52nd IEEE Conference on Decision and Control
December 10-13, 2013. Florence, Italy

Optimal and Feedback Control for Light-Based Circadian Entrainment

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***Abstract*— With the emergence of solid state lighting, light-based circadian rhythm control is becoming increasingly feasible. In this paper, we use a popular empirical model proposed by Richard Kronauer to study the entrainment with the light intensity as the control input. Given a reference circadian oscillation, we formulate the entrainment problem as a tracking problem: adjusting the light intensity to drive the circadian rhythm to the reference trajectory. We compare four cases: periodic light entrainment, active open loop optimal entrainment (using both the Kronauer model and a first-order approximation of only the phase response), active feedback entrainment, and subtractive feedback entrainment. Results from this study provide new insight and guideline to light intensity control for circadian rhythm regulation.**

I. Introduction

The disruption of human circadian rhythm has serious potential detrimental consequences ranging from increased sleepiness and decreased attention span during the day, lower productivity, gastrointestinal disorders, to long-term health problems such as increased risk for cancer, diabetes, obesity, and cardiovascular disorders [1]–[10]. The circadian disruption may be caused by, for example, irregular sleep patterns of soldiers in the battlefield [11], artificial deprivation of light of submariners or mine workers [12], [13], frequently shifted sleep-wake cycles of night nurses [2], and shifted light-dark cycles for travelers across multiple time zones [14].

Light is a strong circadian rhythm synchronizer. Light-based circadian entrainment has long been proposed. A commonly used tool is 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.

An open loop circadian entrainment method has been proposed based on the PRC constructed from the Kronauer model to design a light-dark pattern for jet lag treatment [15]. A 10-state circadian oscillation model of Drosophila was used to construct the PRC and closed loop model predictive control based on the phase measurement [16]. By adjusting only the timing of the light pulse (intensity and duration are constant), the simulation result shows that a 12-hour phase shift was achieved within 3.5 days. The shape and amplitude of PRC is highly dependent on the pulse amplitude and duration [17] and the transient response is ignored.

Phase control using first order model has been proposed in [18] [19]. In [18], the control strategy is a discrete form of proportional control, which can reduce the phase tracking error using small stimuli. In [19], the stimuli are limited to short pulses with fixed intensity and duration. The controller determines the timing of the pulses, and only one pulse is applied every cycle. Necessary conditions for optimality are not considered in [18] [19].

We focus on light control strategies based on a popular empirical model developed by Richard Kronauer [20]–[23] which describes the relationship between light stimulus and the oscillation of human core body temperature, an acceptable phase marker of the circadian system. The entrainment problem is formulated as a trajectory tracking problem where the reference trajectory is given by the desired circadian oscillation. Based on active lighting control (adding or blocking circadian light, wavelengths that stimulate the human circadian system), we have proposed feedback circadian control strategy [24] and optimal open loop control strategy [25] based on this model.

In this paper, we further investigate the entrainment strategies proposed in [24] and [25]. The local stability of periodic light input is demonstrated using Poincarè map. The minimum time control strategy is extended to first order approximation inspired by the phase model in [26], which only requires the knowledge of the phase response curve. The minimum time control computed using this first order model is actually very close to the optimal controller based on the Kronauer model, but is much quicker to compute. The local stability of reference-tracking feedback controller is demonstrated using reachable set of hybrid system. The entrainment simulation results are discussed and the insight has potential application to light intensity control for circadian rhythm regulation.

