Published in final edited form as:

J Theor Biol. 2007 August 21; 247(4): 583–599. doi:10.1016/j.jtbi.2007.04.001.

Addition of a non-photic component to a light-based mathematical model of the human circadian pacemaker

Melissa A. St Hilaire⁽¹⁾, Elizabeth B. Klerman⁽¹⁾, Sat Bir Khalsa⁽²⁾, Kenneth P. Wright Jr.⁽³⁾, Charles A. Czeisler⁽²⁾, and Richard E. Kronauer^{(1),(4)}

⁽¹⁾ Biomathematical Modeling Unit, Division of Sleep Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, 02115, USA

⁽²⁾ Division of Sleep Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, 02115, USA

⁽³⁾ Department of Integrative Physiology, Sleep and Chronobiology Laboratory, Center for Neuroscience, University of Colorado, Boulder, CO, 80309, USA

⁽⁴⁾ Division of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138, USA

Abstract

Mathematical models have become vital to the study of many biological processes in humans due to the complexity of the physiological mechanisms underlying these processes and systems. While our current mathematical representation of the human circadian pacemaker has proven useful in many experimental situations, it uses as input only a direct effect of light on the circadian pacemaker. Although light (a photic stimulus) has been shown to be the primary synchronizer of the circadian pacemaker across a number of species, studies in both animals and humans have confirmed the existence of non-photic effects that also contribute to phase shifting and entrainment. We modified our light-based circadian mathematical model to reflect evidence from these studies that the sleep-wake cycle and/or associated behaviors have a non-photic effect on the circadian pacemaker. In our representation, the sleep-wake cycle and its associated behaviors provides a non-photic drive on the pacemaker that acts both independently and concomitantly with light stimuli. Further experiments are required to validate fully our model and to understand the exact effect of the sleep-wake cycle as a non-photic stimulus for the human circadian pacemaker.

Keywords

human; circadian rhythms; mathematical model

Introduction

A number of mathematical models have been developed to understand the physiology and to predict the observable behavior of the human circadian timekeeping system [for review, see

Corresponding Author & Reprint Requests: Melissa A. St. Hilaire, Analytic and Modeling Unit: Division of Sleep Medicine, Brigham & Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, msthilaire@rics.bwh.harvard.edu, Telephone: 617-278-0620, Fax: 617-732-4015.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(Czeisler and Brown, 1999)]. Such models are used to report the essential features of the system, to make predictions for new experimental protocols and real-life situations, and to generate new hypotheses to be tested. The most accurate and useful mathematical models attempt to reflect the physiology of the dynamic process being studied while remaining simple and functional enough to be used by modelers and experimentalists alike. When new features of the system are discovered, or the existing system is found to be incorrect or inadequate to explain experimental results, the mathematical models must be refined to reflect these new findings. A model refinement may be as simple as a change of a parameter value or as complex as the addition of a new model structure. It is important to ensure that throughout the modeling process, refinements do not change the ability of the model to make predictions to previous datasets on which it was developed.

Endogenous circadian (~24-hour) rhythms are present in most living organisms, including single-celled organisms, plants, and mammals. These rhythms are responsible for organizing many physiological phenomena, including the sleep/wake cycle, hormone secretion, and subjective alertness and performance in humans. Light is the strongest known stimulus for affecting the circadian pacemaker [(for review, see Czeisler and Wright 1999)]. A dedicated single synaptic pathway, the retinohypothalamic tract (RHT), exists in mammals between the retina and the suprachiasmatic nucleus (SCN), the site of the circadian pacemaker. Even very dim levels of light have been shown to have an effect on the circadian pacemaker (Zeitzer et al., 1997, 2000; Duffy and Wright, 2005). However, non-photic stimuli have also been reported to have weak but independent effects on the SCN. A mathematical model of the circadian system should include a self-sustaining endogenous rhythm, effects of exogenous stimuli, and a mechanism by which the exogenous and endogenous components interact. Here we updated the light-based circadian model developed by Kronauer et al. (1999, 2000) to incorporate more recent studies of the effect of light on the human circadian pacemaker. More notably, we also refined the model to include the sleep-wake cycle and its associated behaviors as a non-photic zeitgeber of the circadian pacemaker.

The effects of non-photic stimuli on the mammalian circadian pacemaker

A non-photic stimulus is any stimulus independent of light that affects the endogenous circadian pacemaker. A variety of non-photic stimuli have been primarily studied in animals [for review, see (Mistlberger and Skene, 2004)], including fetal entrainment to maternal signals in some rodents (Reppert et al., 1987), entrainment via food-anticipatory activity in rats (Mistlberger, 1994), entrainment by melatonin administration in rats (Redman et al., 1983), and intermittent cage agitation and water sprinkling in marmosets (Glass et al., 2001). One well-known non-photic stimulus in animals is locomotor activity, the effects of which have been documented across a number of species [for review, see (Mrosovsky, 1996)], most notably in the Syrian hamster. For example, it has been observed that continuous wheel running during a 3-h dark pulse in the mid-subjective day (the rest phase in nocturnal species such as the Syrian hamster) induces large phase advances averaging up to 3.5 h. The results from these studies suggest that high-intensity locomotor activity can phase-shift the endogenous circadian pacemaker. Recent experiments have sought to determine whether this observed circadian clock resetting in the Syrian hamster was due to the locomotor activity itself or to wake during the rest phase. Antle and Mistlberger (2000) reported that sleep deprivation by gentle handling (without locomotor activity) resulted in phase shifts (up to 4 hours) similar to those induced by locomotor activity during a 3-h dark pulse. Mistlberger et al. (2002) further reported that continuous wheel running was not necessary to induce phase shifts and that enforced wakefulness is sufficient to induce phase shifts averaging 4.35 ± 1.83 hours, although a subsequent review determined that at least low levels of activity were necessary to induce significant phase shifts (Mistlberger et al., 2003). These results suggest that wakefulness, with minimal locomotor activity, induced the observed phase shifts. These

results also suggest that non-exercise control groups of hamsters in previous studies, in which no phase shifts were observed during the 3-h dark pulse, were not kept sufficiently aroused throughout the duration of the pulse.

A number of Phase Response Curves (PRCs) to non-photic stimuli have been reported in animals. In one study, novelty wheel-running, as well as the benzodiazepine triazolam, produced phase shifts in the Syrian hamster (Rosenwasser and Dwyer, 2001). PRCs generated from these data show that the pacemaker is most sensitive (i.e. shows the largest phase advance shifts) to non-photic stimuli during the subjective day (normal rest phase) and shows minimal phase delays to non-photic stimuli during the subjective night (normal activity phase). This non-photic PRC has phase responses that are 180 degrees opposite the phase responses of a photic PRC generated from light responses in Syrian hamsters, which features large phase advances when light is given during the normal activity phase (Daan and Pittendrigh, 1976; Takahashi et al., 1984). Extrapolating from the results of Mistlberger et al. (2002) described above, the sensitivity to non-photic stimuli during the subjective day may be related to arousal, as opposed to activity, during these phases in which the hamster would otherwise be asleep.

Studies in animals have indicated that the possible neuroanatomical pathway for non-photic stimuli to affect the circadian pacemaker may include the intergeniculate leaflet, which can transfer non-photic information to the suprachiasmatic nucleus (SCN) via neuropeptide-Y (Biello et al., 1994; Lewandowski and Usarek, 2002). These studies do not differentiate between behavioral state (i.e. sleep or wake) and activity. However, an experiment by DeBoer et al. (2003) suggests that sleep states alter the activity of neurons in the SCN, supporting theories of a non-photic effect of the sleep-wake cycle on the circadian pacemaker.

A variety of non-photic stimuli have also been studied in humans, including the effect of carbohydrate-rich meals (Kräuchi et al., 2002), auditory stimuli (Goel 2005), and exercise. Exercise was reported to facilitate phase advances to a 23.67-h sleep-wake cycle by advancing the pacemaker ~1.6 h over 12 cycles, compared to ~0.8 h delays in the non-exercise control group (Miyazaki et al., 2001). A PRC to 1-h high-intensity exercise scheduled in the morning, afternoon, evening, or biological night (nocturnal) reported sensitivity to exercise across the circadian phases studied, with the maximum phase delays in the nocturnal exercise group (Buxton et al., 2003). Both of these studies were conducted in light intensities that could affect the interpretation of these results (50 lux and 40 lux, respectively), since these light intensities have been shown to phase-shift the pacemaker (Zeitzer et al., 2000). In a separate study, three 45-min bouts of moderate intensity exercise separated by 1-h intervals of rest in very dim light (<1 lux) scheduled during the subjective night across 7 days were reported to induce significant phase delays in the exercise group (~3.17 h) compared to the non-exercise group (~-1.67 h) (Barger et al., 2004).

Studies of another non-photic stimulus in humans, melatonin administration (Sack et al., 1992, 2000; Lockley et al., 2000), revealed that daily administration of melatonin before habitual bedtime entrained some blind subjects, who were not entrained, to a 24.0-h sleep-wake schedule. PRCs to melatonin in sighted humans have been constructed [for review, see (Lewy and Sack, 1997)]. The human melatonin PRC reported in Lewy et al. (1998) features phase advances in the late subjective day/early subjective night and phase delays in the late subjective night/early subjective day, which is 12 hours opposite the light PRC. The magnitude of the phase shifts are small compared to the light PRC, reaching a maximum phase advance of ~1.0 h and a maximum phase delay of ~0.9 h over 4 days of melatonin administration. In sighted individuals, phase shifts after melatonin administration may be

due to both direct effects of melatonin on the circadian pacemaker and the soporific effects of melatonin, increasing the probability of sleep onset and its associated behaviors.

