Modifying The Human Circadian Pacemaker Using Model Based Predictive Control[1]

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Abstract

The human circadian pacemaker is a biological timekeeping mechanism that governs alertness as well as many other physiological processes of the human body. It is widely accepted that daytime alertness is maximized when an individual's sleep/wake schedule and circadian pacemaker are synchronized. Unfortunately today's world is characterized by widely distributed activity schedules which often make this difficult. However research in chronobiology indicates that ambient light stimulus can be used to phase advance or delay the human circadian pacemaker. To optimally control the human circadian pacemaker using light, the authors present a model based predictive control system. This approach readily facilitates closed-loop control and elegantly handles the constraints present in a typical human environment, thus has merit for a number of practical applications.

Keywords: Circadian Rhythm, Constrained Nonlinear Control, State-Feedback Linearization, Model Based Predictive Control, MBPC, MPC.

1 Introduction

Research in the field of chronobiology, the study of time-varying biological systems, has shown that humans possess an endogenous circadian pacemaker: a self-oscillating chemical process in the suprachiasmatic nucleus region of the brain with a period very near to 24 hours [2]. The human circadian pacemaker is understood to synchronize the rhythm of many physiological processes and govern daily fluctuations in core body temperature [8], hormone levels [12], and alertness [14].

Given the fact that the period of the circadian cycle is 24 hours, it is not surprising that light is the strongest stimulus that affects the human circadian pacemaker [1][3]. In fact, light stimulus has been shown to phase shift the human circadian pacemaker [1][6][7][9]. The effect of this phenomenon on the cycle of alertness is of particular interest, as it is desirable to maximize alertness during waking hours. This can be achieved by shifting the phase of the human circadian pacemaker, using light, to achieve synchronicity with a given activity schedule. The authors present a means of optimal controlling light in a closed loop manner, accounting for inherent constraints connected with introducing light stimulus to a human.

Increasingly accurate models of the effect of light on the human circadian pacemaker have been developed over the past two decades. Early models [3] led to qualitative approaches for modifying circadian rhythms in laboratory and clinical applications. The use of a mathematical Van der Pol oscillator equation to model the circadian pacemaker was first suggested in 1982 by Kronauer et al. [10] and led to the development of more precise algorithms to determine the intensity and duration of light pulses required to produce circadian phase shifts [9]. Subsequent refinements of this model by Jewett et al. [5] to match empirical data now accurately describe a continuous distribution of light stimuli and corresponding circadian phase shifts.

The authors present a means to optimally achieve desired circadian phase shifts through the application of control system theory. In developing an approach to the problem, the following unique features of the system are considered:

- there are practical constraints to light levels in a typical human environment
- the model of the human circadian pacemaker is nonlinear
- processing time is not a critical factor since the circadian process happens over 24 hours

The authors describe an approach based on model based predictive control (MBPC) that addresses these features by making use of model based predictions in order to optimize inputs in the presence of constraints. Incorporating a state-feedback compensation block deals with the nonlinearities

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2 Model of Human Circadian Pacemaker

A mathematical model of the effect of light on the human circadian pacemaker was developed by Jewett and Kronauer in 1999 [5] based on data from many empirical observations. This model describes a human as a single-input single-output (SISO) system in which light and an indicator of circadian state are the input and output respectively. The model is a set of differential equations that captures the oscillatory nature of the circadian pacemaker and the nonlinear effects of light.

Oscillator Equations: The self-sustaining rhythm of the circadian pacemaker is modeled by a modified Van der Pol oscillator with a natural period of slightly more than 24 hours:

$$\dot{x} = \frac{\pi}{12}\left[x_c + \mu\left(\frac{1}{3}x + \frac{4}{3}x^3 - \frac{256}{105}x^7\right) + B\right] \quad (1)$$

$$\dot{x_c} = \frac{\pi}{12}qBx_c - \left[\left(\frac{24}{\tau_x(0.99729)}\right) + kB\right]x \quad (2)$$

where $\mu = 0.13$, $q = 1/3$, $\tau_x = 24.2$, $k = 0.55$, and B is a driving input due to light. The state variables x and x_c are two sinusoids that are out of phase by $90\,^\circ$.