II. Problem Formulation

A. Model

Models of varying complexity have been proposed for circadian rhythm. We will consider the Kronauer model [21] which is an empirical model consisting of a second order nonlinear oscillator (modified Van der Pol oscillator) with a 24.2-hour period, called the *P*-process, driven by a photoreceptor model, called the *L*-process. *P*-process has a stable limit cycle, and the oscillator output is related to the oscillation of core body temperature (CBT) variation which is used as a phase marker of the circadian system. The simplified Kronauer model has the following form

$$\dot{z} = f_0(z) + f_1(z)u, \quad z = \begin{bmatrix} x_1 & x_2 \end{bmatrix}^T, \qquad (1)$$

where u is the light induced circadian drive, and x_1 represents the oscillation of CBT. The details of the model are described in [25]. We limit the maximum light intensity at $I_{\max} = 9500$lux, and according to [25] the corresponding maximum drive is $u_{\max} = 0.2392$. Light intensity cannot be negative, so $u \geq 0$. The radius of the limit cycle in the phase plane, (x_1, x_2), is approximately 1 (Figure 1). The oscillator rotates in the clockwise direction, with the 45° direction ($x_1 = x_2$) roughly corresponding to the mid-day (12pm). f_1 is the input drive which can shift the phase and change the amplitude of the oscillation.

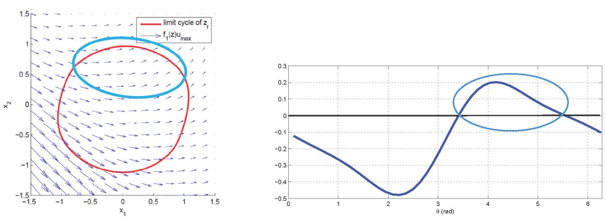

Fig. 1. Left: The input drive function, $f_1(z)$, shown as a vector field, superimposed on the limit cycle. The circled portion at the top of the limit cycle indicates where light input will speed up the oscillation (shorten the period). For the rest of the limit cycle, light input will slow down the oscillation (lengthen the period). Right: The phase response curve, $f(\theta)$ in (6), identified using the Kronauer model. The circled portion where $f(\theta) > 0$ corresponds to the circled portion in left panel where light input speeds up the oscillation.

B. Problem Statement

A motivating example of using light to quickly entrain the circadian cycle is a traveler traveling through multiple time zones. At the arrival of the destination, the circadian rhythm will be different from the local population who have already been entrained to the local time. Our goal is to find the light pattern which can help the traveler's circadian rhythm synchronize with to the local circadian rhythm as fast as possible. In terms of practical implementation, this would require controllable light input as well as blockage of natural light (only need to block the blue spectrum, to which the circadian system is most sensitive). Denote the traveler's circadian rhythm z as in (1) and local circadian rhythm z_r as the reference, which is governed by

$$\dot{z}_r = f_0(z_r) + f_1(z_r)u_r(t) \tag{2}$$

where u_r is the local light cycle, modeled as a 12-hour light (9500lux) and 12-hour dark pattern:

$$u_r(t) = \frac{u_{\max}}{2}\left(1 + \mathrm{sgn}(\sin(\frac{\pi}{12}(t + t_0)))\right). \tag{3}$$

The time variable t refers to the traveler's time at the origin. The time shift t_0 is the time shift between the light pattern of the destination and origin. Entrainment is considered to have been achieved when $z = z_r$ (In numerical simulation, this condition is relaxed to $\|z - z_r\| < 0.1$, which is approximately 10% of the limit cycle radius). We are interested in fast entrainment, so the optimization index is defined as the total entrainment time, t_f:

$$J = t_f = \int_0^{t_f} 1\, dt. \tag{4}$$

III. Circadian Rhythm Entrainment

A. Periodic Light Entrainment

Without the addition of artificial light or the blockage of daylight, the traveler will receive the natural daylight pattern of the local time zone. The dynamics of the circadian rhythm is given by (1) with local light input u_r in (3):

