

# PARAMETER ESTIMATION FOR A BIOMATHEMATICAL 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<sup>1,2</sup>. Biomathematical models have been used to predict performance impairment due to sleep loss<sup>3</sup>, but these models have failed to predict the cumulative deficits resulting from chronic sleep restriction<sup>4</sup>. To overcome this limitation, a novel “slow” process modulating the setpoint of sleep/wake homeostasis over days has been proposed<sup>5</sup>; 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)<sup>2</sup> and for serial add/subtract throughput across 2 days of total sleep deprivation<sup>6</sup>. 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 regulation<sup>7</sup>, which has been used to predict waking alertness<sup>8</sup> 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 deprivation<sup>1</sup>, 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 equations<sup>7</sup>:

$$\begin{aligned} S_t - U_t &= (S_{t-\Delta t} - U_{t-\Delta t}) e^{-\Delta t / T_r} && \text{during wake;} \\ S_t - L_t &= (S_{t-\Delta t} - L_{t-\Delta t}) e^{-\Delta t / T_d} && \text{during sleep;} \end{aligned}$$

where  $U_t = 1$  and  $L_t = 0$  for all times  $t$ ;  $T_r$  and  $T_d$  are the published values of the model’s time constants<sup>7</sup>; and  $\Delta t$  is the time step for computing numerical predictions. We implemented process  $U$  by manipulating the asymptotes  $U$  and  $L$ , as follows:

$$\begin{aligned} U_t &= U_{t-\Delta t} + M_w \Delta t && \text{during wake;} \\ U_t &= U_{t-\Delta t} + (1 - U_{t-\Delta t}) (1 - e^{-M_s \Delta t}) && \text{during sleep;} \\ L_t &= U_t - 1 && \text{during both wake and sleep.} \end{aligned}$$

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<sup>9</sup> of the set of equations for  $S$ ,  $U$  and  $L$ , for laboratory experiments of chronic sleep restriction and total sleep deprivation<sup>1</sup>. Assuming stable sleep/wake patterns with 8 hours sleep in the week before the experiments (in agreement with actigraphy and diary data<sup>1</sup>), we established the initial values for  $S$ ,  $U$  and  $L$  upon baseline awakening to be given by (where “h” indicates hours):

$$\begin{aligned} S_0 &= U_0 - (1 - e^{-8h/T_d}) / (1 - e^{-[16h/T_r + 8h/T_d]}); \\ U_0 &= 1 + 16h \cdot M_w / (e^{8h \cdot M_s} - 1); \\ L_0 &= U_0 - 1. \end{aligned}$$

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)<sup>10</sup> 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<sup>1</sup>. 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<sup>11</sup>, 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  $y_t$  (containing 5,443 data points) was subjected to regression against the biomathematical model predictions using the following equation<sup>4</sup>:

$$y_t \sim a(S_t - C_t) + b.$$

In this equation,  $C_t$  represents the equation for process  $C$  in the two-process model<sup>7</sup>:

$$C_t = A \sum_k \gamma_k \sin(2\pi k(t - t_0) / 24h),$$

where  $\gamma_k$  is a series of constants for  $k = 1, \dots, 5$ . 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<sup>1,4</sup>. Parameter assessment was performed by maximum likelihood estimation using the computer program NONMEM (GloboMax LLC).

