Optimal Phase-Tracking of the Nonlinear Circadian Oscillator

Neda Bagheri, Jörg Stelling, and Francis J. Doyle III

Abstract— **Through investigation of transient phase characteristics, a methodology is developed to optimize the phase resetting properties of robust nonlinear biological oscillators; in particular, those of the circadian rhythm. This pacemaker is an autonomous chemical oscillator with a period close to 24 hours. Research in chronobiology indicates that light stimuli can be used to delay or advance the phase of the oscillator, allowing it to synchronize physiological processes and govern daily fluctuations in the core body. This paper proves that a circadian oscillator optimally recovers extreme phase difference (half the nominal period) within 4-days.**

I. Introduction

Many biological systems exhibit a characteristic period and amplitude described by oscillatory models [13]. They are found to be robust to parametric perturbation, resuming normal behavior in finite time. Robustness measures, based on sensitivity analysis, can be used to gain a better understanding of biological phenomena while advancing medical technology [12]. In this paper, a closed-loop optimal phase tracking control system is developed for a nonlinear biological oscillator and applied to the 10-state *Drosophila* circadian model [6]. The circadian gene network has proven to be an ideal model for this type of study. This self-sustained 24-hour free-running oscillator has been studied extensively and is apparent in many organisms such as *Neurospora*, *Drosophila*, and mammals. The system consists of two coupled negative feedback loops that model the transcription, translation, phosphorylation, and time delays associated with *per* and *tim* genes and proteins in *Drosophila* (Fig. 1).

Through use of entrainment factors, such as light [7], researchers have been able to manipulate circadian dynamics. Studies have shown that admitting light pulses to the oscillator under dark-dark conditions resets the limit cycle. Such pulses induce a phase shift, resulting in either a phase delay or advance [13]. Previous studies have investigated light-based optimal control applied to a model without gene regulation [8]. This paper presents a real-time method of optimally controlling light pulses to recover, or reset, the phase of a circadian model. Directing this type of system shows promise for alleviating sleeping disorders, depression, and travel stresses while improving alertness and performance through synchronizing the biological clock with its environment [2], [3].

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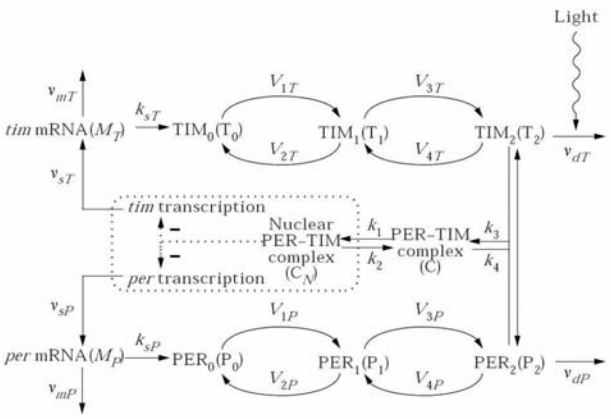

Fig. 1. **The 10-State Circadian Model [6].** Negative regulation of *per* and *tim* gene expression occurs via the PER-TIM nuclear complex. *per* and *tim* genes are transcribed in the nucleus, after which their mRNAs are transported into the cytosol where they undergo protein synthesis. The newly formed PER and TIM proteins are phosphorylated, yielding P_1/T_1 and P_2/T_2 protein elements. The doubly phosphorylated proteins (P_2 and T_2) form a PER-TIM complex, C, that enters the nucleus and closes the feedback loop by suppressing gene expression.

II. System

A. Nonlinear Oscillators

Three main characteristic outputs of oscillators (or biological rhythms) are *amplitude*, *period*, and *phase* [3]. The *amplitude* of a system relates state maximum values to their respective minimum values. In the case of circadian rhythms, this amplitude reflects a ratio of maximum to minimum mRNA concentrations. *Period* may be expressed as the time interval for a reference point in successive waves to pass a fixed point [3]. In other words, it is the time measure between peak state values; the circadian clock has an entrained period of 24 hours. *Phase* is defined as the measure of time capturing a system's advance or delay relative to a nominal reference (Fig. 2).

