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Circadian Phase Entrainment via Nonlinear Model Predictive Control

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A nonlinear model predictive control algorithm is developed to investigate the phase resetting properties of robust nonlinear biological oscillators; in particular, those of the circadian rhythm. This pacemaker is an autonomous biochemical oscillator with a free-running period close to 24 hours. Research in chronobiology indicates that a light stimuli may delay or advance the phase of the oscillator, allowing it to synchronize physiological processes and entrain to the environment. In this paper, a closed-loop optimal phase tracking control algorithm is developed and applied to a *Drosophila* circadian model. Through use of nonlinear MPC, optimal phase entrainment is investigated and compared to natural phase resetting via light:dark cycles.

Motivation

A well-studied example of a biological oscillator is the circadian clock. The term *circa-* (about) *diem* (a day) describes a biological event that repeats every 24-hours. Such rhythms are possessed by most organisms, acting as a biological clock. They are observed at all cellular levels since oscillations in enzymes and hormones affect cell function, cell division, and cell growth [1]. Circadian rhythms serve to impose internal alignments between different biochemical and physiological oscillations. Their ability to anticipate environmental changes enables organisms to organize their physiology and behavior such that they occur at biologically advantageous times during the day [1]. An inability to entrain circadian phase to the environment or anticipate change causes many functional disorders.

Circadian disorders include non-24-hour sleep-wake syndrome (often due to blindness), rapid time-zone change syndrome (jet lag), work-shift syndrome (impaired sleep and alertness due to unusual work times), advanced or delayed phase sleep syndrome, and irregular sleep-wake pattern syndrome [2]. Such disorders are often caused by circadian oscillators that are out of phase with the environment, and thereby hinder one's performance. Many researchers have studied the clock in an attempt to both understand and resolve existing phase discrepancies. Daan and Pittendrigh, for instance, discussed light-induced phase shifts as a function of circadian time and the role phase response curves play in achieving entrainment [3]. Watanabe *et al.* confirmed Daan and Pittendrigh's work through experimental procedures proving that the basis for phase adjustment involves rapid resetting of both advance and delay components of the phase response curve [4]. Boulos *et al.* performed similar experiments establishing bright light treatment as a means to accelerate circadian re-entrainment following transmeridian travel [5]. Despite the decades of work put forth in understanding circadian phase and entrainment properties, the idea of optimally controlling phase via a closed-loop control algorithm is a recent area of interest.

Background

In this study, the *Drosophila melanogaster* (fruit fly) 10-state mathematical model [6] demonstrates the utility of nonlinear model predictive control specific to nonlinear oscillators. This moderately complex system consists of two coupled negative feedback loops that model the transcription, translation, phosphorylation, and effective delays associated with *period* and *timeless* genes, and their

protein counterparts (Fig. 1). Experimental data proves that a change in light pattern controls phase-resetting properties of the *Drosophila melanogaster* circadian clock [7].

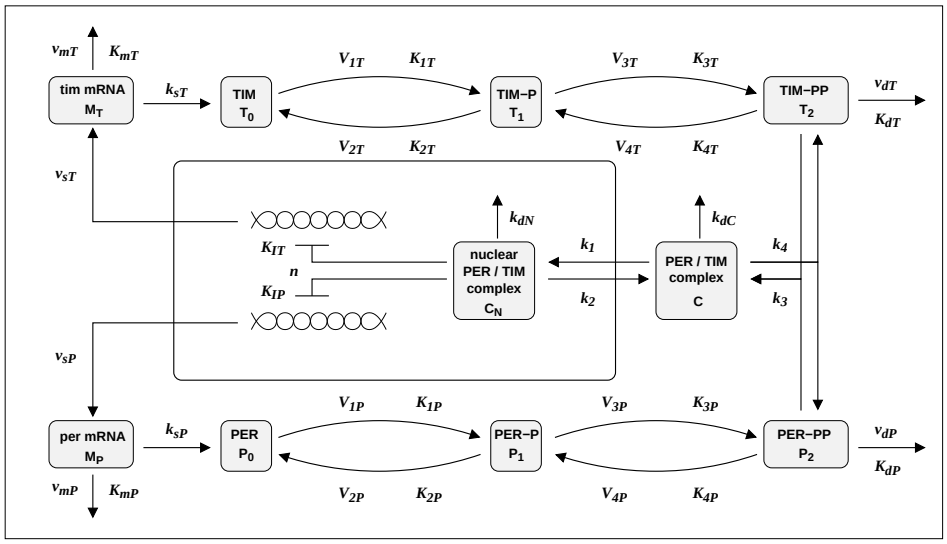

Figure 1: **The 10-state circadian model (adapted from [6]).** Negative regulation of *per* and *tim* gene expression occurs via the nuclear PER/TIM complex. *per* and *tim* genes are transcribed in the nucleus, after which their mRNAs are transported into the cytosol where they undergo protein synthesis. 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/T_2) form a PER/TIM complex, C, that enters the nucleus and closes the feedback loop by suppressing gene expression. Bright light doubles the T_2 degradation rate, ν_{dT}, and serves as a control input for phase resetting.

Admitting light pulses under free-running (dark:dark) conditions resets the oscillator by inducing a phase advance or delay [8]. If the stimulated rhythm, $\mathbf{x}(t)$, leads the unperturbed reference, $\mathbf{r}(t)$, by less than one-half cycle upon admission of a light pulse, there exists a phase advance; or, if it lags by less than one-half cycle, a delay [8]. The mapping of light pulses and their resulting phase shift is captured in a phase response curve (PRC) (Fig. 2) [8]. It characterizes the clock's time-dependent sensitivity toward the given stimulus. Through use of PRCs, one may predict how biological oscillators respond to a light input, and reset the system's phase by manipulating the duration and intensity of control.

