Interactive Mathematical Models of Subjective Alertness and Cognitive Throughput in Humans

Megan E. Jewett*[,1] and Richard E. Kronauer[†]

*Circadian, Neuroendocrine and Sleep Disorders Section, Division of Endocrinology-Hypertension, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Avenue, Boston, MA, 02115 USA, [†]Division of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138 USA

Abstract The authors present here mathematical models in which levels of subjective alertness and cognitive throughput are predicted by three components that interact with one another in a nonlinear manner. These components are (1) a homeostatic component (*H*) that falls in a sigmoidal manner during wake and rises in a saturating exponential manner at a rate that is determined by circadian phase during sleep; (2) a circadian component (*C*) that is a function of the output of our mathematical model of the effect of light on the circadian pacemaker, with the amplitude further regulated by the level of *H*; and (3) a sleep inertia component (*W*) that rises in a saturating exponential manner after waketime. The authors first construct initial models of subjective alertness and cognitive throughput based on the results of sleep inertia studies, sleep deprivation studies initiated across all circadian phases, 28-h forced desynchrony studies, and alertness and performance dose response curves to sleep. These initial models are then refined using data from nearly one hundred fifty 30- to 50-h sleep deprivation studies in which subjects woke at their habitual times. The interactive three-component models presented here are able to predict even the fine details of neurobehavioral data from sleep deprivation studies and, after further validation, may provide a powerful tool for the design of safe shift work and travel schedules, including those in which people are exposed to unusual patterns of light.

In this modern era of continuous operations, shift work, and transmeridian travel, there is a real need to be able to predict human ability to perform under a variety of different sleep / wake schedules, including those in which people are exposed to unusual light patterns. To that end, several models of subjective alertness and performance have been developed (Folkard and Åkerstedt, 1992; Achermann and Borbély, 1994; Jewett et al., 1996a, 1996b). One of the earliest models to be presented was Folkard and Åkerstedt's (1992) three-process model of subjective alertness. Their model is composed of (1) a homeostatic component that rises during sleep and falls during wake, (2) a sinusoidal 24-h circadian component (*C*), and (3) a wake component (*W*) that represents reduced levels of alertness, referred to as "sleep inertia," that are typically observed upon awakening (Jewett et al., 1999c). Achermann and Borbély (1994) have proposed a very similar three-process model of subjective alertness in which they modified *W* so that it contains both sleep inertia and "wake inertia," which reflects the time it takes to fall asleep.

These models both have their roots in mathematical models of sleep propensity and regulation. For exam-

1. To whom all correspondence should be addressed.

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ple, their homeostatic component of alertness (called *S* after Borbély's [1982] homeostatic sleep drive) falls exponentially during wake and rises exponentially toward an asymptote during sleep, which is the exact opposite of the homeostatic sleep drive component in models of sleep propensity (Borbély, 1982; Daan et al., 1984). The connection between these subjective alertness models and models of sleep propensity is further illustrated by the fact that the time-course of the exponential rise of *S* during sleep in the three-process subjective alertness model has been validated against the rate of decline of slow-wave activity during sleep (Folkard and Åkerstedt, 1992), rather than against the rise of alertness due to sleep. Not surprisingly, this three-process model has been shown to be able to predict duration of sleep (Åkerstedt and Folkard, 1996), sleep latency (Åkerstedt and Folkard, 1994), and alpha power density of waking EEG recordings (Åkerstedt and Folkard, 1994, 1995).

Now that extensive subjective alertness and cognitive performance data sets are available, we no longer need to rely on sleep propensity models for the development and validation of neurobehavioral models. For example, in the original three-process model, the decline of the homeostatic component after >22 h of wakefulness was formulated largely from data collected in a 72-h sleep deprivation experiment that was conducted at only one circadian phase (Folkard and Åkerstedt, 1992), because at the time that was one of the largest data sets of prolonged wakefulness available. In addition, their derivation of the homeostatic and circadian components was based on the assumption that the circadian and homeostatic components were linearly independent (Folkard and Åkerstedt, 1992). Since then, forced desynchrony (FD) studies have been conducted in which subjects are placed for several weeks on a 28-h sleep-wake cycle that is well outside their ranges of entrainment. This allows alertness and performance to be measured after different lengths of wakefulness (up to 18.7 h) across all circadian phases. Detailed analyses of FD data have revealed that the circadian and homeostatic components of alertness and performance do in fact interact with one another in a nonlinear manner. Dijk et al. (1992) and Czeisler et al. (1994) have shown that the amplitude of the circadian component of subjective alertness and cognitive throughput is dependent on length of prior wakefulness, which is itself dependent on the level of the homeostatic component (assuming that the homeostatic component declines monotonically as wakefulness increases). Wyatt et al. (1997) have demonstrated a similar interaction between the homeostatic component and the amplitude of the circadian component for a psychomotor vigilance task. These FD findings have been confirmed and extended by a recent analysis of nearly two hundred 30- to 50-hour sleep deprivation experiments initiated across all phases of the circadian cycle (Jewett, 1997). That analysis revealed that the amplitude of the circadian component of alertness and performance is quite low upon awakening, increases gradually during the first ~15 h of wakefulness, and then remains relatively constant. Thus, any mathematical model of alertness or performance must incorporate these nonlinear interactions between *H* and *C* to accurately predict neurobehavioral functioning during the first ~15 h of wakefulness (Jewett et al., 1996a).