$$\dot{z} = f_0(z) + f_1(z)u_r(t) \tag{5}$$

To show the stability of the limit cycle of this periodic system, we use the Poincaré map which relates the state variables at each light-onset. Based on the numerical simulation of (5), we observe that $z_s = [-0.7858, 0.6338]^T$ is a fixed point of the Poincaré map. The eigenvalues of the Poincaré map linearized about z_s are $[0.6461, 0.0131]$, which are within the unit circle. This means that z_s is a locally stable fixed point, and the limit cycle is a stable periodic orbit of (5). We shall use this local lighting entrainment case as the baseline to compare with cases where we manipulate the light intensity u. We can extend this analysis to other lighting patterns (for open loop entrainment using artificial lighting) in terms of period (maybe other than 24 hours, e.g., for submariners, miners, space travelers), duty cycle (percentage of the period where light input is applied), and light intensity. If the Poincaré map converges, we check the eigenvalues of the linearized return map about the limit point to ascertain the stability of the entrainment. If the Poincaré map does not converge, then the entrainment is unstable.

Figure 2 shows the entrainment stability for different duty cycles, light intensity and periods. As shown in Figure 1, light tends to delay oscillation. Hence, for longer (than 24-hour) periods, higher duty cycle is needed. Conversely, shorter periods requires lower duty cycle (shown in Figure 2).

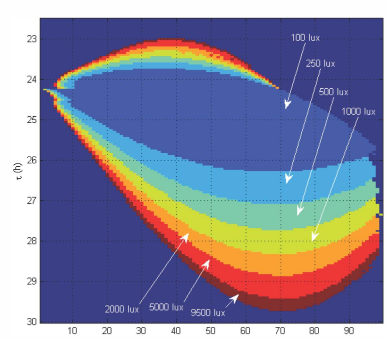

Fig. 2. The entrainment stability for different duty cycles (horizontal axis) and periods (vertical axis) with different light intensities.

B. Active open loop Optimal Entrainment

Active open loop optimal entrainment aims to establish a lower bound on how fast light control can shift the circadian cycle by a specified phase. The goal is to find $u(t)$, $0 \le u \le u_{\max}$ to minimize the cost function (4). In [25], we showed faster entrainment comparing with baseline by applying optimal entrainment to the Kronauer model.

In this paper, we extend the optimal entrainment to the first order approximation of Kronauer model using Pontryagin's Minimum Principle. This approach is attractive as it is much less computationally demanding, and consequently has the potential to serve as the basis for model predictive control.

The phase response (along the limit cycle) may be approximated by a first order model [26]

$$\dot{\theta} = \omega_0 + f(\theta)u \tag{6}$$

where $2\pi/\omega_0$ is the free running period and $f(\theta)$ is the phase response curve (Figure 1). This approximation is close to the actual phase if the actual trajectory is close to the limit cycle.

We formulate the optimal control problem as following:

$$\dot{\Theta} = \Omega + F(\Theta)u \tag{7}$$

where

$$\Theta = [\theta, \theta_r]^T,\ \Omega = [\omega_0, \omega_r]^T,\ F(\Theta) = [f(\theta), 0]^T$$

θ is the circadian phase of the traveler. θ_r is the circadian phase of the local population, which is already entrained, therefore, $\omega_r = \frac{2\pi}{24}$. The boundary conditions are:

$$\Theta(0) = [\theta_0, \theta_{r0}]^T, \tag{8}$$

$$\underbrace{\sin\left(\frac{[1,-1]\Theta(t_f)}{2}\right)}_{\triangleq m(\Theta(t_f))} = 0. \tag{9}$$

The cost function is the same as (4). The Hamiltonian of the system is

$$H = 1 + p^T(\Omega + F(\Theta)u) \tag{10}$$

where $p = [p_1, p_2]^T$ is the co-state and satisfies

$$\dot{p} = -\frac{\partial H}{\partial \Theta} = \underbrace{-\frac{\partial (F(\Theta)u)^T}{\partial \Theta}}_{\triangleq f_2(\Theta,u)} p. \tag{11}$$

