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Modeling Fatigue over Sleep Deprivation, Circadian Rhythm, and Caffeine with a Minimal Performance Inhibitor Model

Patrick L. Benitez^{*}, Gary H. Kamimori[†], Thomas J. Balkin[†], Alexander Greene[‡], and Michael L. Johnson^{*}

^{*} Departments of Pharmacology and Medicine, University of Virginia Health System, Charlottesville, VA [†] Department of Behavioral Biology, Walter Reed Army Institute of Research, Division of Neuroscience, Silver Spring, Maryland [‡] School of Medicine, University of Florida, Gainesville, Florida

Abstract

Sleep loss, as well as concomitant fatigue and risk, is ubiquitous in today's fast-paced society. A biomathematical model that succeeds in describing performance during extended wakefulness would have practical utility in operational environments and could help elucidate the physiological basis of sleep loss effects. Eighteen subjects (14 males, 4 females; age 25.8 ± 4.3 years) with low levels of habitual caffeine consumption (<300 mg/day) participated. On night 1, subjects slept for 8 h (2300–0700 h), followed by 77 h of continuous wakefulness. They were assigned randomly to receive placebo or caffeine (200 mg, i.e., two sticks of Stay Alert gum) at 0100, 0300, 0500, and 0700 during nights 2, 3, and 4. The psychomotor vigilance test (PVT) was administered periodically over the 77-h period of continuous wakefulness. Statistical analysis reveals lognormality in each PVT, allowing for closed-form median calculation. An iterative parameter estimation algorithm, which takes advantage of MatLab's (R2007a) least-squares nonlinear regression, is used to estimate model parameters from subjects' PVT medians over time awake. In the model, daily periodicity is accounted for with a four-component Fourier series, and a simplified binding function describes asymptotic fatigue. The model highlights patterns in data that suggest (1) the presence of a performance inhibitor that increases and saturates over the period of continuous wakefulness, (2) competitive inhibition of this inhibitor by caffeine, (3) the persistence of an internally driven circadian rhythm of alertness, and (4) a multiplicative relationship between circadian rhythm and performance inhibition. The present inhibitor-based minimal model describes performance data in a manner consistent with known biochemical processes.

1. Introduction

In industrialized society, sleep loss has become a fact of life (Rajaratnam and Arendt, 2001). Ever more common for a wider swath of individuals, schedules that preclude adequate nightly sleep deleteriously impact alertness, performance, and quality of life. In certain operational (e.g., military and transportation) environments, the consequences of inadequate sleep can be especially dire. In such scenarios, the calculus involves weighing the need for pilots, firefighters, soldiers, and so on to operate during nighttime for sustained periods or under other conditions that prevent adequate sleep versus the increased risk of sleep loss-induced lapses in performance (Johnson *et al.*, 2007; Kryger *et al.*, 2000; Petrie and Dawson, 1997). Such lapses pose a threat to operator health and safety, odds of mission success, and so on.

Traditional biomathematical homeostatic models of sleep deprivation predict performance in terms of simple forms such as linear or exponential decrements and daily sinusoids (Achermann, 2004). Such homeostatic models assume a “performance capacity reservoir” that is depleted during wakefulness and replenished, at a rate proportional to sleep need, during

subsequent sleep (Achermann, 2004; Akerstedt and Folkard, 1997). However, such models fail to accommodate data from acute sleep deprivation studies, which often reveal asymptotic and/or nonsinusoidal behavior (Kamimori *et al.*, 2006). Furthermore, such models lack a clear physiological basis, with the “performance capacity reservoir” remaining a hypothetical construct.

This chapter presents a biochemically relevant model that adequately describes the variation in performance data over a 77-h period of wakefulness. In this model, sleep deprivation-related fatigue (i.e., increased reaction time relative to baseline) occurs as a function of two processes: saturation of a performance inhibitor and a driven 24-h (circadian) rhythm. This model can be extended to account for the effects of caffeine, which decreases PVT reaction time for sleep-deprived subjects (Rupp *et al.*, 2007), by assuming that the drug competitively inhibits the performance inhibitor (Boutrel, 2004). In this vein, the present “performance inhibitor”-based model constitutes the first attempt to describe, in physiological terms, the effects of pharmacological fatigue countermeasures in behavioral studies.