In addition, current neurobehavioral models must take into account the effects of light on the phase and amplitude of the circadian component of alertness and performance. This is of practical importance, since shift workers and transmeridian travelers are often exposed to light-dark schedules that could reset the phase and amplitude of their circadian systems, and thereby affect the circadian component of their neurobehavioral functioning. Achermann and Borbély (1994) and Jewett et al. (1996a, 1996b) have incorporated Kronauer's (1990) mathematical model of the effect of light on the human circadian system into their models of subjective alertness to simulate phase resetting and photoperiodic studies. In the neurobehavioral models we present here, we incorporate our most recent model of the effects of light on the human circadian pacemaker (see Jewett et al. 1999a and Kronauer et al. 1999). This model, shown in equations (1) through (6) below (*I* represents ambient light intensity [in lux], CBT_{min} represents the timing of the fitted minimum of the core body temperature measured during a constant routine protocol), more accurately predicts the findings of a wide variety of light experiments in humans, including studies in which subjects were exposed to brief pulses of bright light.

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

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

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

$$B = G(1-n)\alpha\left(1-0.4x\right)\left(1-0.4x_c\right) \tag{4}$$

$$\alpha = \alpha_0\left(\frac{I^p}{9500^p}\right) \tag{5}$$

$$CBT_{min} = x_{min} + 0.8. \tag{6}$$

The parameter values are $\mu = 0.13$, $q = 1/3$, $\tau_x = 24.2$, $k = 0.55$, $\beta = 0.013$, $G = 19.875$, $\alpha_o = 0.16$, and $p = 0.6$. The initial conditions at normal habitual bedtime are $x = -0.17$, $x_c = -1.22$, and $n = 0.50$.

In this paper, we construct and refine mathematical models of both subjective alertness and cognitive throughput using data kindly provided by the authors of 15 reports published over the past 12 years (Duffy et al., 1996; Khalsa et al., 1997; Jewett et al., 1997, 1999b, 1999c; Boivin et al., 1994, 1996; Zeitzer et al., 1997; Rimmer et al., 1995; Johnson et al., 1992; Dijk et al., 1992; Czeisler et al., 1994; Dinges et al., 1987, 1994, 1997). We are very grateful to the many experimentalists who allowed us to use their data in the construction and refinement of the models presented here.

CONSTRUCTING INITIAL MODELS OF SUBJECTIVE ALERTNESS AND COGNITIVE THROUGHPUT

For ease of understanding, the models of subjective alertness and cognitive throughput presented here have been scaled so that 1.0 represents the maximum measurable level of alertness or throughput and 0.0 represents the minimum measurable level of alertness or throughput. Alertness and throughput can only be measured during wakefulness, so at any given time the models' predictions of "alertness" and "throughput" during sleep represent the levels of alertness or throughput that would be expected if the person were to awaken at that moment.

As originally suggested by Folkard and Åkerstedt (1992), we have assumed that both subjective alertness and cognitive throughput are determined primarily by three factors: the circadian system, a sleep-wake homeostat, and sleep inertia. A schematic diagram of these neurobehavioral models is shown in Figure 1.

