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Fatigue from sleep loss and circadian misalignment jeopardizes the cognitive performance and safety of individuals during sustained Air Force operations. Mathematical models of fatigue and performance provide a useful tool for the prediction of cognitive impairment resulting from sleep loss and circadian disruption. However, currently available models do not accurately predict the effects of chronic sleep restriction, and do not make reliable predictions at the level of persons or small teams. In this project, a new model for the sleep/wake homeostatic regulation of fatigue was developed to improve predictions of performance deficits under conditions of chronic sleep loss. Furthermore, Bayesian forecasting was implemented to predict performance responses to sleep loss and circadian displacement for individuals. This project resulted in significant advances in fatigue and performance modeling, addressing the Air Force's need to understand and help mitigate the effects of fatigue on cognitive capability.

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EXECUTIVE SUMMARY

Fatigue from sleep loss and circadian misalignment jeopardizes cognitive performance and safety of individuals during sustained Air Force operations and in other around-the-clock operational environments. Mathematical models of fatigue and performance provide a useful methodology for the prediction of cognitive impairment resulting from sleep loss and circadian disruption. However, currently available models do not have the capability to make predictions for individuals, which makes them unreliable at the level of persons or small teams. Also, currently available models do not accurately predict the effects on performance of chronic sleep restriction, which reduces their usefulness in sustained operations. To deal with these problems, we implemented and extended a cutting-edge statistical technique called Bayesian forecasting to predict performance responses to sleep loss and circadian displacement for individuals. Furthermore, we developed a new model for the sleep/wake homeostatic regulation of fatigue to improve predictions of performance deficits under conditions of chronic sleep loss. As such, this project resulted in significant advances in fatigue and performance modeling, addressing the Air Force's need to understand and help mitigate the effects of fatigue on cognitive capability.

Current mathematical models of fatigue and performance do not accurately predict cognitive performance for individuals with a-priori unknown degrees of trait vulnerability to sleep loss; do not predict performance reliably when initial conditions are uncertain; and do not yield statistically valid estimates of prediction accuracy. These limitations diminish their usefulness for predicting the performance of individuals during Air Force missions and in other operational environments. To overcome these limitations, we developed a new modeling approach based on the extension of a statistical technique called Bayesian forecasting. The extended Bayesian forecasting procedure was implemented in the two-process model of sleep regulation, which has been used to predict performance on the basis of a sleep homeostatic process and a circadian process.

Employing the two-process model with the Bayesian forecasting procedure to predict performance for individual subjects in the face of unknown traits and uncertain states entailed subject-specific optimization of three trait parameters (homeostatic build-up rate, circadian amplitude and basal performance level) and two initial state parameters (initial homeostatic state and circadian phase angle). Prior information about the distribution of the trait parameters in the population at large was extracted from psychomotor vigilance test (PVT) performance measurements in ten subjects who had participated earlier in a laboratory experiment with 88h of total sleep deprivation. The PVT performance data of three additional subjects in this experiment were set aside beforehand for use in prospective computer simulations.

The simulations involved updating the subject-specific model parameters every time the next performance measurement became available, and then predicting performance 24h ahead. Comparison of the predictions to the subjects' actual data revealed that as more data became available for the individuals at hand, the performance predictions became increasingly more accurate and had progressively smaller 95% confidence intervals, as the model parameters converged efficiently to those that best characterized each individual. Even when more challenging simulations were run (mimicking a change in the initial homeostatic state; simulating the data to be sparse), the predictions were still considerably more accurate than would have

been achieved by the two-process model alone. Although the work described in this report is limited to periods of consolidated wakefulness with stable circadian rhythms, and follow-up translational efforts are needed, the results obtained demonstrate that the Bayesian forecasting procedure can successfully overcome some of the major outstanding challenges for mathematical prediction of cognitive performance in operational settings.

As a foundation for the development of the Bayesian forecasting procedure, we used the two-process model of sleep regulation. However, in and of itself, the two-process model does not accurately predict the effects on performance of chronic sleep restriction. This diminishes the usefulness of the model during sustained Air Force operations and in many other operational scenarios. To overcome this limitation, we developed a new sleep/wake homeostatic model of fatigue and performance. We showed that the two-process model belongs to a broader, new class of models formulated in terms of coupled non-homogeneous first-order ordinary differential equations, which have a dynamic repertoire capturing waking cognitive functions across a much wider range of wake/sleep schedules.

We selected a specific case of the new model class, and demonstrated the existence of a bifurcation: for daily amounts of wakefulness less than a critical threshold, cognitive performance (as represented by PVT measurements) is predicted to converge to an asymptotically stable fixed point (equilibrium); whereas for daily wakefulness greater than the critical threshold, cognitive performance is predicted to diverge from an unstable fixed point. Comparison of model simulations to laboratory observations of lapses of attention on the PVT, in experiments on the effects of chronic sleep restriction and acute total sleep deprivation, indicated that this bifurcation is an essential feature of performance impairment due to sleep loss.

We also considered two new predictions, that may be experimentally verified to validate the model. These predictions, if confirmed, challenge conventional notions about the effects of sleep and sleep loss on cognitive performance. The new model class implicates a biological system analogous to two connected compartments containing interacting compounds with time-varying concentrations as being a key mechanism for the regulation of cognitive performance as a function of sleep loss. The dynamics of the new model suggests that the adenosinergic neuromodulator/receptor system may provide the underlying neurobiology.

This final report covers the work performed from 1 Jan 2005 through 30 Sep 2005 at the University of Pennsylvania (AFOSR grant FA9550-05-1-0086), and the subsequent work performed from 1 Oct 2005 through 29 Feb 2008 at Washington State University (AFOSR grant FA9550-06-1-0055) where the project was transferred when the PI (Van Dongen) moved there. The products of this project include the first method for on-line individualization of mathematical model prediction of fatigue and performance; and a substantially improved mathematical model of fatigue and performance under conditions of chronic sleep restriction. The results of the project represent significant advances in fatigue and performance modeling. They contribute to accurate, subject-specific prediction of cognitive impairment in Air Force operations, and provide useful approaches to help optimize mission safety and success. The results of this project are also highly relevant for the many operational settings in today's 24/7 society that put individuals at risk of performance deficits due to sleep loss and circadian displacement.

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PREDICTING FATIGUE AND PERFORMANCE IN INDIVIDUALS: ACCOUNTING FOR UNKNOWN TRAITS AND UNCERTAIN STATES

Introduction

Increased fatigue and degraded cognitive performance due to sleep loss and night work are a concern in Air Force operations and many other operational settings (e.g., transportation, health care, emergency response, space flight). Mathematical models of fatigue and performance may be useful to help predict performance impairment resulting from sleep loss (Neri, 2004). As such, mathematical models may be seen as fatigue management tools, supporting the anticipation and prevention of high-risk situations, the implementation of safe and productive work schedules, and/or the timely delivery of fatigue countermeasures.

In the AFOSR-sponsored "Fatigue and Performance Modeling Workshop" (June 2002; Seattle, Washington), a number of mathematical models were discussed and evaluated (Mallis et al., 2004; Van Dongen, 2004). In the proceedings of that workshop, scientists and stakeholders alike pointed out that to be useful and reliable in operational settings, performance models must be able to deal with inter-individual differences in performance impairment from sleep loss (Dinges, 2004; Friedl et al., 2004; Van Dongen, 2004). Laboratory experiments have revealed that these inter-individual differences are substantial, and that they represent *trait* vulnerability (Van Dongen et al., 2004a). Thus, inter-individual differences are important determinants of sleep-deprived performance (Van Dongen et al., 2005b), and should be captured by models deployed in operational settings (Dinges and Achermann, 1999).

Performance models can be made to account for inter-individual differences by first assessing every subject's individual response to sleep deprivation, and then adjusting the model parameters to match each subject's specific response. In most operational environments, however, assessing everyone's response to sleep deprivation is unpractical or unfeasible. It is a problem, therefore, that none of the currently available mathematical models of performance can handle inter-individual differences unless the individuals are characterized in advance.

One procedure to overcome this limitation was recently demonstrated by Olofsen et al. (2004): Bayes posterior distribution estimation, also known as Bayesian forecasting. This approach is grounded in Bayesian statistics, and as such it makes use of the advance characterization of the inter-individual variability in the population as well, for instance by studying performance changes over time during a sleep deprivation experiment. However, this can be done in a representative sample drawn from that population—it is not necessary to include the specific individuals for whom the mathematical model will ultimately be used. Modern statistical techniques referred to as mixed-effects modeling (Vonesh et al., 1997) allow the data from the studied sample to be separated into consistent changes over time, systematic between-subjects variance (i.e., trait-like variability), and residual within-subjects variance or error variance (Olofsen et al., 1999; Van Dongen et al., 2004b). This yields information about the prior probability that any given level of impairment would be observed at a specific time point in a person randomly drawn from the population at large. Importantly, it also produces probability estimates of the contributions to that impairment level from the person's trait characteristics on

the one hand, and from error variance (e.g., random short-term variations in alertness) on the other hand.

To illustrate this with an example, consider a population of Air Force pilots, whose responses to sleep loss could be characterized by subjecting a representative sample of them to sleep deprivation in a laboratory. By repeatedly measuring each subject's performance during the laboratory sleep deprivation period, and subsequently analyzing the collective measurement data with mixed-effects modeling, the pattern of consistent changes over time, the between-subjects variance and the within-subjects variance for performance impairment due to sleep loss could be assessed for this population. For the sake of argument, let's assume that the primary performance assay in the sleep deprivation experiment was a choice reaction time task. Let's say that the group-average response to sleep loss as measured at midnight, expressed relative to baseline, was an increase of 6 in the number of response errors. Because of trait inter-individual differences as well as random fluctuations, there may be some individual in the population whose response to sleep loss at midnight would show an increase of 11 errors relative to baseline, i.e., 5 additional errors compared to the group average. Using the between-subjects variance and within-subjects variance as assessed for the representative sample, a statement could be made about the probability of observing such a response to sleep loss. Moreover, it could be estimated to what extent this would likely be caused by trait vulnerability to sleep loss, and to what extent a random fluctuation would likely have contributed. For instance, if the between-subjects variance were somewhat larger than the within-subjects variance in this population, then further calculations might show that the individual's trait characteristics most probably led to 3 additional errors in the response to sleep loss (as compared to the group average), and that random variability most probably contributed the remaining 2 additional errors observed at midnight.

Thus, even if nothing is a-priori known about a given person, it is possible to acquire probability-based information regarding that person's performance during sleep deprivation—owing to first having studied the inter-individual differences in a sample of the population to which the person belongs. The Bayesian forecasting procedure can use this information to optimize the parameters of a mathematical model of performance for any individual of interest. Initially, the model parameters would be set to those that would best describe the average person in the population, and model predictions for the individual's performance would be based on this population-average version of the model. This makes sense, for if nothing is as yet known about the individual, the probability is greatest that the individual's response is approximately average. However, if it is possible to take one or more measurements of the individual's performance, then the likely contribution of his or her actual trait characteristics to the observed performance could be estimated, as outlined above. Using Bayesian probability statistics, this trait information can be utilized to optimize the model parameters for the individual at hand (Olofsen et al., 2004). In this manner, Bayesian forecasting allows a mathematical model to account for inter-individual differences even when performance predictions are applied to individuals not studied beforehand.