Generally, within a defined state space, limit-cycle oscillators are structurally stable and produce steady state oscillations whose amplitudes are independent of initial conditions [4]. For instance, the limit cycle of the Van der Pol oscillator has the property that all trajectories in the vicinity of the limit cycle ultimately tend toward the orbit as time approaches infinity. Such limit cycles are classically known as stable [4]. Biological oscillators exhibit similar behavior; their limit cycles are assumed to be global attracting sets in a given parameter space. Upon

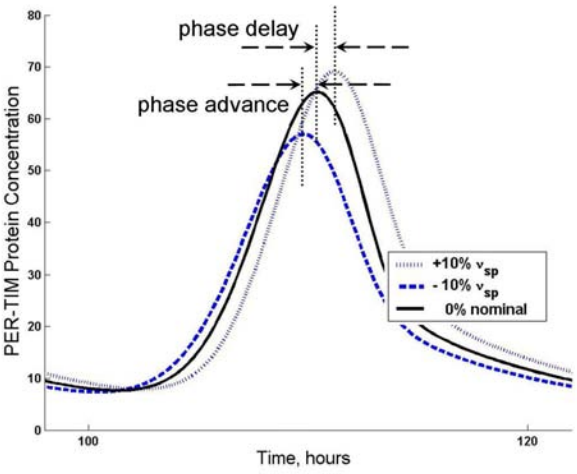

Fig. 2. **Characteristics of Oscillators.** In circadian rhythms, the *per* transcription rate, v_{st}, is perturbed to positive and negative 10-percent of its nominal value. This disturbance causes the amplitude and period of oscillation to either increase or decrease, respectively. If the peak of the perturbed trajectory crosses a time point before that of the nominal, there exists a phase advance. The reverse yields a phase delay.

perturbation, states deviate from the nominal (undisturbed) trajectory, and return to the periodic orbit asymptotically.

B. Circadian Rhythms

The most prominent characteristics of circadian rhythms are persistence, temperature compensation, and entrainment [3]. Biological oscillators are persistent, or robust, due to their ability to maintain period and phase behavior under environmental and structural variation [12]. Environmentally induced phase-tracking is possible through the existence of control inputs, such as light, that entrain the cycle to naturally-occurring rhythms.

The gene network underlying the *Drosophila* model consists of two coupled negative auto-regulatory transciption/translation feedback loops (Fig. 1). Although period and timeless genes and proteins undergo similar oscillations, TIM is known to be unstable in the presence of light. More specifically, light-induced TIM degradation requires neither the involvement of PER, nor any other functional clock protein [10]. Therefore, its response to light is considered a direct control input pathway that catalyzes entrainment. The circadian model is based on the assumption that a 1-minute light pulse induces a multiplication of the maximum TIM degradation rate, v_{dt}, by a factor of two over a 3-hour period [7]. While this numerical combination is not unique, it meets the necessary requirements: when incorporating light-induced TIM degradation, the model displays damped oscillations during constant light, entrainment of the rhythm by light-dark cycles, and phase shifts through pulses of light [7].

C. Entrainment

Entrainment occurs once the period of the overt reaction matches the period of the entraining cycle. In the case of circadian rhythms, several entraining factors exist; none of these factors, however, prove to be more influential than changes in light [2], [3]. Light triggers TIM protein degradation, leading to a variable maximum degradation rate, v_{dt}. The consequence of such a parameter change can be long-lasting: a 1-minute pulse of light can indeed turn on a gene and elicit the activity of enzyme synthesis for hours [7].

An increase in TIM degradation causes a phase delay if light is applied during increasing *per* or *tim* mRNA concentrations. A phase advance is acquired if the input is applied during decreasing mRNA concentrations. The absence of a phase shift corresponds to times at which mRNA are at near minimum concentration. This time interval roughly corresponds to natural hours of daylight: between 08:00 and 20:00 hours. Note that an increase in TIM degradation hinders negative regulation of *per* and *tim* transcription by decreasing the concentration of the cytoplasmic PER-TIM complex (Fig. 1).

D. Response Curves

Since biological oscillators are generally stable within a defined parameter space, a finite stimulus will force the oscillator's trajectory to deviate from its periodic orbit and return to the limit cycle asymptotically. Upon completion of this transient, the system incurs a phase shift. If this initial stimulus is applied at different times throughout the period, the resulting change in phase will vary. In other words, as depicted in Fig. 3, a stimulus applied at 5-hours results in a different change of phase relative to the same stimulus applied at 10-hours.