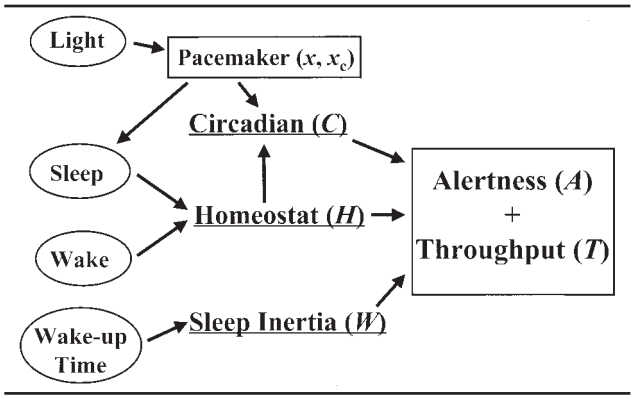

Figure 1. Schematic diagram of subjective alertness and cognitive throughput models developed in this paper. The light/pacemaker model is described in equations (1) to (6). The circadian component (*C*)of the neurobehavioral models is described in equations (7) and (8), the homeostatic component (*H*) during sleep is described by equation (11) and during wake by equation (16) for subjective alertness and by equation (9) for cognitive throughput, and the sleep inertia component (*W*) is described by equations (12) and (13). Cognitive throughput (*T*) is described by equation (14), and subjective alertness (*A*) is described by equation (15).

The sleep inertia component (*W*) represents the relatively brief period of reduced levels of alertness and throughput that are associated with awakening (Jewett et al., 1999c). As noted above, experimental FD data indicate that the amplitude of circadian component (*C*) is dependent on the level of the homeostatic component (*H*). Since *C* is a repeating function, we have defined *H* during wakefulness to be the level of alertness or performance for a given length of wakefulness averaged across all circadian phases (Kronauer et al., 1996). We then define *C* for any given level of *H* (or length of prior wakefulness) to be the repeating function representing the ~24-h rhythmic fluctuations observed in subjective alertness and cognitive throughput (see Jewett, 1997 for details). In the models presented here, *C* is governed by both the output of a light-sensitive circadian pacemaker and the level of the homeostatic component. During sleep, *H* recovers in a saturating exponential manner, the rate of which is dependent on the phase of the circadian pacemaker.

Circadian Component

As was shown in Jewett (1997), the circadian components of alertness (measured using a 100-mm visual analog scale, VAS) and cognitive throughput (measured using a 4-min addition task, ADD) are sinusoidal, with minima that occur ~1.5 h after CBT_{min}. The amplitude of the circadian component is modulated

by the level of the homeostat such that when the homeostat is near its peak (just after waketime), the amplitude of the circadian component is quite low, and as the homeostat drops during wakefulness, the amplitude of the circadian component grows in a saturating exponential manner (see Jewett, 1997 for details). Thus, the circadian component (C) of alertness and throughput was initially modeled using equations (7) and (8), where x and x_c represent the state variables of the circadian pacemaker model described in equations (1) through (6), A_C represents the amplitude of the circadian component, u_C represents the upper asymptote of A_C, H represents the homeostatic component, and h_{Ac} represents the scale of H, which causes the exponential function to decrease by e^{-1}. A weighted average of the two pacemaker state variables was used in equation (7) to force the minimum of C to occur ~1.5 h after CBT_{min} (~2.3 h after x_{min}, see equation (6)). The values of the parameters in equations (7) and (8) were derived from the saturating exponential curves (scaled to a range of 1.0) fit to the amplitudes of the circadian components of alertness and throughput data (Jewett, 1997).

$$C = A_C(0.91x - 0.29x_c) \tag{7}$$

$$A_C = u_C - ae^{H/h_{Ac}}. \tag{8}$$

For subjective alertness, $u_C = 0.1512$, $a = 1.8 \times 10^{-5}$, and $h_{Ac} = 0.11$; for cognitive throughput, $u_C = 0.1503$, $a = 6.2 \times 10^{-6}$, and $h_{Ac} = 0.098$.

Homeostatic Component

The homeostatic component (H) of subjective alertness and cognitive throughput is represented by two differential equations: one that describes the rate of recovery of H during sleep and one that describes the rate of decay of H during wake. As was shown in Jewett (1997), both subjective alertness (measured using the VAS) and cognitive throughput (measured using the ADD) decay during wakefulness in a sigmoidal manner and can be fit well with Gaussian curves. Thus, in equation (9) the rate of decay of H is modeled using the derivative of the Gaussian curves (scaled to a range of 1.0) fit to the alertness and throughput data in Jewett (1997). In equation (9), r_{Hw} represents the rate of decay of H, and t_w represents length of prior wakefulness.

$$\text{During wake, } \dot{H} = -2t_w(r_{Hw})^2(H - u_C). \tag{9}$$

For subjective alertness, $r_{Hw} = 1/28.9\ h^{-1}$; for cognitive throughput, $r_{Hw} = 1/32.0\ h^{-1}$.