This project dealt with implementation of the Bayesian forecasting procedure for mathematical modeling of performance, but also extended this effort to simultaneously account for subject-specific states. The latter issue has been largely overlooked in the published literature, but is no

less important in operational settings. For example, the sleep history of personnel reporting for a mission is typically undocumented, and therefore individuals' initial sleep homeostatic state may be a-priori unknown. Hence, to be truly useful and reliable in operational settings, performance models must also be able to deal with this initial state uncertainty. In this report, it is shown that this matter can be approached with the Bayesian forecasting procedure as well.

Performance Prediction with the Two-Process Model

To develop a tool for mathematical model prediction of individual subjects' performance in the face of a-priori unknown inter-individual differences in traits as well as uncertain states, the seminal two-process model of sleep regulation (Borbély, 1982; Borbély and Achermann, 1999) was used as a model platform. The two-process model postulates two primary sleep/wake regulatory processes: a sinusoidal *circadian process* and a saturating exponential *homeostatic process*.

The equation for the circadian process C is a closed-form equation of the form:

$$C(t) = \sum_k a_k \sin(2k\pi(t-\varphi)/\tau), \quad (1)$$

where t denotes clock time (in hours, relative to midnight), φ is a parameter for the circadian phase angle (i.e., the timing of the circadian process relative to clock time), and τ is a parameter for the circadian period. Since circadian phase shifts and temporary changes in the circadian period are mathematically equivalent (Van Dongen et al., 1998), τ is redundant with φ in most operational environments, and is therefore fixed here at τ = 24h. The summation over the index k serves to allow for harmonics in the sinusoidal shape of the circadian process. For application of the two-process model for alertness prediction, k has been taken to go from 1 to 5, with the constants a_k being fixed as a_1 = 0.97, a_2 = 0.22, a_3 = 0.07, a_4 = 0.03, and a_5 = 0.001 (Achermann and Borbély, 1994).

The equation for the homeostatic process S during wakefulness is a difference equation of the form:

$$S_t = 1-(1-S_{t-\Delta t})\ e^{-\Delta t/\tau_r} \quad (2)$$

($S > 0$), where t denotes (cumulative) clock time, Δt denotes the time step (of arbitrary length, but typically taken as Δt = 0.5h), and τ_r represents the time constant for the build-up of the homeostatic process during wakefulness. For the present purposes, only consolidated periods of wakefulness are considered; the equation for S during sleep is therefore not discussed here.

By replacing time constant τ_r with an equivalent rate constant ρ, and substituting S with reversed sign (i.e., $S < 0$) for $S - 1$, Eq. (2) can be simplified to:

$$S_t = S_{t-\Delta t}\ e^{-\rho\ \Delta t}. \quad (3)$$

Iteratively tracking this difference equation back in time to an arbitrary modeling start time t_0, it follows that:

$$S(t) = \xi\ e^{-\rho(t-t_0)}, \quad (4)$$

where ξ is the initial homeostatic state (i.e., at time t_0). Here, we select t_0 to be the time of the most recent awakening, and so ξ represents the homeostatic state upon awakening.

As conceptualized by Achermann and Borbély (1994), performance may be modeled by assuming an additive interaction of the circadian and homeostatic processes. The general equation for this would be:

$$P(t) = \beta\ S(t) + \gamma\ C(t) + \kappa, \quad (5)$$

where P is the predicted level of performance, β is a parameter for the relative impact of the homeostatic process on performance, and γ is a parameter for the amplitude of the effect of the circadian process on performance. The intercept parameter κ offsets the two processes and thereby modulates the basal performance level. Substituting Eqs. (1) and (4) into Eq. (5), and noting that β is redundant with ξ (i.e., they only occur together as $\beta\,\xi$ and may therefore be replaced by a single, rescaled parameter ξ), it follows that:

$$P(t) = \xi\ e^{-\rho(t-t_0)} + \gamma \sum_k a_k \sin(2k\pi(t-\varphi)/\tau) + \kappa. \quad (6)$$

The free parameters in this performance model are ρ, γ, κ, ξ and φ. There is experimental evidence that the homeostatic build-up rate ρ (Finelli et al., 2000; Aeschbach et al., 2001), the circadian amplitude γ (Van Dongen et al., 2004a, footnote a), and the basal performance level as determined by κ (Kane and Engle, 2002) depend on individual subjects' trait characteristics. These parameters are therefore considered *trait parameters*.

The homeostatic state and the circadian phase cannot normally be considered trait parameters; they may change for any given individual depending on the circumstances (e.g., due to recent sleep loss and/or circadian phase shifting from a bout of shift work) and are therefore *state parameters*. However, within a consolidated period of wakefulness, the *initial* homeostatic state ξ (i.e., the homeostatic state at the time of the most recent awakening t_0) is not subject to change. Thus, the initial homeostatic state is an enduring condition. Although the initial homeostatic state cannot be inferred from population-based data, its enduring quality makes it otherwise indistinguishable from a trait for the purpose of parameter estimation with the Bayesian forecasting procedure. When applying that procedure to a consolidated period of wakefulness, therefore, the parameter ξ may be treated as equivalent to a trait parameter. This important property is implied throughout this report whenever the term *initial state parameter* is used.

In general, the circadian phase angle cannot be considered an enduring condition—for many operational settings, especially those involving shift work or transmeridian travel, this would be a poor approximation of reality. However, while it is possible to deal with transitory states in the Bayesian forecasting procedure, this goes beyond the scope of the present project. The work described here is limited to those circumstances under which circadian phase angle is stable and may therefore be assumed to represent an enduring condition. With this qualification, circadian phase angle is not distinguishable from a trait for the purpose of parameter estimation with the Bayesian forecasting procedure. When applying the procedure, therefore, the parameter φ is also an initial state parameter which may be treated as equivalent to a trait parameter.

Population Model for the Two-Process Model

As described in the introduction, the Bayesian forecasting procedure makes use of the advance characterization of inter-individual variability in the population. In the present context, the

procedure depends on the advance estimation of the two-process model parameters and their between-subjects variance in a sample of n subjects drawn from the population. It is assumed that an appropriate data set is available. For illustration purposes, such a data set is introduced later in this report.

The two-process model parameters and their between-subjects variance can be estimated on the basis of the available data using the following mixed-effects regression equation:

$$y_{ij} = P_i(t_{ij}) + \varepsilon_{ij}, \quad (7)$$

where y_{ij} represents the data for subjects i (i = 1, ..., n) at time points t_{ij} (with j indexing the data points), and ε_{ij} stands for independent, normally distributed residual error with mean zero and variance σ^2. P_i is the subject-specific version of the performance model in Eq. (6):

$$P_i(t_{ij}) = \xi_i e^{-\rho_i (t_{ij} - t_{i0})} + \gamma_i \sum_k a_k \sin(2k\pi(t_{ij} - \varphi_i)/\tau) + \kappa_i. \quad (8)$$

Here ρ_i, γ_i, κ_i, ξ_i and φ_i are the subject-specific model parameters, and t_{i0} is the subject-specific modeling start time.

To estimate between-subjects variance in the trait parameters, it is assumed a priori that ρ_i and γ_i are lognormally distributed over subjects around ρ_0 and γ_0, respectively, and that κ_i is normally distributed over subjects around κ_0. It is also assumed that there is no covariation over subjects among ρ_i, γ_i and κ_i. The assumptions about the distribution types for these "random effects" are weak (Olofsen et al., 2004). It is not critical for the shape of the assumed distributions to describe the data very precisely, as the effect thereof on the results of the Bayesian forecasting procedure is limited. Some statistical and numerical efficiency may be gained by explicitly modeling the covariation between pairs of random effects, but that issue is beyond the scope of the project.

The distributions of the initial state parameters ξ_i and φ_i depend on the conditions under which the available data were collected. Specifically, for the data set introduced in the next section of this report, by design the initial homeostatic state ξ and the circadian phase angle φ should be approximately the same for all subjects—say, ξ_0 and φ_0, respectively. (Later, however, for simulation purposes we consider ξ and φ as uncertain.)

Taken together, these assumptions, or prior distributions, can be translated into the following mathematical equations:

$$\rho_i = \rho_0 \, e^{\nu_i}, \quad (9a)$$

$$\gamma_i = \gamma_0 \, e^{\eta_i}, \quad (9b)$$

$$\kappa_i = \kappa_0 + \lambda_i, \quad (9c)$$

$$\xi_i = \xi_0, \quad (9d)$$

$$\varphi_i = \varphi_0, \quad (9e)$$

where ν_i, η_i and λ_i are independent, normally distributed with means of zero and variances ψ^2, ω^2 and χ^2, respectively. Characterization of the trait inter-individual variability in the population in the framework of the two-process model thus entails the assessment of the normal distributions for ν_i, η_i, and λ_i by estimating the parameters ψ^2, ω^2 and χ^2. For reference purposes, the relevant model parameters are recapitulated in Table 1.

Table 1: Summary descriptions of the trait parameters (distinguishing their fixed effects, the associated subject-specific random effects, and the variances thereof across the population) and other model parameters (initial state parameters, residual error) involved in the Bayesian forecasting procedure.

Trait Parameters	Homeostatic build-up rate	ρ (fixed effect) v (random effect) ψ^2 (population variance)
	Circadian amplitude	γ (fixed effect) η (random effect) ω^2 (population variance)
	Basal performance level	κ (fixed effect) λ (random effect) χ^2 (population variance)
State Parameters	Initial homeostatic state	ξ (subject-specific)
	Circadian phase angle	φ (subject-specific)
Residual Error	Error variance	σ^2 (population variance)

Substitution of Eqs. (8) and **Error! Reference source not found.** into Eq. (7) leads to the following formulation of the mixed-effects regression equation:

$$y_{ij} = \xi_0 e^{-\rho_0 e^{v_i}(t_{ij}-t_{i0})} + \gamma_0 e^{\eta_i} \sum_k a_k \sin(2k\pi(t_{ij}-\varphi_0)/\tau) + \kappa_0 + \lambda_i + \varepsilon_{ij}. \quad (9)$$

The parameters of this regression equation can be estimated by means of maximum likelihood estimation. Let the probability density function (pdf) of a normal distribution with mean m and variance s^2 for a variable x be denoted as $p[x; m, s^2]$. The likelihood l_i of observing the data y_{ij} for a given subject i can be expressed as a function of the regression parameters, as follows:

$$l_i(\rho_0,\gamma_0,\kappa_0,\xi_0,\varphi_0,v_i,\eta_i,\lambda_i,\sigma^2) = c\prod_j p[y_{ij};\ \xi_0 e^{-\rho_0 e^{v_i}(t_{ij}-t_{i0})} + \gamma_0 e^{\eta_i}\sum_k a_k \sin(2k\pi(t_{ij}-\varphi_0)/\tau) + \kappa_0 + \lambda_i,\ \sigma^2], \quad (10)$$

where σ^2 is the variance of the residual error, and c is an (irrelevant) normalization constant.

