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Entrainment Control of Phase Dynamics

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***Abstract*—First order phase reduced model is a good approximation of the dynamics of forced nonlinear oscillators near its limit cycle. The phase evolution is determined by the unforced frequency, the forcing term, and the phase response curve (PRC). Such models arise in biological oscillations such as in circadian rhythm, neural signaling, heart beat, etc. This technical note focuses on the phase regulation of the circadian rhythm using light intensity as the input. Though the model is simple, the circle topology of the state space needs to be carefully addressed. The most common entrainment method is to use a periodic input, such as in our daily light-dark cycle. We obtain the complete stable entrainment condition based on the entraiment input and the PRC. Motivated by the jet-lag problem, we also consider the minimum time entrainment control to achieve a specified phase shift. Application of the Pontryagin Minimum Principle leads to an efficient solution strategy for the optimal control, without solving the two-point boundary value problem. The optimal control may be further represented as a feedback control law based on the current and desired phases. Our analysis allows the answer to questions such as: When traveling from New York to Paris, is it faster to use light to shift the phase forward by 6 hours or delay the phase by 18 hours? The answer is somewhat counter-intuitive—delaying by 18 hours requires less time. The general answer depends on the light intensity level and the shape of the PRC. PRCs for human and *Drosophila* from the literature are used to illustrate the results.**

***Index Terms*—Circadian rhythm, entrainment, optimal feedback control, phase control.**

I. Introduction

Phase response curve (PRC) is widely used to model the phase change of circadian rhythm in various organisms in response to light pulse input [1], [2]. Around the limit cycle of the circadian oscillation (based on, e.g., the empirical nonlinear oscillator models such as those by Richard Kronauer [3] or high-order biomolecular models for *Drosophila* and *Neurospora* [4], [5]) and mammals [6], the phase dynamics may be approximated by the first order phase reduced model [7]

$$\dot{\theta} = \omega + f(\theta)u \tag{1}$$

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where $2\pi/\omega$ is the free running (i.e., $u = 0$) period, $f(\theta)$ is the PRC, and u is the intensity of the light input.

This technical note considers the circadian phase control problem: choose $u(t) \in [0, u_{\max}]$ to shift θ to a reference θ_r asymptotically. We assume $u_{\max}$ is chosen so that $\omega + f(\theta)u_{\max} > 0$ for all θ. Though the model is very simple, the circle topology of the state space, S^1, needs to be addressed with care. For example, a 6-hour advance is equivalent to an 18-hour delay, so the phase-shift controller needs to decide which route to take. Circadian phase control has been investigated for *Drosophila* using model predictive control with quadratic cost in [8] and [9] and for empirical human oscillator model using optimal control [10]–[12]. General PRC-based control methods have been proposed [13], [14], but a detailed analysis of open loop entrainment and minimum time phase shift for the phase reduced model is not available.

Time optimal control for spiking neurons modeled by phase dynamics has been solved in [15] and [16]. Though the dynamics is similar to our case, we consider reference trajectory tracking instead of controlling to a target terminal phase. Also, exploiting the circular topology of the state space, we address both phase advance and lag strategies for reference trajectory tracking. We also have the additional constraint that the light input can only be positive, Specifically, this technical note presents three new results:

1) For open loop entrainment using a periodic input, the condition for the existence of a stable phase periodic solution on the circular state space is completely characterized. This condition depends on the entrainment period T (which may be different than the free running period) and the input profile.
2) The solution of the minimum time phase shifting control is reduced to two one-dimensional line search problems instead of solving a nonlinear two-point boundary value problem.
3) The minimum time control may be represented as a feedback law dependent on $\theta(t)$ and $\theta_r(t)$, easily implemented as a table lookup.

The feedback control law has an intuitive structure: If θ is ahead of θ_r, then apply $u_{\max}$ at the delaying portion of the PRC $(f(\theta) < 0)$ and zero input at the advancing portion $(f(\theta) \geq 0)$ of the PRC; reverse the procedure if θ is behind θ_r. However, since θ and θ_r evolve on a circle, there needs to be a threshold for $\theta - \theta_r$ to interpret "ahead" vs. "behind." Based on the shape of PRC, we can compute this threshold. For the PRC from [3] with 9500lux maximum light intensity, this threshold corresponds to about 3-hour advance. Hence, for the 6-hour advance from New York to Paris, using light to delay 18 hours is faster than advancing 6 hours.

Throughout the technical note, we will use the PRC (shown in Fig. 1) identified from the model developed by Richard Kronauer's group [3] (we shall refer to it as the Kronauer model) as an illustrative example. With the maximum light intensity of 9500lux (full daylight but not direct sun), the equivalent $u_{\max}$ is 0.2392. Application to *Drosophila* with PRC from [4] is also considered.

II. Periodic Entrainment

Perhaps the most obvious form of entrainment is to impose a periodic input of desired period T (which may be different than the free running period). For example, the regular 24-hour light/dark cycle

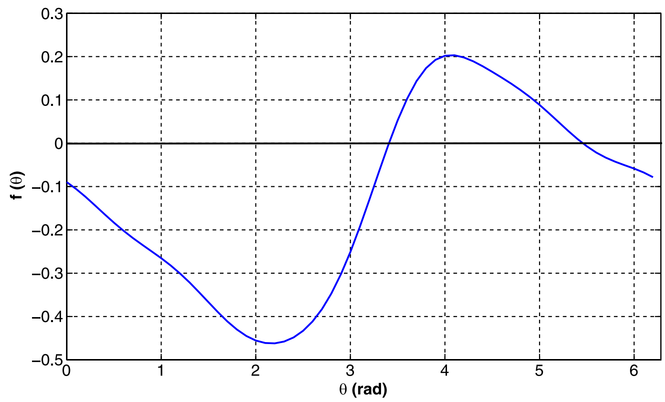

Fig. 1. Human phase response curve (normalized with respect to light intensity and duration) identified using the Kronauer model [3].