The rates of rise of the homeostatic components of alertness and throughput during sleep were estimated from dose response curves (DRCs) to sleep (Jewett et al., 1999b). The sleep DRCs were constructed using alertness and performance data that were measured after subjects had slept 0, 2, 5, or 8 h in the previous night. Unlike the other studies used to construct the models presented here, in the sleep DRC study, subjective alertness was measured using the Stanford Sleepiness Scale (SSS) rather than the VAS, and performance was measured using a Psychomotor Vigilance Task (PVT) rather than the ADD. However, the recovery rates measured in those DRCs provide a good first estimate for the rates of recovery of subjective alertness and cognitive throughput during sleep. Those data showed that the recovery of both alertness and performance during sleep is described well by a saturating exponential function. Therefore, the derivative of the exponential functions fit to the sleep DRCs (scaled to range of 1.0) in Jewett et al. (1999b) was used here to model the recovery of H during sleep. This derivative is shown in equation (10), where r_{Hsl} represents the rate of recovery during sleep, and u_H represents the upper asymptote of homeostatic recovery.

$$\text{During Sleep, } \dot{H} = r_{Hsl}(u_H - H). \tag{10}$$

For subjective alertness, $r_{Hsl} = 1/9.09\ h^{-1}$ and $u_H = 0.9949$; for cognitive throughput, $r_{Hsl} = 1/2.14\ h^{-1}$ and $u_H = 0.9896$.

Equation (10) describes the recovery of H for sleep episodes that are scheduled to occur during the nighttime hours, since in the experiments analyzed by Jewett et al. (1999b) the subjects all slept at their habitual times. However, FD studies have shown that when subjects are scheduled to sleep at different circadian phases, the amount of sleep they actually obtain during their scheduled sleep episodes fluctuates by ~20% across the circadian cycle, with the most sleep obtained near CBT_{min} and the least sleep obtained ~12 h after CBT_{min} (Dijk and Czeisler, 1994, 1995). Thus, even if the homeostat recovers during sleep at the same rate at all circadian phases, we must still take into account the fact that the amount of sleep that a

person obtains during a scheduled sleep episode varies with circadian phase. As shown in equation (11), we have incorporated this circadian variation in sleep propensity into our model by modulating the rate of recovery of H during sleep such that near the minimum of the circadian temperature cycle (represented by x from equation (1)), the recovery rate of H is faster, and near the maximum of x the recovery rate is slower.

$$\text{During Sleep, } \dot{H} = r_{Hsl}(1 - 0.1x)(u_H - H). \quad (11)$$

Sleep Inertia Component

It has been widely demonstrated that subjects show reduced levels of subjective alertness and cognitive throughput immediately upon wakening (referred to as "sleep inertia"). Since we have defined our predictions of alertness and throughput during sleep to represent the levels expected if a person were to awaken at that moment, sleep inertia (W) is set to a constant (W_o) during sleep. In that way, the models predict that any time a person awakens from sleep, a deficit of magnitude W_o will be observed. As is shown in equation (12), the absolute value of W_o is forced to be always less than ($H + C$), so that the models' predictions of alertness and throughput will never be less than zero. The magnitude of W_o was determined from the saturating exponential curves (scaled to a range of 1.0) fit to the sleep inertia data in Jewett et al. (1999c).

$$\begin{aligned} &\text{During sleep, For } H + C \geq |W_o|, \; W = W_o \\ &\qquad\qquad \text{For } H + C < |W_o| \;\; W = -(H + C). \end{aligned} \quad (12)$$

For subjective alertness, $W_o = -0.5346$; for cognitive throughput, $W_o = -0.2868$.

Once subjects have awakened, sleep inertia dissipates in an asymptotic manner that is described well by a saturating exponential function (Jewett et al., 1999c; Folkard and Åkerstedt, 1992; Achermann et al., 1995). Thus, we model the dissipation of sleep inertia during wake using the derivative of the saturating exponential functions (scaled to a range of 1.0) that were fit to the alertness (measured using the VAS) and cognitive throughput (measured using a 2-min ADD) data recorded during the first 4 h after awakening (Jewett et al., 1999c). This derivative is shown in equation (13), in which the rate of dissipation of W is represented by r_W.

$$\text{During wake, } \dot{W} = -r_W W. \quad (13)$$

For subjective alertness, $r_W = 1/0.79$ h^{-1}; for cognitive throughput $r_W = 1/0.86$ h^{-1}.