2. Methods

2.1. The Walter Reed Army Institute of Research Stay Alert caffeine gum study

Data were obtained from the Walter Reed Army Institute of Research (WRAIR) study on the efficacy of Stay Alert caffeine gum over a period of continuous (77 h) wakefulness (Kamimori *et al.*, 2006). The 18 subjects, all mild or noncaffeine users (<300 mg/day), included 14 ($N = 14$) males and 4 ($N = 4$) females, none of whom used hormonal contraceptives. Subjects gave informed consent, and officials confirmed their health status with a review of medical history, routine laboratory tests, and a physical examination. The Human Subjects Research Review Board of the Office of the Surgeon General of the Army approved the protocol for the study. Study administrators provided standardized meals and sleep was encouraged from 2300 to 0700 h on the night prior to sleep deprivation. Water was provided *ad libitum*.

For the 77-h period of wakefulness, the protocol called for assigning the subjects randomly into two groups: caffeine and placebo. In a double-blind fashion, the caffeine group received the Stay Alert caffeine gum (two sticks = 200 mg caffeine) four times per night (at 0100, 0300, 0500, and 0700 h), while the placebo subjects received Amurol confectioners gum at those times. Over the 3 days, subjects undertook a 5-min psychomotor vigilance test (PVT) three times between 2400 and 0100 h, nine times every 2 h between 0100 and 0900 h, and once every 2 h between 0900 and 2400 h. For reference, initial time awake took place at 700 h, and the initial PVT battery took place at 0940 h, both on the first day.

As an assessment of performance, the PVT has several advantages over other tests (Kaida *et al.*, 2007). The test itself measures the time it takes for a subject to push a button after presentation of a visual stimulus. Thus, learning curve and cognitive bias effects are minimized, increasing the signal-to-noise ratio (SNR), reducing systemic error, and making aggregate analysis (for the purposes of population parameter estimation) possible.

2.2. Data processing

Psychomotor vigilance test T data that fall into three categories thought to describe behavior other than canonical PVT reactions are excluded from analysis. First, PVT error events (such as anticipation, wrong key, or false start) are omitted. Second, tests with reaction times under 180 ms are omitted (i.e., considered too fast to represent actual reactions to the stimuli). Third, tests with reaction times over 2000 ms are omitted because independent studies have suggested that these PVT include periods of microsleep (Moller *et al.*, 2006).

After filtering, reaction time data from each PVT battery are summarized on a distribution basis (Adam *et al.*, 2006). As in Fig. 16.1, the distribution of reaction times for each battery is found to be threshold lognormal. This distribution can be described as Gaussian with mean μ and standard deviation σ under the shift θ (the threshold) and then a natural logarithm transform as in Eq. (16.1),

$$\ln(RT - \theta) \equiv \text{Gaussian}(\mu, \sigma). \quad (16.1)$$

Three statistical tests support this finding: (1) cumulative distribution function (CDF) comparison, (2) linearity in the threshold lognormal plot, and (3) Kolmogorov–Smirnov test. Given the distribution as described in Eq. (16.1), parameters θ , μ , and σ are calculated using a CDF-fitting method that took advantage of MatLab's (R2007a) nonlinear regression algorithm. With parameter estimates, a distribution median can be calculated,

$$\text{median} = \theta + \exp(\mu), \quad (16.2)$$

as well as its confidence interval (using a Monte Carlo simulation). This statistic is a robust measure of the center of the skewed distribution and is much more stable than the open-form calculation of the median, as it is resistant to the individual values in the center of the distribution. Figure 16.1 depicts a graphical representation of the distribution fitting and median estimation.

Finally, the distribution medians are shifted on a subject-by-subject basis so that the initial distribution's median (from the battery that took place at 0940 h on the first day) is 0 ms. Subtracting the baseline from each subject shifts data in a way that, to an extent, removes subject-to-subject variation and allows the medians from all subjects to be treated as one data set. Performing a regression on the aggregate data increases the SNR and yields reliable parameters for the population of subjects.