The optimal control u^* minimizes H and is given by the following "bang-off control" (assuming no singular arcs):

$$u^*(\Theta, p) = \frac{u_{max}}{2}(1 - \mathrm{sgn}(p^T F(\Theta))) \tag{12}$$

Substituting the optimal control into the state and co-state equations, we obtain the following two-point boundary value problem (TPBVP):

$$\begin{aligned} \dot{\Theta} &= \Omega + F(\Theta)u^*(\Theta, p), \\ \dot{p} &= f_2(\Theta, u^*(\Theta, p))p. \end{aligned} \tag{13}$$

Since t_f is free, the transversality conditions are

$$1 + p(t_f)^T(\Omega + F(\Theta(t_f))u^*(t_f)) = 0, \tag{14}$$

$$d\frac{\partial m(\Theta(t_f))}{\partial \Theta} + p(t_f) = 0. \tag{15}$$

where d is a variable to be determined by (13) and m is defined in (9). To solve this 6th-order TPBVP efficiently, we make the following observations:

- According to (9) and (15), $p_2(t_f) = -p_1(t_f)$.
- In (12), u^* is determined by θ and p_1.
- For the costate, $\dot{p}_2 = 0$ and p_2 does not influence the trajectory of $\Theta(t)$.

Furthermore, we utilize Proposition 1 in [25]:

Proposition 1: If $(\Theta(t), p(t))$ is a solution of (13), so is $(\Theta(t), \alpha p(t))$ for any positive constant α.

This Proposition states that if the initial co-state p_1 is scaled by a positive constant α, the trajectory of Θ will not change, and the co-state trajectory $p_1(t)$ will also be scaled by α. Suppose $(p_1(0), t_f)$ is found to satisfy the terminal state condition (9). If, furthermore, $[p_1(t_f), -p_1(t_f)](\Omega + F(\Theta(tf))u^*(tf)) \neq 0$, then p_1 may be scaled by α,

$$\alpha = -\left([p_1(t_f), -p_1(t_f)](\Omega + F(\Theta(tf))u^*(tf))\right)^{-1}.$$

After scaling of p_1, set

$$p_2(0) = -p_1(t_f),\ d = -\frac{p_1(t_f)}{\frac{\partial m}{\partial \theta}}$$

and the transversality conditions are satisfied. Hence, the solution of the TPBVP reduces to just finding $(p_1(0), t_f)$, with $|p_1(0)|$ arbitrarily chosen to be 1, to satisfy (9). $|p_1(0)| = 0$ should be avoided because it can generate singular arch. This leads to the following algorithm to solve the minimum time control problem:

Algorithm 1: Arbitrarily choose $p_2(0) = 1$. For $p_1(0) \in \{-1, 1\}$, simulate (13) and denote the trajectory as $\Theta_{p_1}(t)$. Find the minimum convergence time:

$$t_f = \min_{p_1(0)\in\{-1,1\}} \left\{\min\left(\arg\min_t |m(\Theta_{p_1}(t))| < \varepsilon, T_{\max}\right)\right\} \tag{16}$$

where ε is the convergence criterion and $T_{\max}$ is the upperbound for t_f (which could be chosen as the baseline entrainment time).

Remark 1: We can observe that $\dot{p}_1 = -\frac{\partial(f(\theta)u)}{\partial \theta} p_1$ and the sign of $p_1(t)$ is the same as $p_1(0)$. According to (12), if $p_1(0)$ is positive, $u^* = u_{max}$ when $f(\theta) < 0$ and the phase θ is delayed whenever possible until (9) is achieved; if $p_1(0)$ is negative, phase θ is advanced whenever possible until (9) is achieved. The algorithm tries both cases, and select the one which takes less time.

As a numerical illustration, consider the active entrainment starting at 3pm origin time on the limit cycle. The corresponding initial condition is $\theta(0) = 0$. The convergence criterion is $\varepsilon = 0.05$. The results of optimal phase shifting for $(\theta(0) - \theta_r(0)) \in \{1..23\} \times \frac{\pi}{24}$ are plotted in Figure 4. The optimal control of the first order phase model has similar time cost comparing with the optimal control of the Kronauer model.