Several studies have also attempted to determine whether the sleep-wake cycle has an effect on the circadian pacemaker in humans. Studies that attempt to determine the effect of the sleep-wake cycle as a non-photic zeitgeber are often difficult, because under most experimental conditions the light-dark cycle coincides with the sleep-wake cycle [for review see (Klerman, 2001)]. Because even dim light (~12 lux) has been reported to have an effect on the circadian pacemaker (Zeitler et al., 1997, 2000; Duffy and Wright, 2005), studies conducted to determine the non-photic effect of the sleep-wake cycle should be conducted at very dim light levels (ideally 0 lux) to avoid confounding observations with photic effects. One study of a forced 24-h sleep-wake schedule in dim light (~5 lux) suggests that the imposed rest-activity cycle may be sufficient to entrain the pacemaker of some subjects to the 24-h day (Nakamura, 1996). In a more recent experiment, subjects scheduled to a protocol that advanced the sleep-wake schedule by less than one hour each day ($T = \sim 23.67$ h) in <0.2 lux phase advanced towards the entraining stimuli compared to control subjects in the same lighting condition scheduled to a $T = 24.0$ -h protocol (Danilenko et al., 2003). In studies that examined the effect of sleep deprivation on the circadian pacemaker, it has been reported that a 40-h sleep deprivation in dim light (between ~1.5 and 13 lux) induced, on average, a phase delay shift (Cajochen et al., 2003; Wright et al. 2005) that was larger than that which could be explained by the drift due to intrinsic period of the circadian pacemaker (Wright et al. 2005). Because light levels during these studies were between ~1.5 and 13 lux in the angle of gaze, the phase delay seen during sleep deprivation could be attributed to the extended exposure to these comparably low levels of light. It is also possible that the extended duration of arousal may have an effect on phase shifts similar to that observed in hamsters (Mistlberger et al., 2002). Sleep deprivation protocols conducted in complete darkness are needed to verify this hypothesis.

The recent findings of entrainment in response to a scheduled very dim light (~1.5 lux)/dark activity/rest wakefulness/sleep cycle (Wright et al., 2001) and entrainment of a completely blind subject (no light effects) to a forced non-24-hour rest-activity cycle (Klerman et al., 1998) can also be used to guide further investigations of the sleep-wake cycle as a non-photic stimulus. We have incorporated the results from these studies into an existing mathematical model of the circadian pacemaker (Kronauer et al. 1999, 2000). Although there are a number of mathematical models of the human circadian pacemaker that already incorporate the effects of non-photic stimuli (e.g. Gundel and Spencer, 1999; Nakao et al., 2002), these models do not consider the sleep-wake cycle as a non-photic zeitgeber nor do they contain both a direct photic drive and a direct non-photic drive on the circadian pacemaker. We propose to modify a well-tested model of the effects of light on the circadian pacemaker to incorporate an additional non-photic effect from the sleep-wake cycle. In this model the non-photic effects of the rest-activity cycle are introduced as a drive independent from light that acts on the pacemaker. We will also modify the existing photic effect built into the model to improve predictions of the model to single pulses of light and to light intensities under 100 lux (Zeitler et al., 2000).

Methods

Description of Light Model

The previous version of our light-based mathematical model (Kronauer et al., 1999, 2000) for the human circadian pacemaker includes two dynamic systems: the dynamic stimulus processor, Process L, and the circadian pacemaker, Process P. The Equations of Process L represent the physiological process by which light initiates a chemical reaction within the photo-pigments of the retinal photoreceptors that transmit photon energy from the retina

through the RHT to the circadian pacemaker within the SCN. This chemical reaction assumes a forward rate constant

$$\alpha = \alpha_0 \left(\frac{I}{I_0} \right)^p \quad (1)$$

where $\alpha_0 = 0.05$, $I = 9500$ and $p = 0.5$. Equation 1 converts ready elements into a drive $\hat{B}$ onto the pacemaker such that

$$\hat{B} = G(1 - n)\alpha \quad (2)$$

where G is a scaling constant and n is the fraction of elements in the system that are “used”. Used elements are recycled back into the ready state at a rate of β . In general, the rate at which elements are activated (processed from “ready” to “used”) in Process L is given at any time by the formula

$$\dot{n} = 60[\alpha(1 - n) - \beta n] \quad (3)$$

The drive generated in Equation 2 acts onto Process P. Process P is divided into two components: the circadian pacemaker and the circadian sensitivity modulator. The coupled pacemaker Equations are

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

$$\dot{x}_c = \frac{\pi}{12} \left\{ qBx_c - x \left[\left(\frac{24}{0.99729\tau_x} \right)^2 + kB \right] \right\} \quad (5)$$

Equations 4 and 5 represent a higher-order limit cycle oscillator, and the coefficients in Equation 4 were chosen so that the amplitude of the limit cycle would equal 1.00, as in previous iterations of the model (Kronauer 1990).

$\hat{B}$ enters Process P via the circadian sensitivity modulator, where it is converted into a direct drive, B , onto the pacemaker that is dependent on the state variables x and x_c such that

$$B = \hat{B}(1 - 0.4x)(1 - 0.4x_c) \quad (6)$$

to characterize the feature that the human circadian pacemaker has varying sensitivity to light throughout the circadian day (Jewett et al., 1997). The term qBx_c on the left side of Equation 5 produces, for $q > 0$, the “divergence” effect that enhances the stimulus precision necessary to realize Type 0 resetting, in which large phase shifts up to 12 hours can be achieved via antecedent reductions of circadian amplitude (Winfree, 1980). The term kB on

the right side of Equation 5, for $k > 0$, lowers the period of the pacemaker in response to light, thereby embodying the “Aschoff Rule” (Aschoff 1960). The intrinsic period of the pacemaker is represented by τ_x . Equation 5 includes a correction factor on τ_x , 0.99729, which is required for the observed period to equal τ_x due to the oscillator’s non-linear terms. The correction factor is significant to 5 figures because the intrinsic period may be stable and precise down to 1 minute each day (i.e. precision of $1/1440 = 0.00069$) (Czeisler et al., 1999).

To compare the results of the model to core body temperature (CBT) data in humans, a phase relationship was derived (May et al., 2002) such that

$$\text{Time of } CBT_{\min} = \text{Time of } \varphi_{xcx} + \varphi_{ref} \quad (7)$$

where $CBT_{\min}$ is the CBT minimum, $\varphi_{ref} = 0.97$, and φ_{xcx} is defined as the polar phase angle between the state variables x and x_c such that

$$\arctan \frac{x_c}{x} = -170.7^\circ \quad (8)$$

The mathematical model reports $CBT_{\min}$ as the circadian phase marker. The rhythms of CBT and melatonin are highly correlated (Shanahan and Czeisler, 1991) but melatonin has been found to be a more accurate marker of phase (Klerman et al., 2002). Therefore, although both CBT and melatonin were recorded for each experiment, either $DLMO_{25\%}$ (dim light melatonin onset calculated as 25% of the fitted peak of melatonin) or $DLMO_{UC}$ (dim light melatonin onset calculated as the upward crossing of the mean) was used in the analysis of the entrainment data. A conversion factor was found to relate $CBT_{\min}$ to $DLMO_{25\%}$ or $DLMO_{UC}$ for each individual subject in order to compare model simulations to experimental data. To find this conversion factor, we calculated the difference between the experimental $CBT_{\min}$ and the experimental $DLMO_{25\%}$ (or $DLMO_{UC}$) during an initial Constant Routine (CR, described below) (if available) and the difference between the $CBT_{\min}$ and $DLMO_{25\%}$ (or $DLMO_{UC}$) during a second CR (if available), and averaged the two differences. We subtracted this factor from the $CBT_{\min}$ predicted by the model simulations to convert the $CBT_{\min}$ predictions into $DLMO_{25\%}$ or $DLMO_{UC}$ predictions to enable comparisons between experimental results and model simulations.

Description of data sets

A number of datasets were used to develop, test, and validate the addition of a non-photopic component to our existing light-based circadian model and to refine the existing parameters of Process L in our light-based circadian model.

General conditions—For each of the protocols discussed below, subjects were tested individually in an environment free of time cues with timed bedrest:activity episodes scheduled in a 1:2 ratio (e.g., 7.93-h bedrest:15.87-h activity for a cycle of 23.8 h, 8-h bedrest:16-h activity for a cycle of 24.0 h, 8.2-h bedrest:16.4-h activity for a cycle of 24.6 h, 9.33-h bedrest:18.67-h activity for a cycle of 28.0 h). Light levels were set at 0 lux during a scheduled bedrest episode, unless otherwise noted. During some days within the protocols, subjects were exposed to a constant routine (CR) procedure designed to minimize or distribute evenly across a 24-h interval factors that influence the endogenous circadian rhythm. During a CR, subjects remain awake in a semi-recumbent posture in constant dim

light with meals distributed at hourly intervals. The conditions of the CR procedure enable more accurate assessment of circadian phase and amplitude (Duffy, 1993).

Dim Light Entrainment Protocol—Wright et al. (2001) conducted a study to determine whether a weak synchronizing stimulus consisting of a ~1.5 lux:0 lux activity:rest wake:sleep cycle would entrain a subject to an imposed “entrainment cycle” or “T-cycle” of T=23.5 h, T=24.0 h or T=24.6 h. This protocol began with a 24.0-h rest-activity schedule for 3 to 6 days, followed by a 40-h CR. After this initial CR, subjects were assigned to 18 cycles of T-cycle = 23.5 h, or 25 cycles of T = 24.0 h or T = 24.6 h. Subjects were maintained in ~1.5 lux during wake episodes. CBT and plasma melatonin rhythms were monitored throughout the protocol in order to determine the observed period of the circadian pacemaker, using CBT_{min} and $DLMO_{25\%}$ as phase markers. Between 8 - 11 $DLMO_{25\%}$ values were available per subject for analysis. Following the entrainment cycles, subjects underwent a second CR to reassess circadian phase. Following this second CR, subjects underwent 12 cycles of a T = 28.0 h forced desynchrony protocol (described under “*forced desynchrony protocols*” below).

This study reported that 0/3 subjects entrained to T = 23.5 h; 0/6 subjects entrained to T = 24.6 h; and 5/6 subjects entrained to T = 24.0 h. The results from the subjects scheduled to T = 24.0 h and T = 24.6 h were used to develop and test the non-photoc component of our model.