Integration over the assumed normal distributions for v_i, η_i and λ_i to account for the relative probabilities of all possible values of these parameters yields the marginal likelihood L_i:

$$L_i(\rho_0,\gamma_0,\kappa_0,\xi_0,\varphi_0,\psi^2,\omega^2,\chi^2,\sigma^2) = C\int_{v_i}\int_{\eta_i}\int_{\lambda_i} l_i(\rho_0,\gamma_0,\kappa_0,\xi_0,\varphi_0,v_i,\eta_i,\lambda_i,\sigma^2)\ p[v_i;\ 0,\psi^2]\ p[\eta_i;\ 0,\omega^2]\ p[\lambda_i;\ 0,\chi^2]\ dv_i\ d\eta_i\ d\lambda_i,$$

where the integrals each run from $-\infty$ to ∞, and C is an (irrelevant) normalization constant. It follows that the likelihood L of observing the entire data set, for all subjects collectively, can be expressed as a function of the regression parameters, as follows:

$$L(\rho_0,\gamma_0,\kappa_0,\xi_0,\varphi_0,\psi^2,\omega^2,\chi^2,\sigma^2) = \prod_i L_i(\rho_0,\gamma_0,\kappa_0,\xi_0,\varphi_0,\psi^2,\omega^2,\chi^2,\sigma^2). \quad (11)$$

Maximum likelihood estimation entails assessment of those parameter values that would make it maximally likely for the data to be observed as they were, i.e., those parameters that maximize L. This is typically done by minimizing $-2 \log L$, which is equivalent to maximizing L but is easier to perform numerically. The ensuing parameter estimates establish what is called the *population model*. Here, the population model characterizes the consistent changes in performance over time

according to the two-process model, the systematic between-subjects variance (i.e., trait-like variability) in the parameters of the two-process model, and the residual within-subjects variance (i.e., error variance) in the sample representing the population.

Bayesian Forecasting with Unknown Traits and Uncertain States

Once the population model has been established, it can be used in the Bayesian forecasting procedure to optimize the parameters of the two-process model and to make subject-specific predictions of future performance for an individual not studied beforehand. Let's indicate this individual with index "a". The subject's trait parameters are thus represented by ν_a, η_a and λ_a, and the subject's initial state parameters are ξ_a and φ_a. Recasting Eq. (9) yields:

$$y_{aj} = \xi_a e^{-\rho_0 e^{\nu_a}(t_{aj}-t_{a0})} + \gamma_0 e^{\eta_a} \sum_k a_k \sin(2k\pi(t_{aj}-\varphi_a)/\tau) + \kappa_0 + \lambda_a + \varepsilon_{aj}. \quad (12)$$

Fixing ρ_0, γ_0, κ_0, ψ^2, ω^2, χ^2 and σ^2 at their established population values, the subject-specific parameter optimization task focuses on estimating ν_a, η_a, λ_a, ξ_a and φ_a.

At first, when no performance data are as yet available for the subject, the most likely estimates for the subject's traits are those that correspond to the "average" subject in the population—i.e., $\nu_a = 0$, $\eta_a = 0$ and $\lambda_a = 0$. Such reasoning would not normally be valid for the subject's initial homeostatic state ξ_a and circadian phase angle φ_a. With ν_a, η_a and λ_a fixed at zero, however, Eq. (12) would reduce to:

$$y_{aj} = \xi_a e^{-\rho_0 (t_{aj}-t_{a0})} + \gamma_0 \sum_k a_k \sin(2k\pi(t_{aj}-\varphi_a)/\tau) + \kappa_0 + \varepsilon_{aj}, \quad (13)$$

in which only ξ_a and φ_a are free parameters. With three performance measurements for the individual at hand, first estimates for the initial state parameters ξ_a and φ_a can generally be obtained from this equation. This suggests that, as a rule of thumb, Bayesian forecasting estimates for the subject's model parameters may begin to be reliable when the third performance measurement becomes available (and with every measurement thereafter).

Let the pdf of a uniform distribution over the interval from a to b for a variable x be denoted as $u[x; a, b]$. Assuming that the distributions represented by the parameters ν_a, η_a, λ_a, ξ_a and φ_a in Eq. (12) are independent of each other and of the noise term ε_{aj}, a-posteriori estimates for the state and trait parameters are obtained by maximizing the Bayesian expression:

$$l_a(\xi_a, \varphi_a, \nu_a, \eta_a, \lambda_a)\, p[\nu_a;\ 0, \psi^2]\, p[\eta_a;\ 0, \omega^2]\, p[\lambda_a;\ 0, \chi^2]\, u[\xi_a;\ -\infty, 0]\, u[\varphi_a;\ 0, \tau] / L_a, \quad (14)$$

given the subject's available data y_{aj} (j = 1, 2, 3, ...). Here l_a is the likelihood function taken from Eq. (10) with ρ_0, γ_0, κ_0 and σ^2 fixed; and L_a is defined analogous to the marginal likelihood in Eq. **Error! Reference source not found.**:

$$L_a = C \int_{\nu_a} \int_{\eta_a} \int_{\lambda_a} \int_{\xi_a} \int_{\varphi_a} l_a(\xi_a, \varphi_a, \nu_a, \eta_a, \lambda_a)\ p[\nu_a;\ 0, \psi^2]\ p[\eta_a;\ 0, \omega^2]\ p[\lambda_a;\ 0, \chi^2] \cdot \quad (15)$$

$$u[\xi_a;\ -\infty, 0]\ u[\varphi_a;\ 0, \tau]\ d\nu_a\ d\eta_a\ d\lambda_a\ d\xi_a\ d\varphi_a.$$

Here the integrals for ν_a, η_a and λ_a run from $-\infty$ to ∞; and the integrals for ξ_a and φ_a run from $-\infty$ to 0 and from 0 to τ, respectively.

The normal distribution factors in Eq. (14) represent the prior probability information about the trait parameters, as engendered in the population model. No such prior information is available for the initial state parameters, which is why they are assigned uniform distributions across the ranges of their possible values. For the purpose of maximization, the uniform distributions for ξ_a and φ_a cancel out; and the denominator L_a, being invariant to the free parameters (ξ_a, φ_a, ν_a, η_a and λ_a) also cancels out. As such, for maximization, Eq. (14) may be simplified to

$$l_a(\xi_a, \varphi_a, \nu_a, \eta_a, \lambda_a) \; p[\nu_a;\, 0, \psi^2] \; p[\eta_a;\, 0, \omega^2] \; p[\lambda_a;\, 0, \chi^2]. \quad (16)$$

Maximization of Eq. (16), using all the available performance data y_{aj} for the subject at hand, yields the most likely estimates for the parameters ξ_a, φ_a, ν_a, η_a and λ_a. By repeating this maximization (iteratively) each time additional performance data become available, the parameter estimates improve with every such update, converging rapidly to those that statistically optimally represent the individual. Consequently, the accuracy of predictions for future performance, based on the updated parameter estimates, increases progressively. Due to first having characterized a sample of the population at large, this improvement in prediction accuracy for a previously unstudied individual occurs much more efficiently than would be possible if the individualized predictions were attempted without the use of population information (Olofsen et al., 2004).

As an additional advantage, Eq. (16) allows estimation of how accurate the subject-specific parameter estimates and performance predictions actually are, via assessment of (95%) confidence intervals. How this is best approached depends on the numerical procedure used to deal with Eq. (16), and a detailed discussion is beyond the scope of this report (but see Smith et al., 2007). One approach currently implemented is described below.

Numerical Implementation

A computer program was developed for the numerical maximization of Eq. (16) to estimate the parameters, and for the assessment of 95% confidence intervals for the parameter estimates and performance predictions. The computer program was written in Matlab version 7.0 (The MathWorks, Inc., Natick, Massachusetts), and was run under the Microsoft Windows XP operating system on a 1.7GHz Intel Pentium desktop computer.

Eq. (16) was maximized through a 5-dimensional grid search, which involved calculating the outcome across many combinations of possible parameter values and recording the largest outcome encountered. The parameter grid was made up of ν_a ranging from –3 to 3 in intervals of 0.5; η_a ranging from –2 to 2 in intervals of 0.25; λ_a ranging from –30 to 30 in intervals of 3; ξ_a ranging from –120 to 0 in intervals of 15; and φ_a ranging from 0 to 21 in intervals of 3 (due to the 24h circularity of φ_a there was no need to evaluate φ_a at 24). The grid ranges for the (non-circular) parameters ν_a, η_a, λ_a and ξ_a were selected such that the probability density represented by Eq. (16) vanished toward the boundaries. To increase the computational efficiency, calculation of Eq. (10) as embedded in Eq. (16) was done recursively, and the irrelevant constant c in the formula was ignored (i.e., set to 1). To enhance the numerical resolution of the parameter estimates, the parameter grid was interpolated by a factor 4 in each dimension using piecewise cubic splines. The parameter values corresponding to the interpolated maximum were entered

into Eq. (12) (minus the error term ε_{aj}) to yield the most probable prediction of future performance (for given time t).

For each performance prediction, a 95% confidence interval was calculated by first identifying the smallest contiguous portion of the (interpolated) parameter grid that captured 95% of the total area under the curve given by Eq. (18). All combinations of parameter values included in this portion of the grid were then entered into Eq. (12) to compute the corresponding predictions of future performance (for given time t). The minimum and maximum of the performance predictions encountered in this process were taken as estimates of the boundaries of the 95% confidence interval (which was thereby allowed to be asymmetrical).

Bayesian 95% confidence intervals for the parameter estimates proper were derived by constructing the marginal pdfs. These are the pdfs for every parameter considered individually while accounting for the probability densities of the other parameters. The marginal pdf for each parameter was computed by integrating over the other four parameters across the parameter grid. All marginal pdfs thus obtained were interpolated by a factor 30 using piecewise cubic splines. Their maxima were identified in order to obtain more precise estimates for the individual model parameters. Lastly, 95% confidence intervals for the parameter estimates were computed by assessing the shortest contiguous interval capturing 95% of the area under the curve of each marginal pdf (Sivia, 1996).

Average prediction bias (i.e., systematic under- or over-prediction) was quantified by calculating the average difference between predictions and actual observations. Furthermore, average prediction error (i.e., point by point deviation) was quantified by computing the square root of the average squared difference between predictions and actual observations (i.e., the root mean square error).

Experimental Data and Corresponding Population Model

To illustrate the potential of the Bayesian forecasting approach, a previously established data set was employed to run simulations. The data were collected during a laboratory study involving 88h of total sleep deprivation, as described by Van Dongen and Dinges (2005). During the sleep deprivation period, a range of cognitive performance outcomes was measured every 2h, from 07:30 until 23:30 three days later. Performance on the psychomotor vigilance test (PVT) was selected as the outcome measure to model, because of demonstrated validity and sensitivity to the homeostatic and circadian processes (Dorrian et al., 2005). The number of lapses (reaction times ≥ 500ms) on the PVT was recorded as the primary outcome variable y.

Data from n = 10 subjects in the study, drawn from a population of healthy males aged 21 to 50, were used to derive a population model based on the two-process model, as per Eq. (9). Fig. 1 displays the data from this sample, averaged over subjects. As discussed in Van Dongen and Dinges (2005), performance deteriorated across days of sleep deprivation in accordance with the homeostatic process, Eq. (4), and varied rhythmically within each day in accordance with the circadian process, Eq. (1). The average level of performance impairment reached after multiple days of total sleep deprivation was considerable—it appeared to exceed the average level of

performance impairment resulting from being legally intoxicated by alcohol (Dawson and Reid, 1997). However, there were substantial inter-individual differences in the effects of sleep deprivation on psychomotor vigilance performance, as illustrated by the inset in Fig. 1. The bar shows the interval of ±1 standard deviation for systematic between-subjects variability, determined by mixed-effects analysis of variance (Van Dongen et al., 2004c).