The mapping of such parametric influences to the resultant phase shift is captured in a phase response curve (PRC) (Fig. 4). It characterizes the clock's time-dependent sensitivity toward the given stimulus, a 1-minute light pulse [13]. Another means of defining the PRC is through measuring the effect of a temporary change in period of oscillation on the relative phase when a pulse-like perturbation is applied at different points in the cycle. If the controlled rhythm, $\mathbf{x}(t)$, leads the unperturbed reference, $\mathbf{r}(t)$, by less than one-half cycle, there exists a phase advance, or if it lags by less than one-half cycle, a delay [13]. It is conventional to plot these phase advances and delays against the relative time index, k, at which a resetting stimulus is employed. This index represents the real-time, t, normalized by the period of oscillation, T, such that $k \in [0,1)$.

Let $\phi(t)$ be the measure of time between the system and reference. Equation 1 describes the PRC function as an input/output mapping of light applied at relative time k, to an acquired change in phase, $\phi^+(k)$. The greatest possible phase advance (Fig. 4. top plot) results from a one-minute light pulse applied at approximately $k = \frac{2}{3}$ in relative time: $\phi^+(\frac{2}{3}) = 3.2$-hours.

$$\phi^+(k) = g_{prc}(u(k)) \tag{1}$$

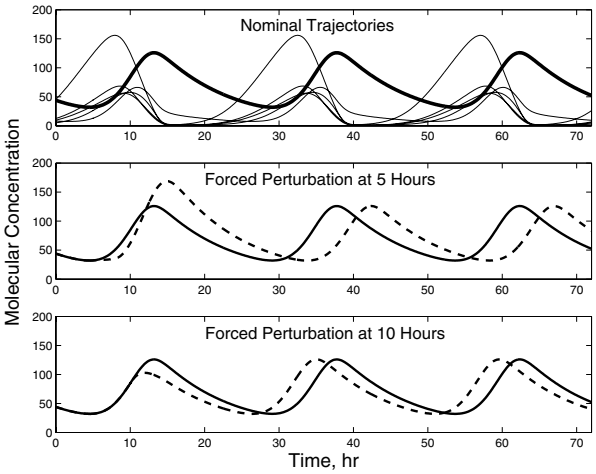

Fig. 3. **Open Loop Circadian Dynamics with Forced Perturbations.** The first plot depicts the nominal behavior of the circadian 10-state model over a three-day period. The heavy-weight line denotes concentrations of the PER-TIM complex within the nucleus, C_N. This complex is tracked in the following two plots as a light pulse is applied to the system at 5-hours and 10-hours, respectively. This disturbance temporarily represses the complex by increasing the maximum degradation rate of the TIM protein. The first perturbation recovers from the repression by gaining amplitude and delaying its relative phase; in other words, by acquiring a negative phase shift. The second perturbation decreases amplitude, gains a relative advance, and acquires a positive phase shift.

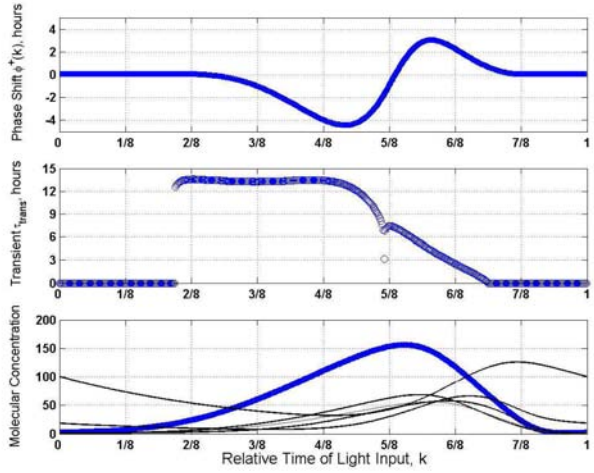

Fig. 4. **Phase Response Curve of the Circadian Model.** (upper plot) Applying a one-minute light pulse at various times within an oscillation results in a set of phase shifts captured by the PRC. The maximum phase advance through a use of a single stimulus is 3.2-hours while the maximum phase delay is 4.6-hours. (middle plot) Transient response of the circadian model states for a one-minute light pulse exerted at various times within a cycle are depicted on the vertical axis. The horizontal time-axis corresponds directly to that of the PRC and state concentrations. (lower plot) The heavy-weighted state trajectory in the lower plot denotes nominal *per* and *tim* mRNA concentration. Its peak value associates with the sharp zero-crossing of the PRC. The TRC discontinuity existing just before relative time $k = \frac{5}{8}$ relates to a PRC phase shift of -1.7-hours. An input applied at this exact point will provide a small phase shift with almost no transient behavior.