Non-photoc Entrainment Protocol—In Klerman et al. (1998), one blind subject with no ocular light perception was reported to have stable entrainment to a 24.0-h scheduled sleep-wake cycle while living at home. During a T=28.0-h FD protocol (described below), the subject was found to have a τ of 24.1 h. To determine the presence and strength of a non-photoc effect on the circadian pacemaker, the subject was scheduled to 24 cycles of a T = 23.8 h, followed by 14 cycles of T = 24.0 h. During both scheduled sleep and wake times, light levels were <0.03 lux, achieved by placing blue acrylic light filters (Roscolux 74, Rosco, Port Chester, NY) over the light source. However, because the subject had no ocular light perception, it was assumed that no light reached the circadian pacemaker. CBT and plasma melatonin rhythms were monitored throughout the protocol. CBT_{min} and $DLMO_{UC}$ were used as phase markers to determine the phase angle of entrainment. A total of 24 $DLMO_{UC}$ values for this subject were available for analysis. This study reported that the subject entrained to T = 23.8 h. The results of this study were used to validate the addition of a non-photoc component to our model.

Forced Desynchrony Protocols—The cycle length in a forced desynchrony (FD) protocol (e.g., T = 20.0 hr or T = 28.0 hr) is outside the normal range of entrainment of the circadian pacemaker and provides an accurate assessment of τ for the subject (Czeisler et al., 1999). In Wright et al. (2001), subjects were exposed to 25 cycles of T = 24.0 h or T = 24.6 h (as described under the “*dim light entrainment protocol*”), followed by a 40-h CR. This portion of the protocol was followed by 12 cycles of T = 28.0 h, concluding with another 40.0-h CR. Light levels were ~1.5 lux during the wake episodes. CBT and plasma melatonin rhythms were monitored throughout the protocol. A total of 12 $DLMO_{25\%}$ values per subject were available for analysis. In Klerman et al. (1998), prior to the T=23.8-h entrainment protocol (as described under “*non-photoc entrainment protocol*”), the blind subject was scheduled to 24 cycles of T = 28.0 h following three baseline days and a 40.0-h CR. After the FD, the subject underwent another 40.0-h CR and a final sleep episode. Light levels were ~150 lux during wake episodes on baseline days and 10 lux during wake for the remainder of the protocol. CBT and plasma melatonin rhythms were monitored throughout the FD protocols in order to determine the intrinsic period for this subject. A total of 14 $DLMO_{UC}$ values for this subject were available for analysis. The intrinsic periods

determined from these protocols were used as the input parameter, τ_x (Equation 5), for simulations of our model.

1-Pulse Intermittent Light Protocol—Gronfier et al. (2004) performed a series of experiments to determine the response of the pacemaker to a single sequence of intermittent bright light pulses compared to a continuous bright light or dim light pulse. In these experiments, subjects were scheduled to two 24.0-h days in ~90 lux followed by a 26.2-h CR. After the initial CR, subjects were scheduled to 8 h of sleep in 0 lux. For the next wake episode, subjects were randomly assigned to a 6.5-h stimulus in one of three lighting conditions: 1) continuous bright light (BL) at ~9500 lux; or 2) intermittent bright light consisting of six 15-minute bright light pulses of ~9500 lux separated by 60 minutes of very dim light of < 1 lux; or 3) continuous very dim light of <1 lux. In each condition, the stimulus was preceded and followed by 30 minutes of <1 lux. The stimulus day was followed by a 64-h CR. CBT and plasma melatonin rhythms were assessed throughout the protocol. Circadian phase was assessed during both CRs using CBT_{min} and DLMO_{25%}. The light level during wakefulness was ~1.5 lux from the start of the initial CR until the end of the second CR, except during the stimulus. The phase response to the light stimulus was determined by subtracting initial phase found during the initial pre-stimulus CR from the final phase found during the post-stimulus CR. This study reported that the phase delays observed after intermittent bright light were comparable to the phase delays observed after BL, despite 67% less duration of light in the intermittent bright light condition. The data from this study were used to refine parameters in Process L.

1-Pulse Intensity Response Curve Protocol—Zeitzer et al. (2000) performed a series of experiments to determine the response of the pacemaker to phase-delaying light pulses of varying intensities. In these experiments, subjects were scheduled to two 24.0-h days in 150 lux followed by a ~50-h CR. After the initial CR, subjects were scheduled to 8 h of sleep in 0 lux. During the following wake episode, subjects were randomly assigned to receive a single 6.5-h light pulse centered ~3.5 h before CBT_{min} with intensities ranging from 3 lux to 9100 lux. The stimulus day was followed by a 30-h CR. CBT and plasma melatonin rhythms were assessed throughout the protocol. Circadian phase was assessed during both CRs using CBT_{min} and DLMO_{25%} as phase markers. The light level during wakefulness was ~10 lux from the start of the initial CR until the end of the second CR, except during the stimulus. The phase response to the light stimulus was determined by subtracting initial phase found during the initial pre-stimulus CR from the final phase found during the post-stimulus CR. This study reported that the resetting response to a single 6.5-h light pulse has a non-linear relationship to illuminance and that half of the maximal phase-delaying response to ~9000 lux can be achieved by ordinary room light of ~100 lux. The data from this study were used to refine parameters in Process L.

1-Pulse and 3-Pulse PRC Protocols—Khalsa et al. (2000) performed a series of experiments to determine the effect of a dim-background 3-cycle bright light stimulus on the human circadian pacemaker. In these experiments, subjects were scheduled to two 24.0-h days in 150 lux followed by a 26 to 52-h CR (depending on the desired center of the bright light stimulus). After the initial CR, subjects were scheduled to 8 h of sleep in 0 lux. During the following three wake episodes, subjects were exposed to a 5-h 9,500 lux pulse centered in the middle of the 16-h wake episode (which occurred at different circadian phases). The 3-cycle bright light stimulus was followed by a 40-h CR. CBT and plasma melatonin rhythms were assessed throughout the protocol. Circadian phase was assessed during both CRs using CBT_{min} and DLMO_{25%} as phase markers. The light level during wakefulness was ~10 lux from the start of the initial CR until the end of the second CR, except during the bright light stimuli. The phase response to the light stimulus was determined by subtracting

initial phase found during the initial pre-stimulus CR from the final phase found during the post-stimulus CR. This study reported that a 3-cycle bright light stimulus could achieve Type 0 resetting when light exposure was centered at CBT_{min}, phase delays when light exposure was centered before CBT_{min}, and phase advances when light exposure was centered after CBT_{min}. Khalsa et al. (2003) performed a similar 1-pulse PRC experiment with a single 6.7-h 9,500 lux light pulse centered during a wake episode between the pre- and post-stimulus CRs, using CBT_{min}, melatonin midpoint, DLMO_{25%} and dim light melatonin offset (DLMO_{off25%}) as a circadian marker to assess phase shift (for the purposes of this analysis we used the CBT_{min} values). This study reported that a 1-cycle bright light stimulus could achieve Type 1 resetting with phase delays when light exposure was centered before CBT_{min} and phase advances when light exposure was centered after CBT_{min}. The 3-cycle bright light stimulus data have been incorporated into previous iterations of our model and were used here to check that our updated model retains the ability to accurately predict this data. The 1-cycle bright light stimulus data have not been included in previous iterations of the model and were used here to validate the refinements made to Process L and the addition of a non-photoc component to the model.

Revisions to the Light Model

Although the light-based Kronauer et al. (1999, 2000) model predicts accurately the effects of light on the circadian pacemaker for light intensities between 150 and 9,500 lux, the model is less accurate at light levels lower than 150 lux. The exponent $p = 0.5$ appearing in the relation between light intensity, I , and element utilization rate, α , (Equation 1) was derived from data taken at high lux levels (several thousand lux) and was observed to be consistent with exponents appropriate to strong phase shifting in hamsters (Nelson and Takahashi, 1991; Kronauer et al., 1999). Furthermore, at the time the model was published, there were few data available for experiments conducted at lower light levels. When extrapolated to I values 1,000 times weaker, the exponent $p = 0.5$ predicts a photic drive that is far too strong. In fact, the derivative of α becomes singular as I approaches 0. Consequently, we have introduced a multiplicative logistic function that shows a linear behavior for small I and saturates to unity at large I . The transition from linear to saturation is centered at the 100 lux value, in recognition of the data of Zeitzer et al. (2000) that show 119 lux to be the stimulus for 50% of maximum response. With the inclusion of this factor, Equation 1 is replaced by

$$\alpha = \alpha_0 \left(\frac{I}{I_0} \right)^p \frac{I}{I + 100} \quad (9)$$

The inclusion of this logistic function gives α a proportionality of $I^{1.5}$ for values well below $I = 100$, which is comparable to the proportionality of $I^{1.42}$ that Zeitzer et al. (2000) fit to low I in their intensity response curve. Recently, Gronfier et al. (2004) published data from the *1-Pulse Intermittent Light Protocol* (described above) that permit a more accurate assessment of the dynamics embodied in Process L. Most importantly, the forward rate parameter, α_0 , was found to be significantly higher than had been proposed earlier (Kronauer et al., 1999, 2000). Small changes have also been incorporated in β and G . The revised parameters are $\alpha_0 = 0.1 \text{ min}^{-1}$, $\beta = 0.007 \text{ min}^{-1}$ and $G = 37$.

Process N_S

The input of non-photoc stimuli to the circadian pacemaker is postulated to be via the intergeniculate leaflet of the thalamus (Lewandowski and Usarek, 2002), a separate pathway from the photic RHT. The non-photoc component has been incorporated into the model as an

independent drive on Process P (the circadian pacemaker) to reflect the physiological difference between photic and non-photoc pathways. The input to Process N_S is the square waveform of the sleep-wake cycle. The choice to model the sleep-wake cycle as the non-photoc stimulus derives from entrainment studies in very dim light by Wright et al. (2001) and in blind subjects by Klerman et al (1998), in which it is assumed that the observed changes in phase are not due to photic effects, but to another factor, i.e. the strict timing of sleep and wake. Note that scheduled sleep and wake, rather than actual sleep and wake, are being modeled since the putative factors (e.g., posture, eating, exercise) are associated with the scheduled activity rather than sleep or wake themselves. The choice to model the sleep-wake cycle as a square wave derives from evidence that wake-sleep transitions are governed by a flip-flop neural circuit, the “sleep switch” described by Saper et al. (2001, 2005), between the ventrolateral preoptic nucleus (VLPO) and arousal systems. The sleep switch model works as a neural circuit with mutually inhibitory elements: 1) during sleep VLPO neurons fire to inhibit wakefulness, promoting monoaminergic cell groups, which in turn disinhibits and reinforces VLPO neuron firing to promote sleep, and 2) during wakefulness monoaminergic neurons fire to inhibit VLPO neurons, which in turn disinhibits monoaminergic neuron firing to promote wakefulness. Furthermore, inhibition of VLPO neurons disinhibits other wakefulness promoting neurons such as orexin and cholinergic neurons. The sleep switch model avoids transitional states; either the switch is “on” (for sleep) or “off” (for wake). In addition, many associated behaviors are present during one (e.g. activity, eating, posture changes, social interactions) but not the other state. Therefore, our model defines the square wave of the sleep-wake cycle, $\hat{N}_s$ as follows:

$$\hat{N}_s = \rho \left(\frac{1}{3} - \sigma \right) \quad (10)$$

where σ equals either “1” (for sleep/rest) or “0” (for wake/activity), and ρ is a rate constant with a value of 0.032. In the available data, sleep comprises 1/3 of a cycle and wake

comprises 2/3 of a cycle. Therefore, the factor $\left(\frac{1}{3} - \sigma \right)$ is a square wave that achieves zero mean for conventional sleep/wake schedules by weighting the drive during sleep by a factor of $-2/3$ and weighting the drive during wake by a factor of $1/3$.