2.3. Caffeine modeling

In addition to time awake, a normalized caffeine concentration is included as an independent variable. (Placebo subjects always have a caffeine norm of zero.) Caffeine concentration is normalized so that one 200-mg dose resulted in 1 unit of normalized concentration. In Fig. 16.5, the solid line shows the caffeine norm over the period of wakefulness for caffeine subjects. In this method, it is assumed that body volumes and mastication/extraction rates are approximately equal across subjects.

The concentration of caffeine in the body is modeled using a simplified convolution integral of an input and an elimination process (Johnson and Straume, 1999; Johnson and Veldhuis, 1995; Syed *et al.*, 2005; Veldhuis *et al.*, 1987). The input process is approximated as an instantaneous dose_{*i*} at time *T_i* (the time of mastication), which allows the unbounded integral to be written as a sum of doses, one to *N* = 12. In this summation form, a Heaviside function *H* “turns on” dose_{*i*} at its mastication time *T_i*:

$$[C] = \sum_{d=1}^N H\{t - T_d\} \cdot 2^{-(t-T_d)/\lambda}. \quad (16.3)$$

After time T_i , the elimination process is projected as a single-compartment exponential decay with half-life $\lambda = 8.25$ h and an offset so that the concentration due to the dose is unity at time T_i .

2.4. Performance inhibitor model

Whereas a performance reservoir that decrements over time awake is assumed in the classic homeostatic model, the assumption of a performance inhibitor that increases over time awake is central to the model described here. The proposed model is a more useful description of data since it is derived from physiologically relevant and theoretical concepts. The model includes two components: a binding equation and a circadian modulator.

The binding equation at the core of the model is derived from the equilibrium statement of free performance inhibitor X , unbound receptor R , and receptor–inhibitor complex RX , as well as a conservation statement on the receptor:

$$k_{eq} = \frac{[RX]}{[R][X]} \quad (16.4)$$

$$[R_0] = [R] + [RX]. \quad (16.5)$$

The total receptor concentration $[R_0]$, equilibrium quotient k_{eq} , and body volumes are constant. From here a binding equation can be derived, one that calculates the concentration of the inhibitor–receptor complex as a function of constants and the concentration of the inhibitor itself:

$$[R_x] = [R_0] \frac{k_{eq}[X]}{1 + k_{eq}[X]}. \quad (16.6)$$

To extend the binding equation to include caffeine effects, it was assumed that caffeine acts as a competitive inhibitor of the performance inhibitor. Under this minimalist assumption, the binding equation includes a new term in the denominator—the normalized caffeine concentration $[C]$ and its coefficient k_c . The estimated coefficient reflects a combination of dose amount, body volume, and relative affinity between caffeine and the performance inhibitor:

$$[RX] = [R_0] \frac{k_{eq}[X]}{1 + k_{eq}[X] + k_c[C]}. \quad (16.7)$$

To make the binding function relevant to data, it is necessary to express the concentrations' relation to reaction time and time awake. For the purpose of simplicity, it is assumed that the concentration of the performance inhibitor is proportional to time awake, with constant α , and that relative reaction time is proportional to the concentration of bound inhibitor, with constant β :

$$t_{reaction} = \alpha[RX] \quad (16.8)$$

$$[X] = \beta t_{wake} \quad (16.9)$$

While the actual relationships between concentration and the physical analog may be more complex, the assumption of direct proportionality is the minimum required for the present model.

The model also includes a factor to allow for circadian modulation in reaction time (Dijk and Czeisler, 1994). This factor is a Fourier series to the fourth daily harmonic plus one, which allows for a nonperiodic, saturating time trend.

$$\text{Circadian Factor} = 1 + \sum_{i=1}^4 \left(A_i \sin \left[\frac{2\pi \cdot i \cdot t_{wake}}{24} \right] + B_i \cos \left[\frac{2\pi \cdot i \cdot t_{wake}}{24} \right] \right) \quad (16.10)$$

Within this factor, the magnitude of the periodic component is normalized to the magnitude of the time trend. The Fourier series, while more complicated than a one-component sinusoidal oscillation, allows for the model to account for a greater variety of periodic patterns in data. Generalizing the form of the circadian oscillation allows the model to sift through the periodicity of data to better describe any potential evidence of a performance inhibitor's action. The Fourier series, due to the mutual orthogonality of the components, also allows the circadian oscillation's form to arise from data rather than to be imposed upon them.