C. Active Feedback Entrainment

Measuring circadian rhythm experimentally as characterized by SCN activities is challenging [27]–[29]. The most trusted method for estimating circadian rhythm is based on the onset of melatonin secretion under dim light conditions (dim light melatonin onset, or DLMO). Melatonin (or other hormones such as cortisol or alpha amyloid) may be measured through lab test in saliva or plasma, but such measurements are inconvenient, time consuming, and expensive. Other indirect biomarkers have also been used, the most reliable one being the core body temperature (which is the basis for the Kronauer model [20]), but it is also inconvenient to deploy for extended periods. Other more highly "masked" markers such as activity, heart rate, and body surface temperature also show rhythmic patterns, but are affected by many other environmental factors. Wearable sensors with integrated light and activity sensors such as daysimeter [5], model-based (with the Kronauer model) sensor fusion approach [30] and model-free approach [31] [32] have been developed to provide continuous estimate of the circadian rhythm. Together with personalized lighting product (e.g., [33], [34]), feedback circadian entrainment may be feasible in the not-too-distant future.

Compared with open loop optimal control, feedback control rejects the environmental disturbance, and provides tolerance for modeling error. We pose the feedback entrainment problem as a reference trajectory tracking problem using light intensity as input and the full circadian state z for feedback. In [24], we proposed an active feedback control strategy:

$$u = -u_{\max} \min\{\mathrm{sgn}(f_1^T(z)(z-z_r)), 0\}). \tag{17}$$

The stability of the feedback tracking strategy is difficult to prove analytically. Instead, we use the reachable set analysis from hybrid system analysis [35] to demonstrate closed loop stability. The idea is similar to the return map. Instead of propagating a single initial condition, we propagate a set of initial conditions around the limit cycle and show that this set converges to a fixed point. We choose the initial set to be a square in the phase plane

$$P = \{z = [x_1, x_2]^T : \; -1.2 \le x_1 \le 1.2, \; -1.2 \le x_2 \le 1.2\} \tag{18}$$

which encloses the limit cycle. This set is divided up into grids of different sizes. The size of each grid is chosen so that an upperbound of the reachable set in some future time t may be found from a single simulation trajectory from a point in the grid. A MATLAB toolbox called *Breach* has been developed in [35] to automate the process. Fig. 3 shows the progress of the reachable set. After four steps, the reachable set is confined to the 0.1-neighborhood of z_r, demonstrating the worst case convergence in 192 hours.

D. Subtractive Feedback Entrainment

We can modify the feedback algorithm to allow only blockage of the destination ambient light. This removes the requirement of controllable artificial lighting, replacing with just circadian-light blocking sunglasses at select times. We call this the subtractive feedback entrainment. The circadian light blockage may be achieved by selectively removing the short wavelength component of daylight using optical filters, such as goggles and shades, while the long wavelength component light can still be used to enable vision. In this case, the light input is modulated by daylight, so (17) becomes

$$u_{sub} = -u_r \min\{\mathrm{sgn}(f_1^T(z)(z-z_r)), 0\}. \tag{19}$$

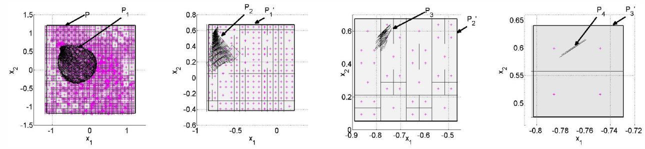

Fig. 3. The reachable set analysis result using 'Breach'. The reachable set after 48h-propagation is calculated in each step. For $t = 24k,\; k \in \{0,1...\}$, $z_r = [-0.7858,\; 0.6338]^T$. At $t = 0$, the set of initial condition of z is defined in (18). *Breach* is capable of partitioning the rectangular set P and computing P_1, the reachable set of P at $t = 48h$. P_1 is relaxed to a rectangular set P_1', and the reachable set of P_1' at $t = 96h$ is P_2. P_2 is relaxed to a rectangular set P_2', and the reachable set of P_2' at $t = 126h$ is P_3. P_3 is further relaxed to a rectangular set P_3', and the reachable set of P_3' at $t = 192h$ is contained in the 0.1-neighborhood of z_r.