Measurement of the state of the human circadian pacemaker can be accomplished by monitoring any of a number of physiological markers that display corresponding circadian fluctuations. Core body temperature (CBT) is one of these markers and fluctuates approximately sinusoidally. The time at which CBT reaches a minimum is a reliable marker of circadian phase and in the model is used to relate the state of the mathematical model to the actual physiological state of a human subject [5]. The time of the minimum of variable x is defined to occur 0.8 hours before the time of CBT minimum:

$$CBT_{min} = x_{min} + 0.8 \text{ hours}$$

Note that for the purposes of this work, the authors make the assumption that the relation between core body temperature and variable x can be extended to all phases with

$$CBT = x + 0.8 \text{ hours},$$

and subsequently treat the state variable x as the measured output of the human circadian pacemaker model. In practice, measuring an individual's circadian CBT fluctuations requires 'demasking' signal processing techniques [13]. To allow a focus on the control algorithms, this state estimation step is simplified and the circadian state is assumed to be directly measured.

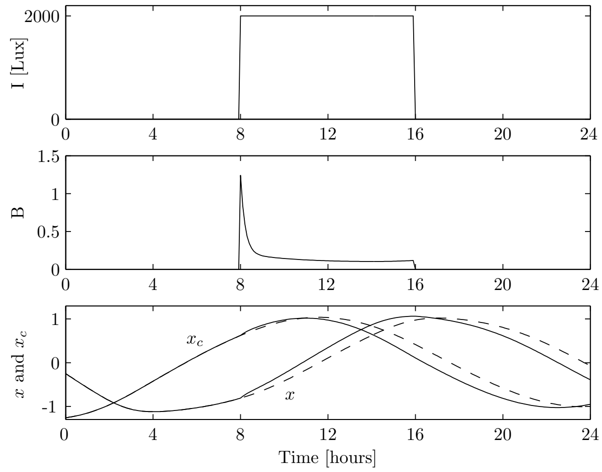

Figure 1: The response of the human circadian pacemaker to a light pulse. a) light intensity input (I) b) driving input (B) to the circadian pacemaker c) response of x and x_c to the light input (solid line) and unforced response (dashed line)

Light Equations: The light input is specified as the ambient light intensity in units of Lux. The following equations relate the light intensity (I) experienced by a human into a driving input (B) on the circadian pacemaker.

The logarithmic response (α) of the human eye to light is modelled by:

$$\alpha = \alpha_0\left(\frac{I}{9500}\right)^p \quad (3)$$

where I is the ambient light intensity in units of Lux, $\alpha_0 = 0.16$, and p=0.6. Further, I is related to a driving input (B) on the circadian pacemaker as follows:

$$\dot{n} = 60[\alpha(1-n) - \beta n] \quad (4)$$

$$B = G\alpha(1-n)(1-mx)(1-mx_c) \quad (5)$$

where β=0.013 and G=19.875. Equation (4) models a filter (n) acting upon (α) and equation (5) models the modulation of the driving input (B) by the current state of the circadian pacemaker and the filter.

Open Loop Model Response: The response of the human circadian pacemaker to a pulse of light and the corresponding driving input (B) is shown in Figure 1. The driving input (B) exhibits an initial peak that decays to a steady state value. Further it is seen how the primary effect of B is to apply an upward force on the state variable x. Depending on the phase of x, B can cause either a phase-advance or phase-delay.

3 Model Linearization

The model equations described in Section 2 lend themselves well to a nonlinear state space representation. To enable the use of MBPC, the original model with light intensity (I) as the manipulated variable is transformed into a linear model where the manipulated variable is the driving input (B). This transformation is achieved by the use of a nonlinear state feedback compensation block together with a nominal linear approximation.