The effect of Process N_S on the circadian pacemaker is directed by two basic principles. The first is that phase shifts generated by non-photoc stimuli are timed 12-h opposite to phase shifts generated by photic stimuli. The circadian times for which light is most effective are those at which sleep ordinarily occurs. Light exposure before the circadian temperature nadir produces phase delays, while light exposure after the temperature nadir produces phase advances. Non-photoc time cues are reported to have PRCs that are out of phase with the photic PRC. Both light and sleep stimuli act to entrain the circadian pacemaker stably to near-conventional circadian phases. Under most environmental conditions in sighted individuals awake during the day and asleep at night, it is difficult to separate and observe photic and non-photoc effects.

The second principle proposes that Process N_S is strongly modulated by the circadian pacemaker, just as photic drive is strongly modulated. The modulation is different for the two processes, as befits a separate neural pathway. The action of circadian modulation on the photic pathway yields a PRC biased in favor of delay shifts. We find that circadian modulation of Process N_S similarly acts to reduce the relative strength of advance phase shifts.

The value of the rate constant, ρ , in Equation 10, is based on the force of the non-photoc stimuli, f_{NP} , acting on the circadian pacemaker, which was determined from subjects in the dim light entrainment protocol (described above) scheduled to a $T = 24.6$ -h cycle in ~ 1.5 lux. Under this imposed T-cycle, subjects were unable to entrain: the observed period for each subject (the period that their circadian pacemaker oscillated at during the imposed T-cycle) was less than 24.6 h. However, analysis of a subsequent $T = 28.0$ -hr FD protocol revealed that the estimate of each subject's intrinsic period [the period emanating within the pacemaker at a given time (Wright et al., 2001)] was shorter than their observed period (the period as measured by markers of the circadian pacemaker (e.g., melatonin or CBT) and influenced by extrinsic stimuli acting on the pacemaker during the time of observation), indicating that their observed period lengthened during exposure to the $T = 24.6$ -h schedule. Because light levels were ~ 1.5 lux, it can be assumed that the daily phase delay required to lengthen the observed period was due to f_{NP} and not the force of the photic stimulus (f_P). To quantify f_{NP} , the following formula was used:

$$\Delta\Psi_{M,S(i+1)} = \Delta\Psi_{M,S(i)} + (f_P + f_{NP})T - \tau \quad (11)$$

where $\Delta\Psi_{M,S}$ is the phase angle between the scheduled sleep time (S) and the DLMO (M) for day, i , of the protocol, T is the imposed T-cycle length, τ is the intrinsic period (not the observed period), and f_P is assumed to be near zero. This analysis revealed that, for each subject, f_{NP} reached a maximum delay of 0.27 h. The rate coefficient of Process N_S was fit using this data to determine the value, $\rho = 0.032$, in which the maximum f_{NP} was ~ 0.27 .

The analysis outlined above using Equation 11 not only revealed the maximum force of the non-photoc stimuli to be 0.27-h, but also revealed how f_{NP} varies across circadian phases. The maximum delay occurred when $\Psi_{M,S}$ fell within the range of $\Psi_{M,S} = 5$ to $\Psi_{M,S} = 9$. Process N_S is presumed to be modulated by a circadian sensitivity function expressed as

$$N_S = \hat{N}_S (1 - \tanh 10x) \quad (12)$$

To appreciate how this modulator performs, recall that in a pacemaker unaffected by time cues, x is an approximate sinusoid of amplitude unity, taking on a value close to -1 at CBT_{min} and a value close to 1 twelve hours later. For $x = -0.2$, $(1 - \tanh 10x) = 1.96$, while for $x = +0.2$, $(1 - \tanh 10x) = 0.04$. The modulator acts like a somewhat smoothed step-function between the limits of 2 for $x < -0.2$ and zero for $x > 0.2$. Thus, for about 10 hours centered over CBT_{min} , the modulator weighs $\hat{N}_S$ by the factor ~ 2 , while for about 10 hours centered at the opposite circadian phase, the weighting is essentially zero.

Analyzing the experimental data from the blind subject scheduled to an entrainment cycle of $T = 23.8$ h with Equation 11 also revealed that f_{NP} was inconsistent across the protocol, with f_{NP} particularly diminished during the first ~ 10 days of the $T = 23.8$ -h cycle (Klerman et al., 1998), at a point where $\Psi_{M,S}$ fell within a low negative range (approximately $\Psi_{M,S} = 0$ to $\Psi_{M,S} = -2$). Low negative $\Psi_{M,S}$ corresponds to the region of the circadian cycle in which the scheduled sleep episode occurs in advance of $DLMO_{25\%}$ by a few hours. It can be observed that this region corresponds approximately to the circadian phases for which initiation of sleep appears difficult (Lavie, 1986) also referred to by Strogatz et al. (1987) as the “wake maintenance zone”.

A term was added to Process N_S that limits the drive of f_{NP} within this region of the circadian cycle. We introduce a new term $\Psi_{C,X}$ such that

$$\Psi_{C,X} = C - CBT_{min} \quad (13)$$

where C represents the clock time relative to midnight = 0, and the time of CBT_{min} is the circadian minimum of the pacemaker, defined in Equations 7 and 8.

Under this definition, the values for which $\Psi_{C,X}$ correspond to low negative $\Psi_{M,S}$ are set by the region of $\Psi_{C,X}$ for which

$$16.5 < \Psi_{C,X} < 21 \quad (14)$$

where 16.5 and 21 are optimized by parameter fitting to data from subject 1451 (Klerman et al., 1998), as it is not well-established how wide an interval the wake maintenance zone occupies. The model assumes that when sleep initiation is attempted within the region defined in Equation 14, Process N_S remains at a drive associated with wake (representing a long sleep latency), such that

$$\widehat{N}_s = \frac{1}{3}\rho \quad (15)$$

to limit the f_{NP} drive on the pacemaker. When $\Psi_{C,X}$ reaches a boundary of the region in Equation 14, Process N_S transitions to a sleep drive.

The nonphotic drive, N_S , incorporating both the circadian sensitivity modulation and sensitivity to sleep initiation, is included in Equation 4 to give

$$\dot{x} = \frac{\pi}{12} \left[x_c + \mu \left(\frac{1}{3}x + \frac{4}{3}x^3 + \frac{256}{105}x^7 \right) + B + N_s \right] \quad (16)$$

Figure 1 shows a schematic diagram of the model with the incorporation of Process N_S .

Comparison of Model Simulations to Data

To determine whether the refinements to the light-based circadian model and the addition of a non-photoc component to the model improved predictions to experimental data, Model P (Kronauer et al., 1999, 2000) (photoc only) and Model PNP (updated photic and non-photoc) were fit to experimental data. Model PNP retains the same structure of Model P but includes the additional non-photoc component, N_S , and updated parameter values in Process L, as described above.

The initial conditions of Model P and Model PNP assume relative sleep from 2400 to 0800 h. Furthermore, both models assume that CBT_{min} occurs ~2.5 h prior to waketime under baseline conditions. Due to inter-individual variability in habitual sleep-wake times and circadian phase, the phase angle between sleep time and circadian phase, i.e. Ψ , varies across subjects. When comparing model simulations to experimental data, it is important that the initial conditions of the model correspond to the initial conditions of the experimental data. Because the parameters of Process N_S were fit using entrainment data, simulations were run from the start of the entrainment portion of the protocols. Therefore,

the initial conditions of the model were adjusted to the ψ for each subject based on the values at the initial constant routine immediately preceding entrainment. The intrinsic period of the circadian pacemaker, τ , used in the model simulations as the input parameter τ_x (Equation 5) for each subject, was calculated from data during a FD protocol using a non-orthogonal spectral analysis (Czeisler et al., 1999).

To determine which model - Model P or Model PNP - fit the experimental data better, the mean square error (*MSE*) was calculated by determining the sum of the square of the differences between experimental data ($DLMO_{25\%}$ or $DLMO_{UC}$) and the predicted circadian phase of the model and dividing by the total number of points. This was done for each model, Model P and Model PNP, and the model with the smaller *MSE* is the better fit to the experimental data (Wallach and Goffinet, 1989).

The Akaike Information Criterion (AIC) was also used to determine the “goodness of fit” of each model. The AIC was calculated as $n \log(\hat{\sigma}^2) + 2k$, where $\hat{\sigma}^2$ is the residual sum of squares, n is the number of samples, and k is the number of parameters estimated for each model (Anderson et al., 2000). The “ $2k$ ” term imposes a penalty for adding new parameters to a model. The initial conditions, x and x_c , were estimated for both Model P and Model PNP. Additionally, ρ and the boundary in Equation 14 were estimated for Model PNP. Therefore, for Model P $k = 2$, and for Model PNP $k = 4$. The model with the lower AIC is the better fit to the experimental data.