## RESULTS AND DISCUSSION

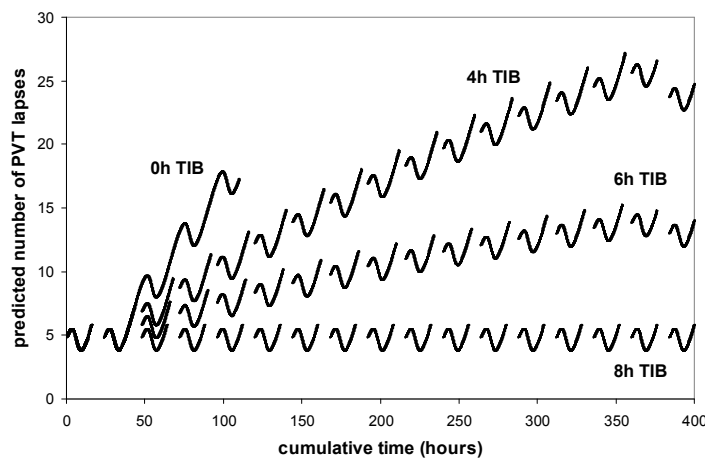
The parameter estimates ( $\pm$  standard error) were  $M_w = 0.553 \pm 0.788$  / h;  $M_s = 0.0115 \pm 0.0040$  / h;  $A = 4.77 \pm 6.67$ ;  $t_0 = 6.15 \pm 0.69$ ;  $a = 0.305 \pm 0.427$ ; and  $b = -24.5 \pm 10.5$ . Based on these estimates, Figure 1 shows the predictions of the two-process model 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<sup>5</sup> 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  $T_r$  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  $L_t = U_t - 1$ ) 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<sup>12</sup> relative to the original two-process model, the “excess wakefulness” model introduced by us earlier<sup>1</sup> 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.

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## REFERENCES

- <sup>1</sup> Van Dongen, H.P.A., Maislin, G., Mullington, J.M., Dinges, D.F., 2003. The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26, 117-126.
- <sup>2</sup> Belenky, G., Wesensten, N.J., Thorne, D.R., Thomas, M.L., Sing, H.C., Redmond, D.P., Russo, M.B., Balkin, T.J., 2003. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *Journal of Sleep Research* 12, 1-12.
- <sup>3</sup> Mallis, M.M., Mejdal, S., Nguyen, T.T., Dinges, D.F., 2004. Summary of the key features of seven biomathematical models of human fatigue and performance. *Aviation, Space, and Environmental Medicine* 75, A4-A14.
- <sup>4</sup> Van Dongen, H.P.A., 2004. Comparison of mathematical model predictions to experimental data of fatigue and performance. *Aviation, Space, and Environmental Medicine* 75, A15-A36.
- <sup>5</sup> Johnson, M.L., Belenky, G., Redmond, D.P., Thorne, D.R., Williams, J.D., Hursh, S.R., Balkin, T.J., 2004. Modulating the homeostatic process to predict performance during chronic sleep restriction. *Aviation, Space, and Environmental Medicine* 75, A141-A146.
- <sup>6</sup> Thorne, D.R., Genser, S., Sing, H., Hegge, F., 1983. Plumbing human performance limits during 72 hours of high task load. *Defence and Civil Institute of Environmental Medicine: Proceedings of the 24<sup>th</sup> DRG Seminar on the Human as a Limiting Element in Military Systems*, Toronto, pp. 17-40.
- <sup>7</sup> Borbély, A.A., Achermann, P., 1999. Sleep homeostasis and models of sleep regulation. *Journal of Biological Rhythms* 14, 557-568.
- <sup>8</sup> Achermann, P., 2004. The two-process model of sleep regulation revisited. *Aviation, Space, and Environmental Medicine* 75, A37-A43.
- <sup>9</sup> Avinash, D., Crudele, C.P., Amin, D.D., Vacs, E.F., Dinges, D.F., Van Dongen, H.P.A., 2005. Goodness-of-fit of an expansion of the two-process model to predict cumulative performance impairment due to chronic sleep restriction. *Sleep* 28, A133-A134.
- <sup>10</sup> Dinges, D.F., Powell, J.W., 1985. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behavior Research Methods, Instruments, & Computers* 17, 652-655.
- <sup>11</sup> Hoffman, J.M., Van Dongen, H.P.A., Dinges, D.F., 2005. Time of day and sleep inertia effects on cognitive performance and sleepiness during chronic sleep restriction. *SLEEP-WAKE Research in The Netherlands*; this vol.
- <sup>12</sup> Amin, D.D., Avinash, D., Crudele, C.P., Vacs, E.F., Dinges, D.F., Van Dongen, H.P.A., 2005. Expanding the two-process model to describe cumulative performance impairment from chronic sleep loss. *Sleep* 28, A130.