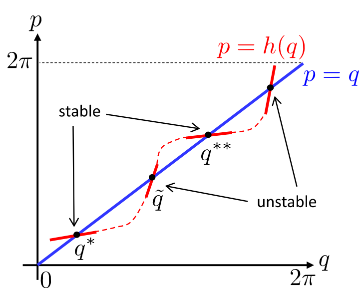

Fig. 2. Illustration for Proposition 3.

entrains the daily circadian rhythm. Given a T-periodic input $u(t)$, denote the solution of the phase dynamics (1) with initial condition $\theta(0) = q$ as $\varphi(t, q)$. Define

$$h(q) \triangleq \varphi(T, q) - 2\pi. \tag{2}$$

We first show that h is strictly increasing.

Proposition 1: For any $q \in [0, 2\pi)$, $h'(q) > 0$.

Proof: Observe that $h'(q) = \partial\varphi(T, q)/\partial q$ is the sensitivity function that satisfies the differential equation

$$\frac{d}{dt}\frac{\partial\varphi(t,q)}{\partial q} = u(t)\left.\frac{\partial f}{\partial\theta}\right|_{\theta=\varphi(t,q)}\frac{\partial\varphi(t,q)}{\partial q}, \quad \frac{\partial\varphi(0,q)}{\partial q} = 1. \tag{3}$$

This implies that $\partial\varphi(t, q)/\partial q$ does not change sign over time and thus is always positive. ■

If $q^* \in [0, 2\pi)$ is a fixed point of $h(\cdot)$, i.e., $h(q^*) = q^*$, then $\varphi(t, q^*)$ is a periodic orbit under the entrainment signal $u(t)$. We say that q^* is an asymptotically stable fixed point of $h(\cdot)$ if there exists an $\varepsilon > 0$ such that $q_0 \in (q^* - \varepsilon, q^* + \varepsilon)$ implies that the sequence $\{h^k(q_0)\}$ converges to q^*, where

$$h^k(q_0) \triangleq \underbrace{h\left(h\left(\cdots h(q_0)\right)\right)}_{k \text{ times}}.$$

The following result states a necessary and sufficient condition for a stable fixed point.

Proposition 2: q^* is a stable fixed point of $h(\cdot)$ if and only if the curve $p = h(q)$ crosses the line $p = q$ at q^* downward (see Fig. 2); that is, there exists a $\varepsilon > 0$ such that $q \in (q^* - \varepsilon, q^*) \Rightarrow h(q) > q$, and $q \in (q^*, q^* + \varepsilon) \Rightarrow h(q) < q$.

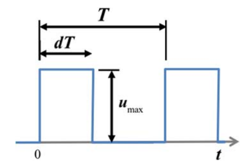

Fig. 3. Periodic square wave entrainment input.

Proof: **(if)** From Proposition 1, $h(\cdot)$ is monotonically increasing. Therefore, for any $q \in (q^* - \varepsilon, q^*)$, we have $h(q) < h(q^*) = q^*$. Further, since $h(q)$ curves downward at q^*, we have $h(q) > q$. Hence, the sequence $\{h^k(q)\}$ is monotonically increasing and bounded by q^*. Since q^* is the only fixed point in $[q^* - \varepsilon, q^*]$, we conclude $\{h^k(q)\}$ converges to q^*. The same argument can be used to show that for any $q \in (q^*, q^* + \varepsilon)$, $\{h^k(q)\}$ converges to q^*.

(only if) Suppose that $\varepsilon > 0$ is such that $q \in (q^* - \varepsilon, q^* + \varepsilon)$ implies that the sequence $\{h^k(q)\}$ converges to q^*. This means $h(q) - q \neq 0$ in $(q^* - \varepsilon, q^*) \cup (q^*, q^* + \varepsilon)$ First consider $q \in (q^* - \varepsilon, q^*)$. Suppose $h(q) - q < 0$. Then $\{h^k(q)\}$ is monotonically decreasing and therefore cannot converge to q^*. Hence, $h(q) - q > 0$. Similarly, for $q \in (q^* + \varepsilon, q^*)$, it follows that $h(q) - q < 0$. Hence $p = h(q)$ is downward crossing at q^*. ■

We next show that the stable and unstable fixed points of h must interlace.

Proposition 3: For every stable fixed point, there is at least one unstable fixed point. Moreover, between two stable fixed points (in the sense of S^1, i.e., a point q is identified with $q + 2L\pi$ for any integer L) there is at least one unstable fixed point.

Proof: From Proposition 2, at a stable fixed-point q^*, the curve $p = h(q)$ intersects with the line $p = q$ downward. Let q^{**} be another stable fixed point, or $q^{**} = q^* + 2\pi$ if q^* is the only fixed point. The intersection between $p = h(q)$ and $p = q$ must similarly curve downward. Between q^* and q^{**}, $p = h(q)$ must intersect $p = q$ upward at some point. If $\tilde{q}$ is the fixed point corresponding to the upward intersection, then $h'(\tilde{q}) >$ and thus $\tilde{q}$ is an unstable limit point. ■

With the above properties of $h(\cdot)$, we can now completely characterize the domain of attraction for the stable fixed points of $h(\cdot)$.