Results

Entrainment Predictions

Comparison of Model PNP and Model P using dim light entrainment data—As described in the dim light entrainment protocol above (Wright et al., 2001), 5 of 6 subjects entrained to a $T = 24.0$ -h schedule under exposure to ~ 1.5 lux during scheduled wakefulness, while no subjects entrained to either a $T = 23.5$ -h or $T = 24.6$ -h schedule under the same lighting conditions. Figure 2 shows simulations of Model P and Model PNP compared to experimental $DLMO_{25\%}$ data from one of the subjects scheduled to $T = 24.0$ h, subject 18G6, who was found to have an intrinsic $\tau = 23.88$ hr. The circadian phase predicted by Model P (represented here as $DLMO_{25\%}$) advances each day due to $\tau < 24.0$, with a small counter-effect from the f_p generated by the ~ 1.5 lux stimulus to entrain to the $T = 24.0$ h. Graphically Models P and PNP generate similar fits to the experimental data. The *MSE* values indicate that Model PNP (*MSE* = 0.51) is a better fit to the data than Model P (*MSE* = 0.84), while the opposite is true for the AIC values (Model P AIC = 3.39, Model PNP AIC = 5.69) for this subject. In general, we would expect Model P and Model PNP to fit equally well when the circadian phase is at a normal phase angle to scheduled sleep time, because this is where the non-photic drive is weak (due to modulation in Equation 12). Table 1 compares the *MSE* and AIC of Model P to Model PNP with respect to the experimental data for each subject who was scheduled to $T = 24.0$ h (Wright et al., 2001). The average *MSE* and AIC was found across all subjects scheduled to $T = 24.0$ h for each model. The average *MSE* was lower for Model PNP than Model P (Model P average *MSE* = 0.97, Model PNP average *MSE* = 0.91); however, the average AIC was lower for Model P than Model PNP (Model P average AIC = 2.87, Model PNP average AIC = 6.48). Although subject 1842 was reported to entrain to $T = 24.0$ h in the original study, this subject was excluded from this analysis, because the intrinsic τ of this subject was not reported in the original study: intrinsic τ is necessary to compare predictions of Model P and Model PNP to an individual's data.

None of the 6 subjects scheduled to $T = 24.6$ h entrained to that schedule. Figure 3 compares Model P and Model PNP to the experimental $DLMO_{25\%}$ data of one subject scheduled to T

= 24.6 h, subject 1947, who was found to have intrinsic $\tau = 24.23$ hr. Because $\tau > 24.0$, both Model P and Model PNP predict that $DLMO_{25\%}$ drifts to a later clock hour each day. However, in Model P the phase angle between the sleep time and the $DLMO_{25\%}$, $\Psi_{M,S}$, advances due to the difference between intrinsic period and the T-cycle ($\tau - T = -0.44$ hr), while the extra drive provided by the non-photic component in Model PNP accelerates the pacemaker shift towards $T = 24.6$ h. Graphic examination, MSE values, and AIC values all reveal that Model PNP (MSE = 0.16, AIC = -0.76) is a better fit to the data than Model P (MSE = 1.74, AIC = 6.64) for this subject. Table 1 compares the MSE and AIC of Model P to Model PNP with respect to the experimental data for each subject scheduled to $T = 24.6$ h. One subject from the original study, subject 1715, was excluded from this analysis because the intrinsic τ of this subject was not reported. For 3 of the 5 subjects that were scheduled to $T = 24.6$ h that we analyzed, the MSE and AIC are lower for Model PNP, indicating that it is a better fit with respect to the experimental data for these subjects. However, for subjects 18J5 and 19a9, the MSE and AIC values both indicate that Model P fits these data better than Model PNP. It is unclear why this is the case; these subjects may have little non-photic drive or the variability of measurement may be too large. The average MSE and AIC was found across all subjects scheduled to $T = 24.6$ h for each model. The average MSE was lower for Model PNP than Model P (Model P average MSE = 1.33, Model PNP average MSE = 0.73); however, the average AIC was lower for Model P than Model PNP (Model P average AIC = 4.27, Model PNP average AIC = 4.77).

Comparison of Model PNP and Model P using non-photic entrainment data—

The blind subject studied under the *non-photic entrainment protocol* described above and in Klerman et al. (1998) appeared to be entrained to a $T = 24.0$ -h schedule. Analysis of FD data revealed that the intrinsic period of the subject was 24.1 h. Because $\tau \neq T$, it was concluded that the subject was entrained to the imposed T-cycle by an unknown non-photic zeitgeber. The subject was placed on a schedule of $T = 23.8$ h for 24 cycles, followed by $T = 24.0$ h for 14 cycles, to determine whether the subject could entrain to a T-cycle further from his intrinsic period: $T - \tau = -0.30$ h. Results indicated that the subject entrained to the $T = 23.8$ -h schedule. Figure 4 shows simulations of Model P (MSE = 20.13, AIC = 53.54) and Model PNP (MSE = 0.27, AIC = -13.62) compared to the $DLMO_{UC}$ of subject 1451 scheduled to 24 cycles of $T = 23.8$ h, followed by 14 cycles of $T = 24.0$ h (Klerman et al., 1998). Because the subject had no ocular light perception, it was assumed that no light information reached the pacemaker; therefore, 0 lux was used in model simulations. Model P predicts that the pacemaker will run at its intrinsic period in 0 lux and delay by 0.1 h per day, due to drift at intrinsic period. The f_{NP} drive generated by the non-photic component in Model PNP counteracts the natural drift of the intrinsic period and advances the pacemaker towards the $T = 23.8$ -h cycle. A comparison of the models during $T = 24.0$ h reveals that Model P continues to drift to a later phase due to the intrinsic period. The force of the non-photic component in Model PNP continues to advance the pacemaker in response to the $T = 24.0$ h stimuli. The behavior of the pacemaker observed in the simulations of Model PNP is similar to the behavior observed in the experimental data for subject 1451.

In subject 1451, it was observed that the $DLMO_{UC}$ did not advance for the first ~10 cycles of the $T = 23.8$ h protocol. As we described in Methods, this was attributed to diminished f_{NP} due to circadian sensitivity in sleep initiation. Figure 5a compares simulations of Model PNP with and without the circadian sensitivity of sleep initiation function included in the model to the experimental data from subject 1451 when the subject was scheduled to a $T = 23.8$ -h schedule with an intrinsic period of $\tau = 24.1$ hr. Simulations reveal that predictions are phase-advanced compared to the experimental results when circadian sensitivity is not considered in Model PNP (MSE = 0.47, AIC = -6.44). For subject 1451, $\Psi_{C,X}$ fell within the range defined in Equation 14 for most of the protocol, which can be observed in the reduction of phase advance for both the experimental data and Model PNP predictions when

the circadian sensitivity to sleep initiation function was included ($MSE = 0.27$, $AIC = -13.62$). Figure 5b reports the same feature in subject 18G1 of the dim light entrainment protocol scheduled to a $T = 24.0$ -h schedule with an intrinsic period of $\tau = 24.36$ hr (Wright et al., 2001). The combined f_P and f_{NP} drive is insufficient to entrain the subject to a $T = 24.0$ -h cycle. The circadian sensitivity to sleep initiation limits the amount of drive that reaches the pacemaker by reducing the advance drive of f_{NP} when sleep is initiated at an adverse circadian phase. The reduction of f_{NP} at this circadian phase decreases the magnitude of the phase advance of the circadian pacemaker because of this circadian sensitivity to sleep initiation. In this particular subject, a phase advance would counter the phase delay from $T = 24.0$ -h evoked by the drift in $\tau = 24.36$ hr. The reduction of phase advance can be observed in the Model PNP simulation that includes this circadian sensitivity to sleep initiation ($MSE = 0.59$, $AIC = 5.74$). Without this function, Model PNP predicts larger phase advances than are observed experimentally ($MSE = 0.79$, $AIC = 4.96$). Thus, while MSE is significantly decreased, the AIC is slightly worsened.

PRC Predictions

Circadian modulation of non-photoc drive—The circadian modulation of the light drive in Equation 6 was incorporated to mimic the observed modulation of human visual sensitivity throughout the day (Knoerchen et al., 1976). The sensitivity modulator enhances the light drive during phases of the circadian cycle in which the pacemaker is more sensitive to the effect of light. As described above, the pacemaker is also differentially sensitive to non-photoc stimuli at different phases of the circadian cycle. The circadian modulation of the non-photoc stimulus, Equation 12, interacts with the state variable x of the pacemaker to determine the strength of the drive that reaches the pacemaker. This modulation of the drive is important for phase shifts encountered near the CBT_{min} , particularly when the sleep-wake cycle is inverted (e.g., PRC studies).

Figure 6 reports the circadian modulation of the non-photoc stimulus, f_{NP} , across all phases of the circadian cycle, $\Psi_{M,S}$, where $\Psi_{M,S}$ is the difference between $DLMO_{25\%}$ and scheduled sleep time ($\Psi_{M,S}$ is positive when sleep time occurs after $DLMO_{25\%}$). The maximum advance drive occurs around $\Psi_{M,S} = -2.00$, which corresponds to sleep initiated ~2 hour prior to $DLMO_{25\%}$. The maximum delay drive occurs around $\Psi_{M,S} = 7.00$, which corresponds to sleep time that occurs 7 hours after $DLMO_{25\%}$. When the sensitivity to sleep initiation function is included in Model PNP, there is a drop in f_{NP} corresponding to sensitivity to sleep initiation occurring during the ~2 hours following $DLMO_{25\%}$ (see Results above). Figure 6 shows the corresponding circadian phase of the center of the sleep episode with respect to CBT_{min} , which reveals a non-photoc PRC with phase advances observed when the center of the sleep episode occurs prior to CBT_{min} and phase delays observed when the center of the sleep episode occurs after CBT_{min} . This non-photoc PRC is 12 hours opposite the light PRC, which reports phase delays when light is centered prior to CBT_{min} and phase advances when light is centered after CBT_{min} . There is no effect of the non-photoc drive at CBT_{min} , which is the critical phase of light stimulus in a Type 0 PRC. This predicted non-photoc PRC is similar in shape and timing to non-photoc PRCs of melatonin administration and exercise in humans as well as non-photoc PRCs observed in animals.

