Poincaré-Bendixson Theorem, there exists a limit cycle around the origin. We can estimate the period and amplitude of the limit cycle by using the describing function method (also known as harmonic balance) [14], [15]. The system may be written as a feedback interconnection of $G(s) = B^T(sI-A)^{-1}B$ and an odd nonlinearity $g(\cdot)$. The Bode plot of $G(s)$ shows a peak at $\omega = 0.26$rad/hr which corresponds to a period of 24 hours. The sharp drop from the peak means that the effect of higher harmonics will be attenuated, thus, the describing function method has a good chance of making a reasonable prediction of the limit cycle. The describing function approach approximates the periodic solution $x(t)$ by $a\sin\omega t$. Since g is a static function, $g(x(t))$ is also periodic. Retaining only the fundamental harmonic of $x(t)$ and $g(x(t))$, we may replace g by its describing function [14], [15]:

$$\eta(a) = \frac{\pi}{12}\mu\left(a^2 - \frac{4}{3}a^6\right). \qquad (3)$$

We then solve for a such that $A + B\eta(a)B^T$ has purely imaginary eigenvalues, $j\omega$. For the Kronauer model, $a = 1$, and $T = 2\pi/\omega = 24.13$hr.

IV. Circadian Rhythm Control

The natural light-dark pattern involves the switching of I: a constant value of I during the light state and $I = 0$ in the dark state. The corresponding steady state u would switch between 0 and $u_{\max} = G\alpha\beta/(\alpha+\beta)$ where α is given by (1). Figure 1 shows the result of a 12-hour light-dark cycle which maintains the 24-hr period while introducing a phase shift of about 1 hour as compared with the free running oscillation. This synchronization of the oscillation with the external light-dark pattern is called entrainment.

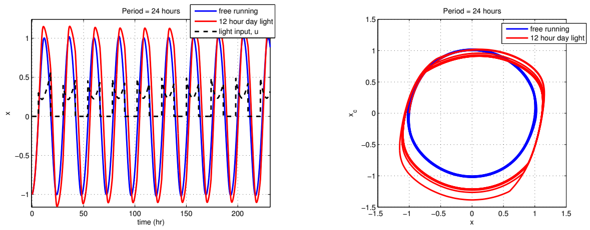

Fig. 1. Effect of 12-hour light-dark pattern

The light input may be manipulated, through artificial lighting, to achieve different objective, such as:

- *Entrainment Control*: In the presence of disturbances, e.g., spurious light, sleep disorder, or other stimuli as in the case of shift workers, that affect the circadian rhythm, light control may be used to ensure regular period and phase of the circadian oscillation.
- *Phase Control*: To achieve specified phase shift, which is useful to address jet lag recovery, light control may be useful to reduce the recovery (re-synchronization) time.

A. PRC based Phase Control

The phase response curve, or PRC, obtained experimentally or numerically, may be used to develop entrainment strategy. However, the PRC is highly dependent on the pulse amplitude and duration. In the case of a pulse train input or even a single pulse with sufficient strength (product of amplitude and duration), the numerically generated PRC is a slanted straight line (also as shown in [16]). At lower light pulse strength, PRC can take on different shapes.

If the light pulse strength is large enough, one may even be able to change the period of the circadian rhythm (e.g., for submariners) [17]. Figure 2 shows the effect of light pulses at 30hr intervals. When there is insufficient light input (6-hr light and 24-hr darkness), there is no entrainment. With sufficient light input (12-hr light and 18-hr darkness), the oscillation is entrained at 30-hr period.

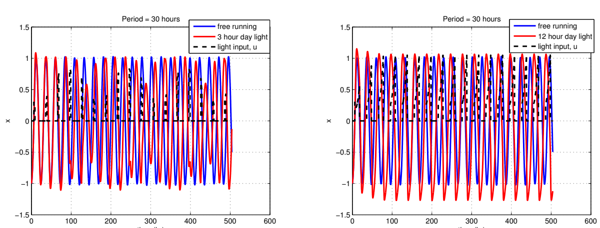

Fig. 2. Entrainment control using 30-hour light/dark pattern. At 3-hour light pulse (left), circadian rhythm entrainment is not achieved. At 12-hour light pulse (right), circadian rhythm is entrained.