Theorem 1: Suppose a stable fixed point of $h(q)$, q^*, has adjacent unstable fixed points $\tilde{q}_1$ and $\tilde{q}_2$: $q^* \in (\tilde{q}_1, \tilde{q}_2)$. Then the domain of attraction for q^* is $(\tilde{q}_1, \tilde{q}_2)$.

Proof: First consider $q \in (\tilde{q}_1, q^*)$. As q^* is a stable fixed point, $h(q) > q$. As h is monotonically increasing, $h(q) < h(q^*) = q^*$. Hence $\{h^k(q)\}$ is a strictly monotonically increasing sequence that is bounded by q^*. Since q^* is the only fixed point in $(\tilde{q}_1, q^*]$, $h^k(q)$ converges to q^*. Similarly for $q \in (q^*, \tilde{q}_2)$, $h(q) < q$ and the sequence $\{h^k(q)\}$ is bounded below by q^*. Hence, $h^k(q)$ converges to q^* as stated. ■

In the case that there is only one pair of stable/unstable fixed points, $(q^*, \tilde{q})$, we can apply the above result to $q^* \in (\tilde{q} - 2\pi, \tilde{q})$ or $q^* \in (\tilde{q}, \tilde{q} + 2\pi)$ to conclude the convergence on S^1 is semi-global, i.e., $h^k(q)$ converges to q^* for all q except for $q = \tilde{q}$.

Given the PRC and the input, the return map $h(q)$ in (2) may be conveniently used to ascertain the existence and stability of periodic solutions. In particular, consider $u(t)$ as a T-periodic square wave with maximum $u_{\max}$ and duty cycle $d \in (0, 1)$ in each period (i.e., $u(t) = u_{\max}$ for d portion of the period), as shown in Fig. 3. Note that, without loss of generality, the start time of the duty cycle may be set to 0. The fixed point q^* is the relative phase shift between the starting points of the light input and circadian rhythm in each cycle. The existence of a stable periodic solution depends on T, $u_{\max}$, and d. For the Kronauer PRC with $T = 24$ hr and 50% duty cycle square wave input (12 hr/12 hr light-dark cycles), $h(q)$ intersects the diagonal at $q^* = (2.77, 3.72)$ as shown in Fig. 4. The slope of h at fixed point

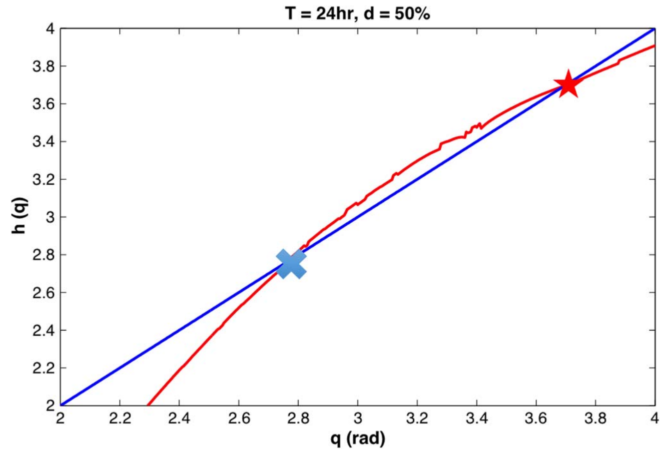

Fig. 4. Graph of $h(q)$ for duty cycle $d = 50\%$ and $T = 24$ hr. The intersections between $h(q)$ and q indicates the existence of two periodic solutions: unstable solution at $q^* = 2.77$ ($h'(q^*) > 1$) and stable solution at $q^* = 3.72$ ($h'(q^*) < 1$).

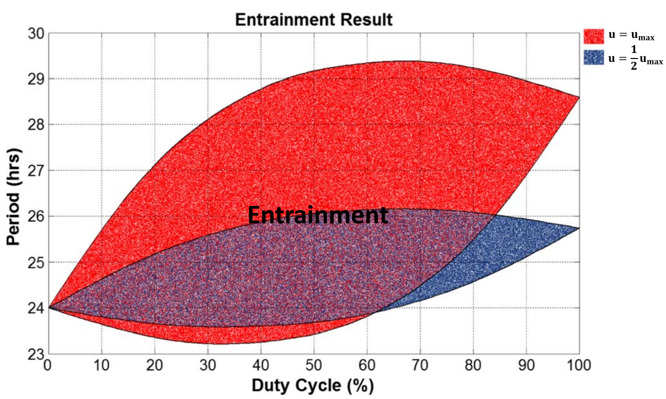

Fig. 5. Stable entrainment region with respect to period T and duty cycle d for $u_{\max}$ (red shaded area) and $u_{\max}/2$ (blue shaded area).

$q^* = 2.77$ is greater than 1 and is therefore unstable. The slope at $q^* = 3.72$ is less than 1 and is stable. At 70% duty cycle, $h(q)$ and q do not intersect, and therefore no fixed point exists. More generally, the stable entrainment portions of the (T, d) parameter space for $u_{\max}$ and $u_{\max}/2$ are shown in Fig. 5.