Subjective Alertness and Cognitive Throughput

Finally, as described in equations (14) and (15), subjective alertness (A) and cognitive throughput (T) are defined to be the sum of the circadian, homeostatic, and sleep inertia components. Although it may appear from these equations that the models are simply additive, it is important to recall the nonlinear interactions between H and C that occur in equation (8) and between H and x that occur in equation (11).

$$A = C + H + W \quad (14)$$

$$T = C + H + W \quad (15)$$

SIMULATIONS USING THE INITIAL MODELS OF SUBJECTIVE ALERTNESS AND COGNITIVE THROUGHPUT

Description of the Simulation Program

Simulations were performed on an IBM-compatible personal computer using the software "Stella" (High Performance Systems, Hanover, NH) for dynamic modeling. The equations were integrated using Euler's method, with an integration interval of 0.1 h. For each version of the models, the initial conditions for H were chosen so that the value of H at bedtime was stable under 24-h sleep-wake cycles of 16 h of wake beginning at 0800 h (defined as waketime) and 8 h of sleep beginning at midnight (defined as bedtime). Simulations were run of the baseline constant routine experimental protocol (*baseCR*) described below. The inputs for the simulations were light intensities (in lux), scheduled bedtimes, and scheduled waketimes. These inputs were set so that they matched those of the *baseCR* protocol.

Simulations of Baseline Constant Routine Protocol

The full *baseCR* protocol began with three baseline days in which subjects slept in darkness at their habitual times for 8 h (here defined to be 2400 to 0800 h) and

were awake in ~150 lux for 16 h (here from 0800 to 2400 h). This was followed by a 30- to 50-h constant routine (CR) during which subjects remained awake in ~10 lux in a constant semirecumbent posture (for details, see Jewett et al., 1997). During waking periods, subjective alertness was measured every 20 min using the VAS, and cognitive throughput was measured every hour using the ADD. VAS data were available for 147 *baseCR* studies, and ADD data were available for 94 *baseCR* studies. Thus, the *baseCR* study provides an extensive data set for the refinement of the initial alertness and throughput models described above. Although the entire protocol was simulated, only alertness and throughput data from the CR portion of the study were analyzed.

Analysis of Experimental Data and Scaling Factors

The VAS was scored as millimeters from the "sleepy" end of the 100-mm scale, and the ADD was scored as number of addition problems attempted in 4 min (see Jewett, 1997 for details). The VAS and ADD scores are reported as deviation from the subject's mean score, defined to be the average score between 2 and 26 h of wakefulness during the subject's CR. The VAS and ADD data were first averaged in 2-h bins of length of wakefulness within subjects, and then the bins were averaged across subjects.

In the sleep deprivation experiments from which our functions for H and C were derived (Jewett, 1997), fitted VAS scores ranged from a maximum of ~14.4 above the mean to a minimum of ~42.9 below the mean. Thus, for subjective alertness, $A = 1$ was set equivalent to 14.4 and $A = 0$ was set equivalent to –42.9. The fitted ADD scores from Jewett (1997) ranged from a maximum of ~9.6 above the mean to a minimum of ~42.1 below the mean. Therefore, for cognitive throughput, $T = 1$ was set equivalent to 9.6 and $T = 0$ was set equivalent to –42.1.

REFINEMENT OF THE INITIAL MODELS

Subjective Alertness Model

As can be seen in Figure 2, the initial model of subjective alertness (dashed line) fit the general shape of the *baseCR* data (filled squares) fairly well. However, the model underestimated the level of alertness at waketime, indicating that the rate of recovery of the