A complement of the PRC, the transient response curve (TRC) defines the amount of time it takes for the system trajectory to return to its limit cycle upon stimulus (Fig. 4, middle plot). Equation 2 describes the TRC function as mapping a light input at relative time k to a measure of the ensuing transient period, $\tau_{trans}(k)$. Therefore, the greatest phase advance generates a transient of about 5-hours: $\tau_{trans}(\frac{2}{3}) = 5$-hours. Transients are determined numerically by observing the amount of time required for the minimum distance between the perturbed and nominal limit cycles to fall within a given tolerance once subject to a light input.

$$\tau_{trans}(k) = g_{trc}(u(k)) \tag{2}$$

III. Controlling the Circadian Oscillator

A. Model Dynamics

The present analysis assumes a general nonlinear system such that $\mathbf{x}(t)$ defines the n-length state vector, ρ defines the m-length parameter vector, $\mathbf{u}(t)$ defines the control input, and $f(\mathbf{x}(t), \rho(t), \mathbf{u}(t))$ defines system dynamics. In the case of circadian rhythms, the key entrainment factor, light, functions as a multiplicative input affecting v_{dt} exclusively. Thus, all other parameters are static over time. Such entrainment yields a model of the form in equation (3).

$$\begin{aligned} \dot{\mathbf{x}}(t) &= f(\mathbf{x}(t), \rho(u(t))) \\ &\quad \mathbf{x}(t) \in \mathbf{R}^m \\ &\quad \rho(t) \in \mathbf{R}^n \end{aligned} \tag{3}$$

The reference (4) oscillates according to the system's nominal dynamics and is assumed to have no light-input.

$$\begin{aligned} \dot{\mathbf{r}}(t) &= f(\mathbf{r}(t), \rho) \\ &\quad \mathbf{r}(t) \in \mathbf{R}^m \\ &\quad \rho(t) \in \mathbf{R}^n \end{aligned} \tag{4}$$

Given an oscillatory system such that $\mathbf{x}(t) = \mathbf{x}(t+T)$, where T represents the period of oscillation, relative phase measures are obtained by minimizing the difference between the mapping of reference and system trajectories onto a nominal set of state concentrations, $\mathbf{x}_n(t)$ (Fig. 5). At each time point t, this mapping provides indices, k_r and k_s (5): k_r is the reference index and k_s is the system index .

$$\begin{aligned} k_r &= \min_k |\mathbf{r}(t) - \mathbf{x}_n(k)| \\ k_s &= \min_k |\mathbf{x}(t) - \mathbf{x}_n(k)| \\ &\quad k,\, k_r,\, k_s \in [0,1) \end{aligned} \tag{5}$$

As a result, the relative positions of k_r and k_s at time t characterize the difference in phase, ϕ (6).

$$\phi = (k_r - k_s) \cdot T \tag{6}$$

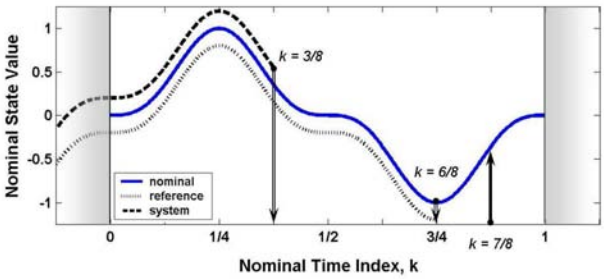

Fig. 5. **Relative Time Mapping.** An example oscillatory system and reference are mapped onto a single cycle of a known nominal set. Projecting real-time dynamics onto this set provides indices used to relate phase differences. The example above shows a phase difference of 9-hours: $\phi = \left(\frac{6}{8} - \frac{3}{8}\right) \cdot 24$. Assuming the time index of the next control input is known, $k = \frac{7}{8}$, the resulting delay is 12-hours: $\tau_{delay} = \left(\frac{7}{8} - \frac{3}{8}\right) \cdot 24$.