III. Minimum Time Optimal Entrainment

Consider a traveler passing through multiple time zones. It usually takes days to entrain the circadian rhythm to the local schedule using the destination light/dark cycle (which is just the open loop periodic input as in Section II). Could active lighting control help reduce this entrainment time? We pose this problem as a minimum time control problem using the constrained input u to drive $\theta(t)$ to the reference $\theta_r(t)$ (local phase) in the least amount of time. To avoid the possibility of singular control or non-uniqueness of the optimal control, we assume f has isolated roots.

A. Open Loop Optimal Control

Applying the Pontryagin minimum principle and accounting for the circular state space leads to the solution of the minimum time control problem.

Theorem 2: Given the phase dynamics (1) with $u(t) \in [0, u_{\max}]$, and a reference phase trajectory $\theta_r(t)$. Define

$$v(\theta, \rho) = \begin{cases} u_{\max} & \text{if } \rho f(\theta) < 0 \\ 0 & \text{otherwise} \end{cases} \tag{4}$$

where $\rho \in \{-1, 1\}$. Let $\tau(\rho, L)$ be the smallest positive solution of τ in

$$g\left(\theta(0), \theta_r(\tau) + 2L\pi; v(\theta, \rho)\right) = \tau \tag{5}$$

where $L \in \{0, -1, 1\}$ and g is defined as

$$g(q, q_1; u) := \int_q^{q_1} \left(\omega + f(\theta)u(\theta)\right)^{-1} d\theta. \tag{6}$$

Then the minimum time at which $\theta(t_f) = \theta_r(t_f) + 2n\pi$ for an integer n, is $t_f = \min_{L,\rho} \tau(\rho, L)$. The corresponding optimal control is $u^*(t) = v(\theta(t), \rho^*)$ with ρ^* given by the minimization of $\tau(\rho, L)$.

Proof: The cost function for the minimum time control problem is given by $J = \int_0^{t_f} 1 dt$. The Hamiltonian is

$$H = 1 + \lambda\left(\omega + f(\theta)u\right).$$

The input that minimizes H, subject to the maximum input constraint, is

$$u^* = u_{\max} \mathbb{1}\left(-f(\theta)\lambda\right) \tag{7}$$

where $\mathbb{1}$ is the unit step function. The costate equation is

$$\dot{\lambda} = -\partial H/\partial\theta = -\lambda f'(\theta)u. \tag{8}$$

Since $\lambda = 0$ is an equilibrium, $\lambda(t)$ cannot change sign. In (7), u^* only depends on the sign of λ. Hence we can replace (7) by (4) with ρ either 1 or -1 (only the sign matters). For a given ρ, v is a function of only θ. Apply separation of variables as before for the terminal condition

$$g\left(\theta(0), \theta_r(t_f) + 2L\pi; v(\theta, \rho)\right) = t_f. \tag{9}$$

We only need to consider $L = \{0, -1, 1\}$ as other choices would incur longer time.

For the finite set of (L, ρ) (6 combinations), find the solutions of (9) (e.g., using line search). The smallest value of the six candidates is the minimum time solution. Substituting the corresponding ρ in (4) gives the optimal control. ■

The above result may be used to solve the two-point boundary value problem (TPBVP): (1), (7), (8), with the initial and terminal state conditions. Since the optimal control only depends on the sign of λ which does not change with time, we may choose $\lambda(0)$ to be either $+1$ or -1 and solve $\theta(t)$ until the terminal condition is satisfied (9). The one with smaller t_f is then the optimal solution. The true $\theta(0)$ will need to scaled to satisfy the transversality condition [17], but the condition is not needed for the solution of the optimal control. The transversality condition does eliminate the only possible case of singular arc with $\lambda \equiv 0$. The solution in Theorem 2 is equivalent to solving TPBVP but only involves two line search operations.

In the jet lag example, θ_r is given by the destination phase. The dynamics of θ_r is governed by (1) with $u = u_r$, the local lighting condition. Write the solution as

$$\theta_r(t) = \varphi\left(t; \theta_r(0), u_r\right). \tag{10}$$

With this θ_r, (5) becomes

$$g\left(\theta(0), \varphi\left(t_f; \theta_r(0), u_r\right) + 2\pi L; v(\theta, \rho)\right) = t_f. \tag{11}$$

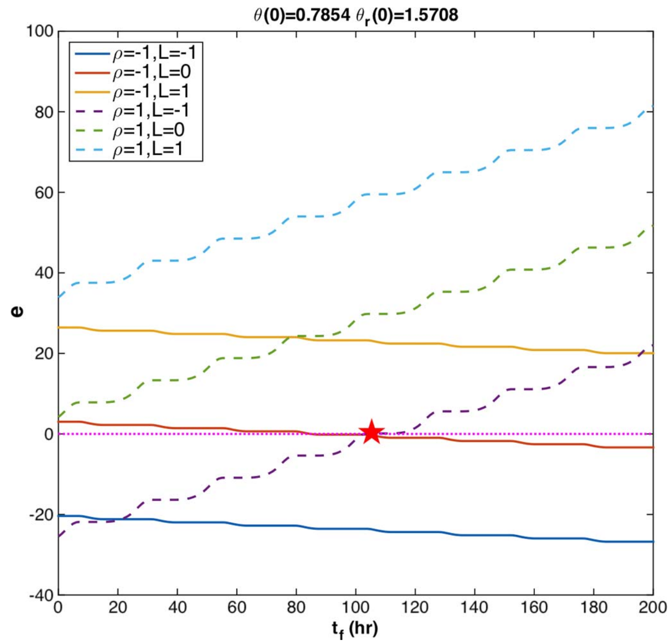

Fig. 6. When $\theta_r(0) - \theta(0) \approx \pi/4$, the two line searches yield the same result.