The model multiplies the circadian factor by the binding equation and, for purposes of parameter estimation, combines several multiplicative constants. A baseline modifier is added to the model.

2.5. The minimal biomathematical model

$$t_{reaction} = K \frac{k_I t_{awake}}{1 + k_I t_{awake} + k_C [C]} \cdot \text{Circadian Factor} + RT_0 \quad (16.11)$$

Table 16.1 contains estimates for the aforementioned equation's parameters. Regarding the *Circadian Factor*, parameters A_i and B_i , i range [1, 4] are also estimated simultaneously.

2.6. Least-squares parameter estimation

Model parameter estimations were performed using MatLab's nonlinear least-squares regression method, a Gauss–Newton algorithm. Medians were weighted to account for the fact that some represented more individual PVT than others, but no weighting function is used in the regression. The reported parameter errors were estimated by taking the square root of the diagonal of the covariance matrix, that is, the asymptotic standard errors. Table 16.1 presents the parameters of the performance inhibitor model.

To enhance the stability of the nonlinear regression process (which can depend on the initial guess values of the parameters) the individual parameters were added one at a time to the model with the following algorithm:

1. Holding previously estimated coefficients constant, the new parameter was estimated.
2. Utilizing this estimate and the previous estimates as initial guesses, a simultaneous parameter estimation was performed.

Estimates were made in the order indicated in Table 16.1, with the initial guesses for K and RT_0 being derived from the coefficients of the linear regression with respect to time awake.

3. Results

Data plotted in Figs. 16.2 and 16.3 are reaction time distribution medians, normalized so that the first (in terms of time awake) median for each subject is zero (Adam *et al.*, 2006). The scatter plots in Fig. 16.2 and 16.3 are placebo and caffeine data, respectively; the fitted model is also shown. This analysis includes both caffeine and placebo data in a simultaneous, nonlinear least-squares parameter estimation.

The performance inhibitor model provides a sound description of caffeine and placebo data for the study. The model adequately characterizes the asymptotic (rectangular hyperbola) behavior (see Fig. 16.2) in the data: as the inhibitor saturates, it can only increase the concentration of bound receptor to the point where (almost) all receptors are bound. For comparison, a model assuming linear increments in reaction time would predict an interminable increase in reaction time, a behavior not supported by data. The inhibitor-based model, along with the multiplicative circadian modulation, provides an improved description of the data over the period of acute sleep deprivation.

Apart from the saturation component, the generalized circadian modulation estimate provides some insight into how the rhythm relates to the time trend. Data support a multiplicative interaction—the fatigue response to sleep deprivation depends on the time of day, as well as concentration of the inhibitor–receptor complex. In Fig. 16.2 the asymptotic increase in *amplitude* of the periodic function results from this multiplier effect. Moreover, data reject the relationship in which the concentration of performance inhibitor itself fluctuates in a 24-h cycle. This would predict attenuation in the circadian rhythm with regards to reaction time, that is, the rhythm would eventually disappear as the concentration of inhibitor approached saturation. As Fig. 16.2 demonstrates, the rhythm increases before stabilizing.

Using this minimal performance inhibitor model for sleep deprivation allows a natural segue into modeling the effect of caffeine. Figure 16.3 shows that assuming caffeine to be a competitive inhibitor of the performance inhibitor sufficiently describes data. In fact, the model does a superior job describing caffeine data, which could possibly be attributed to the fact that the caffeine set contains fewer lapses. Furthermore, caffeine data confirm features found in placebo data. The amplitude of the circadian component on the first evening is much lower than its placebo counterpart. This finding makes sense in light of the multiplicative relationship and competitive inhibition. At this point in the study, the caffeine concentration sufficiently blocks binding of the performance inhibitor to the extent that circadian rhythm is suppressed.

4. Discussion

Results indicate a performance inhibitor that increases over time awake may actually underlie sleep loss mediated performance decrements. Viewed in this manner, caffeine can be seen to act as a competitive inhibitor of this performance inhibitor. This model adequately describes data from this WRAIR sleep deprivation study.