State feedback linearization: The most significant nonlinear aspect of the model is the relation between the light intensity (I) and the driving input (B) that is applied to the circadian oscillator. To hide these nonlinearities from the controller, a nonlinear compensator is designed to perform a reverse transformation, from B to I, that will allow the controller to manipulate B rather than I. An estimate of the current circadian state (x), that is derived as discussed in Section 2, is used in the compensator.

To begin creating the B to I transformation, equation (5) is rearranged as:

$$\alpha = \frac{B}{G(1-n)(1-mx)(1-mx_c)} \tag{6}$$

A complication arises due to the presence of the state variable n that has itself a nonlinear dependance on the value of α in equation (4). Equation (4) describes a decaying exponential function that approaches its steady state value within a short amount of time relative to the length of an average light pulse (16 hours). Thus, the authors simplify equation (6) by approximating n as a constant:

$$n_{approx} = \lim_{t\to\infty} n = \frac{\alpha}{\alpha+\beta} \tag{7}$$

Substituting the value of n_{approx} from equation (7) for n in equation (6) leads to:

$$\begin{aligned} \alpha &\approx \frac{B}{G\left(1-\frac{\alpha}{\alpha+\beta}\right)(1-mx)(1-mx_c)} \\ &= \frac{\beta B}{G\beta(1-mx)(1-mx_c)-B} \end{aligned} \tag{8}$$

Further, equation (3) is rearranged to:

$$I = 9500\left(\frac{\alpha}{\alpha_0}\right)^{\frac{1}{p}} \tag{9}$$

To complete the transformation equations (8) and (9) combine to:

$$I \approx 9500\left(\frac{\beta B}{\alpha_0[G\beta(1-mx)(1-mx_c)-B]}\right)^{\frac{1}{p}} \tag{10}$$

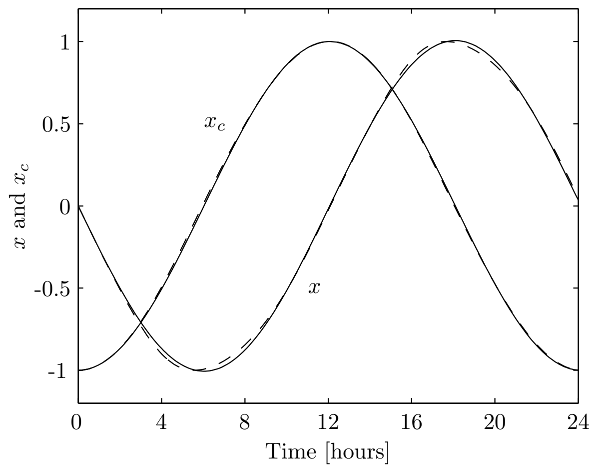

Figure 2: Unforced response (I=0) of x and x_c with linear approximation (μ=0) of equation (1) (solid line) versus the original nonlinear form (dashed line).

Equation 10 is a transfer function of the form $I = f(B, x, x_c)$ that serves as a nonlinear compensation block to convert from B to I. Note that since the terms x and x_c are states of the plant it is implemented using state-feedback.

Nominal linear model approximation: With a nonlinear compensation block allowing B to serve as the manipulated variable, the next goal is to describe the oscillator equations (1) and (2) as a linear state space system with B as the input. A quasi-LPV [4][11] approach was considered here. However, an analysis of the nonlinearities present in this system led to the conclusion that a nominal linear approximation would provide a sufficiently accurate model over the operational envelope of this plant for a length of time corresponding to the prediction horizons used within the MBPC.