To change the phase, we will focus on using light inputs to change the phase of the free running oscillation. The approach is equally applicable to phase change in the presence of a given light-dark pattern. The PRC approach has been proposed in [4], [5], except the PRC is generated with a single light pulse with specified amplitude and duration applied at different time. The resulting *steady state* phase shift, ϕ, is then plotted as a function of the time of the applied light pulse, T: $\phi = h(T)$. If the desired phase shift is within the range of h, then T may be directly selected. Otherwise, a simple iterative approach may be applied to sequentially reduce the phase error to zero. A multi-parameter PRC may also be generated by varying the magnitude and duration of the light pulse. The resulting phase shift is then $\phi = h_1(T, A, T_d)$, and a constrained minimization may be performed to select (T, A, T_d) to sequentially and optimally reduce the phase error to zero. This type of approach has been popular and used in various forms by many researchers [3].

B. Phase Plane Analysis

We now look more closely how light input would affect the phase by considering the effect of a light pulse on the phase of the free running oscillation through a phase plane analysis. As shown in Figure 3, the pulse input kicks the state off the limit cycle to z_a, resulting in an immediate phase shift of $\Delta\phi_a$. The resulting orbit then converges back to the limit cycle, with an additional phase shift of $\Delta\phi_b$.

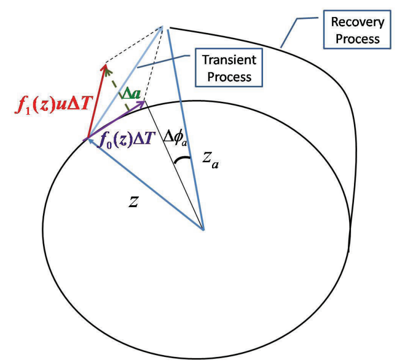

Fig. 3. Effect of light pulse on phase

Transient Process: The phase shift, $\Delta\phi_a$, due to a light pulse u of magnitude J and duration ΔT, may be estimated from:

$$cos(\Delta\phi_a) = \frac{r_a^2 + r_b^2 - r_c^2}{2 r_a r_b} \tag{4}$$

where

$$\begin{aligned} r_a &= \|z + (f_0(z) + f_1(z)J)\Delta T\| \\ r_b &= \|z + f_0(z)\Delta T\| \\ r_c &= \|f_1(z)\| J\Delta T. \end{aligned}$$

The corresponding time shift is $\Delta T_a = (24/2\pi)\Delta\phi_a$.

Recovery Process: The phase shift due to the convergence back to the limit cycle may be computed numerically by running simulations using initial conditions all round the limit cycle. The resulting phase shift map as a function of the deviation from the limit cycle, Δa, and the angle on the limit cycle, ϕ, is shown in Figure 4(a). It may be observed that the map is approximately separable in the sense that

$$\Delta\phi_b = b(\phi)c(\Delta a) \tag{5}$$

where b and c are two different functions depending on the sign of Δa (inside or outside of the limit cycle). The comparison of the approximation versus the simulated shows very small difference as indicated in Figure 4(b).

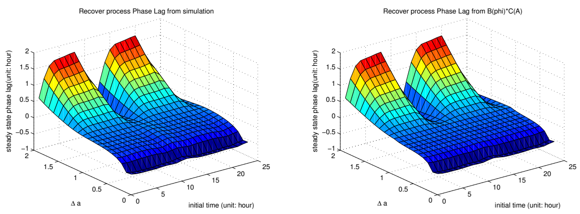

Fig. 4. (a) Phase lag from recovery process based on simulation as a function of initial Δa and time. (b) Phase lag map using separability approximation

The describing function method is also useful in characterizing effect of the light input on the limit cycle. The limit cycle given approximated by the describing function is given by

$$\dot{z}^{(\ell)} = (A + BB^T\eta(1))z^{(\ell)} = \begin{bmatrix} 0 & \omega_1 \\ -\omega_2 & 0 \end{bmatrix} z^{(\ell)} \qquad (6)$$

where $\sqrt{\omega_1\omega_2} = \omega$. The solution is

$$z^{(\ell)} = \begin{bmatrix} -\omega_1\cos(\omega t + \psi) & \omega\sin(\omega t + \psi) \end{bmatrix} \qquad (7)$$

where ψ given by the initial condition. Linearize about this approximate period orbit, and after removing the higher order harmonics and higher order terms, the deviation from the periodic orbit, $\delta z := z - z^{(\ell)}$, is given approximately by

$$\delta\dot{z} = \bar{A}(t)\delta z + \bar{B}(t)u \qquad (8)$$

$$\bar{A}(t) = A + BB^T(\eta(1) + g'(z^{(\ell)}(t))),\ \bar{B}(t) = f_1(z^{(\ell)}(t)). \qquad (9)$$