The minimal inhibitor model can account for nonlinear features in data in a theoretically valid, physiologically based way. Saturation (i.e., beyond a certain point, an increased concentration of the inhibitor fails to increase the number of bound receptors) explains how reaction time (and amplitude of circadian variation in reaction time) approaches an asymptote. Moreover, the notion of a performance inhibitor as opposed to a reservoir fits into a modern understanding of the molecular biology of sleep deprivation (Boonstra and Stins, 2007). This model also unites the study of acute sleep deprivation with that of the effect of caffeine as a stimulant.

Unlike previous models, it succeeds in simultaneously describing data under caffeine and placebo conditions, eliminating the artificial barrier between the two conditions of sleep deprivation. Using the estimated parameters, effective time awake and effective caffeine concentration can be estimated under the conditions of the study, if we ignore circadian effects. In Fig. 16.4, the dashed line plots effective time, which is, according to the assumptions in the model,

$$t_{eff} = t \left(\frac{1}{1 + k_c [C]} \right) \approx t \left(\frac{1}{1 + 0.356 \cdot [C]} \right) \quad (16.12)$$

and, in Fig. 16.5, the dashed line plots the effective normalized concentration:

$$[C]_{eff} = [C] \left(\frac{1}{1 + k_t t} \right) \approx [C] \left(\frac{1}{1 + 0.0264 \cdot t} \right) \quad (16.13)$$

Effective time awake is the time that would give rise to the same reaction time given a caffeine concentration of zero.

The model also confirms findings about the nature of the effect of caffeine. According to Fig. 16.5, the model-based analysis predicts that the half-life of the effect of the caffeine is 7.08 h on day 2 and 7.33 h on day 3. This diverges from the established half-life of caffeine in the body of 8.25 h (Syed *et al.*, 2005). This prediction, however, is in line with other studies that show that the half-life of the effect of caffeine is shorter than the half-life of its concentration in the blood (Ammar *et al.*, 2001; Kynastgales and Massey, 1994; Myers, 1988; Robertson *et al.*, 1978; Whitsett *et al.*, 1984). This common finding of the abbreviated effect of caffeine is consistent with the possibility of competitive inhibition.

This inhibitor-based minimal model predicts that the positive effect of caffeine will not be followed by a negative rebound effect as the caffeine concentration decreases. This is consistent with the observed effects of caffeine (Hewlett and Smith, 2007; Killgore, 2008).

While this minimal model can explain performance decrements over time awake, it has several limitations. The model takes the simplest possible route when dealing with concentrations. The relationship between time awake and the concentration of a performance inhibitor and between reaction time and the concentration of bound inhibitor may be nonlinear. The equilibrium statement, moreover, could contain nonunity stoichiometry, necessitating Hill coefficients in the binding equation of values other than 1 (Farhy, 2004).

These limitations result from the desire to start from the simplest assumptions. The circadian component, estimated under a Fourier series to allow maximal generality, appears to be in the form of a driven oscillation. This oscillating factor persists despite abrogation of the sleep cycle and the light cycle, suggesting that the circadian rhythm originates internally (Dardente and Cermakian, 2007). According to Figs. 16.2 and 16.3, the driven oscillation is similar to the pattern found in daily modulation of the concentration of growth hormone in the blood (Straume *et al.*, 1995), and perhaps similar mathematical methods can be applied to the sleep/alertness cycle.

More studies and analyses of other PVT data sets are needed in order to verify the performance inhibitor and the effect of caffeine. For the purposes of this analysis, data collected with a fixed frequency over the period of sleep deprivation are preferable as this would allow for time-series and variance analysis (Mulligan *et al.*, 1994). Also, from a numerical analysis prospective, a

better design for the PVT batteries would be to fix the number of valid response times instead of the time duration of the battery. This change, in addition to making data more comparable across time awake, would create an incentive for subjects to give maximal effort (so as to escape the tedium of a PVT battery), and thus help remove the effort bias (Kecklund *et al.*, 2006). With regard to the WRAIR study, there was a dip in reaction times in some of the placebo subjects at around 12 h of continuous wakefulness (Kamimori *et al.*, 2006). Experimental measurement uncertainties may explain why this dip occurs in some of the placebo subjects and in none of the caffeine subjects. This aberration occurs before caffeine administration, meaning that both groups should be identical at this point.

