PARAMETER ESTIMATION FOR A BIOMATHMATICAL
MODEL OF PSYCHOMOTOR VIGILANCE PERFORMANCE
UNDER LABORATORY CONDITIONS OF CHRONIC SLEEP
RESTRICTION

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INTRODUCTION
Laboratory experiments have demonstrated that cognitive performance deteriorates
progressively under conditions of chronic sleep restriction.1,2. Biomathematical models have
been used to predict performance impairment due to sleep loss3, but these models have failed
to predict the cumulative deficits resulting from chronic sleep restriction.4. To overcome this
limitation, a novel “slow” process modulating the setpoint of sleep/wake homeostasis over
days has been proposed5; this process will be referred to here as “process $U$”. The process $U$
approach was shown to provide reasonable predictions for psychomotor vigilance
performance impairment across 7 days of chronic sleep restriction (3, 5, 7 or 9 hours time in
bed per day)2 and for serial add/subtract throughput across 2 days of total sleep deprivation6.
However, this finding was based on the combined outcome variables from two different
cognitive performance tasks, transformed to percentages of baseline, and measured across a
limited number of days.

Here we integrated process $U$ with the two-process model of sleep regulation7, which has
been used to predict waking alertness8 by subtracting the model’s process $S$ (the sleep/wake
homeostat) from its process $C$ (the circadian pacemaker). We estimated the parameters of the
integrated process $U$ on the basis of (non-transformed) psychomotor vigilance data from 14
days of chronic sleep restriction (4, 6 or 8 hours time in bed per day) and 3 days of total sleep
deprivation1, and evaluated the viability of process $U$ for predicting the cognitive
performance deficits resulting from cumulative sleep loss.

METHODS
The equations for process $S$ in the two-process model have fixed upper and lower asymptotes
($U$ and $L$), as can be seen when rewriting the published equations7:

\[
\begin{align*}
S_i - U_i &= (S_t - U_t - \Delta t) e^{-\Delta t/ T_w} \\
S_i - L_i &= (S_t - L_t - \Delta t) e^{-\Delta t/ T_d}
\end{align*}
\]

during wake;

during sleep;

where $U_t = 1$ and $L_t = 0$ for all times $t$, $T_w$ and $T_d$ are the published values of the model’s time
constants7; and $\Delta t$ is the time step for computing numerical predictions. We implemented
process $U$ by manipulating the asymptotes $U$ and $L$, as follows:

\[
\begin{align*}
U_i &= U_{t-\Delta t} + M_w \Delta t \\
U_i &= U_{t-\Delta t} + (1 - U_{t-\Delta t}) (1 - e^{-M_s \Delta t}) \\
L_i &= U_i - 1
\end{align*}
\]

during both wake and sleep.
In these equations, $M_w$ and $M_s$ are the rate parameters of process $U$ during wake and sleep, respectively. To estimate optimal values for these parameters, we derived a closed-form version of the set of equations for $S$, $U$ and $L$, for laboratory experiments of chronic sleep restriction and total sleep deprivation. Assuming stable sleep/wake patterns with 8 hours sleep in the week before the experiments (in agreement with actigraphy and diary data), we established the initial values for $S$, $U$ and $L$ upon baseline awakening to be given by (where “h” indicates hours):  

\[
S_0 = U_0 - \left(1 - e^{-8h / T_d}\right) / \left(1 - e^{-[16h / T_d + 8h / T_d]}\right); \\
U_0 = 1 + 16h \cdot M_w / (e^{8h \cdot M_s} - 1); \\
L_0 = U_0 - 1.
\]

Model predictions were fitted to experimental observations of psychomotor vigilance performance lapses (reaction times $\geq 500$ milliseconds), as measured on a 10-minute psychomotor vigilance task (PVT) every 2 hours during scheduled wakefulness in our laboratory studies with 14 days of chronic sleep restriction (4, 6 or 8 hours time in bed per day) and 3 days of total sleep deprivation. We used the observations from two baseline days (8 hours time in bed per day) and all experimental sleep loss days for a total of $n = 47$ subjects, as well as data from one recovery day (8 hours time in bed) for the subset of 34 subjects exposed to chronic sleep restriction. To exclude sleep inertia effects from the data set, we removed data points collected immediately after awakening; and on the basis of analyses presented elsewhere in this volume, we also removed data points collected 2 hours after awakening for the 13 subjects in the condition with 4 hours time in bed per day. The entire data set $y$, containing 5,443 data points was subjected to regression against the biomathematical model predictions using the following equation:

\[y_i \sim a \left(S_i - C_i\right) + b.\]