The approximation may be improved if $z^{(\ell)}(t)$ in $A(t)$ and $B(t)$ is replaced by $z^*(t)$, the true periodic solution.

The solution of (8) is of the following general form

$$\delta z(t) = \Sigma(t,t_0)\delta z(t_0) + \int_{t_0}^{t} \Sigma(t,\tau)\bar{B}(\tau)u(\tau)\,d\tau \qquad (10)$$

where $\Sigma(t,t_0)$ is the state transition matrix corresponding to $A(t)$. For an initial deviation Δa from the orbit at angle ϕ, the initial state is

$$\delta z(t_0) = \begin{bmatrix} -\cos(\phi) & \sin(\phi) \end{bmatrix}^T \Delta a. \qquad (11)$$

This shows the ensuing orbit and hence the phase is linear in Δa, explaining the separability property in (5). The time varying linear equation (8) may also facilitate the computation of the phase response curve by using the discrete time approximation of the differential equation.

In general, by examining the vector field, we can gain some intuition of the effect of light input. As shown in Figure 5, define e_t as the clockwise vector perpendicular to z and e_n as the outward pointing vector perpendicular to $f_0(z)$. We have the following characterizations:

Phase Change: $f_1(z)^T f_0(z)$
Amplitude Change: $f_1(z)^T e_n$
Efficiency: $\left|f_1(z)^T e_t\right| / \|z\|$.

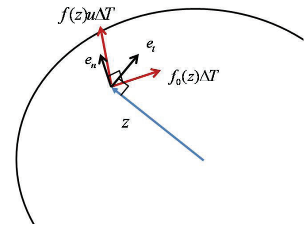

Fig. 5. Definition of phase plane vectors e_n and e_t.

The calculation of efficiency is based on the approximation that magnitude of the angular velocity, $\dot{\phi}$, is given by linear tangential velocity divided by the radius.

By using these three characterizations, the effect of light pulses in different portion of the state space is shown in Figure 6. When the amplitude is small, i.e., closer to the origin, the phase change efficiency is high. Therefore, a judicious combination of the light pulses in different regimes will achieve faster phase change. For example, one may want to suppress amplitude by using light pulses in the amplitude suppression region, change the phase in the high efficiency region, and then regain the amplitude.

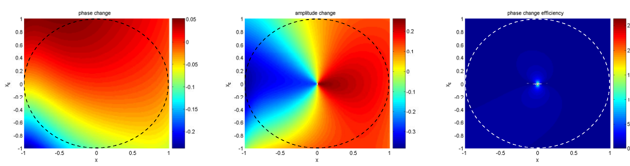

Fig. 6. Effect of a light pulse on amplitude, phase, and efficiency in different portions of the phase plane

C. Phase Control with Reference Pacemaker

An alternate approach is to use lighting control to drive the circadian rhythm towards a reference oscillator (pacemaker). Let z_r denote the state of the reference oscillator with the desired phase. Since it is simply the free running oscillator with a different initial condition, it satisfies the unforced dynamics:

$$\dot{z}_r = f_0(z_r),\ z_r(0) = z_{ro}. \qquad (12)$$

Since the goal is to drive z towards z_r by using u, we define a standard error function (a Lyapunov function candidate):

$$V = \frac{1}{2}\|z - z_r\|^2. \qquad (13)$$

The derivative of V along the trajectory is

$$\begin{aligned} \dot{V} &= (z-z_r)^T(f_0(z) - f_0(z_r)) + (z-z_r)^T f_1(z)u \\ &= (z-z_r)^T A(z-z_r) + (z-z_r)^T B(g(B^T z) - g(B^T z_r)) \\ &\quad + (z-z_r)^T f_1(z)u. \end{aligned}$$