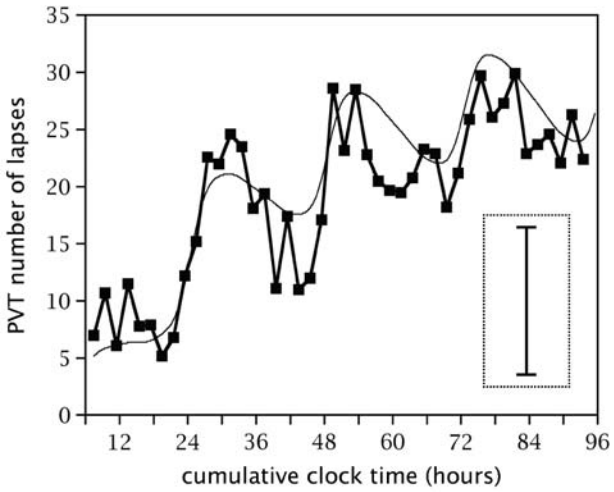

Figure 1: Performance measurements during a laboratory study involving 88h of total sleep deprivation, and population model of performance based on the two-process model. The solid boxes show the number of lapses (reaction times ≥ 500ms) on a psychomotor vigilance test administered every 2h, averaged over subjects (n = 10). Upwards in the graph corresponds to greater performance impairment. The thin curve shows the population model as plotted for the "average" subject. The averaged data are captured well by this curve. However, the averaged data do not show the considerable inter-individual differences throughout the sleep deprivation period. The bar in the inset depicts the interval of ±1 standard deviation for between-subjects variability in the data. Although difficult to illustrate graphically, these inter-individual differences are captured well by the population model also.

The population model was assessed using Eqs. **Error! Reference source not found.** through (11), as evaluated with the computer software NONMEM version V (GloboMax LLC, Hanover, Maryland). Time t was expressed as cumulative clock time (in hours) with time 0 defined as the midnight preceding the total sleep deprivation period. The sleep deprivation began at 07:30, and this time point was used to define the modeling start time, so that $t_0 = 7.5$ for all subjects. Subject selection criteria and experimental controls (Van Dongen and Dinges, 2005) standardized the initial homeostatic state ξ and circadian phase angle φ at the beginning of sleep deprivation. For the purpose of assessing the population model, therefore, these two parameters were considered the same for all 10 subjects in the sample. The circadian phase angle was relatively stable during the 88h of total sleep deprivation (Van Dongen et al., 1998), indicating that the initial state parameter φ represented an enduring condition under these circumstances.

The parameter estimates (± standard errors) for the population model were found to be as follows: $\rho_0 = 0.0350$ (± 0.0156), $\gamma_0 = 4.30$ (± 1.05), $\kappa_0 = 29.7$ (± 3.7), $\xi_0 = -28.0$ (± 4.4), $\varphi_0 = 0.6$ (± 0.2), $\psi^2 = 1.15$ (± 0.41), $\omega^2 = 0.294$ (± 0.191), $\chi^2 = 36.2$ (± 26.2), and $\sigma^2 = 77.6$ (± 7.3). Fig. 1 shows that the population model closely matched the data as averaged over subjects. Not readily observed in Fig. 1 is that the population model also matched the data of the individual subjects well, since the parameters of the population model were optimized relative to the data of the whole sample of n = 10 subjects without averaging out the considerable inter-individual differences. Compared to the same model without inter-individual differences, the population model reduced the residual error variance by a factor 1.64.

The population model described here characterized the changes in performance during total sleep deprivation in accordance with the two-process model, as well as the inter-individual differences in the model parameters, and the residual error, in a population of healthy males aged 21 to 50.

This provided all the information necessary to run simulations for the Bayesian forecasting procedure, in order to demonstrate the predictability of individual subjects' performance in the face of a-priori unknown traits and uncertain states.

Bayesian Forecasting Simulations

Besides the ten subjects used to establish the population model, three additional subjects drawn from the same population participated in the total sleep deprivation study described above. These three subjects were selected to represent considerable inter-individual differences in performance impairment during sleep deprivation, and their data were set aside prospectively to run simulations with the Bayesian forecasting procedure. The trait parameters ν_a, η_a and λ_a for these subjects were not known a priori. Furthermore, even though the initial state parameters ξ_a and φ_a were approximately the same for all subjects due to the design of the study (Van Dongen and Dinges, 2005), for the purposes of simulations these parameters were considered uncertain.

The objective of the first of our simulations was to make predictions of the three subjects' performance during total sleep deprivation, at 1h intervals for up to 24h in the future (i.e., 24h-ahead predictions); and to update the predictions using Bayesian forecasting each time the next performance measurement became available. The population model parameters ρ_0, γ_0, κ_0, ψ^2, ω^2, χ^2 and σ^2 remained fixed at their previously established population averages (see the previous section). Modeling start time t_{a0} was fixed at 7.5 (i.e., 07:30, the scheduled time of awakening). Time t_{aj} was incremented in 2h steps beginning at t_{a0}, so as to coincide with the time points for data collection in the sleep deprivation experiment. At each increment, parameter estimates were updated by maximizing Eq. (16) using the numerical approach outlined previously. With the updated parameter estimates, Eq. (12) (minus the error term ε_{aj}) was evaluated at 1h intervals from t_{aj} to $t_{aj} + 24$ in order to predict performance up to a 24h prediction horizon.

Fig. 2 shows the results of the simulation, in snapshots taken at 8h intervals. The three subjects are indicated as "A", "B" and "C". The first snapshot (top row panels in Fig. 2) occurred at 11:30, at 4h awake, when the third performance measurement was taken. Based on the rule of thumb suggested by Eq. (13), this is the first occasion when there may have been enough data points (black circles) to reasonably estimate the initial state parameters ξ_a and φ_a. Even at this early stage, the 24h predictions for the three subjects (solid curves) were already notably different, accounting with remarkable accuracy for the different performance profiles that would subsequently be observed in the actual measurements (gray circles). However, the 95% confidence intervals for the performance predictions were still large. The last snapshot (bottom row panels in Fig. 2) was taken 40h later, well before the end of the 88h sleep deprivation period, but sufficiently far along for the present purposes. By this time (i.e., at 44h awake), the 24h predictions had diverged substantially among the three subjects, as had the actual observations. Also, the 95% confidence intervals for the performance predictions were much narrower. There was no overlap between the 95% confidence intervals for subjects B and C at any of the evaluated time points (at 1h intervals) across the 24h prediction horizon (center and right bottom panels in Fig. 2). This implies that at 44h awake, the predictions for these two individuals were statistically distinct with a type I error of much less (Payton et al., 2003) than 0.05 for every prediction time point.

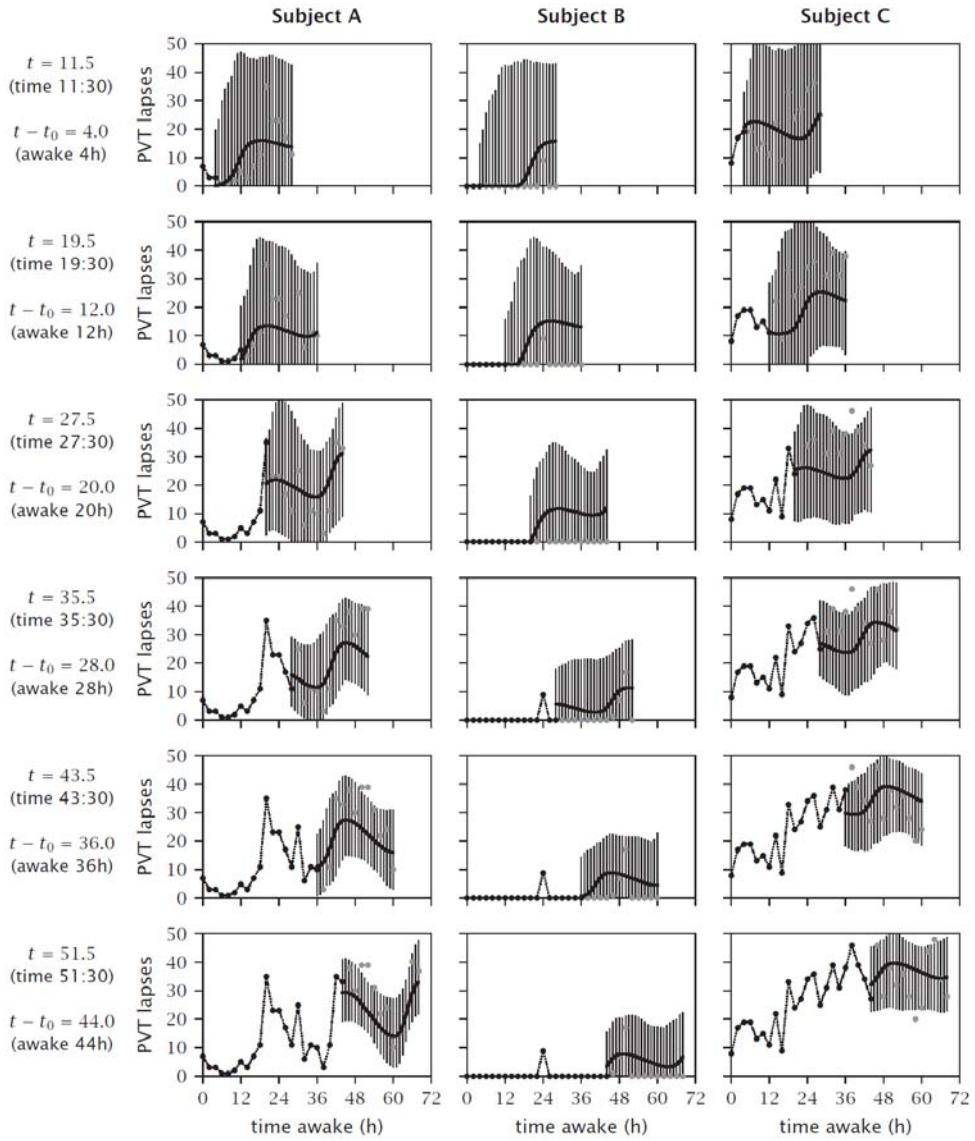

Figure 2: Simulation using the Bayesian forecasting procedure to predict performance over time for three individuals exposed to acute total sleep deprivation. Each column of panels represents a different individual. Subject "A" exhibited a fairly average response to sleep deprivation (cf. Fig. 1); subject "B" displayed considerable resistance to the effects of sleep deprivation; and subject "C" had relatively high vulnerability to performance impairment due to sleep deprivation. However, these subject-specific characteristics were not clear in advance—in this simulation, the trait parameters ν, η and λ were assumed a-priori unknown, and the initial state parameters ξ and φ were considered a-priori uncertain as well. The first row of panels shows the performance predictions for each of the three individuals upon acquisition of the third performance measurement, at 4h awake (11:30 clock time). The black circles show the number of lapses (reaction times ≥ 500ms) on a psychomotor vigilance test administered every 2h up to that time point. The thick curve shows the psychomotor vigilance performance predictions for the subsequent 24h period. The thin vertical lines display the corresponding 95% confidence intervals (in 1h steps). For comparison, the gray circles show the actual performance measurements during the 24h prediction period. (Since this was a simulation based on data acquired previously, these observations were already known, even though they were not yet made available to the Bayesian forecasting procedure.) Note that any data points that visually seem to be missing have the prediction curve right on top of them. The second row of panels shows the situation 8h later, when four additional performance measurements were available and the model parameters had been updated accordingly by the Bayesian forecasting procedure. The third through sixth rows show the situation in further 8h increments.