B. Optimal Phase-Tracking

The ultimate purpose of the optimal control design is to drive the states to track a reference signal or desired output, $\mathbf{r}(t)$. Since this method is designed to determine the control input that minimizes the performance criterion, one typically employs a weighted objective function (7) that reflects this operation directly. Variables $\mathbf{Q}$ and $\mathbf{R}$ represent positive-definite real symmetric matrices that serve to weigh the cost according to specific design problems. The utility of such a formulation is that it allows one to tune the aggressiveness of the control response:

$$S = \int_0^\infty \mathbf{x}^T(t)\mathbf{Q}\mathbf{x}(t) + \mathbf{u}^T(t)\mathbf{R}\mathbf{u}(t)dt. \tag{7}$$

In the case of circadian rhythms, the optimal control problem [11] is simplified by setting $\mathbf{R}$ to zero, yielding a potentially aggressive cost function. Additionally, the infinite horizon objective function is reduced to horizon encompassing a single period of oscillation. As a result, the controller minimizes the error by weighing the amount of time needed to track the reference. Given the nature of the PRC, each *desired* phase shift, $-\phi$, may have more than one solution. The combination of relative control indices, k_{cont}, are determined by minimizing the difference between $-\phi$ and the PRC function output (8).

$$\begin{aligned} k_{cont} &= \min_k \left|\phi - \phi^+\right| \\ & k \in [0,1) \end{aligned} \tag{8}$$

During this procedure, it is important to address two special conditions. If the desired positive phase difference is beyond the maximum achievable phase advance, the controller defaults to perturbing the system at $k = \frac{2}{3}$. Similarly, if the desired negative phase difference is less than the maximum achievable phase delay, the controller defaults to perturbing the system at $k = \frac{9}{16}$.

The vector τ is comprised of the relative time inputs and related transients provided by the PRC and TRC, respectively. The first entry denotes the time delay, τ_{delay}, between the current time and the relative time at which the control may be applied (9).

$$\begin{aligned} \tau_{delay} &= (k_{cont} - k_s) \cdot T \\ & if \ \ \tau_{delay} < 0 \\ & then \ \ \tau_{delay} = (k_{cont} - k_s + 1) \cdot T \end{aligned} \tag{9}$$

The second entry, τ_{trans}, denotes the transient time associated with this input (10).

$$\tau_{trans} = g_{trc}(u(k_{cont})) \tag{10}$$

The $\mathbf{Q}$-matrix is set equal to a two-dimensional identity matrix if time factors are weighted uniformly. Subsequently, the performance criterion minimizes the cost of j possible control inputs over the next period of oscillation (11). If the cost of existing in transient is more stringent than the controller's time delay, w_{trans} has greater magnitude than w_{delay}.

$$\begin{aligned} S_j &= \tau_j^T(t) \begin{bmatrix} w_{delay} & 0 \\ 0 & w_{trans} \end{bmatrix} \tau_j(t) \\ & t \in [t, t+T) \\ \tau &= [\tau_{delay} \ \ \tau_{trans}]^T \end{aligned} \tag{11}$$

Minimizing the cost function yields the optimal control time $\tilde{k}_{cont}$ along with its respective time delay $\tilde{\tau}_{delay}$ and transient period $\tilde{\tau}_{trans}$. The real-time control input occurs when current time t is equal to: $t_{cont} = t + \tau_{delay}$.

C. Model Predictive Control

The main idea of model predictive control (MPC) is to choose a control action by repeatedly solving an optimal control problem. This optimality aims at minimizing a performance criterion over a future horizon, while subjecting system properties to constraints [5]. Future behavior for a variety of control inputs are computed according to a model of the plant (3). The most ideal behavior determines the next control action. Through use of PRC and TRC's, a closed-loop optimal control algorithm is applied to the circadian oscillator, resetting the phase to that of an entraining cycle. This control system mimics an MPC by assuming a stage cost involving a one-step ($m = 1$) horizon over an entire cycle of oscillation ($p \in [t, t+T)$), while driving the phase to a target reference signal. Successful implementation of such an algorithm shows promise for more strict control over a longer horizon.

D. Results

Using the weight $\mathbf{Q} = diag(1,1)$, the controller is able to recover approximately 12-hours of phase difference within four days (Fig. 6). Specifically, in the case of an initial -11.5-hour phase difference, the control tracks the reference with 0.2-hours accuracy in approximately 3.5-days. Tracking a difference in the other direction is less time consuming due to the asymmetric attributes of the PRC. An initial phase of +11.5-hours requires 3.25-days of recovery.