To make $\dot{V}$ more negative, we can choose u to be

$$u = -u_0\,\mathrm{sgn}(\min\{f_1^T(z)(z-z_r), 0\}) \qquad (14)$$

which states that if the light input can reduce the tracking error, then we turn on the light with intensity u_0. Otherwise, the light is kept off. Then we have

$$\dot{V} = \underbrace{(z-z_r)^T A(z-z_r)}_{\dot{V}_1} + \underbrace{(z-z_r)^T B(g(B^T z) - g(B^T z_r))}_{\dot{V}_2} + \underbrace{\left(-u_0 \left|\min\{f_1^T(z)(z-z_r), 0\}\right|\right)}_{\dot{V}_3}.$$

At the present, we do not have a proof for the stability of the closed loop system, and only have simulation results showing convergence for various test scenarios. The stable behavior that we have observed in simulation may be justified by the following heuristic argument. Recall that A is unstable (one of the eigenvalues of $A+A^T$ is negative, and the other is close to zero), so $\dot{V}_1$ is almost always positive. The function g is incrementally negative when its argument is larger than 0.82. Therefore, if the error $B^T(z-z_r) = x - x_r$ is large, the second term becomes negative. The third term is negative when the vectors $f_1(z)$ and $z-z_r$ form an obtuse angle. Figure 7 shows the control of x with 6-hour initial phase shift. The phase difference is almost completely removed in 20 hours with a single light pulse. Plotting the three terms of $\dot{V}$, as shown in Figure 8, illustrates the closed-loop behavior. When the initial error is large, the $(x-x_r)(g(x)-g(x_r))$ term is large and negative, driving $z-z_r$ towards 0. When $\|z-z_r\|$ is small, the negative term due to the feedback action dominates, driving $z-z_r$ further towards zero. During the period where lighting is off, $\dot{V}$ does become positive, and the tracking error increases. However, since the free running periodic orbit is stable, the increase is bounded. As the lighting control portion continues to reduce $\|z-z_r\|$, the overall tracking error converges to zero. The plot of V in Figure 9 shows that the convergence is not monotonic. For the low light case, the convergence is slower but is still towards zero.

Note that in the high lighting case, the amplitude is first reduced. Once the phase difference is reduced, the amplitude then increases back to the full magnitude.

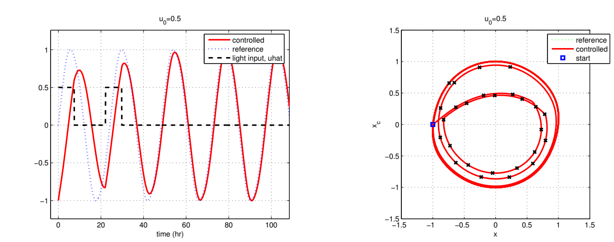

Fig. 7. Phase compensation with trajectory error feedback, $u_m = 0.5$

Figure 10 considers another example. Using the proposed control law, a 12-hour jet lag recovery is shortened to 3.5 days. Figure 11 plots the entrainment time versus the initial phase difference. It is surprising to note that the 12-hour entrainment time is 1 day shorter than the 7-hour entrainment time! In fact, the 10-hour entrainment cost shows a local minimum. This result appears to be counter-intuitive as one may expect the entrainment time to be monotonically increasing with respect to the initial phase difference. The explanation of this phenomenon may be seen from the trajectory in the phase plane. In Figure 12, the trajectory of the 7-hour case winds around the origin while the trajectory of the 10-hour case passes almost through the center. From the efficiency analysis and the phase response map shown in Figure 6, we observe that near the origin of phase plane, both phase advancing efficiency and phase delaying efficiency are much larger. Hence, the 10-hour trajectory can catch up with the reference trajectory more quickly.