Note that since u_r is T-periodic

$$\varphi(t_f; \theta_r(0), u_r) + 2\pi L = \varphi(t_f; \theta_r(0) + 2\pi L, u_r).$$

Define the terminal condition error as

$$e(\theta(0), \theta_r(0), \rho, L, t_f) := g(\theta(0), \varphi(t_f; \theta_r(0) + 2\pi L, u_r); v(\theta, \rho)) - t_f. \quad (12)$$

Fig. 6 shows e vs. t_f for the six combinations of ρ and L for $\theta(0) < \theta_r(0)$ and $\theta(0) > \theta_r(0)$. The graph of e with $L = \pm 1$ is simply the graph of e with $L = 0$ shifted up and down. For $\rho = 1$, only the delay (negative) portion of the PRC is used resulting in super-linear growth in t_f, so e monotonically increases in t_f (the integrand is larger than $1/\omega$). Similarly, for $\rho = -1$, e is monotonically decreasing. Hence, for $\rho = 1$, we only need to consider L with the largest negative e at $t_f = 0$, and for $\rho = -1$, only L with the smallest positive e at $t_f = 0$. Define

$$L_d = \arg\min_L \{h_d(L) : h_d(L) := g(\theta(0), \theta_r(0) + 2\pi L; v(\theta, 1)) < 0\}$$
$$L_a = \arg\min_L \{|h_a(L)| : h_a(L) := g(\theta(0), \theta_r(0) + 2\pi L; v(\theta, -1)) > 0\}. \quad (13)$$

Then only two line searches are needed: For $(L, \rho) = (L_d, 1)$, input is used to delay the phase using the delay portion of the PRC, and for $(L, \rho) = (L_a, -1)$, input is used to advance the phase using the advance portion of the PRC. The smaller of the two solutions of t_f is the minimum entrainment time. When both t_f solutions coincide, the phase delay and advance strategies are both optimal, as shown in Fig. 6, where $t_f^* = 102$ hr. For the 9 hr phase advance case (from $\theta(0) = \pi/4$ to $\theta_r(0) = \pi$), the two search cases are $L_d = -1$, $L_a = 0$, and $t_f^* = 71$ hr corresponds to $\rho = 1$ (delay strategy). For the 9 hr delay case from $\theta(0) = \pi$ to $\theta_r(0) = \pi/4$), the search cases are $L_d = 0$ and $L_a = 1$, and $t_f^* = 53$ hr for $\rho = 1$.

B. Feedback Minimum Time Control

The optimal control depends only on $\theta(0)$ and $\theta_r(0)$. This suggests a feedback implementation in the same spirit as model predictive control [18]: At each time t, consider it as the starting time of the optimal control, then $u^*(t)$ may be written as

$$u^*(t) = v(\theta(t), \rho^*(\theta(t), \theta_r(t))). \quad (14)$$

We now show that this feedback control law may be expressed in an intuitive form based on the PRC and is minimum time.

Theorem 3: Given the reference phase trajectory $\theta_r(t)$. Define the phase tracking error as $e_\theta = \theta_r - \theta$. Let δ be the solution of

$$g(\theta, \varphi(t_\delta; \theta - \delta; u_r) + 2\pi L_d; \nu(\theta, 1)) = g(\theta, \varphi(t_\delta; \theta - \delta; u_r) + 2\pi L_a; \nu(\theta, -1)) := t_\delta. \quad (15)$$

Assume δ is unique. Then $e_\theta \to 0$ in minimum time using the following feedback control law:

$$u^* = \begin{cases} u_{\max} & \begin{cases} \text{If } f(\theta) < 0 \text{ and } \operatorname{mod}(e_\theta, 2\pi) \in [\delta, 2\pi), \\ \text{or } f(\theta) > 0 \text{ and } \operatorname{mod}(e_\theta, 2\pi) \in [0, \delta) \end{cases} \\ 0 & \text{otherwise.} \end{cases} \quad (16)$$

Proof: If $e_\theta = \delta$, the two e curves [corresponding to L_a and L_d, with e defined as in (12)] intersect at t_δ. Perturb e_θ slightly to $\delta + \varepsilon$. If $\varepsilon > 0$, the integral in g with L_a (phase advance strategy) increases, implying $t_f > t_\delta$, and the integral in g with L_d (phase delay strategy) decreases, implying $t_f < t_\delta$. Hence, $\rho = 1$ corresponds to the optimal control. In this case, if $f(\theta) < 0$, then it follows from (4) that the optimal control action is $u_{\max}$. Similarly, if $f(\theta) < 0$, then optimal u is 0. Conversely, if $\varepsilon < 0$, $\rho = -1$ corresponds to the optimal control. Therefore, if $f(\theta) > 0$, then the optimal control u from (4) is $u_{\max}$. Similarly, if $f(\theta) < 0$, the optimal control is 0. Since δ is assumed to be unique, this reasoning may be extended until $e_\theta = 2n\pi$. The optimal feedback control law just described is exactly (16). ■