Since the sleep deprivation study took place in the past and all the data were already available, the simulation predictions could be compared directly to actual observations of performance impairment. Looking at all the snapshots in succession (from top to bottom through Fig. 2), the performance responses to sleep deprivation varied systematically among the three individuals. The model predictions were progressively tailored to these subject-specific responses, and the 95% confidence intervals consistently reduced in size, revealing a steady increase in model precision. Of course, this does not mean that the predictions were highly accurate throughout. Occasionally, performance at specific time points was considerably under- or over-predicted. However, the observations at those time points typically stood out from the surrounding data points, and did not fit the expected profile of gradual change over time in accordance with the homeostatic and circadian processes. Whether these data points represent outliers or whether they may reflect systematic aspects of performance regulation not captured by the two-process model is difficult to establish. Ultimately, the Bayesian forecasting procedure can only predict performance as accurately as allowed by the comprehensiveness of the mathematical model in which it is implemented, and the quality of the data it uses to update the model parameters. Given these caveats, the simulation demonstrated a high degree of success in predicting performance 24h ahead during laboratory sleep deprivation.

Fig. 3 shows the evolution of the model parameter estimates with every step in the simulation, from 4h awake up to 70h awake, for subject "A". The figure illustrates that the three trait parameters as well as the two initial state parameters could be estimated with increasing precision as more data became available over time. However, this "sharpening up" of the parameter estimates did not always occur in a gradual fashion. Occasional abrupt changes reflected variability in how informative the newly acquired performance data were for the parameters in question. After about 50h of wakefulness, there was hardly any new information in the performance data, and the parameters converged on their best estimable values. The estimates of the trait and initial state parameters for each of the three subjects at the end of the simulation, after 88h of total sleep deprivation, are shown in Table 2. For comparison, the population averages of the trait parameters were zero by definition, and the population averages of the initial state parameters were $\xi_0 = -28.0$ and $\varphi_0 = 0.6$.

Table 2: Estimates of the trait and initial state parameters for the three individual subjects, as converged on after 88h of total sleep deprivation in computer simulations starting at awakening.

	Trait Parameters			State Parameters	
Individual	v	η	λ	ξ	φ
A	0.12	0.75	2.8	–44.5	0.0
B	–2.37	–0.44	–3.1	–30.0	3.3
C	0.88	–0.13	3.5	–39.5	–2.8*

*Even though circadian phase angle φ was estimated in the range from 0 to 24, it is shown here on a scale from –12 to 12 to facilitate comparison among individuals.

It is instructive to assess the performance prediction accuracy of the Bayesian forecasting procedure relative to that of the population average model (i.e., with the traits and initial states fixed at the estimates obtained when establishing the population model). The latter is illustrated in Fig. 4 for a snapshot taken at 44h of wakefulness. A visual comparison of this simulation with the one in Fig. 2 (last row panels) suggests that using the population average model had limited

consequences for subject "A" (because this subject's response to sleep deprivation turned out to be approximately average), but resulted in substantial over-prediction of performance impairment for subject "B" and under-prediction of performance impairment for subject "C". The average prediction bias at 44h awake for the three subjects combined was –4.4 lapses, and the average prediction error was 16.3 lapses. In contrast, for the simulation with the Bayesian forecasting procedure (Fig. 2), the average prediction bias at 44h awake was only –0.2 lapses, and the average prediction error was 8.0 lapses. These numbers demonstrate the improvement achieved by using the Bayesian forecasting procedure to predict performance under conditions of unknown traits and uncertain states.

Because the three subjects set aside for simulations were taken from the same study as the ten subjects used to establish the population model, their initial homeostatic and circadian state parameters may have been relatively close to the population averages. Indeed, the parameter values at the end of the simulation (Table 2) confirmed this. To rule out that our evaluation of the Bayesian forecasting procedure under conditions of state uncertainty constituted a poor test because of this, another simulation was run similar to the first one (Fig. 2), but starting at a different homeostatic state. This was accomplished by ignoring the first 24h of sleep deprivation and the performance data collected during this period, and beginning the simulation at $t_{a0} = 31.5$ (i.e., 07:30 on the second day of sleep deprivation). All other aspects of the simulation were kept the same.

Fig. 5 shows the results of this new simulation for subject "A", in snapshots taken at 8h intervals. In terms of time spent awake, the top panel in Fig. 5 corresponds to the fourth panel in the left column of Fig. 2—both represent the situation at 28h awake. Since the performance data acquired during the first 24h of wakefulness were ignored in the new simulation, however, the 24h performance predictions made at 28h awake were slightly different, and the 95% confidence intervals were much larger. Still, over time (from top to bottom through Fig. 5), the Bayesian forecasting procedure displayed the same behavior, progressively tailoring the predictions to the subject-specific responses with the 95% confidence intervals consistently reducing in size. At 44h of wakefulness (i.e., the third snapshot), the average prediction bias across all three subjects was –1.5 lapses, and the average prediction error was 8.9 lapses—not much different from the first simulation (Fig. 2) and still much better than the population average model simulation (Fig. 4). The estimates of the trait and initial state parameters for each of the three subjects at the end of the simulation, after 88h of total sleep deprivation, are shown in Table 3. By and large, these estimates are close to those obtained in the first simulation (Table 2). These results confirm that the Bayesian forecasting procedure, as extended by us from the trait-only procedure presented by Olofsen et al. (2004), can handle the a-priori uncertainty of initial states well.

Table 3: Estimates of the trait and initial state parameters for the three individual subjects, as converged on after 88h of total sleep deprivation in computer simulations starting 24h after awakening.

	Trait Parameters			**State Parameters**	
Individual	ν	η	λ	ξ	φ
A	0.47	0.76	0.0	–44.5	0.0
B	–2.05	–0.32	–3.9	–31.0	3.2
C	1.38	0.11	3.4	—*	–3.0

*ξ could not be estimated from subject C's data after 24h of wakefulness, as this parameter no longer had a noticeable effect on the subject's performance predictions.

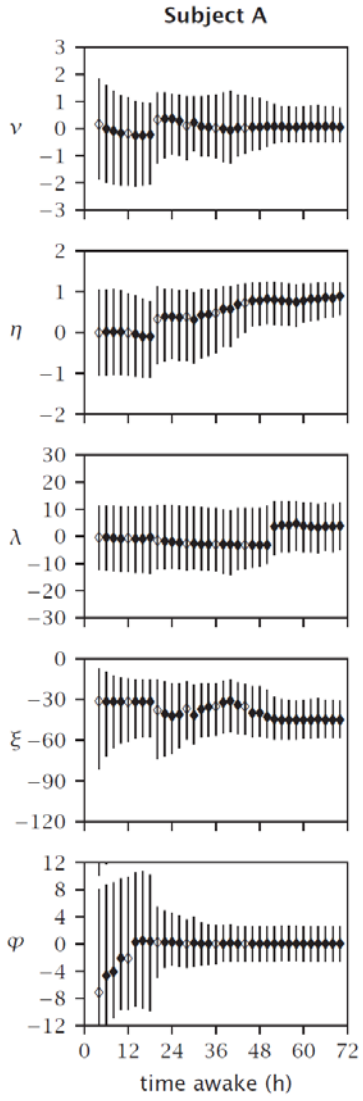

Figure 3: Bayesian forecasting estimates of the trait and initial state parameters for subject "A". This figure illustrates the optimization process for the estimates of trait parameters ν, η and λ and initial state parameters ξ and φ during the simulation shown in Fig. 2. The panels display the parameter estimates (diamonds) with 95% confidence intervals (vertical bars), as updated upon the availability of new performance measurements at 2h intervals (beginning with the third measurement at 4h of wakefulness). Note that even though circadian phase angle φ was estimated in the range from 0 to 24, it is plotted here (last panel) on a scale from –12 to 12 to facilitate visual interpretation. The confidence intervals for the first two estimates of φ extend below the bottom of the panel, and are continued at the top of the panel because of the circular nature of this parameter. For reference purposes, the open diamonds mark the parameter estimates that were underlying the performance predictions for subject "A" as shown successively in the six panels in the left column of Fig. 2.

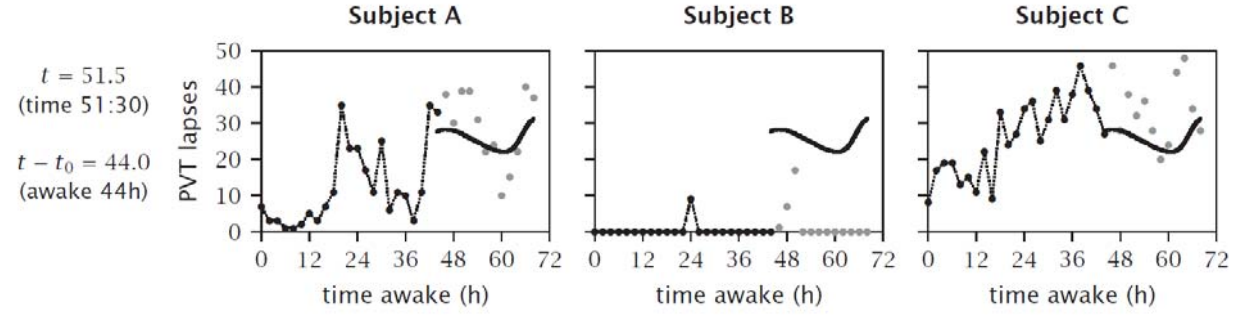

Figure 4: Simulation using the population model based on the two-process model to predict performance over time, without employing the Bayesian forecasting procedure. Details are the same as for the last row of panels (awake 44h) in Fig. 2, except that the state and trait parameters of the performance prediction model remained fixed at their population averages and were not updated based on subject-specific performance information acquired during the sleep deprivation period. As a consequence, the performance predictions were equal for each individual, and there was no flexibility in the level or shape of the 24h predictions curves. Note also that no suitable equivalent was available for the 95% confidence intervals.

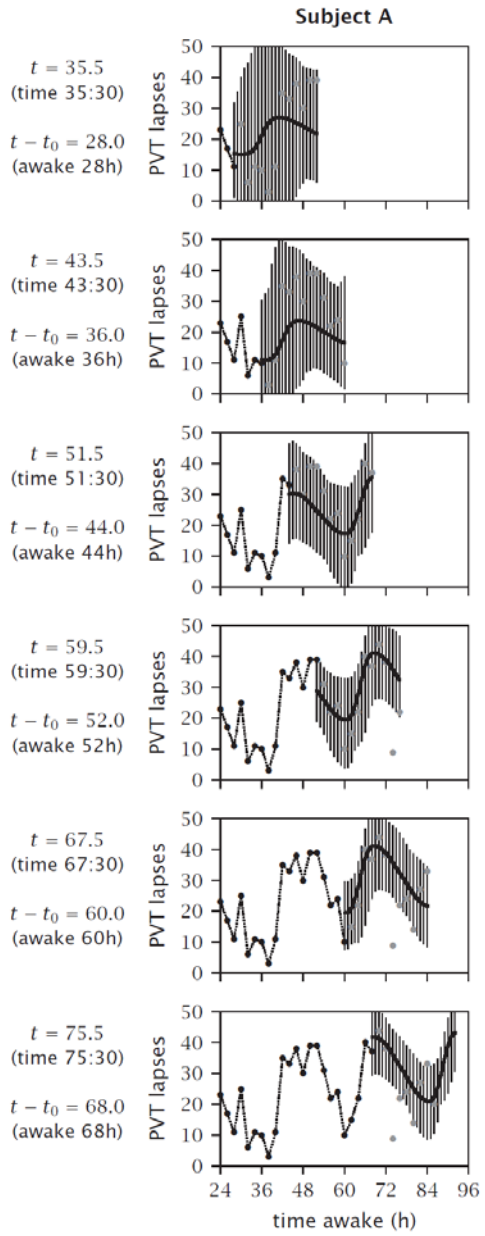

Figure 5: Simulation using the Bayesian forecasting procedure to predict performance over time for subject "A", starting at a later time during the sleep deprivation period. Details are the same as for Fig. 2 (left column panels), except that here the initial homeostatic state was different because the simulation was started at 24h awake (but for the purpose of the simulation the amount of prior wakefulness was considered not known). Timewise, the top panel in this figure corresponds to the fourth panel in the left column of Fig. 2. The second through sixth panels display the updated 24h performance predictions as time passed, shown in 8h increments. Note that there were only nine actual observations (gray circles) to compare to in the last panel, because data acquisition stopped at 88h awake in the laboratory experiment.