In addition to verification via replication, more distribution-based analysis, such as is depicted in Fig. 16.1, is needed to establish an accepted method of summarizing reaction time data (Adam, 2006). While summary statistics help account for variation and the inherent inadequacy of reaction time as a measure of performance over a period of sleep deprivation, there may be more appropriate ways by which to describe the center, spread, and shape of reaction time data.

Further areas of exploration include individualization, recovery from sleep deprivation, and chronic sleep restriction. Subjects have been shown to have interindividual variability in the following areas: chronotype (Mongrain and Dumont, 2007; Taillard *et al.*, 1999), sensitivity to caffeine (Rétey *et al.*, 2007), and sensitivity to sleep deprivation (Frey *et al.*, 2004; Murray *et al.*, 2006; Rétey *et al.*, 2006; Tucker *et al.*, 2007).

Extensions of this minimal model to these areas will make inhibitor-based modeling more applicable to real-world problems. For example, adding a second component to the recovery process (Johnson *et al.*, 2004) of the homeostatic model allows the model to better reflect the cumulative effects of sleep deprivation. This second component has a theoretical interpretation that is consistent with the inhibitor hypothesis, specifically slow increments in the number of receptors over time awake and slow decay over time asleep.

Adenosine, which increments in concentration during acute sleep loss (Rétey *et al.*, 2007) is a strong potential candidate for the performance inhibitor. Caffeine is a known adenosine antagonist (Fredholm *et al.*, 1999). It is anticipated that further study along these lines will lead to pharmacological therapies to regulate sleep pathology (Mignot *et al.*, 2002).

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Figure 16.1.

A graphical example showing a typical PVT set's empirical cumulative distribution function (ECDF), fitted lognormal CDF, and distribution median calculation. PVT data are shown to be lognormal (with a threshold) under several statistical tests. Using a nonlinear least-squares method, a lognormal CDF is fitted to data, which gives rise to a distribution median estimate. Confidence on the median is calculated with a Monte Carlo simulation.

Figure 16.2.

Plot of the placebo subjects' relative medians over time awake, along with the projected relative median reaction times according to the fitted model with a caffeine concentration of zero. Zero "relative reaction time" is defined as the subject's median reaction time for the first PVT set in terms of hours awake. In other words, relative reaction time measures the change in reaction time since the first PVT set. Overall, the model, which assumes a multiplicative relationship between circadian rhythm, succeeds in describing data. Figures 16.2 and 16.3 are less accurate for times awake under 5 h, perhaps due to sleep lag effects (Akerstedt and Folkard, 1997).

Figure 16.3.

Plot of caffeine subjects' relative medians over time awake, along with projected relative median reaction times according to the fitted model with the projected normalized caffeine concentration. The plot is of the same form as the placebo plot. Again, the model succeeds in describing data, although multiplicity between saturation and circadian effects is even more apparent.

Figure 16.4.

A plot of effective sleep deprivation under the placebo and caffeine regimens in the study. This figure is an implication of the model. Although caffeine seems persistently effective in this graph, it is important to remember that the difference between 20 and 30 h awake is more substantial than the difference between 40 and 70 h awake. This disparity can be explained in terms of saturation of the performance inhibitor.

Figure 16.5.

A plot of the effective strength of the caffeine concentration relative to the normalized concentration at zero hours awake. This figure is an implication of the inhibitor-based model. The normalized concentration is such that 1 unit equals the concentration that results from one 200-mg dose. As time awake increases, the performance inhibitor competitively swamps the caffeine so the relative strength decays. The established half-life of caffeine is 8.25 h, whereas the approximate half-life of the effect on the second day is 7.08 h and on the third day is 7.33 h. This is in agreement with other studies that have shown the half-life of the effect to be shorter than that of the concentration.

Table 16.1

Parameter estimates with asymptotic standard error for the simultaneous fit of placebo and caffeine data

Parameter	Estimate	Error
K	230.9	1.4
RT_0	-51.7	1.0
K_t	0.0264	0.0006
K_c	0.356	0.004
A_1	-0.0474	0.0034
B_1	0.384	0.005
A_2	-0.0990	0.0034
B_2	0.0811	0.0031
A_3	-2.94E-03	2.89E-03
B_3	-1.43E-03	3.22E-03
A_4	0.0277	0.0026
B_4	0.0287	0.0026