IV. Entrainment Result Comparison

In this section, we compare the following control strategies for the entrainment of the circadian rhythm to the reference trajectory with a specified phase shift:

1) *Baseline*: Entrainment by the periodic daylight of the destination as described in Section III-A.
2) *Active open loop Optimal Entrainment*: The minimum time open loop control using the Kronauer model and first order phase model as described in [25] and Section III-B.
3) *Active Feedback Entrainment*: The active light control based on the circadian state feedback as described in Section III-C.
4) *Subtractive Feedback Entrainment*: The subtractive light control (active blockage of the destination daylight) based on the circadian state feedback, as described in Section III-D.

The entrainment times for different target phase shifts are shown in Figure 4. We make the following observations:

- Active entrainment is effective in phase delay. This is built into the input vector field, f_1 in (1), as shown earlier in Fig. 1 superimposed onto the limit cycle. Since the light input is non-negative, the effect of light is mostly to add delay to the oscillation, except for about the upper quarter of the limit cycle. This is not entirely surprising, since light (in the blue spectrum) tends to suppress the secretion of melatonin which would delay the circadian oscillation.
- Active entrainment is ineffective in phase advance. This is just the corollary of the observation above, again due to the direction of the input vector field f_1. In this case, a good strategy is to block the ambient light at appropriate times, which would reduce the inherent delay due to the ambient light, leading to phase advance. For small phase advance (up to 4 hours), the optimal entrainment

time is almost identical to the subtractive feedback case, as shown in Figure 4. The control strategies for both cases, optimal and subtractive, are almost identical as shown in Figure 6. Both strategies consist of blocking the light input several hours before the onset of darkness at destination.

- Active entrainment based on minimum time control or feedback control are both effective in achieving phase delay entrainment, significantly improving over the baseline. For example, for the 12-hour phase shift, the entrainment time is reduced from about 8 days using the destination daylight to $2\frac{1}{2}$ days using the optimal control. For the worst case 16-hour phase delay (or 8-hour phase advance), the improvement is the largest: 10 days vs. 3 days. For small phase advance, the optimal control just requires strategic blocking of the natural light.
- The time costs for active open loop optimal entrainment based on the first order phase model and the Kronauer model are very similar. According to [24] , in the neighborhood of the limit cycle, the isochrone curves are almost orthogonal to the free running limit cycle. Small variation of the amplitude will introduce very little phase shift after convergence. For small u_{max} which cannot significantly deviate the trajectory from the limit cycle, the first order phase model is a good approximate of the Kronauer model. In the numerical simulation, for 6h, 12h and 18h phase delaying, the optimal lighting input generated using the first order phase model is fed into the Kronauer model, and the results are compared with the optimal lighting input generated directly from the Kronauer model [25] (Figure 5). The light patterns and the trajectories are similar for 6h and 12h delaying cases. For 18h delaying, the lighting pattern generated using the first order phase model is different from the pattern using the Kronauer model, and the discrepancy in the trajectories can be observed, especially in terms of amplitude. The first order phase model does not capture the dynamics of the amplitude, and the terminal conditions is only phase-matching instead of full-state-matching. One observation is for 18h delaying case, the trajectory of the traveler's circadian rhythm is still catching up the reference trajectory using the optimal lighting input generated using the first order phase model.
- In the cases of delaying 21h, 22h and 23h, $p_1(0)$ is negative for the optimal solution in the first order phase model. According to the *Remark* 1 in III-B, for these three cases advancing the phase to catch up the reference takes less time; for the cases of delaying $1-20$ hours, keeping on delaying the phase is a better strategy. This asymmetry can again be explained by Figure 1: on the limit cycle, the vector field of $f_1(z)$ is easier to delay the phase than to advance the phase. As a result, feedback control using the first order phase model, e.g. based on Lyapunov like function $m^2(\Theta)$, may not have the optimal results. For example, to achieve 13h delay, feedback control will keep on advancing the phase to achieve the terminal condition, while the optimal strategy is delaying the phase. Model predictive control, on the other hand, can determine the optimal strategy using Algorithm 1 at each time step.
- Subtractive feedback entrainment is optimal for small phase advances (up to 4-6 hours) but becomes ineffective for phase delays. This is due to the fact that light blockage only has a small window of opportunity in the circadian cycle to add delay: when there is daylight and the input vector field advances the phase (around late morning in traveler's clock).