Equation (1) contains an expression of terms of x that slightly modifies the original Van der Pol equation so that it matches experimental results. Two terms contain higher order terms of x and therefore introduce nonlinearities. However, the significance of the these terms is reduced by the scaling factor (μ). Also, the expression contains only odd powers of x, and forms an odd function which has an integral of 0 over the normal operating range of $x \in$ [-1,1]. So, due to the small instantaneous effects that average to zero over a full period these terms are eliminated from equation (1) by setting μ=0. A simulation showing the effect of this simplification is shown in Figure 2.

The remaining nonlinearities in the model equations are the two B terms in equation (2). In a similar manner, these terms only serve to make minor adjustments to the behavior of the system as shown by the small values of the multiplicative parameters q and k. The simplification to linearity is performed by setting q=0 and k=0.

The above simplifications result in a nominal linear version of equations (1) and (2) that can be expressed, in state space form, by:

$$\begin{bmatrix} \dot{x} \\ \dot{x_c} \end{bmatrix} = \begin{bmatrix} 0 & \frac{\pi}{12} \\ \left(\frac{24}{\tau_x(0.99729)}\right)^2 & 0 \end{bmatrix} \begin{bmatrix} x \\ x_c \end{bmatrix} + \begin{bmatrix} \frac{\pi}{12} \\ 0 \end{bmatrix} B \tag{11}$$

$$[x_{out}] = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} x \\ x_c \end{bmatrix} \tag{12}$$

4 The application of MBPC

Putting together the linearized state space model and the nonlinear compensation block, a predictive controller is developed. An MBPC based on the linear state-space model from equations (11) and (12) is used to determine the optimal control moves in terms of B. The nonlinear compensation block then converts from B to the light intensity I. This control architecture is shown in Figure 3.

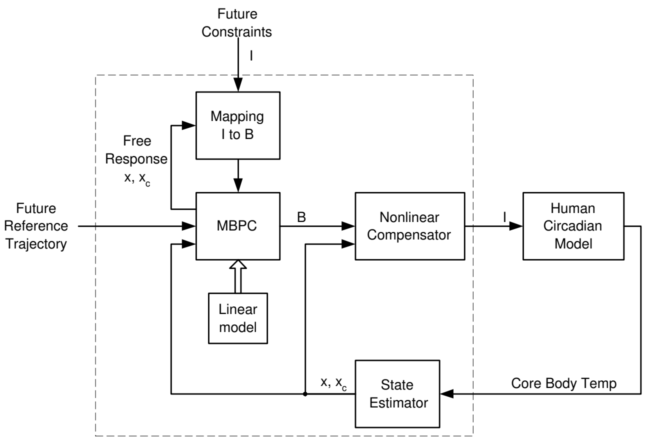

Figure 3: Controller architecture.

The reference trajectory is the desired path of the circadian state variable x. During normal conditions x follows a nearly sinusoidal rhythm with slight aberrations due to the nonlinearities present in the plant. For simplicity the authors chose to use a pure sinusoid as the reference trajectory. Accordingly, the MBPC tolerates small deviations from the reference trajectory, but tracks the fundamental phase and period. These tracking goals are achieved through the implementation of an appropriate error tracking cost function.

The cost function has in its expression the time-varying reference error weight, δ, and the cost for manipulated variable changes, λ, respectively:

$$J = \sum_{k=1}^{p} \left\| \delta(k)[\hat{x}(t+k|t) - r(t+k)] \right\|^2 + \sum_{k=1}^{p} \left\| \lambda(k)\Delta B(t+k-1) \right\|^2 \tag{13}$$

where p is the prediction and control horizon. In the unconstrained case, the nonlinearities in the system are hidden from the MBPC and optimal control moves can be calculated from the cost function (13).

In practical applications however there will be constraints on the light intensity (I). In many situations future constraints on illumination input can also be anticipated from knowledge of an individual's sleep/wake schedule. Therefore the authors designed the MBPC to handle such time-varying constraints on I. Some nonlinear complications arise since constraints on the MBPC's manipulated variable must be expressed in terms of B.