The phase threshold δ depends on θ and θ_r, but in numerical simulations, it hovers around a constant. For the Kronauer PRC with maximum input $u_{\max} = .2392$, $\delta \approx \pi/4 = .785$ (or 3 hours). We can actually obtain a good estimate of δ based on the relative areas of advance and delay in the PRC. Specifically, in each period- T cycle, using $u_{\max}$ in only the phase advance portion results in time t_a to traverse one period (smaller than T since phase is speeding up) and using $u_{\max}$ in only the phase delay portion results in time t_d to cover one period (larger than T since phase is slowed down)

$$t_a = \int_{\{\theta: f(\theta) > 0\}} \frac{d\theta}{\omega + f(\theta) u_{\max}}$$
$$t_d = \int_{\{\theta: f(\theta) < 0\}} \frac{d\theta}{\omega + f(\theta) u_{\max}}. \quad (17)$$

Let $t_\delta = \delta \cdot T/(2\pi)$ be the switching time corresponding to δ. Then using phase advance to cover $-t_\delta$ would take $\alpha_a = -t_\delta/(t_a - T)$ cycles for θ to catch up. Using phase delay to cover $(\delta - 2\pi) \cdot T/(2\pi) = t_\delta - T$ would take $\alpha_d = (t_\delta - T)/(t_d - T)$. Equating the two, we can solve for t_δ and δ

$$t_\delta = \frac{T}{(1 - (t_d - T)/(t_a - T))}$$
$$\delta = \frac{2\pi t_\delta}{T}. \quad (18)$$

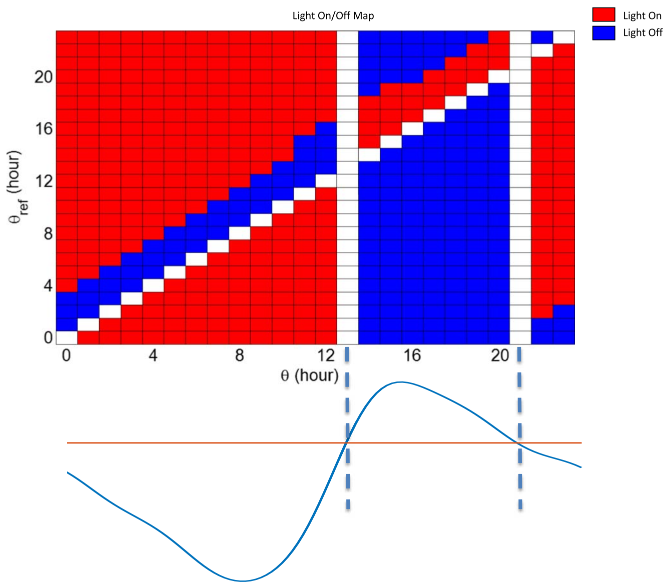

Fig. 7. Graphical depiction of feedback control law (14) where blue indicates $u = 0$ and red indicates $u = u_{\max}$. The PRC is shown in the lower portion. The zero crossing of the PRC corresponds transitioning between using light to delay and to advance.

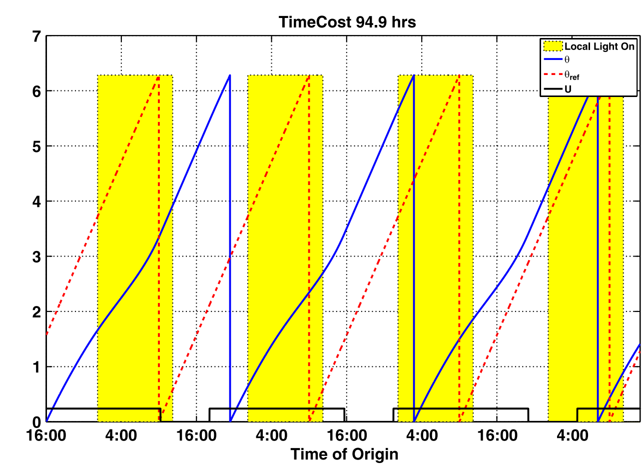

Fig. 8. Optimal control strategy for 6-hour advance or 18-hour delay. Long periods of awake time are required to achieve the required delay.

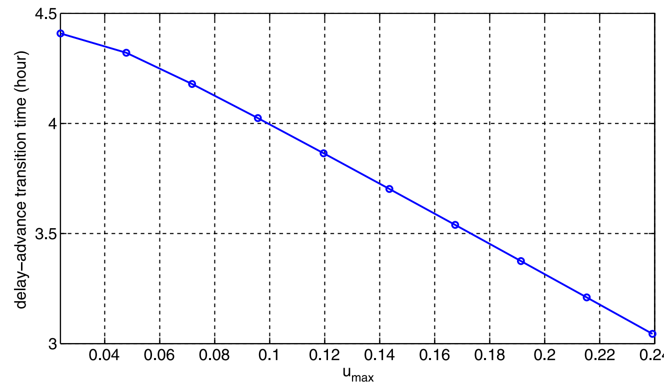

Fig. 9. Transition time t_δ versus maximum light intensity $u_{\max}$.