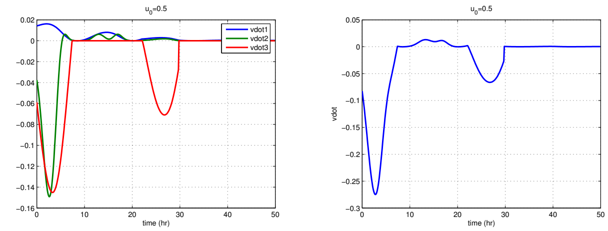

Fig. 8. Comparison of the contribution of the three terms in $\dot{V}$ and the overall $\dot{V}$, $u_m = 0.5$

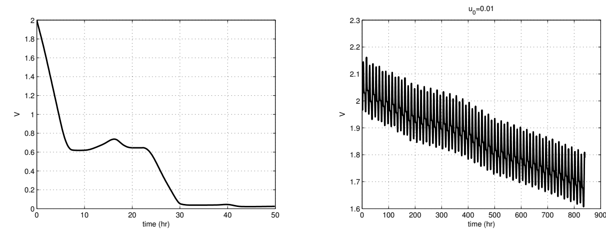

Fig. 9. Comparison of V for $u_m = 0.5$ and $u_m = 0.01$

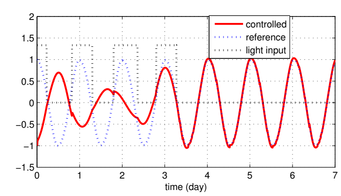

Fig. 10. 12-hour jet lag recovery with phase plane tracking. Red line is the 10,000lux light stimulus

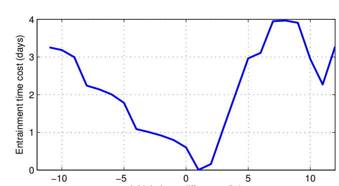

Fig. 11. entrainment time cost versus initial phase difference

D. A Two-Step Approach to Phase Control

The observation of reducing the amplitude to gain efficiency motivates a modified two-step strategy: first drive the oscillator into the center and then let it catch up with the reference trajectory. To drive the oscillator to the center, we apply light when the oscillator is in the suppressed-amplitude region. However, from simulation and experiments, driving a oscillator into the center region takes about 3 days [18], which adds to the entrainment time . Hence, we first drive the trajectory toward the center until it comes within a predefined

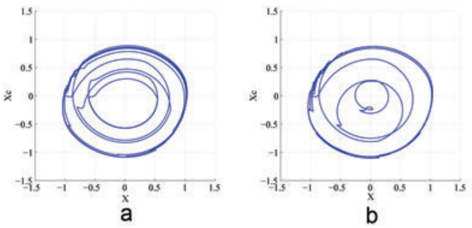

Fig. 12. The phase plane trajectories for the (a) 7-hour and (b) 10-hour phase shift. The 10-hour phase shift trajectory passes near the origin where the phase shifting efficiency is high.

distance R from the origin. The control law (14) is then applied to match up the phase. The optimal distance R is may be be found for each initial phase difference using nonlinear optimization. It can then be encoded in a look-up table. Figure 13 shows the entrainment time versus initial phase difference with this modified method, demonstrating a significant reduction of the entrainment time.

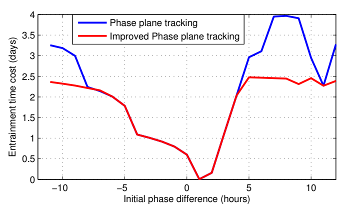

Fig. 13. With improved phase plane tracking method, the entrainment time cost is shortened by up to 1.5 days.

V. Conclusion and Future Work

This paper analyzed an empirical circadian rhythm model developed by Kronauer. We showed that in the free running case (no light), the describing function method gives excellent prediction of the oscillation. The linearization about this approximate periodic solution has the potential of being used for forced oscillation analysis as well. By using the nonlinear empirical model, we show two approaches to shift the phase of the oscillation. The first approach is similar to the PRC method, but with a more detailed analysis of the impact of a pulse at different portions of the orbit. The second approach is based on a reference oscillation, and the feedback of the state error. A Lyapunov-like analysis is used to heuristically argue that the system is stable. Simulation shows that the approach has excellent transient performance, reducing jet lag recovery from 7 days to 2.5 days.

We are currently working with drosophila experiments to compare the biochemical model [3] and the empirical oscillator model [8] by using the activity measurements as an indirect indicator of the circadian rhythm. The experimentally identified model will be used for the estimation of circadian rhythm based on measured activity. We are also investigating the spectral response of the circadian system [19]and the use of spectral-tunable lighting to balance between circadian system control and lighting needed for visual perception.

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