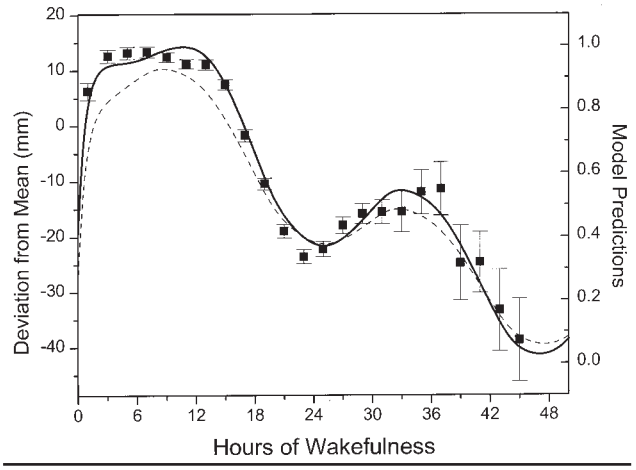

Figure 2. Subjective alertness (filled squares) measured during a baseline constant routine (*baseCR*) protocol using a 100 mm visual analog scale (VAS). Data were averaged in 2-h bins and are reported as millimeter deviation from the mean VAS score measured between 2 and 26 h of the *baseCR* for each subject. Error bars represent the standard error of the mean of each bin. Predictions of the initial (dashed line) and revised (solid line) subjective alertness model are shown.

homeostat during sleep (r_{Hsl}) needed to be increased. This may have been due in part to the fact that r_{Hsl} was calculated using SSS scores, while VAS scores were used in the validation studies. Thus, r_{Hsl} was increased to 2.3^{-1} for all further simulations. Once the recovery rate during sleep was increased, it became clear that the initial model of subjective alertness overestimated the upper asymptote of H (u_H), so u_H was reduced to 0.955. For the amplitude of the circadian component (C) to then equal zero when H equaled u_H, a in equation (8) was set equal to 3.59×10^{-6}. In addition, the simulation of subjective alertness in the *baseCR* experiment indicated that in the initial model the upper asymptote (u_C) of the amplitude of C was too small and that the amplitude of C increased too slowly as H decreased. Thus, u_C was increased to 0.21 and h_{Ac} was decreased to 0.087.

However, even with these adjustments, the initial model of subjective alertness was still not able to predict the extended period of above-average alertness after waketime that was observed in the *baseCR* experiment. In that study, subjects rated themselves 10 to 20 mm above their mean level of alertness for ~15 h after waketime. Thus, equation (9) describing the rate of decay of H during wakefulness was adjusted to take into account the slow rate of decay of H after waketime, as is shown in equation (16). In this equation, the rate of decay is quite slow until $t = t_o$, after which time H decays more quickly. For large values of

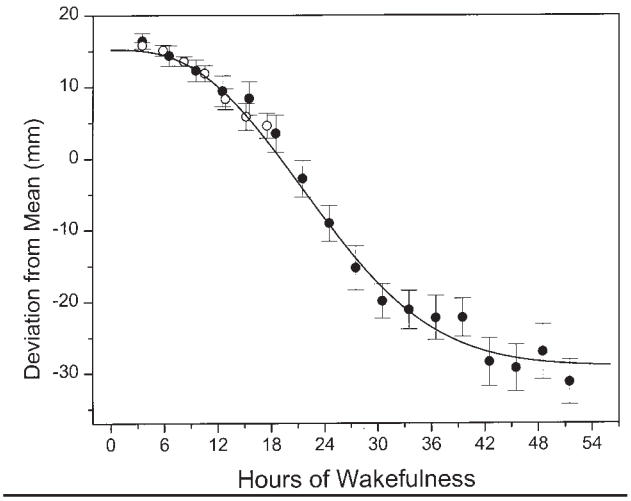

Figure 3. Homeostatic component of the subjective alertness data from approximately two hundred 30- to 50-h sleep deprivation studies initiated across all circadian phases (filled circles) and from 11 forced desynchrony studies (open circles) (see Jewett, 1997 for details). Data plotted as in Figure 2. The solid line represents the fitted equation (17).

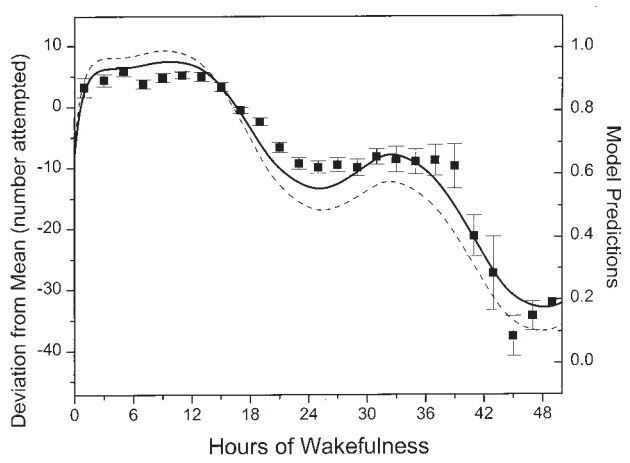

Figure 4. Cognitive throughput (filled squares) measured during the *baseCR* protocol using a 4-min addition task (ADD). Data were averaged in 2-h bins and are reported as deviation from the mean number of problems attempted per ADD test between 2 and 26 h of the *baseCR* for each subject. Error bars represent the standard error of the mean of each bin. Predictions of the initial (dashed line) and revised (solid line) cognitive throughput model are shown.