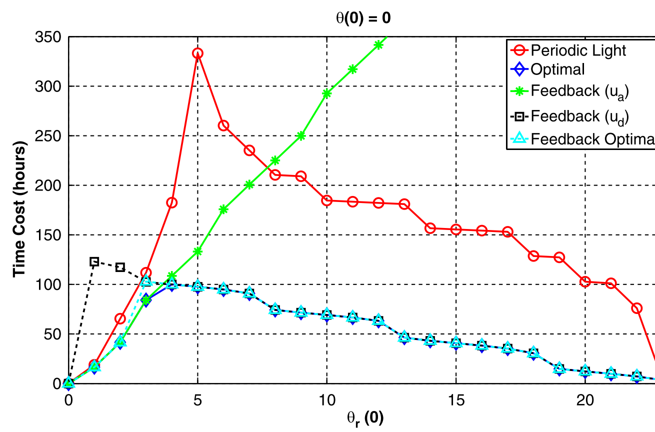

Fig. 10. The entrainment time comparison between open loop periodic light entrainment, minimum time optimal, $u = u_a$, $u = u_d$, and feedback optimal control for $\theta_r(0) \in [0, 23] \cdot \pi/12$ and $\theta(0) = 0$. Convergence criterion is set at 0.1 rad (about 23 min).

For the Kronauer PRC, it is easy to compute $t_a = 23.40$ hr and $t_d = 29.69$ hr. With $T = 24$ hr, we have $t_\delta = 3.07$ hr and $\delta = .796$, which is close to our numerical estimate of $\pi/4 = .785$. This procedure is only an estimate since the initial and final cycles may not involve the complete PRC. However, the estimate provides a good approximation, without explicitly solving (15) for δ and t_δ.

We can visualize the feedback control law as a table where a given pair of (θ, θ_r) determines if the light should be full on or off. The Kronauer PRC case is shown in Fig. 7. This figure shows that if θ is in a phase lag portion of the PRC and θ_r is "sufficiently" lag behind θ, then light input should be used to delay θ towards θ_r. However, since θ and θ_r evolve on S^1, phase lag may be viewed as phase advance with a 2π increment. The separation between lag and advance would depend on the PRC and $u_{\max}$, and is given by $e_\theta = \delta$. For Fig. 7, this means that for 3-hour phase advance, such as going from Los Angeles to New York, one should use light in the phase advance portion of the PRC. But for 6-hour phase advance, such as going from New York to Paris, it is more efficient to use the phase delay portion of the PRC to delay by 18 hours rather than advancing by 6 hours (3.9 day vs. 7.3 days with $u_{\max} = .239$). The caveat is that light input needs to be used for long periods of time, with 18-hours and two 21-hour lights-on periods with intervening 8-hour lights-off periods, as shown in Fig. 8, to achieve the 18-hour delay. Such long periods of awake times may not be practical. Inclusion of requisite rest periods will be part of our future work. The maximum light intensity also affects the entrainment time. Fig. 9 shows t_δ as a function of $u_{\max}$ for the Kronauer PRC. The PRC has an inherent bias towards delay, hence the transition time t_δ favors delay. As $u_{\max}$ decreases, the relative advantage of delay over advance is reduced, and we expect t_δ to increase towards parity.

Fig. 10 shows a comparison of the entrainment strategies presented in this technical note applied to the Kronauer-based PRC. It shows the entrainment time for $\theta_r(0) - \theta(0)$ goes from 0 to 2π (0 to 24 hr advance) with periodic entrainment (using the pulse train input in Section II with 50% duty cycle), optimal entrainment $u^*(t) = v(\theta(t), \rho^*)$ as in Theorem 1 and feedback entrainment (16). The figure also shows the entrainment time using u_d, the controller (4) with $\rho = 1$, and u_a, the controller (4) with $\rho = -1$. These controllers only use the phase delay or advance portions, respectively. Not surprisingly, the entrainment times under u_d and u_a intersect at t_δ. This result is identical to the ones obtained using numerical tools for the full Kronauer model in [19].

As an additional example, consider the 10-state *Drosophila* bio-molecular model [20]. The *Drosophila* PRC [4] and the corresponding

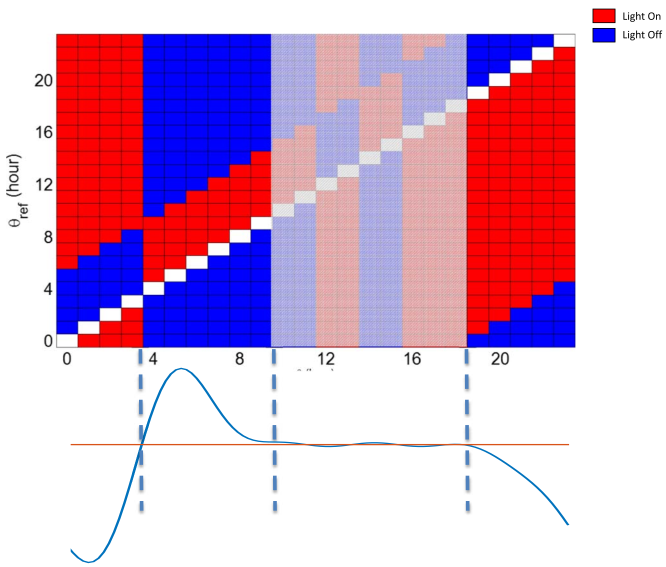

Fig. 11. Drosphila phase response curve identified using 10-state *Drosophila* biomolecular model [20] and the corresponding optimal input map.

optimal input table are shown in Fig. 11. Note that there is a large portion of approximately 9 hours that the PRC is near zero indicating that the input does not have significant effect on the phase. Using this PRC and $u_{\max} = 1$ (chosen as in [20], roughly equivalent to 100lux), we have $t_d - T = 3.25$ hr and $t_a - T = -0.76$ hr. This results in the transition time $t_\delta = 4.59$ hr.