Model predictions of 1-cycle/3-cycle pulses of bright light on the pacemaker

Previous models (Forger et al., 1999; Jewett et al., 1999; Kronauer et al., 1999, 2000) have accurately predicted the results of 3-pulse PRC experiments, which report the response of the pacemaker to 3 consecutive cycles of extended bright light pulses dispersed across all circadian phases. Figure 7 shows the predictions of Model PNP and Model P against the experimental data reported in (Khalsa et al., 1997). The PRC is plotted as initial phase

versus phase shift, where initial phase is defined as the center of the light pulse relative to CBT_{min} as recorded during CR. The CBT_{min} occurs at 0. Based on the MSE and AIC values calculated for each model, Model P (MSE = 3.82, AIC = 102.97) provides a better fit to the data than Model PNP (MSE = 4.08, AIC = 111.74). Graphically, Model P appears to provide a better fit to the data, particularly within the critical zone of the PRC (near $CBT_{min} = 0$). Although changes have somewhat altered the model's predictions to data that have been predicted well by the model in the past, Model PNP retains the ability to predict the type 0 resetting observed experimentally in this 3-pulse PRC.

Results from the 1-pulse experimental PRC (protocol in Khalsa et al., 2003) reported that a single pulse of bright light has the ability to phase-shift the pacemaker significantly. Figure 8 shows the Model P and Model PNP predictions of the 1-pulse PRC compared to CBT data (previously unpublished) from the 1-pulse PRC study (protocol in Khalsa et al., 2003). Model P predicts smaller phase delays (shift to earlier hour) and larger phase advances (shift to later hour) than Model PNP. Both models predict the zero-crossing from phase delay to phase advance at $CBT_{min} = 0$. Based on the MSE and AIC values calculated for each model, Model P (MSE = 3.28, AIC = 13.28) provides a better fit to the data than Model PNP (MSE = 3.89, AIC = 18.62). Graphically, neither model appears to fit well due to the variability in the data. Data from 1-pulse PRC experiments have not been previously included in refinements to this model.

Another experiment tested the efficacy of a single 6.5-h light pulse with light intensities ranging from 3 lux to 9100 lux at a single circadian phase where light exposure was centered 3.5 h before CBT_{min} (Zeitler et al., 2000). It was reported that the half-maximal phase-delaying response is obtained with ~100 lux, with saturation at ~550 lux. Figure 9 reports that simulations of Model P fail to reproduce these results. Model P obtains a half-maximal response at ~300 lux and does not reach saturation. Furthermore, the range of phase delays predicted by Model P is attenuated in comparison to the experimental results, which have been fit with a 4-parameter logistic function. Therefore, it was necessary to modify the definition of light in Process L as described above. The enhancement of the α_0 parameter

effectively raises the saturation point of the I intensity response function, while $\frac{I}{I+100}$ reduces photic effects at intensities below 100 lux. At $I + 100$ values well below $I = 100$, α (Equation 9) is proportional to $I^{1.5}$. This is a proportionality similar to the logistic function fit to the experimental data in (Zeitler et al., 2000), which had a proportionality of $I^{1.42}$ at low I . Graphically, it appears that Model PNP fits the data better than Model P. This result is confirmed by MSE and AIC values that indicate that Model PNP (MSE = 0.27, AIC = -3.98) is a better fit to the data than Model P (MSE = 0.59, AIC = -0.88). This improvement is not due to the non-photoc effects but can be attributed to the photoc enhancements that we have introduced into Model PNP.

Discussion

Our revised mathematical model of the human circadian system is the first to introduce a direct effect of non-photoc stimulus independent from a direct effect of light or darkness exposure. This important step forward in the modeling of the human circadian system demonstrates that an existing mathematical model can be adapted to include new features of the system without disrupting the original model structure or its predictions. The incorporation of a new component for the effect of the sleep-wake cycle as a non-photoc zeitgeber introduces the opportunity for similar components to be added to the model to represent the effects of other non-photoc zeitgebers such as exogenous melatonin and exercise. Furthermore, this refinement of the model allows for the generation of new testable hypotheses about non-photoc effects on the human circadian pacemaker, particularly about

the effect of non-photic zeitgebers in blind subjects with no ocular light perception. While predictions of our photic-only model, Model P, report that the behavior of the pacemaker in the absence of a photic stimulus exhibits only a natural drift guided by the intrinsic period of the pacemaker, predictions of Model PNP would suggest that it is possible to entrain blind subjects and sighted subjects studied in 0 lux to T-cycle lengths $\pm \sim 0.30$ -h different from τ with non-photic stimuli alone.

Comparison of model fits to experimental data in which subjects are scheduled to $T = 24.0$ hr in ~ 1.5 lux are less conclusive. The results suggest that a non-photic component may not be necessary for predictions in which subjects are scheduled to $T = 24.0$ hr; however, the 4 subjects who entrained to $T = 24.0$ hr were found to have $|T - \tau| \leq 0.12$ hr (subject 1842 also entrained, but τ is unknown. The one subject that did not entrain to $T = 24.0$ hr was found to have intrinsic $\tau = 24.36$ hr, and the results for this subject were better predicted by Model PNP. Results from some of the subjects scheduled to $T = 24.6$ hr in ~ 1.5 lux were better predicted by Model PNP than by Model P using the MSE and AIC metrics for comparison, despite the fact that none of these subjects entrained. These results would suggest that ~ 1.5 lux alone is sufficient to entrain subjects for at least $|T - \tau| \leq 0.12$ hr, while non-photic stimuli with or without a weak (~ 1.5 lux) photic stimulus are needed to explain pacemaker behavior for larger differences between T and τ .

Our representation of the sleep-wake cycle as the non-photic drive on the pacemaker is supported by evidence in both animal and human studies demonstrating changes in the circadian pacemaker in response to variations in the sleep-wake schedule. Whether this represents an effect of sleep per se, as distinct from behaviors associated with the sleep episode (e.g., supine posture, fasting, decreased activity, etc.) cannot be determined from present experimental data. Our decision to model the sleep-wake cycle as a square wave, as opposed to a multi-phasic signal such as observed in the SCN electrical activity reported by Deboer et al. (2003), follows from evidence that the transition from wake to sleep is controlled by a “sleep switch” (Saper et al., 2005). Although the square wave is modeled for a sleep-wake cycle consisting of a 1:2 ratio of wake to sleep, this ratio can be adjusted and tested on non-1:2 sleep:wake ratios, such as might be seen in chronic sleep restriction protocols or with naps. The evidence of a sleep switch also supports our decision to model the circadian sensitivity of sleep initiation with an abrupt boundary separating sleep from wake representing the “wake maintenance zone” in which initiation of sleep is difficult.

That Model PNP simulates the experimental data better when the model accounts for the consequences of scheduled sleep at adverse circadian phases, in which scheduled sleep cannot be initiated, suggests that the timing and/or duration of sleep may play a considerable role in the response of the pacemaker to stimuli. The inference of these results is that the timing of the sleep and wake episodes are an important factor in the non-photic effect of the sleep-wake cycle versus the rest/activity state. Supporting evidence for this exists in Syrian hamsters, in which it has been shown that arousal at adverse phases was as effective as locomotor activity to phase shifting of the pacemaker (Mistlberger et al., 2002). Results in humans are not as conclusive and need to be explored further, but may have implications for workers on rotating shift schedules or anyone exposed to chronic sleep restriction.

The non-photic drive generated by Model PNP (Figure 6) indicates that the human circadian pacemaker is sensitive to the timing of sleep across the circadian day, which appears contrary to the results of an experiment in which the effect of a 180-degree inversion of the sleep-wake cycle was studied (Duffy et al., 1996). While significant phase-shifts were not observed in response to inversion of the sleep-wake cycle in that study, the effect of sleep was studied only at two circadian phases, and these phases were chosen to optimize the effect of a light pulse for maximal phase delay or maximal phase advance. Furthermore, the

magnitude of the effect of non-photoc stimuli observed in Model PNP predictions is small enough that it could be (a) masked by the stronger effects of light in that and other studies, (b) lost in the variability of circadian phase markers due to sensitivity of the assays, or (c) confounded by the natural drift in the pacemaker as well as background light levels. Other studies have reported that timing of sleep (Danilenko et al., 2003) may have an effect on the circadian pacemaker, independent of light. Furthermore, our theoretical non-photoc PRC generated by Model PNP has a similar shape as compared to other non-photoc PRCs observed in humans in response to exercise and exogenous melatonin, findings which indicate that there is a 12-h anti-phase relationship to the light PRC. The asymmetry seen in the magnitude of the predicted delays and advances of the non-photoc drive is comparable to the asymmetry seen in photic PRCs. However, no controlled experiment has sought to determine whether the non-photoc PRC of the sleep-wake cycle produces the same response as melatonin or exercise.

The non-photoc drive works both independently and concomitantly to the existing light drive of our Model PNP. Minor changes to the photic drive facilitated the addition of a non-photoc drive with minimal consequences to the dynamics of the model, particularly when photic effects were strong. The logistic function appended to the forward rate, α , in Equation 9 revises the nonlinearity of the light drive to improve model predictions to single pulses of light, to light intensities under 100 lux (Zeitzer et al., 2000), and to intermittent light pulses (Gronfier et al., 2004). While previous versions of our model have not been validated for light intensities under 150 lux, the ability of Model PNP to predict entrainment at both 0 lux and 1.5 lux improves the range of accurate model simulations from $150 < I < 9500$ lux, as reported in (Jewett and Kronauer, 1998), to $0 < I < 9500$ lux, as reported here. These revisions offer promise for using the model to develop more accurate and effective light schedules for shift workers, who are often exposed to a wide range of light levels at adverse circadian phases, resulting in circadian misalignment and other health issues (Klerman 2005).

Although the model in its current form does not account for inter-individual differences in habitual sleep schedules, intrinsic period, phase, or relative response to stimuli, this analysis demonstrates that comparisons of model predictions to experimental data can be made when this information about bedrest times, intrinsic period and circadian phase are known.