t, H decays in a Gaussian manner. The parameter values for equation (16) were estimated by integrating (16) to get equation (17) and fitting (17) to the homeostatic component of the sleep deprivation (Fig. 3, filled circles) and FD (Fig. 3, open circles) data from which the equation for H was originally derived (see Jewett 1997 for details). As in Jewett (1997), the fitting procedure was weighted by the number of tests in each bin. As can be seen in Figure 3 (solid line), equation (17) fits the data quite well.

$$\text{During wake, } \dot{H} = -\frac{t^2}{(t+t_o)} r_{Hw}(H - u_C) \qquad (16)$$

$$H = h_0 + h_1(t+t_o)^{\left(r_{Hw}t_o^2\right)} e^{\left[r_{Hw}/2(t+t_o)(t-3t_o)\right]}. \qquad (17)$$

The fitted parameter values were $t_o = 18.88$, $r_{Hw} = -0.006$ h^{-1}, $h_0 = -29$, and $h_1 = 957$. To improve the fit to the *baseCR* data, these parameters were revised slightly so that $t_o = 18.24$ and $r_{Hw} = 6.64 \times 10^{-3}$ h^{-1}. With these revised parameters, equation (16) fits the data shown in Fig. 3 equally well.

As can be seen in Fig. 2, the revised subjective alertness model (solid line) fit the *baseCR* data quite well throughout the entire CR. The final revised subjective alertness model consists of equations (7), (8), (11-14), and (16) with the following parameter values $u_C = 0.21$, $a = 3.59 \times 10^{-6}$, $h_{Ac} = 0.087$, $r_{Hsl} = 1/2.3$ h^{-1}, $u_H = 0.955$, $W_o = -0.5346$, $r_W = 1/0.79$ h^{-1}, $t_o = 18.24$, and $r_{Hw} = 6.64 \times 10^{-3}$ h^{-1}.

Cognitive Throughput Model

As can be seen in Fig. 4, the initial model of cognitive throughput (dashed line) fit the *baseCR* data fairly well. However, the rate of decline of H was slightly too fast, so r_{Hw} was reduced to 1/38. In addition, the model slightly overestimated the upper asymptote of H, so u_H was reduced to 0.95. For the amplitude of C to then equal zero when H equaled u_H, a in equation (8) was set equal to 9.27×10^{-6}. As can be seen in Fig. 4, the revised cognitive throughput model (solid line) fit the *baseCR* data quite well. The final revised cognitive throughput model consists of equations (7-9), (11-13), and (15) with the following parameter values $u_C = 0.1503$, $a = 9.27 \times 10^{-6}$, $h_{Ac} = 0.098$, $r_{Hsl} = 1/2.14$ h^{-1}, $u_H = 0.95$, $W_o = -0.2868$, $r_W = 1/0.86$ h^{-1}, $t_o = 18.24$, and $r_{Hw} = 1/38.0$ h^{-1}.

DISCUSSION

While only minor parameter adjustments were necessary for the initial cognitive throughput model to fit the *baseCR* data set, more extensive refinements were necessary in the initial subjective alertness model. We found that even though the Gaussian curve used to

model the homeostatic decline of alertness during wakefulness had a very slow rate of decay near waketime, it did not remain near the upper asymptote of *H* long enough to accurately predict the *baseCR* subjective alertness results. Therefore, we replaced the derivative of the Gaussian function in equation (9) with the function shown in equation (16), in which the rate of decay of the homeostat is quite slow until 10 to 15 h of wakefulness (see Fig. 3).

It is possible that the prolonged period of fairly constant, high alertness and throughput scores observed after waketime may reflect a ceiling effect of the tests used to measure alertness and throughput, rather than an underlying feature. Further studies using different alertness and throughput metrics will allow us to determine to what extent, if any, ceiling effects may have influenced the slow decay rate of subjective alertness observed after waketime. However, it is clear from these simulations that to predict subjective alertness and cognitive throughput, the homeostatic component cannot decay in the exponential manner described in the original mathematical models of Folkard and Åkerstedt (1992) and Achermann and Borbély (1994). Rather than a rapid decline of alertness and throughput that begins immediately upon awakening, both alertness and throughput seem to remain fairly stable for many hours after waketime.