IV. Conclusion

This technical note presents new control-theoretic results for light-based circadian entrainment based on a first order phase dynamic model. The entrainment process is formulated as a reference tracking problem. Based on the first order phase dynamics, analytical results are obtained for periodic entrainment, minimum-time control, and feedback optimal control. Examples for the Kronauer phase response curve for human circadian rhythm and the Drosophila phase response curve are included to illustrate the results. The feedback optimal phase control is implementable as a simple table lookup. If the circadian phase is measured using, e.g., wearable biometric sensors, then personalized lighting may be used for effective phase shift. Such scheme would be useful for international travellers faced with long jet lags, and shift workers. The control strategy at the present does not account for sleep schedule. However, the feedback strategy may still be applied whenever the person is awake. This would extend the entrainment time, but the convergence is still faster than the open loop periodic entrainment. As an example, for the 6-hour phase advance, suppose the traveler goes to sleep from 11 P.M. to 7 A.M. local time, the entrainment time goes from 95 hr to 141 hr, while the open loop periodic entrainment time (at 50% duty cycle) is 260 hr.

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References

[1] C. H. Johnson, "Forty years of PRCs—What have we learned?" *Chronobiol. Int.*, vol. 16, no. 6, pp. 711–743, 1999.
[2] P. Sacre and R. Sepulchre, "Sensitivity analysis of oscillator models in the space of phase-response curves: Oscillators as open systems," *IEEE Control Syst. Mag.*, vol. 34, no. 2, pp. 50–74, Apr. 2014.
[3] R. Kronauer, D. Forger, and M. Jewett, "Quantifying human circadian pacemaker response to brief, extended, repeated light stimuli over the phototopic range," *J. Biol. Rhythms*, vol. 14, no. 6, pp. 501–516, 1999.
[4] J. Leloup, D. Gonze, and A. Goldbeter, "Limit cycle models for circadian rhythms based on transcriptional regulation in Drosophila and Neurospora," *J. Biol. Rhythms*, vol. 14, no. 6, pp. 433–448, 1999.
[5] J. Leloup and A. Goldbeter, "Toward a detailed computational model for the mammalian circadian clock," *Proc. Nat. Acad. Sci.*, vol. 100, no. 12, pp. 7051–7056, 2003.
[6] D. Forger and C. Peskin, "A detailed predictive model of the mammalian circadian clock," *Proc. Nat. Acad. Sci.*, vol. 100, no. 25, pp. 14 806–14 811, 2003.
[7] E. Brown, J. Moehlis, and P. Holmes, "On the phase reduction and response dynamics of neural oscillator populations," *Neural Computing*, vol. 16, pp. 673–715, 2004.
[8] N. Bagheri, J. Stelling, and F. Doyle, III, "Circadian phase entrainment via nonlinear model predictive control," *Int. J. Robust Nonlin. Control*, vol. 17, pp. 1555–1571, 2007.
[9] S. R. Taylor, "Computational Methods for the Analysis of Phase Dynamics in Biological Oscillators," Ph.D. dissertation, Univ. California at Santa Barbara, Santa Barbara, CA, USA, 2008.
[10] C. Mott, D. Mollicone, M. Van Wollen, and M. Huzmezan, "Modifying the human circadian pacemaker using model based predictive control," in *Proc. Amer. Control Conf.*, Denver, CO, 2003, pp. 453–458.
[11] D. Dean, II, D. Forger, and E. Klerman, "Taking the lag out of jet lag through model based schedule design," *PLoS Computational Biol.*, vol. 5, no. 6, Jun. 2009. [Online]. Available: http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1000418
[12] K. Serkh and D. Forger, "Optimal schedules of light exposure for rapidly correcting circadian misalignment," *PLoS Computat. Biol.*, vol. 10, no. 4, Art. no. e1003523, 2014.
[13] A. Granada and H. Herzel, "How to achieve fast entrainment? The timescale to synchronization," *PLoS ONE*, vol. 4, no. 9, 2009, Art. no. e7057.
[14] D. Efimov, "Phase resetting control based on direct phase response curve," *J. Math. Biol.*, vol. 63, no. 5, pp. 855–879, 2011.
[15] A. Nabi and J. Moehlis, "Time optimal control of spiking neurons," *J. Math. Biol.*, vol. 64, pp. 981–1004, May 2012.
[16] J. Moehlis, E. Shea-Brown, and H. Rabitz, "Optimal inputs for phase models of spiking neurons," *J. Computat. Nonlin. Dyn.*, vol. 1, no. 4, pp. 358–367, 2006.
[17] D. Liberzon, *Calculus of Variations and Optimal Control Theory: A Concise Introduction*. Princeton, NJ, USA: Princeton Univ. Press, 2011.
[18] M. Morari and J. Lee, "Model predictive control: Past, present and future," *Comp. Chem. Eng.*, vol. 23, no. 4–5, pp. 667–682, 1999.
[19] J. Zhang, J. Wen, and A. Julius, "Optimal circadian rhythm control with light input for rapid entrainment and improved vigilance," in *Proc. Conf. Decision Control*, Maui, HI, USA, Dec. 2012, pp. 3007–3012.
[20] J. Leloupm and A. Goldbeter, "A model for circadian rhythms in Drosophila incorporating the formation of a complex between the PER and TIM proteins," *J. Biol. Rhythms*, vol. 13, pp. 70–87, 1998.