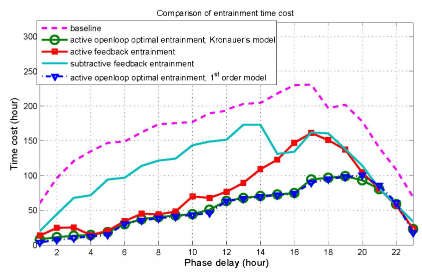

Fig. 4. Comparison of the time cost as a function of the specified phase shift under 12h/12h-light/dark periodic input (baseline), active open loop optimal entrainment (Kronauer model), active feedback entrainment, subtractive feedback entrainment and active open loop optimal entrainment (first order model).

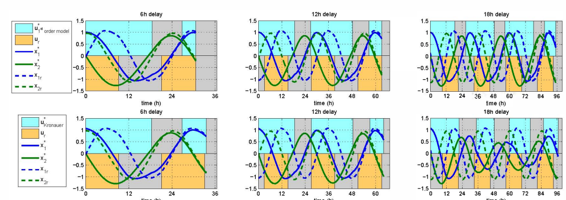

Fig. 5. Comparison of the optimal lighting patterns generated using the first order phase model (first row) and Kronauer model (second row) and resulting trajectories for 6h, 12h and 18h phase delay.

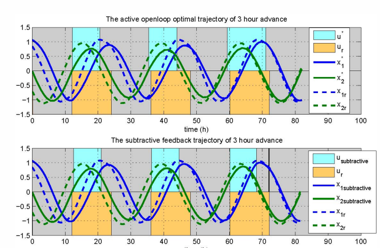

Fig. 6. Light input for optimal active light control (top) and subtractive feedback control (bottom) for 3 hour phase advance. The control input and entrainment time are nearly identical. Only blockage is needed with no active light input.

V. Conclusion

This paper analyzes light-based circadian entrainment using the empirical nonlinear oscillator model of the human circadian system proposed by Kronauer. The entrainment process is formulated as a reference tracking problem, and the entrainment time, or the convergence time to the reference trajectory, is used as performance metric.

We have analyzed the entrainment stability using periodic light input. The optimal control strategy of the first order phase model is presented, and the result is compared with optimal control of the Kronauer model. We have also examined feedback based circadian entrainment using the full circadian state. A hybrid system formulation is used to demonstrate closed loop stability. The entrainment simulation results are discussed and the insight has potential application to light intensity control for circadian rhythm regulation.

ACKNOWLEDGMENT

This work was supported primarily by the National Science Foundation (NSF) Smart Lighting Engineering Research Center (EEC-0812056) and in part by the Center for Automation Technologies and Systems (CATS) under a block grant from the New York State Empire State Development Division of Science, Technology and Innovation (NYSTAR) contract C090145. The authors would also like to thank Drs. Mark Rea, Mariana Figueiro, and Andrew Bierman at the RPI Light Research Center for introducing this topic to the authors.

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