In general, model development has been based on group data and assumes a relative sleep episode from 2400 to 0800 with a corresponding CBT_{min} occurring ~ 2.5 h before wake. For simulations of individual subjects, actual sleep and wake times were adjusted to these values and the initial CBT_{min} of the model was adjusted so that the initial phase angle in the model matched the phase angle observed experimentally in each individual. The correct alignment of phase is imperative to the accurate predictions of individual experimental data, particularly in entrainment studies where the stable phase angle between the scheduled sleep episode and the circadian phase marker is the sole determinant of entrainment. Predictions of entrainment also depend on the accuracy of the estimated intrinsic period of the circadian pacemaker, which has a significant effect on the daily phase shifts observed. Although it has been reported that the average intrinsic period of the human circadian pacemaker following entrainment to $T=24.0$ hr is $\tau = 24.18$ hr (Czeisler et al., 1999), individuals display large variations in intrinsic period that must be taken into account when using the model to compare predictions to experimental data. Furthermore, there are inter-individual differences in the response of the human circadian pacemaker to exogenous stimuli. It has been reported that some non-entrained blind subjects entrained to exogenous melatonin administration, while some subjects were unable to entrain. It was suggested that these individuals may require longer exposure or stronger dosages of the exogenous stimuli to have the same observable effects as the other subjects (Lockley et al., 2000). This suggestion may also be

true for subjects scheduled to a non-24-hr entrainment cycle who did not entrain and for which Model PNP could not sufficiently match their observed behavior. These results suggest an inter-individual variability in sensitivity to both photic and non-photoc stimuli.

It should be noted that Model PNP has been developed with a relatively small amount of data, with parameters depending heavily on a few subjects studied under ~1.5 lux and only 1 subject studied in 0 lux. Comparisons of Model PNP to entrainment data were made to data that was used to develop Model PNP. Therefore, Model PNP needs to be validated on independent entrainment data in subjects scheduled to non-24-hr T-cycles in dim light or 0 lux. Additional experiments are required to test the hypothesis that the sleep-wake cycle itself or any of its associated behaviors are the non-photoc stimulus that has the ability to entrain and phase-shift the human circadian pacemaker. Because the light-dark cycle and the sleep-wake cycle normally coincide, it is necessary to separate the two cycles in order to determine the contribution of the sleep-wake cycle to the observed phase-shifts of the human circadian pacemaker. The advantage of studies on blind subjects with no ocular light perception is that the sleep-wake cycle may be naturally desynchronized from a light-dark cycle (except in cases where intrinsic period is equal to T-cycle length or in those blind subjects who keep a habitual sleep/wake schedule because of work). Because other non-photoc stimuli are linked to the sleep-wake cycle (e.g., meal timing or posture changes), it is also important to consider the possible contribution of these additional effects on the circadian pacemaker. Once data are available, this model can be further refined.

References

- Anderson DR, Burnham KP, Thompson WL. Null hypothesis testing: problems, prevalence, and an alternative. *J Wildl Manage.* 2000; 64:912–923.
- Antle MC, Mistlberger RE. Circadian clock resetting by sleep deprivation without exercise in the Syrian hamster. *J Neurosci.* 2000; 20:9326–9332. [PubMed: 11125012]
- Aschoff J. Exogenous and endogenous components in circadian rhythms. *Cold Spring Harb Symp Quant Biol.* 1960; 25:11–28. [PubMed: 13684695]
- Barger LK, Wright KP Jr, Hughes RJ, Czeisler CA. Daily exercise facilitates phase delays of circadian melatonin rhythm in very dim light. *Am J Physiol Regul Integr Comp Physiol.* 2004; 286:R1077–R1084. [PubMed: 15031136]
- Biello SM, Janik D, Mrosovsky N. Neuropeptide Y and behaviorally induced phase shifts. *Neuroscience.* 1994; 62:273–279. [PubMed: 7816205]
- Buxton OM, Lee CW, L'Hermite-Balériaux M, Turek FW, Van Cauter E. Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. *Am J Physiol Regul Integr Comp Physiol.* 2003; 284:R714–R724. [PubMed: 12571075]
- Cajochen C, Jewett ME, Dijk DJ. Human circadian melatonin rhythm phase delay during a fixed sleep-wake schedule interspersed with nights of sleep deprivation. *J Pineal Res.* 2003; 35:149–157. [PubMed: 12932197]
- Czeisler CA, Brown EN. Commentary: Models of the effect of light on the human circadian system: Current state of the art. *J Biol Rhythms.* 1999; 14:538–543. [PubMed: 10643751]
- Czeisler, CA.; Wright, KP, Jr. Influence of light on circadian rhythmicity in humans. In: Turek, FW.; Zee, PC., editors. *Regulation of Sleep and Circadian Rhythms.* New York, NY: Marcel Dekker, Inc; 1999. p. 147-180.
- Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, Ronda JM, Silva EJ, Allan JS, Emens JS, Dijk DJ, Kronauer RE. Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science.* 1999; 284:2177–2181. [PubMed: 10381883]
- Daan S, Pittendrigh CS. A functional analysis of circadian pacemakers in nocturnal rodents: II. The variability of phase response curves. *J Comp Physiol.* 1976; 106:253–266.
- Danilenko KV, Cajochen C, Wirz-Justice A. Is sleep per se a zeitgeber in humans? *J Biol Rhythms.* 2003; 18:170–178. [PubMed: 12693871]

- Deboer T, Vansteensel MJ, Detari L, Meijer JH. Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci.* 2003; 6:1086–1090. [PubMed: 12958601]
- Duffy JF. Constant Routine. In: Carskadon, MA., editor. *Encyclopedia of Sleep and Dreaming*. New York, NY: Macmillan; 1993. p. 134-136.
- Duffy JF, Kronauer RE, Czeisler CA. Phase-shifting human circadian rhythms: Influence of sleep timing, social contact and light exposure. *J Physiol (Lond).* 1996; 495:289–297. [PubMed: 8866371]
- Duffy JF, Wright KP Jr. Entrainment of the human circadian system by light. *J Biol Rhythms.* 2005; 20:326–338. [PubMed: 16077152]
- Forger DB, Jewett ME, Kronauer RE. A simpler model of the human circadian clock. *J Biol Rhythms.* 1999; 14:532–537. [PubMed: 10643750]
- Glass JD, Tardiff SD, Clements R, Mrosovsky N. Photic and nonphotic circadian phase resetting in a diurnal primate, the common marmoset. *J Physiol.* 2001; 280:R191–R197.
- Goel N. Late-night presentation of an auditory stimulus phase delays human circadian rhythms. *Am J Physiol Regul Integr Comp Physiol.* 2005; 289:R209–R216. [PubMed: 15790749]
- Gronfier C, Wright KP Jr, Kronauer RE, Jewett ME, Czeisler CA. Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phase in humans. *Am J Physiol Endocrinol Metab.* 2004; 287:E174–E181. [PubMed: 15039146]
- Gundel A, Spencer MB. A circadian oscillator model based on empirical data. *J Biol Rhythms.* 1999; 14:516–523. [PubMed: 10643748]
- Jewett ME, Forger DB, Kronauer RE. Revised limit cycle oscillator model of human circadian pacemaker. *J Biol Rhythms.* 1999; 14:493–499. [PubMed: 10643746]
- Jewett ME, Kronauer RE. Refinement of a limit cycle oscillator model of the effects of light on the human circadian pacemaker. *J Theor Biol.* 1998; 192:455–465. [PubMed: 9680719]
- Jewett ME, Rimmer DW, Duffy JF, Klerman EB, Kronauer RE, Czeisler CA. Human circadian pacemaker is sensitive to light throughout subjective day without evidence of transients. *Am J Physiol.* 1997; 273:R1800–R1809. [PubMed: 9374826]
- Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol (Lond).* 2003; 549:945–952. [PubMed: 12717008]
- Khalsa SBS, Jewett ME, Duffy JF, Czeisler CA. The timing of the human circadian clock is accurately represented by the core body temperature rhythm following phase shifts to a three-cycle light stimulus near the critical zone. *J Biol Rhythms.* 2000; 15:524–530. [PubMed: 11106069]
- Khalsa SBS, Jewett ME, Klerman EB, Duffy JF, Rimmer DW, Kronauer RE, Czeisler CA. Type 0 resetting of the human circadian pacemaker to consecutive bright light pulses against a background of very dim light. *Sleep Research.* 1997; 26:722.
- Klerman EB. Non-photic effects on the circadian system: results from experiments in blind and sighted individuals. In: Honma, K.; Honma, S., editors. *Zeitgebers, Entrainment and Masking of the Circadian System*. Sapporo: Hokkaido University Press; 2001. p. 155-169.
- Klerman EB. Clinical aspects of human circadian rhythms. *J Biol Rhythms.* 2005; 20:375–386. [PubMed: 16077156]
- Klerman EB, Gershengorn HB, Duffy JF, Kronauer RE. Comparisons of the variability of three markers of the human circadian pacemaker. *J Biol Rhythms.* 2002; 17:181–193. [PubMed: 12002165]
- Klerman EB, Rimmer DW, Dijk DJ, Kronauer RE, Rizzo JF, Czeisler CA. Nonphotic entrainment of the human circadian pacemaker. *Am J Physiol.* 1998; 274:R991–R996. [PubMed: 9575961]
- Knoerchen, R.; Gundlach, EM.; Hildebrandt, G. Circadian variations of visual sensitivity and vegetative responsiveness to light in man. In: Hildebrandt, G., editor. *Biologische Rhythmen und Arbeit*. Vienna: Springer-Verlag; 1976. p. 244-253.
- Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Alteration of internal circadian phase relationships after morning versus evening carbohydrate-rich meals in humans. *J Biol Rhythms.* 2002; 17:364–376. [PubMed: 12164252]
- Kronauer, RE. A quantitative model for the effects of light on the amplitude and phase of the deep circadian pacemaker, based on human data. In: Horne, J., editor. *Sleep '90, Proceedings of the Tenth European Congress on Sleep Research*. Dusseldorf: Pontenagel Press; 1990. p. 306-309.