In this equation, $C_i$ represents the equation for process $C$ in the two-process model:

\[C_i = A \sum_k y_k \sin \left(2\pi k (t - t_0) / 24h\right),\]

where $y_k$ is a series of constants for $k = 1,\ldots,5$. The amplitude parameter $A$ and the phase parameter $t_0$ were designated free parameters, in order to allow for realignment of process $C$ relative to process $S$ as might be necessary due to the integration of process $U$. The rate constants $M_w$ and $M_s$ of process $U$ were also designated free parameters. Random effects were included for regression parameters $a$ and $b$ to account for inter-individual differences.

Parameter assessment was performed by maximum likelihood estimation using the computer program NONMEM (GloboMax LLC).

RESULTS AND DISCUSSION

The parameter estimates (± standard error) were $M_w = 0.553 \pm 0.788$ / h; $M_s = 0.0115 \pm 0.0040$ / h; $A = 4.77 \pm 6.67$; $t_0 = 6.15 \pm 0.69$; $a = 0.305 \pm 0.427$; and $b = -24.5 \pm 10.5$. Based on these estimates, Figure 1 shows the predictions of the two-process model after integration of process $U$, for the four experimental sleep loss conditions.

Comparison of the biomathematical model predictions with the published data (bottom panels of Figure 2 in ref. 4) revealed that the trends in psychomotor vigilance performance over days were accurately predicted for the conditions with 6 and 8 hours time in bed per day. However, performance impairment in the condition with 4 hours time in bed per day was substantially overestimated, and performance impairment in the total sleep deprivation condition was substantially underestimated. The relatively large standard errors for parameters $M_w$ and $a$ also suggested that the two-process model with integrated process $U$ did not fit the data set well (or that the data were not sufficiently informative to estimate these parameters). The only other published investigation of the slow modulating process...
(i.e., process $U$) failed to expose the problem, because data from only 7 days of chronic sleep restriction and 2 days of total sleep deprivation were used and because data from different performance tasks were combined.

Some improvement in the model fit could be gained by modifying the shape of the circadian process $C$ (which should also reduce the standard error for parameter $A$); by changing the values of the parameters $T_i$ and $T_d$ of the homeostatic process $S$; and by using polysomnographically estimated total sleep time instead of time in bed as a basis for the model predictions (although this would make little difference for the condition with 4 hours time in bed per day and no difference for the total sleep deprivation condition). It is not likely that such adjustments would overcome the mismatch between experimental data and model predictions over the long term (i.e., across days). It is possible that modulation of the relationship between the upper and lower asymptotes $U$ and $L$ (presently fixed via $L_i = U_i - 1$) would constitute a fundamental improvement, but model parsimony may then become an issue.

Even though integration of the novel process $U$ in the two-process model resulted in improved predictions of cumulative performance deficits from chronic sleep restriction\cite{12} relative to the original two-process model, the “excess wakefulness” model introduced by us earlier\cite{1} still appears to be the only published model capable of simultaneously predicting long-term cumulative performance deficits during both chronic sleep restriction and total sleep deprivation. However, that model is incomplete in that it does not make predictions for cognitive performance during recovery days. Laboratory studies are underway to systematically investigate the relationship between recovery sleep duration and performance recuperation, which will help to expand the excess wakefulness model with proper equations for performance recuperation.

![Figure 1. Predictions of the two-process model expanded with slow modulating process U, for psychomotor vigilance task (PVT) performance lapses across two baseline days (8 hours time in bed per day) and 14 days of chronic sleep restriction to 4 hours, 6 hours or 8 hours time in bed per day (4h TIB, 6h TIB or 8h TIB condition, respectively) followed by one recovery day (8 hours time in bed); and across two baseline days and 3 days of total sleep deprivation (0h TIB condition). Time 0 on the abscissa corresponds to awakening on the first baseline day. Gaps in the curves correspond to sleep periods.](image-url)
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