Critical for the usefulness of the Bayesian forecasting procedure in operational settings is its ability to deal with sparse data, collected infrequently at intervals of potentially unequal duration. To examine this property, another simulation was conducted, similar again to the first one (and starting at $t_{a0} = 7.5$), but using only the performance measurements of 8 (instead of 23) randomly selected time points to updated the model parameters. Fig. 6 shows the results of this simulation for subject "A", again in snapshots taken at 8h intervals. In terms of time spent awake, the top panel in Fig. 6 corresponds to the second panel in the left column of Fig. 2—both represent the situation at 12h awake (at 4h awake there were not enough data points yet to expect reasonable estimates for the initial state parameters).

The scarcity of data in the simulation of Fig. 6 caused the 24h-ahead prediction curve at 12h awake to be notably different than in the first simulation (Fig. 2). The 95% confidence intervals

were larger as well. However, as the simulation progressed (from top to bottom through Fig. 6), the 24h predictions became very similar to those seen in the first simulation. At 44h awake, the average prediction bias across all three subjects was –0.5 lapses, and the average prediction error was 8.5 lapses—again similar to what was found in the first simulation (Fig. 2). The estimates of the trait and initial state parameters for each of the three subjects at the end of the simulation, after 88h of total sleep deprivation, are shown in Table 4. These are also close to the estimates obtained in the first simulation (Table 2). Thus, the main effect of the data being sparse appeared to be that the 95% confidence intervals reduced in size less rapidly, but the Bayesian forecasting procedure did not lose its ability to predict.

Table 4: Estimates of the trait and initial state parameters for the three individual subjects, as converged on after 88h of total sleep deprivation in computer simulations with sparse data.

Individual	Trait Parameters			State Parameters	
	v	η	λ	ξ	φ
A	0.48	0.58	2.6	–48.0	0.0
B	–1.97	–0.25	–4.1	–30.5	5.6
C	0.35	–0.17	0.4	–26.0	2.6

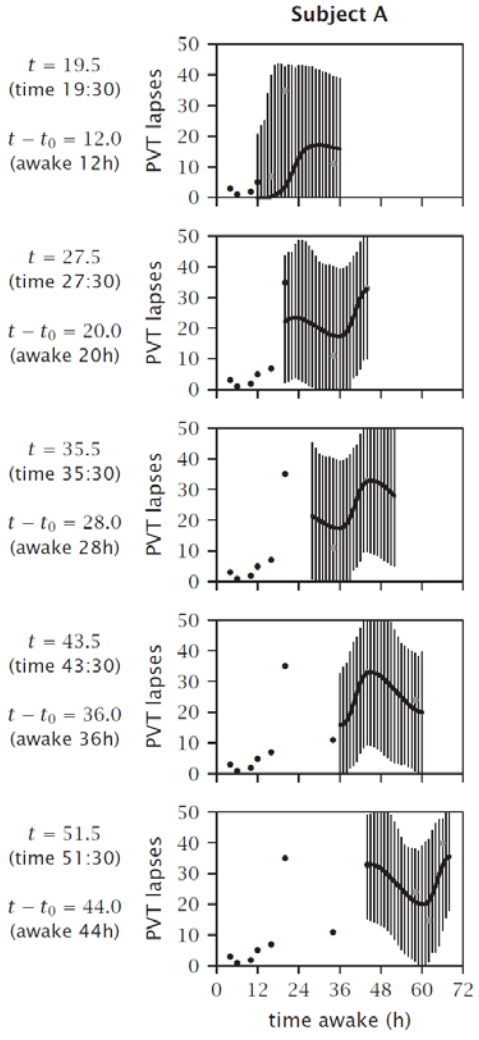

Figure 6: Simulation using the Bayesian forecasting procedure to predict performance over time for subject "A", under conditions of sparse data availability. A large portion of the original data set (see Fig. 2, left column panels) was discarded here, so as to simulate that the available performance measurements occurred infrequently—at random, unequally spaced intervals. Other details are the same as for Fig. 2, except that the first panel in that figure (awake 4h) is not repeated because only one data point was available during the first 4h of wakefulness in this simulation.

Repeated Use of Bayesian Forecasting

After the Bayesian forecasting procedure has been applied to make performance predictions for a given individual, the optimized values for the trait parameters (but not the initial state parameters) can be used again if predictions are needed for this same individual on another occasion. Specifically, the prior normal distributions for the trait parameters v_i, η_i and λ_i in Eq. (16) can be replaced by the pdfs obtained for these parameters at the end of the previous application of the Bayesian forecasting procedure. This way, the data acquired for an individual during scenarios in the past continue to contribute to the precision of the performance predictions for that individual in the future.

To examine this idea, a simulation was run using data from a different experiment (study 2 in Van Dongen et al., 2005a). A person was exposed to 36h total sleep deprivation in the laboratory on two occasions. Laboratory circumstances were similar to those encountered in the other simulations. However, the 36h sleep deprivations began at 10:00, and this time point was used to define the modeling start time for each sleep deprivation period (i.e., $t_0 = 10$). Psychomotor vigilance testing occurred at 2h intervals, beginning at 10:30 ($t = 10.5$), during both sleep deprivations. The performance data were very similar between the two sleep deprivations (see Fig. 7), as was anticipated given that performance responses to sleep deprivation are overall trait-like (Van Dongen et al., 2004a). It was expected that, despite the relatively small number of data points available, the Bayesian forecasting procedure would achieve greater prediction precision more rapidly for the second exposure to sleep deprivation when utilizing the trait information obtained in the first exposure.

The results of the simulation are shown in Fig. 7. The first column of panels shows the results of Bayesian forecasting for the first sleep deprivation period. The second column of panels shows the results for the second sleep deprivation period *without* utilizing the trait information acquired in the first. Although some data points were missing in the first sleep deprivation session, the prediction results and corresponding 95% confidence intervals were nearly identical. The average prediction bias was –4.3 lapses for the first, and –6.0 lapses for the second sleep deprivation; and the average prediction error was 11.2 lapses for the first, and 11.0 lapses for the second sleep deprivation. The third column of panels shows the improvement in the predictions for the second sleep deprivation when employing the pdfs obtained for the trait parameters (but not the initial state parameters) at the end of the first sleep deprivation. Using these pdfs as prior information, the average prediction bias for the second sleep deprivation was reduced to 0.5 lapses, and the average prediction error was reduced to 6.9 lapses.

The improvement stemmed from the fact that the trait and initial state parameters converged more rapidly to the values best characterizing the individual at hand, due to the more informative prior distributions for the trait parameters. As a result, the performance predictions became more accurate, and the 95% confidence intervals were consistently smaller, than without the use of the information from the first exposure to sleep deprivation (compare the second and third columns in Fig. 7). This illustrates that the Bayesian forecasting procedure can become more effective when used repeatedly.

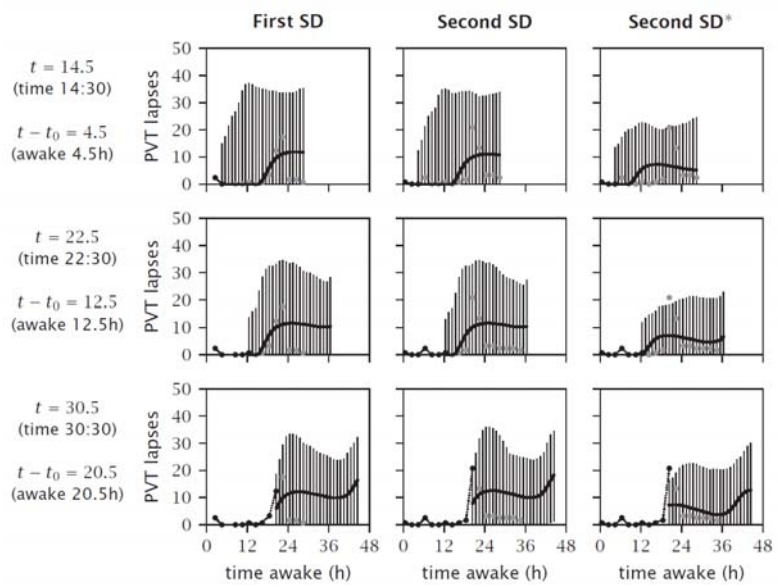

Figure 7: Simulation using the Bayesian forecasting procedure to predict performance over time for a single individual exposed to acute total sleep deprivation twice. The first column of panels shows the simulation for the first time the individual underwent 36h sleep deprivation; graphical details are the same as for Fig. 2. (Note that the 24h ahead predictions displayed in the bottom panel extend beyond the 36h period of sleep deprivation.) The second column of panels shows the simulation for the second time the individual was exposed to 36h sleep deprivation, retaining no information from the first exposure. The third column of panels shows the simulation for the second exposure to sleep deprivation again, but—as denoted by the asterisk—the estimates for the trait parameters at the end of the first exposure to 36h sleep deprivation were used as prior information this time (although the initial state parameters were still considered a-priori uncertain).

Discussion

We demonstrated the usefulness of the Bayesian forecasting procedure for predicting cognitive performance impairment with a mathematical model, in particular the two-process model, in the face of unknown trait characteristics and uncertain initial states in individual subjects. Prospective computer simulations were run using data from the psychomotor vigilance test (PVT), a marker of changes in cognitive performance mediated by the homeostatic and circadian processes (Dorrian et al., 2005), as recorded during a laboratory-based study of total sleep deprivation. The simulations showed that mathematical model parameters converged rapidly to the values that best characterized the individuals concerned, resulting in substantially improved performance predictions relative to the original version of the model. The Bayesian forecasting procedure also yielded estimates of 95% confidence intervals for the parameter estimates and for performance prediction accuracy. The 95% confidence intervals for performance shrunk over time, both in absolute size and relative to the differences in performance predictions among individuals, resulting in statistically relevant differentiation among subjects—i.e., successfully individualized performance predictions. Numerical computations were sufficiently fast on a Pentium-driven desktop computer to be feasible in real time in operational environments (even for keeping track of multiple individuals working in small teams).

Thus, the work presented here provides the first solution to some of the most significant challenges in the development of mathematical models of performance for operational use (Dinges, 2004; Friedl et al., 2004): a) performance prediction for individuals (instead of groups) in the face of a-priori unknown trait inter-individual variability; b) performance prediction for individuals in the face of uncertain initial states; and c) quantification of prediction accuracy.

The Bayesian forecasting procedure as implemented in the two-process model possesses broad generalizability, in that it can be used to predict waking performance in any scenario and in any population for which the two-process model proper is valid. Thus, the procedure should work in total sleep deprivation, acute sleep restriction, acute sleep displacement, and nap sleep scenarios (Achermann, 2004). Furthermore, besides healthy adults, it may work in other populations such as adolescents (Carskadon et al., 2004), people with depression (Borbély, 1987), and patients with seasonal affective disorder (Koorengevel et al., 2002). Although it is important to establish a population model for the target population, it is not necessary to assess the population model under the same circumstances as those for which the Bayesian forecasting will be used. For example, a population model established in a nap sleep scenario should be usable as a basis for Bayesian forecasting in a sleep displacement scenario. The total sleep deprivation scenario considered in this report does not yet offer full generalizability, though, because the data set does not allow estimation of the rate of dissipation for the homeostatic process during sleep (which could be overcome by including performance data from the recovery days following sleep deprivation). Otherwise, the versatility of the Bayesian forecasting procedure is not bounded by the circumstances associated with the population model, as long as the procedure is applied in accordance with the scope of the underlying mathematical model, and the individuals for which performance is being predicted are part of the same population as the sample that yielded the population model.