The *baseCR* study represents our most extensive validation data set available, and thus it is important that our revised models be able to predict those data quite accurately. In both the subjective alertness and cognitive throughput data measured in the *baseCR* study, the standard errors increase as the length of wakefulness increases (see Figs. 2 and 4). This is primarily due to a decrease in the number of tests available because some CRs ended earlier than others, rather than to an increase in response variability. Nevertheless, we found that the revised subjective alertness and cognitive throughput models were able to fit even the fine details of the entire *baseCR* data train quite well (Figs. 2 and 4). However, it will be important to further validate these models using sleep deprivation studies that last for more than the 40-50 h reported here.

Although the models proposed here have taken into account some important interactions between model components, other interactions may exist that have not yet been included. For example, while we have incorporated the effects of circadian phase on the ability to obtain sleep, there may also be an additional effect of circadian phase (x) on the actual recovery rate of the homeostat during sleep (r_{Hsl}). It is also quite likely that the magnitude of the initial deficit (W_o) and / or the rate of dissipation (r_w) of sleep inertia (W) may be dependent on circadian phase at waketime (x) and / or prior sleep debt (H). As more neurobehavioral data measured across different circadian phases after different lengths of prior sleep and wakefulness become available, it will be possible to more carefully characterize these and other potential interactions between model components.

It is important that models be developed for a given neurobehavioral function (e.g., short-term memory, reaction time, cognitive throughput, subjective alertness) as we have done here, since circadian phase and length of prior sleep and wakefulness are likely to have different effects on different functions. While we have relied on only one type of test for our model of each neurobehavioral function (VAS for subjective alertness, ADD for cognitive throughput), it would be preferable to use more than one kind of test to measure a given neurobehavioral function. This would reduce the influence of any test-specific attributes (e.g., ceiling or practice effects) on the models. For example, Achermann (1999) has suggested that the reduced amplitude of C (A_c) at high levels of H in both subjective alertness and cognitive throughput may be due to ceiling effects in each of the tests used to measure those functions. However, if this interaction between H and A_c is observed across several different measurements of alertness and throughput, then it is unlikely to be the result of a ceiling effect (Dijk et al, 1999). In addition, if C is sinusoidal, a low A_c due to ceiling effects in a metric can be distinguished from a low A_c due to an interaction between H and A_c based on the shape of C at high levels of H. Ceiling effects would lead to a circadian component with a flattened peak but a normally-shaped trough, while component interaction would lead to a sinusoidal C with a clear peak and trough but with a reduced amplitude throughout. However, to distinguish the shape of C to this level of detail, circadian phase must be well sampled for each length of prior wakefulness and tests with minimal noise must be used.

Once a final, validated model is in place for a given neurobehavioral function, there are a number of external factors that could then be incorporated into the model. For example, while we have included the phase-shifting effects of light in our current models, we have not yet incorporated any acute effects of bright light on alertness and performance (Czeisler and Wright, 1999). Given sufficient data, we could

also incorporate into our models the effects of pharmacological agents such as caffeine, alcohol, melatonin, and hypnotics. Internal factors that affect neurobehavioral function, such as motivation, boredom, and psychological state, are important but may be more difficult to quantify and model.

In summary, we have constructed and refined mathematical models of both subjective alertness and cognitive throughput. While these models consist of three components, like the three-process models of Folkard and Åkerstedt (1992) and Achermann and Borbély (1994), they contain many significant differences. First of all, as can be seen in equation (8), the models presented here include a nonlinear interaction between the level of the homeostatic component (H) and the amplitude of the circadian component (C). Second, the homeostatic components in these models decline during wake in a Gaussian (or quasi-Gaussian) manner rather than in an exponential manner. Third, the circadian components in these models are governed by a refined limit-cycle pacemaker model that incorporates the effects of light on the circadian pacemaker. Fourth, a circadian rhythm in sleep propensity is included in the recovery of the homeostatic component during sleep. In addition, the models presented here have been scaled to a range of 0.0 to 1.0, which allows for straightforward interpretation of their results. Further validation is required using experiments in which both length of wakefulness and the circadian phase of waketime are varied to ensure that the revised models of subjective alertness and cognitive throughput presented here can provide accurate predictions of alertness and throughput across a wide variety of conditions.

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