- Kronauer RE, Forger DB, Jewett ME. Quantifying human circadian pacemaker response to brief, extended, and repeated light stimuli over the photopic range. *J Biol Rhythms*. 1999; 14:500–515. [PubMed: 10643747]
- Kronauer RE, Forger DB, Jewett ME. Errata: Quantifying human circadian pacemaker response to brief, extended, and repeated light stimuli over the photopic range. *J Biol Rhythms*. 2000; 15:184–186.
- Lavie P. Ultrashort sleep-waking schedule III: “Gates” and “forbidden zones” for sleep. *Electroenceph Clin Neurophysiol*. 1986; 63:414–425. [PubMed: 2420557]
- Lewandowski MH, Usarek A. Effects of intergeniculate leaflet lesions on circadian rhythms in the mouse. *Behav Brain Res*. 2002; 128:13–17. [PubMed: 11755685]
- Lewy AJ, Bauer VK, Ahmed S, Thomas KH, Cutler NL, Singer CL, Moffit MT, Sack RL. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. *Chronobiol Int*. 1998; 15:71–83. [PubMed: 9493716]
- Lewy AJ, Sack RL. Exogenous melatonin’s phase-shifting effects on the endogenous melatonin profile in sighted humans: A brief review and critique of the literature. *J Biol Rhythms*. 1997; 12:588–594. [PubMed: 9406034]
- Lockley SW, Skene DJ, James K, Thapan K, Wright J, Arendt J. Melatonin administration can entrain the free-running circadian system of blind subjects. *J Endocrinol*. 2000; 164:R1–R6. [PubMed: 10607943]
- May CD, Dean DA, Jewett ME. A new mathematical definition of CBTmin improves model predictions of the effect of light on the circadian pacemaker in amplitude suppression protocols. *Society for Research on Biological Rhythms*. 2002
- Mistlberger RE. Circadian food-anticipatory activity: formal models and physiological mechanisms. *Neurosci Biobehav Rev*. 1994; 18:171–195. [PubMed: 8058212]
- Mistlberger RE, Antle MC, Webb IC, Jones M, Weinberg J, Pollock MS. Circadian clock resetting by arousal in Syrian hamsters: the role of stress and activity. *Am J Physiol Regul Integr Comp Physiol*. 2003; 285:R917–R925. [PubMed: 12842864]
- Mistlberger RE, Belcourt J, Antle MC. Circadian clock resetting by sleep deprivation without exercise in Syrian hamsters: Dark Pulses revisited. *J Biol Rhythms*. 2002; 17:227–237. [PubMed: 12054194]
- Mistlberger RE, Skene DJ. Social influences on mammalian circadian rhythms: Animal and human studies. *Biol Rev*. 2004; 79:533–556. [PubMed: 15366762]
- Miyazaki T, Hashimoto S, Masubuchi S, Honma S, Honma K-I. Phase-advance shifts of human circadian pacemaker are accelerated by daytime physical exercise. *Am J Physiol Regul Integr Comp Physiol*. 2001; 281:R197–R205. [PubMed: 11404294]
- Mrosovsky N. Locomotor activity and non-photoc influences on circadian clocks. *Biol Rev*. 1996; 71:343–372. [PubMed: 8761159]
- Nakamura K. Non-photoc entrainment of human circadian clock -- effects of forced sleep-wake schedule on the circadian rhythm in plasma melatonin. *Hokkaido J Med Sci*. 1996; 71:403–422. [PubMed: 8752534]
- Nakao M, Yamamoto K, Honma K-I, Hashimoto S, Honma S. A phase dynamics model of human circadian rhythms. *J Biol Rhythms*. 2002; 17:476–489. [PubMed: 12375623]
- Nelson DE, Takahashi JS. Sensitivity and integration in a visual pathway for circadian entrainment in the hamster (*Mesocricetus auratus*). *J Physiol*. 1991; 439:115–145. [PubMed: 1895235]
- Redman J, Armstrong S, Ng KT. Free-running activity rhythms in the rat: entrainment by melatonin. *Science*. 1983; 219:1089–1091. [PubMed: 6823571]
- Reppert SM, Schwartz WJ, Weaver DR. The circadian-gated timing of birth in rats: disruption by maternal SCN lesions or by removal of the fetal brain. *Brain Res*. 1987; 403:398–402. [PubMed: 3828831]
- Rosenwasser AM, Dwyer SM. Circadian phase shifting: Relationships between photic and nonphotic phase-response curves. *Physiol Behav*. 2001; 73:175–183. [PubMed: 11399309]
- Sack RL, Brandes RW, Kendall AR, Lewy AJ. Entrainment of free-running circadian rhythms by melatonin in blind people. *N Engl J Med*. 2000; 343:1070–1077. [PubMed: 11027741]

- Sack RL, Lewy AJ, Blood ML, Keith LD, Nakagawa H. Circadian rhythm abnormalities in totally blind people: Incidence and clinical significance. *J Clin Endocrinol Metab.* 1992; 75:127–134. [PubMed: 1619000]
- Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci.* 2001; 24:726–731. [PubMed: 11718878]
- Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature.* 2005; 437:1257–1263. [PubMed: 16251950]
- Shanahan TL, Czeisler CA. Light exposure induces equivalent phase shifts of the endogenous circadian rhythms of circulating plasma melatonin and core body temperature in men. *J Clin Endocrinol Metab.* 1991; 73:227–235. [PubMed: 1856258]
- Strogatz SH, Kronauer RE, Czeisler CA. Circadian pacemaker interferes with sleep onset at specific times each day: role of insomnia. *Am J Physiol.* 1985; 253:R172–R178. [PubMed: 3605382]
- Takahashi JS, DeCoursey PJ, Bauman L, Menaker M. Spectral sensitivity of a novel photoreceptive system mediating entrainment of mammalian circadian rhythms. *Nature.* 1984; 308:186–188. [PubMed: 6700721]
- Wallach D, Goffinet B. Mean squared error of prediction as a criterion for evaluating and comparing system models. *Ecol Modelling.* 1989; 44:299–306.
- Winfree, AT. *The geometry of biological time.* New York: Springer-Verlag; 1980.
- Wright KP Jr, Gronfier C, Duffy JF, Czeisler CA. Intrinsic period and light intensity determine the phase relationship between melatonin and sleep in humans. *J Biol Rhythms.* 2005; 20:168–177. [PubMed: 15834113]
- Wright KP Jr, Hughes RJ, Kronauer RE, Dijk DJ, Czeisler CA. Intrinsic near-24-hour pacemaker period determines limits of circadian entrainment to a weak synchronizer in humans. *Proc Natl Acad Sci USA.* 2001; 98:14027–14032. [PubMed: 11717461]
- Zeitler JM, Dijk DJ, Kronauer RE, Brown EN, Czeisler CA. Sensitivity of the human circadian pacemaker to nocturnal light: Melatonin phase resetting and suppression. *J Physiol (Lond).* 2000; 526:695–702. [PubMed: 10922269]
- Zeitler JM, Kronauer RE, Czeisler CA. Photopic transduction implicated in human circadian entrainment. *Neurosci Lett.* 1997; 232:135–138. [PubMed: 9310298]

Figure 1.

Schematic diagram of the circadian mathematical Model PNP. The light pre-processor (Process L) converts light into a drive that acts on the circadian pacemaker (Process P) through a circadian sensitivity modulator (SM_L) before acting on the pacemaker itself ($\sim$). A separate process converts the bedrest timing into a sleep/wake state drive ($\hat{N}_s$) on Process P that enters a circadian sensitivity modulator (SM_N) that is separate from but similar to the one for light, before acting on the pacemaker.

Figure 2.

Simulations of Model P (dashed line) and Model PNP (solid line) of subject 18G6 scheduled to $T = 24.0$ h in ~ 1.5 lux during scheduled wakefulness. Note that the predictions of Model P and Model PNP overlap. Horizontal bars represent scheduled sleep episodes, which are reported in relative clock hour with midnight = 24. $DLMO_{25\%}$ data are represented as filled squares.

Figure 3. Simulations of Model P (dashed line) and Model PNP (solid line) of subject 1947 scheduled to $T = 24.6$ h in ~ 1.5 lux.

Figure 4.

a) Simulations of Model P (dashed line) and Model PNP (solid line) of blind subject 1451 scheduled to $T = 23.8$ h for the first 31 days and then $T=24.0$ h for the remainder of the inpatient protocol. All sleep and wake episodes were in effectively 0 lux, since the subject was blind. DLMO_{UC} data are represented by filled squares.

Figure 5.

A comparison of Model PNP simulations with (solid line) and without (dotted line) circadian sensitivity to sleep initiation to experimental data (filled squares) from subject 1451 (a) and (b) subject 18G1. The simulations of Model PNP that accounted for a circadian sensitivity of sleep initiation report a better fit to the experimental data.

Figure 6.

The force of the nonphotic drive on the pacemaker, with (solid line) and without (dashed line) sensitivity to sleep initiation, integrated over a circadian cycle varies with the phase of the scheduled sleep episode.

Figure 7.

Phase response curves (PRC) to a three-cycle bright light (~9,500 lux, 5 hour duration per cycle) stimulus. Initial phase is defined as the center of the light pulse relative to the minimum of the core body temperature (CBT_{min}) as recorded during CR, where CBT_{min} is defined as 0 h. Final phase is defined as the CBT_{min} assessed during initial and post-stimulus CRs. Simulations from Model PNP (solid line) and Model P (dashed line) are compared to experimental CBT data (filled squares) from Khalsa et al. (1997).

Figure 8. Phase response curves (PRC) to a one-cycle bright light (~9,500 lux, 6.7 hour duration) stimulus. Simulations from Model PNP (solid line) and Model P (dashed line) are compared to experimental CBT data (filled squares) [previously unpublished, protocol in Khalsa et al. (2003)].

Figure 9.

Intensity response curves (IRC) to a one-cycle light stimulus (6.5-hour duration, centered ~3.5 h before $\text{CBT}_{\min}$) with intensities ranging from 0 to 9,500 lux. Simulations from Model PNP (solid line) and Model P (dashed line) are compared to experimental data (filled squares) and the 4-parameter logistic function (dotted line) fit by Zeitzer et al (2000).

Table 1

Mean Square Error (MSE) and Akaike Information Criterion (AIC) of Model P and Model PNP with respect to the experimental data for subjects.

	Subject	Model P MSE	Model PNP MSE	Model P AIC	Model PNP AIC
T = 24.0 h	18G1	0.70	0.59	2.46	5.74
	18G6	0.84	0.51	3.39	5.69
	1814	0.18	0.19	-2.64	1.50
	1983	0.68	0.74	2.81	7.09
	19A4	2.47	2.50	8.32	12.39
T = 24.6 h	18J5	0.32	1.66	-0.41	9.98
	19a9	0.58	1.14	1.37	8.62
	1916	1.40	0.38	5.60	3.44
	1922	2.61	0.29	8.16	2.59
	1947	1.74	0.16	6.64	-0.76

Note: Model with the smaller MSE/AIC is the better fit to the data.