The validity of the two-process model as used to predict performance is limited, primarily, to short-term scenarios with acute sleep-related interventions. While this covers a wide range of operationally relevant scenarios, several common situations are outside the scope of the two-process model, such as chronic sleep restriction (Van Dongen et al., 2003; see also later in this report), circadian phase shifting (Folkard et al., 1999), and use of pharmacological fatigue countermeasures (Balkin et al., 2004). The effect of sleep inertia on cognitive performance immediately after awakening (Dinges, 1990) is also not captured by the two-process model. Various adjustments have been considered to overcome these limitations (Achermann and Borbély, 1994; Åkerstedt and Folkard, 1997; Avinash et al., 2005). Furthermore, other models have been developed to push the envelope on performance prediction (Mallis et al., 2004). The Bayesian forecasting procedure may be implemented in the framework of such alternative models as well, following the same general approach as laid out in this report. Most current mathematical models of performance have more parameters than the two-process model, however, which may increase the number of performance measurements needed to obtain reliable subject-specific parameter estimates and may also increase the size of the 95% confidence intervals. Even so, with Bayesian forecasting, any available performance model may be utilized to make performance predictions for individuals in the face of unknown traits and uncertain states.

This work built on the work by Olofsen et al. (2004), in which Bayesian forecasting was already applied to optimize subject-specific trait parameters. The present work extends this effort by for the first time including initial state parameters in the parameter optimization process. Initial state parameters can be treated as trait parameters in the context of Bayesian forecasting if they represent enduring conditions (i.e., if their values may be assumed stable over the time period for which predictions are made). However, for initial state parameters, unlike trait parameters, the optimization process does not benefit from prior information contained in the population model.

Moreover, if predictions are needed for individuals who were subjected to Bayesian forecasting before, then the previously optimized values of the individuals' trait parameters may be reused to obtain more accurate predictions with fewer data points (see Fig. 7)—but this Bayesian property does not transfer to the initial state parameters. Improved prior information about the initial state parameters may be acquired by other means, though. For instance, actigraphy could be used to track sleep history, and could yield probability estimates for the initial homeostatic state ξ in lieu of the assumed uniform distribution in Eq. (14).

The assumption of enduring initial states implies that the use of the Bayesian forecasting procedure described here is restricted to scenarios in which there are no unexpected changes in initial states—no homeostatic discontinuities (e.g., due to unreported naps) and no circadian phase shifts (e.g., due to exposure to bright light). Considerable work has been done to derive equations for the modeling of circadian phase changes (and even temporary deviations from the limit cycle process determining circadian amplitude) (e.g., Kronauer et al., 1998; St. Hilaire et al., 2007). Incorporation of such equations may allow substitution of the initial state parameter for circadian phase angle by a few trait parameters, thereby lifting the assumption of enduring circadian phase angle in the present work. Other approaches to maintaining performance prediction accuracy under conditions involving dynamic circadian phase changes can be envisioned as well. One such approach could entail the development of procedures relying on on-line measurements for estimating circadian phase.

Implementation of the Bayesian forecasting procedure does not prohibit performance prediction in the absence of any subject-specific data, but the underlying (group-average) mathematical model is only outperformed when at least a few performance measurements are available for the individual at hand. However, in operational environments, it may not be possible or practical to interrupt the ongoing tasks in order to administer performance tests. Automatically measured embedded performance measures, such as lane deviation to track driver performance (Gillberg et al., 1996), may offer a solution to this problem. An additional advantage of using embedded performance measures is that they may be directly relevant to the demands of the operational setting. However, embedded performance measures must be sensitive to the underlying neurobiology in order to be useful, and must not be overly influenced by other factors (e.g., learning, performance strategy, environmental distractions) that can mask the influence of sleep homeostasis and circadian rhythmicity on performance capability. Note also that the same performance measure should be used for assessing the population model as for applying the Bayesian forecasting procedure, because inter-individual differences in vulnerability to sleep loss appear to be dependent on the type of performance being measured (Van Dongen et al., 2004a).

We recently published our work on the Bayesian forecasting procedure in the peer-reviewed literature (Van Dongen et al., 2007a). Since then, an alternative approach for individualized performance prediction has been published (Rajaraman et al., 2008). It involves transformation of the individualized equations of the two-process model into a set of linear optimization problems, which are solved with the least-squares method in order to find estimates for the subject-specific model parameters.

We believe that the Rajaraman et al. (2008) paper contains a number of important inaccuracies. First, the Bayesian forecasting methodology is critiqued, but random effects are mixed up with

intra-individual variability; prediction horizon limitations are mentioned that do not exist (see also Reifman et al., 2007, and Van Dongen et al., 2007b); multimodal distributions are wrongly asserted to cause convergence problems; and the computational cost of our numerical implementation (see above) is confused with the fundamental computational expense of Bayesian forecasting (which can be shown to be merely of order N^2; see Smith et al., in press). Second, the two-process model proper is discredited as a basis for performance prediction in total sleep deprivation (Rajaraman et al., 2008), but this conclusion is based on a critical mistake in the processing of the circadian phase parameter.

These erroneous criticisms of the work of others notwithstanding, there is no a-priori reason to believe that the Bayesian forecasting procedure couldn't be improved. Even so, it is unclear what the advantage of the Rajaraman et al. (2008) approach would be. The approach requires performance data to be available at regular time intervals, and breaks down when data are missing. In addition, parameter convergence is much slower than in the Bayesian forecasting procedure. Because of the effort involved in linearizing the model equations, the Rajaraman et al. (2008) approach cannot readily be applied to other fatigue and performance models. Linearization also prohibits accurate estimation of confidence intervals.

Rajaraman et al. (2008) claim that their approach does not require in-advance assessment of a population model to individualize performance predictions (in fact, even if a population model is available, the approach cannot take advantage of it). However, this feature comes at the cost of considerably greater need for performance measurements from the individual at hand—so much so, that the Bayesian forecasting procedure can as well be used effectively without a population model if that many data points are available. Further, the Rajaraman et al. (2008) approach is claimed to yield a unique solution for the parameter optimization problem, even if the pdf for the multidimensional parameter space is multimodal. However, application of the least-squares method to multimodal pdfs may yield parameter values that, while representative of the statistical mean, do not themselves have a high likelihood (e.g., Sivia, 1996). The usefulness of predicting performance for an individual on the basis of a parameter solution that does not have a high likelihood is questionable. The Bayesian forecasting procedure, on the other hand, yields the parameter set that is most likely for the individual at hand (which is also a unique solution), thereby generating the most probable individualized performance predictions. Furthermore, if multimodality of pdfs is indeed an issue in practice, then it is straightforward in Bayesian forecasting to capture any ensuing multimodality in the performance predictions.

Regardless of ongoing and future efforts to improve the present methodology (e.g., through application of predictive covariates; see Olofsen et al., 2004), we believe that the Bayesian forecasting procedure as presented in this report is powerful and robust enough to be considered for validation in selected operational settings. Such a validation should begin with establishing population models for these operational settings. This is important because the distribution of the trait parameters may be different depending on the population involved, and the error variance (i.e., the estimate for σ^2) may vary from one setting to another. Once demonstrated to be effective in the field, the Bayesian forecasting procedure can be a key component of a reliable and efficient sleep/wake-based fatigue management tool—to predict cognitive performance impairment, and possibly even accident risk (Ingre et al., 2006), at the level of individuals.

NEW MATHEMATICAL MODEL FOR THE SLEEP/WAKE HOMEOSTATIC REGULATION OF FATIGUE AND PERFORMANCE

Introduction

Sleep deprivation and circadian misalignment cause a wide range of cognitive performance deficits (Dinges and Kribbs, 1991; Banks and Dinges, 2007). Various mathematical models of fatigue and performance have been developed to predict such performance impairment (Mallis et al., 2004). However, scientific progress in this area has been limited by difficulties predicting performance under chronic conditions of partial sleep loss (Van Dongen, 2004).

Most of the available fatigue and performance models are based on the seminal two-process model of sleep regulation (Borbély, 1982; Daan et al., 1984). This model posits that sleep and wakefulness are governed by two primary biological mechanisms: a homeostatic process that builds pressure for sleep during wakefulness and dissipates this pressure during sleep (Borbély and Achermann, 1999), and a circadian process that modulates sleep pressure as a function of time of day (Edgar et al., 1993). The two-process model has been successful in predicting various aspects of sleep and of waking cognitive functions across a range of sleep and sleep deprivation paradigms (Borbély and Achermann, 1999; Achermann, 2004). For instance, it was shown that waking cognitive functions could—in many instances—be predicted by the arithmetic difference between the homeostatic pressure for sleep and the circadian pressure for wakefulness (Achermann and Borbély, 1994).

Extending the two-process model from its original focus on sleep (Borbély, 1982) to include predictions of waking functions has been a goal for some time (Borbély and Achermann, 1999; Dinges and Achermann, 1999). However, efforts to achieve this goal have not been universally successful. Several studies have shown that chronic sleep restriction leads to cumulative increases, progressing over days for a week or more, in sleep propensity and cognitive impairment (Carskadon and Dement, 1981; Dinges et al., 1997; Belenky et al., 2003; Van Dongen et al., 2003)—see Fig. 8a. The two-process model does not accurately capture these increasing deficits, predicting instead a stabilization of waking cognitive functions across days after just a few days of chronic sleep loss (Van Dongen et al., 2003)—see Fig. 8b. Other fatigue and performance models have similarly failed to predict the cumulative effects of chronic sleep restriction (Van Dongen, 2004).

Van Dongen et al. (2003) proposed a different model, shifting the emphasis from sleep loss to cumulative wake extension or “excess wakefulness”. This subtle conceptual difference provided a parsimonious explanation for the effects on waking functions of both acute total sleep deprivation and chronic partial sleep deprivation (Van Dongen et al., 2003; Van Dongen and Dinges, 2003b). The excess wakefulness model has theoretical significance, but it is not useful for computational predictions of cognitive impairment, because it does not explicitly state how recovery from the effects of prior sleep loss would be achieved.