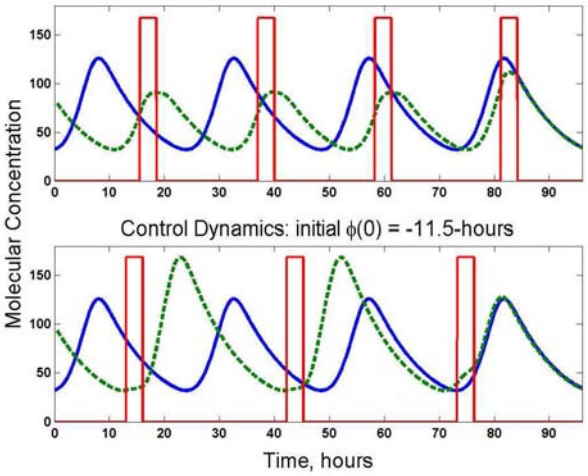

Fig. 6. **Optimal Phase-Tracking of the Circadian Oscillator.** Control inputs are depicted as square waves indicating the time point and duration of light-induced TIM degradation. This light impulse corrects +11.5-hour (upper simulation) and -11.5-hour (lower simulation) initial phase differences, terminating control once the difference in phase is less than or equal to 0.2-hours. The reference is shown as a solid line oscillation while the controlled signal is dashed.

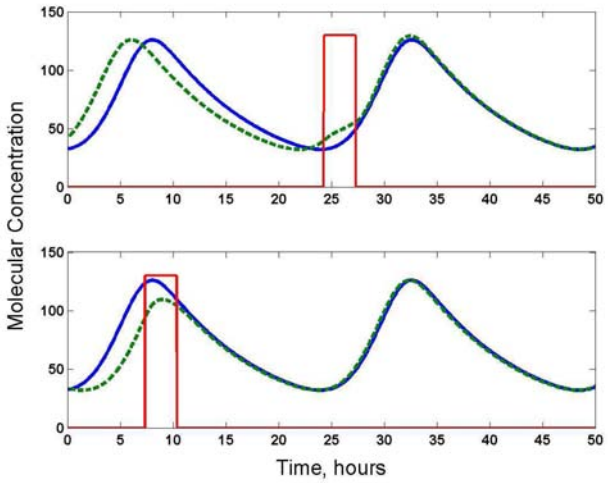

Fig. 7. **Comparing Weight Functions:** $w_{trans} > w_{delay}$**.** Response dynamics for the case when the cost of existing in transient is 1000-times more than the cost of delay. The controlled system tracks the reference as soon as the light input is turned off, minimizing the time spent in transient.

Performance functions are varied in order to optimize specific criteria. When transient weights are greater, $\mathbf{Q} = diag\,(1,1000)$, the system recovers phase almost immediately after the light input has terminated (Fig. 7). When time delay weights are greater, $\mathbf{Q} = diag\,(1000,1)$, the control input is applied sooner, but the total recovery time suffers as it takes the system longer to track the reference (Fig. 8). Both scenarios are able to track a +2-hour phase difference (upper simulation) and a -2-hour difference (lower simulation) within 0.2-hours accuracy. Solid lines symbolize reference trajectories while dashed lines symbolize the controlled system with optimal light inputs as square waves.

E. Phase Recovery

The recovery time is the transient required to reset the circadian clock. Figure 9 indicates that the recovery time is longer for negative desired phase changes, regardless of applying optimal control methods. This discrepancy evolves from the fact that the PRC is asymmetric for positive and negative phase shifts. The maximum achievable phase delay by a single light pulse is 4.6-hours, whereas the maximum phase advance is 3.2-hours (Fig. 4). Due to this asymmetry, capturing a 12-hour phase difference is more efficient by forcing phase advances rather than delays. Figure 9 illustrates the recovery times associated with applying a weight $\mathbf{Q} = diag\,(1,1)$ in the cost function. Previous studies in this group (unpublished data) prove that proportional control methods are less efficient. Through use of proportional control, the system would take 6-days to recover approximately 12-hours of phase with 0.5-hours of accuracy. Through use of a cost function, this initial phase is eliminated within 3.5-days and 0.2-hours accuracy.