The transformation from a light intensity value (I) to a driving input value (B) is given by equations (3),(4), and (5). At a given time k, B is a function of the current circadian state and current and past values of light intensity:

$$B(k) = f(x(k), x_c(k), \sum_{i=-\infty}^{k} I(i))$$

Therefore, to transform a future constraint on I into a constraint on B, the future circadian state and all the future control moves must be known. This leads to an iterative problem since the future circadian state and control moves depend in turn on the constraints. To solve this, two simplifications are made. First the effect of the state variable n is simplified in the same manner as is done in the nonlinear compensation block. Substituting the value of n_{approx} from equation (7) for n in equation (5) results in a time-invariant approximation of B:

$$B(k) \approx G \frac{\alpha(k)\beta}{\alpha(k)+\beta}(1 - mx(k))(1 - mx_c(k)) \tag{14}$$

where α is given by equation (3). Second, the future values of x and x_c are approximated by substituting their predicted free response values. The free response is determined by calculating future values assuming that the current light intensity (I) remains constant. This assumption yields sufficient accuracy since the strong stiffness of the circadian pacemaker causes it to continue oscillating regularly under typical conditions. Thus, future I constraints are transformed to B constraints using equation (14) with the predicted free response values for x and x_c. The optimal control moves are then calculated under the following constraint condition:

$$B_{min}(k) \leq B(k) \leq B_{max}(k) \qquad \text{for } k = 1 \dots p$$

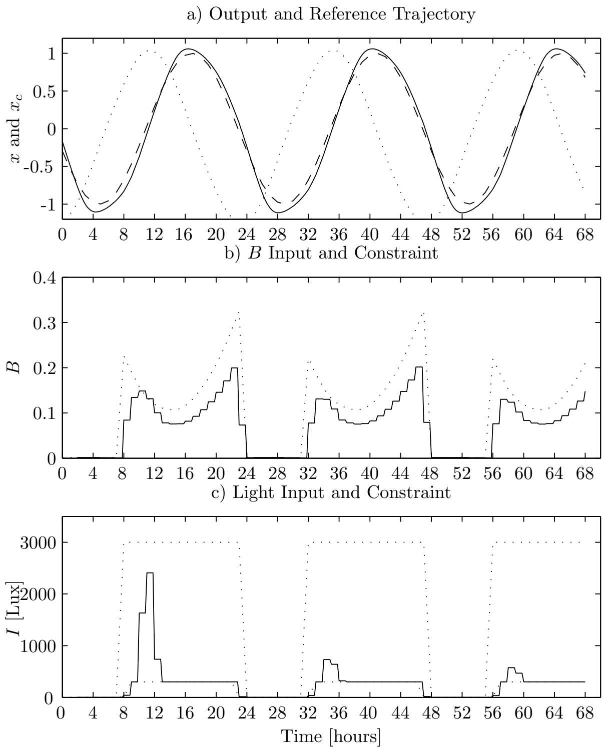

Figure 4: Scenario 1 simulation. In diagram a) the circadian pacemaker x (solid line) is tracked to a reference trajectory (dashed line) with no phase shift. Diagrams b) and c) show the driving input B and the actual light intensity I respectively (solid lines) with their constraint envelopes (dashed lines).