Mott *et al.* uses model-based predictive control to find a set of light pulses necessary to maintain and shift the biological clock within a constrained environment (*i.e.* maintaining an astronaut's rhythm in space) [9]. Their methods are applied to a modified Van der Pol oscillator with a free-running period just over 24 hours. The Van der Pol system is transformed into a linear model through use of both a nonlinear state feedback compensation block and a nominal linear approximation. In our previous work, model-specific data is calculated *a priori* (*i.e.* phase and transient response curves) and used it in combination with a cost function to determine the next control move, simulating an iterative closed-loop look-up table problem [10]. None of these methods, however, take advantage of natural light:dark entrainment.

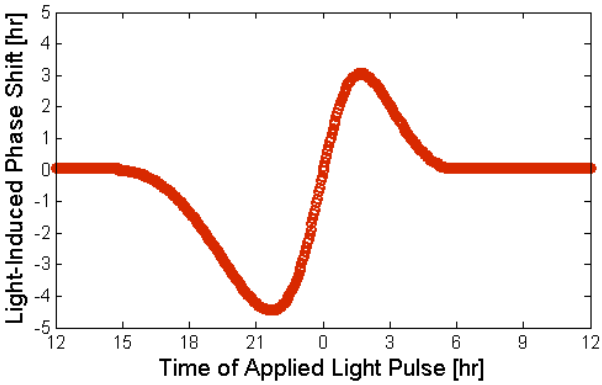

Figure 2: **The 10-state *Drosophila* circadian PRC.** This light input to phase shift relationship illustrates time-dependence and asymmetry as the maximum phase advance of 3.2-hours occurs when light is flashed in the early subjective morning, while the maximum phase delay of 4.6-hours is due to a light pulse in the early subjective night.

Methods

In this study, a closed-loop optimal phase tracking control system is developed for a nonlinear oscillator and applied to a circadian model. Through use of nonlinear MPC, the efficacy of entrainment via natural light:dark cycles is compared to entrainment via light:dark cycles in combination with controlled light pulses. A genetic evolutionary strategy serves as the global optimizer, choosing a set of control moves for a specified move horizon (Fig. 3). Although Mott *et al.* equate the move horizon with the prediction horizon, this algorithm requires that the prediction horizon be longer than the move horizon to minimize transient-effects.

To compare the efficacy of sun cycle, or light:dark, entrainment with model predictive control, a series of simulations are put together that measure the time it takes light:dark cycles to reset $\pm$12-hour phase differences. Due to the nonlinearity of the system, the recovery time associated with a phase shift beginning at dawn may differ from the recovery time of that same phase shift beginning at noon. Therefore, phase recovery data for a set initial conditions spanning the entire circadian period are generated. Once the controlled system's state trajectories are within a certain percent of the nominal reference trajectories, the system is considered to be in phase.

Coupling MPC with light:dark cycles significantly improves phase-resetting, since the prediction horizon allows the MPC to take control action at the current time in response to a forecast of a future error even though the error up to the current time may be zero. Whereas light:dark cycles are consistent, the MPC algorithm is flexible and may manipulate the duration and intensity of light over the set move horizon. While the control algorithm is designed to be general, its application to the nonlinear circadian network is key in resetting the clock's phase, optimizing performance and alertness, and minimizing the effects of circadian disorders. Preliminary data suggests that nonlinear model predictive control is effective at providing optimal control inputs (light pulses) that reset phase differences with minimal *a priori* information. Furthermore, the algorithm minimizes transient effects and may be applied to systems in both constant darkness and natural

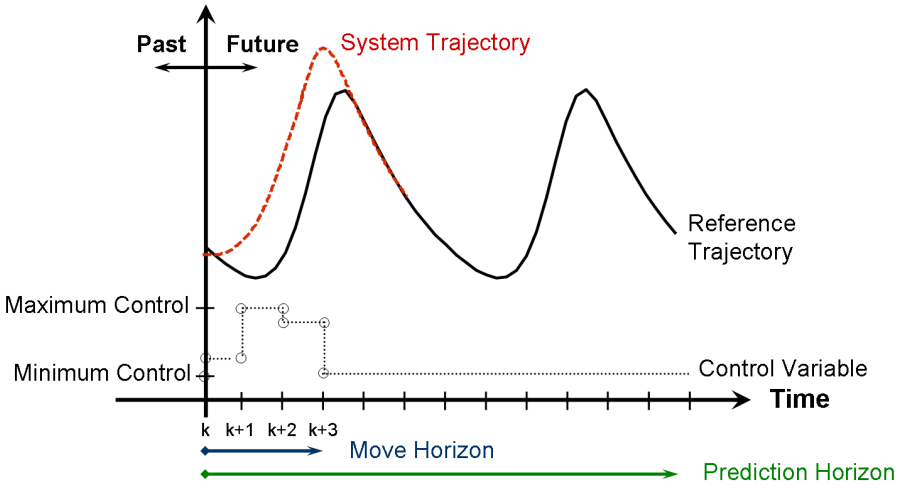

Figure 3: **Nonlinear model predictive control of oscillatory systems.** Model predictive control minimizes the cost of error within the prediction horizon by choosing a set of optimal control moves in the move horizon. The first move is implemented for the duration of a time step, after which the algorithm re-evaluates the forecasted error and control.

light:dark environments, providing greater efficacy in its experimental use. The control algorithm provides certain degrees of freedom – move horizon, prediction horizon, control boundaries, time steps, optimizer, cost function – that may be customized per application. Although the *Drosophila melanogaster* mode serves to prove optimal phase resetting, the algorithm allows researchers to use any asymptotically stable oscillatory model without introducing additional errors due to linearization or approximations, providing a more accurate and robust application of nonlinear model predictive control.

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