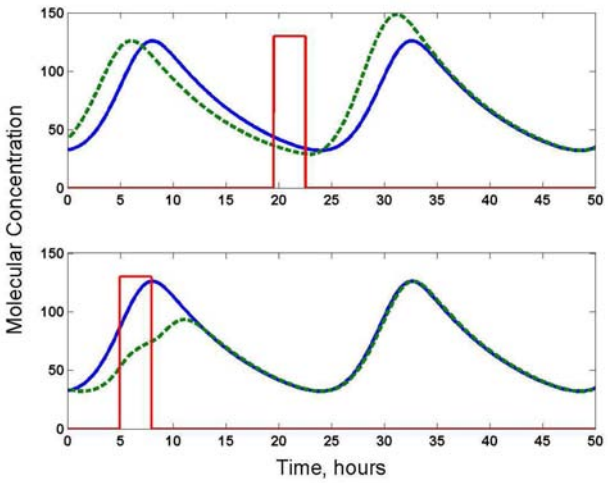

Fig. 8. **Comparing Weight Functions:** $w_{delay} > w_{trans}$**.** Response dynamics for the case when the cost of delay is 1000-times more than that of the transient. Light inputs are applied to the system sooner, minimizing the delay time. Consequently, the system requires more time to track the reference.

There exists one case in which a -10-hour desired phase requires 4.5-days of recovery. The abnormally long recovery time is due to numerical precision. If the tolerance or level of accuracy were less stringent, the -10-hour initial phase recovery time would fit the general pattern.

IV. Conclusions

The application of control theory to complex biological systems has long been a goal for both the engineering and medical communities. This paper develops an optimal phase-tracking control algorithm for an oscillatory biological system, commonly found in bionetwork processes based on a series of activation and deactivation of states. Analysis

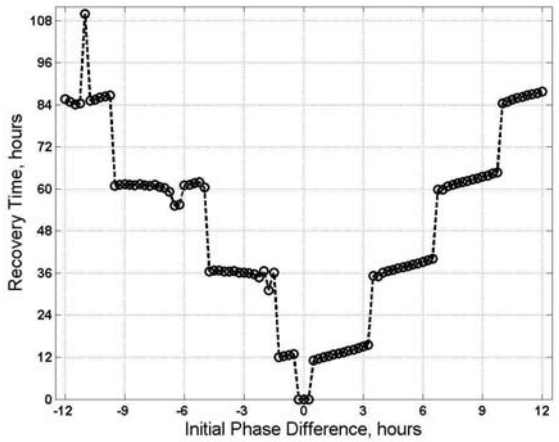

Fig. 9. **The Circadian Recovery Map**. The asymmetry of the recovery time relates directly to the discrepancy between the maximum phase delay versus the maximum phase advance with respect to identical control inputs. Initial phase differences ranging from -12 to +12 hours are reduced to a *maximum* difference of 0.2-hours, after which the signals are considered in phase. This data was constructed from detailed simulations of 97-runs with initial phase difference intervals of 0.25-hours.

of the circadian clock demonstrates a control input (light) that directly influences the parameter ν_{dt}. A phase response curve in addition to a transient response curve may be generated to capture the time-dependent costs of phase-tracking a reference signal for purposes of solving the performance criterion. Optimizing this criterion provides the ideal control input, or times to admit a light pulse. Closed-loop yields the desired change of phase, forcing the controlled signal to track the reference with 0.2-hours of phase accuracy. The use of such pulses as artificial entraining agents may help reduce the recovery time of robust systems when subject to disturbances such as significant changes in daylight patterns. These disturbances may arise from frequent travel resulting in jet lag [2]; or, they may be due to living in more extreme environments where daylight hours are minimal, or nonexistent [3]. Although this study makes use of the *Drosophila* circadian system, the phase tracking control algorithm described in this paper is generic and may be applied to other biological oscillators with stable limit cycle behavior. In the case of mammals, light treatment has proven to be most effective in alleviating symptoms acquired due to jet lag, playing a primary role in human entrainment as it does in many other organisms [2].

Further studies include entrainment of the circadian oscillator in a more natural setting wherein light/dark cycles affect the system's response during control. Dawn and dusk must then be characterized as gradual changes in light intensity instead of the currently employed on/off transitions. Robustness and sensitivity analysis may also encourage studies of entrainment through manipulation of different parameters sets [12]. Parameters with higher sensitivity measures may allow even more time-efficient tracking of the reference cycle [1]. Therefore, studying the control of biological systems provides insight in the manipulation of natural systems for medical purposes, and allows for greater application of control theory.

V. Acknowledgements

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