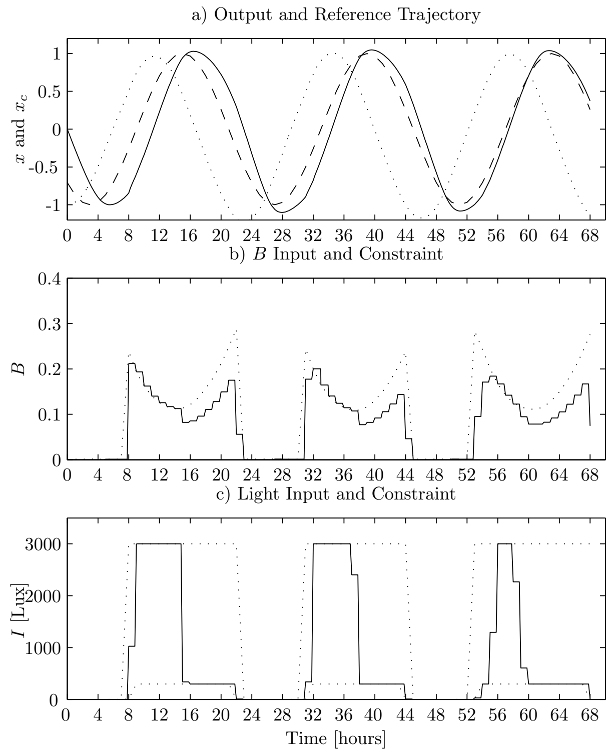

Figure 5: Scenario 2 simulation. In diagram a) the circadian pacemaker x (solid line) is tracked to a reference trajectory (dashed line) with a three hour shift over two days. Diagrams b) and c) show the driving input B and the actual light intensity I respectively (solid lines) with their constraint envelopes (dashed lines).

5 Simulations and Results

Applications for this control system are found in situations where a person's circadian pacemaker needs to be tracked to an optimal rhythm in the presence of input constraints. To demonstrate the operation of the control system the authors created two scenarios involving astronauts.

Astronauts in orbit experience light/dark cycles with greatly reduced periods. It is therefore necessary to artificially maintain 24 hour circadian cycles to ensure optimal alertness and increased quality of sleep during missions.

The following constraints are imposed on the light intensity input (I):

- the range of light extends from darkness to a high intensity light source:
  ($0 \text{ Lux} \leq I \leq 10,000 \text{ Lux}$)
- no light can be received during sleep:
  ($I = 0$ Lux)
- a minimum amount of light is necessary to perform daily activities while awake:
  ($I \geq 300$ Lux)
- for the first hour after rising and the last hour before sleeping the minimum amount of light is reduced to 100 Lux

Scenario 1: In this scenario an astronaut is maintaining a regular 24 hour schedule of 8 hours asleep and 16 hours awake, and the astronaut's circadian rhythm is already synchronized to the reference trajectory (optimal rhythm). As expected, the circadian pacemaker continues naturally on its 24 hour rhythm, and as can be seen in Figure 4, little control effort is needed to maintain it.

Scenario 2: In this scenario the astronaut receives a mission requirement that involves shifting the waking hours ahead by 3 hours. In anticipation of this, the sleep schedule is adjusted over two days and it is left to the control system to ensure that the circadian pacemaker catches up. With knowledge of the schedule change, a reference trajectory with a 3 hour phase lead is introduced and the MBPC determines the optimal light levels over the course of three days. As shown in

Figure 5, the astronaut's circadian rhythm is successfully tracked by the third day.

6 Conclusions

In a novel application of control system theory to the field of chronobiology, the authors have presented a means of optimally controlling the human circadian pacemaker using light stimulus. The control architecture developed consists of a constrained MBPC augmented by a nonlinear block to address nonlinearities present in the model of the circadian pacemaker. In simulated scenarios requiring shifting of the human circadian pacemaker the controller performed successfully.

Areas for further work include improvements to the state estimation and the cost function implementations. To focus on the control aspect, the authors assumed the presence of a means of accurately sensing the human circadian pacemaker state. A more complete treatment of circadian pacemaker state estimation would be beneficial. The inclusion of a nonlinear cost function on the driving input (B) would allow accurate representation of the physical cost of illumination.

The MBPC approach to modifying the human circadian pacemaker described in this paper is a viable means of implementing a practical control system that maximizes an individual's alertness during waking periods. Applications include environmental control systems in environments that have irregular or unnatural illumination patterns, such as those found in submarines and the International Space Station. Other general applications include situations requiring changes in an individual's sleep/wake schedule such as shift work and transmeridian travel.

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