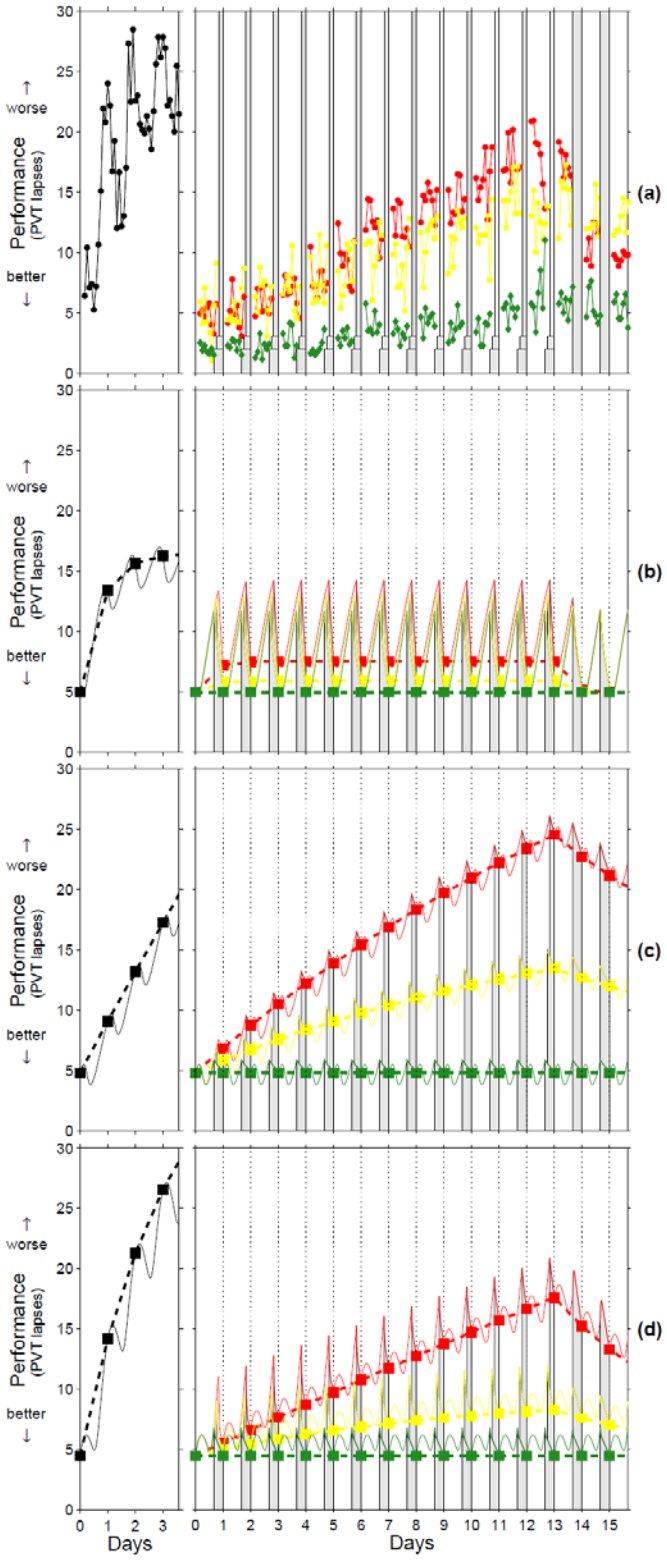

Figure 8: Cognitive performance observations and predictions by different models. A total of 48 healthy young adults were subjected to one of four laboratory sleep deprivation protocols (Van Dongen et al., 2003). Each protocol began with several baseline days involving 8h time in bed (TIB), the last of which is labeled here as day 0. Subsequently, 13 subjects were kept awake (0h TIB) for 3 additional 24h days (left panels). The other subjects underwent various doses of sleep restriction for 14 consecutive days, followed by 2 days with recovery sleep at 8h TIB (right panels). The sleep restriction dose was 4h TIB per day for 13 subjects (red); 6h TIB per day for another 13 subjects (yellow); and 8h TIB per day for the remaining 9 subjects (green). Awakening was scheduled at 07:30 each day. Performance was tested every 2h during scheduled wakefulness using the PVT, for which the number of lapses (RT ≥ 500ms) was recorded.
(a) Observed performance (PVT lapses) for each test bout (dots represent group averages). The first two test bouts of each waking period are omitted in order to avoid confounds from sleep inertia. Gray bars indicate scheduled sleep periods.
(b) Performance predictions according to the original two-process model (Borbély and Achermann, 1999), linearly scaled to the data. Boxes represent performance predictions at wake onset. Thin curves represent predictions within days, but the focus here is on changes across days (dashed lines). Note the rapid stabilization across days predicted to occur in the chronic sleep restriction conditions (right panel), which does not match the observations. (c) Performance predictions according to the extended two-process model (Avinash et al., 2005), linearly scaled to the data. Note the under-prediction of performance impairment in the total sleep deprivation condition (left panel) and the over-prediction of the impairment build-up across days in the 4h TIB condition (right panel), relative to the actual data. (d) Performance predictions according to the new model defined by Eqs. (40) and (45). Note the improved fit to the experimental observations across days for total sleep deprivation (left panel), as well as for the 4h TIB condition (right panel). Performance impairment in the 6h TIB and 8h TIB conditions (right panel) is under-predicted. However, the average impairment levels observed for these conditions are inflated due to a few outliers (Van Dongen et al., 2003).

Alternative solutions were introduced by Hursh et al. (2004) and by Johnson et al. (2004), who each included an additional regulatory process modulating their versions of the homeostatic

process, in order to account for the cumulative effects of chronic sleep restriction. Based on the approach proposed by Johnson et al. (2004), Avinash et al. (2005) then extended the original two-process model, as part of the present project. The objective of this effort was to capture the effects of chronic sleep restriction on waking cognitive performance (Van Dongen et al., 2003), while retaining the successes of the original two-process model in predicting other aspects of waking functions and sleep (Achermann, 2004). The Avinash et al. (2005) approach, which was seminal for further work in this project, can be summarized as follows.

The homeostatic process of the original two-process model is typically represented as a pair of difference equations (Borbély and Achermann, 1999):

$$S_t = 1 - e^{\frac{-\Delta t}{\tau_r}} (1 - S_{t-\Delta t}) \qquad \text{during wake,} \tag{19a}$$

$$S_t = e^{\frac{-\Delta t}{\tau_d}} S_{t-\Delta t} \qquad \text{during sleep.} \tag{19b}$$

Here S is the homeostatic sleep pressure as a function of time t; Δt is the time step; and $\tau_r > 0$ and $\tau_d > 0$ are time constants for the rise and decay of the homeostatic process during wakefulness and sleep, respectively. The reason the two-process model predicts excessively rapid stabilization of performance across days of sleep restriction is related to the asymptotic properties of Eqs. (19). Specifically, the wake equation tends to a steady state represented by an upper asymptote $U = 1$, while the sleep equation tends to a steady state represented by a lower asymptote $V = 0$. This asymptotic behavior can be demonstrated by rewriting Eqs. (19):

$$S_t - U_t = (S_{t-\Delta t} - U_{t-\Delta t}) e^{\frac{-\Delta t}{\tau_r}} \qquad \text{during wake,} \tag{20a}$$

$$S_t - V_t = (S_{t-\Delta t} - V_{t-\Delta t}) e^{\frac{-\Delta t}{\tau_d}} \qquad \text{during sleep.} \tag{20b}$$

The extension of the two-process model by Avinash et al. (2005) involved modulating the homeostatic process through manipulation of the asymptotes U and V in Eqs. (20), as follows:

$$U_t = U_{t-\Delta t} + \mu_r \Delta t \qquad \text{during wake,} \tag{21a}$$

$$U_t = U_{t-\Delta t} + (1 - U_{t-\Delta t})(1 - e^{\frac{-\Delta t}{\mu_d}}) \qquad \text{during sleep,} \tag{21b}$$

$$V_t = U_t - 1. \tag{21c}$$

Here $\mu_r > 0$ represents the slope of a linear rise of the asymptotes during wakefulness, and $\mu_d > 0$ represents the time constant of an exponential decay of the asymptotes during sleep.

The model proposed by Avinash et al. (2005) performed better at capturing the cumulative deficits in cognitive performance across days as induced by chronic sleep restriction, but at the cost of reduced accuracy in describing the magnitude of the effects across days of acute total sleep deprivation—see Fig. 8c. However, it can be shown that the model of Eqs. (21) belongs to a much broader class of homeostatic models based on the same principles, which offer further improvements in predicting performance impairment across days of sleep loss.

New Class of Models Formulated in Terms of Coupled Non-Homogeneous First-Order Ordinary Differential Equations

Beginning with the original two-process model (Achermann and Borbély, 1994), we can write model equations for cognitive performance as:

$$p_n(t) = w_n(t) - c(t) \qquad \text{for } t \in [t_n,\, t_n + W_n] \qquad \text{(i.e., during wake),} \tag{22a}$$

$$q_n(t) = s_n(t) - c(t) \qquad \text{for } t \in [t_n + W_n,\, t_n + T_n] \qquad \text{(i.e., during sleep).} \tag{22b}$$

The variables w_n and s_n denote the homeostatic pressure during wakefulness and sleep, respectively, in the n^{th} wake/sleep cycle (i.e., day), where $n = 0, 1, \ldots$ The function $c(t)$ is the original circadian process (see Borbély and Achermann, 1999). Further, t_n denotes the time of the beginning of the n^{th} wake/sleep cycle, T_n is the total duration of the n^{th} cycle (such that $t_{n+1} = t_n + T_n$), and W_n is the duration of wakefulness in the n^{th} cycle. We require that $0 < W_n \leq T_n$, where $W_n = T_n$ corresponds to total sleep deprivation. Finally, p_n and q_n are the predictions for performance during wakefulness and sleep, respectively, in the n^{th} wake/sleep cycle. The predictions during sleep are notional; they are included strictly for continuity between consecutive wake/sleep cycles. Here p_n and q_n are coupled as follows:

$$p_n(t_n + W_n) = q_n(t_n + W_n), \tag{23a}$$

$$q_n(t_n + T_n) = p_{n+1}(t_{n+1}). \tag{23b}$$

The homeostatic process of Eqs. (19) may be written in the form of a system of first-order ordinary differential equations (ODEs):

$$\frac{dw_n}{dt} = \frac{-1}{\tau_{\text{r}}}(w_n - 1) \qquad \text{for } t \in [t_n,\, t_n + W_n], \tag{24a}$$

$$\frac{ds_n}{dt} = \frac{-1}{\tau_{\text{d}}} s_n \qquad \text{for } t \in [t_n + W_n,\, t_n + T_n]. \tag{24b}$$

Note that w_n and s_n are still functions of time t, but to reduce clutter in later differential equations this is no longer indicated explicitly. From Eqs. (24) it follows that Eqs. (22) can also be written as a system of first-order ODEs:

$$\frac{dp_n}{dt} = \frac{-1}{\tau_{\text{r}}} p_n + \beta(t) \qquad \text{for } t \in [t_n,\, t_n + W_n], \tag{25a}$$

$$\frac{dq_n}{dt} = \frac{-1}{\tau_{\text{d}}} q_n + \gamma(t) \qquad \text{for } t \in [t_n + W_n,\, t_n + T_n], \tag{25b}$$

where p_n and q_n are again coupled as per Eqs. (23). The non-homogeneities $\beta(t)$ and $\gamma(t)$ represent the circadian process, and may be generalized to include other non-homeostatic influences on performance.

The system of Eqs. (25) is an exact representation of the original two-process model (Borbély and Achermann, 1999). In the same manner, the extended two-process model of Avinash et al. (2005) can be written as a system of coupled non-homogeneous first-order ODEs:

$$\begin{bmatrix} \dot{p}_n \\ \dot{u}_n \end{bmatrix} = \begin{bmatrix} -1/\tau_r & 1/\tau_r \\ 0 & 0 \end{bmatrix} \begin{bmatrix} p_n \\ u_n \end{bmatrix} + \begin{bmatrix} \beta_1(t) \\ \beta_2(t) \end{bmatrix} \qquad \text{for } t \in [t_n,\, t_n + W_n], \tag{26a}$$

$$\begin{bmatrix} \dot{q}_n \\ \dot{v}_n \end{bmatrix} = \begin{bmatrix} -1/\tau_d & (1/\tau_d - 1/\mu_d) \\ 0 & -1/\mu_d \end{bmatrix} \begin{bmatrix} q_n \\ v_n \end{bmatrix} + \begin{bmatrix} \gamma_1(t) \\ \gamma_2(t) \end{bmatrix} \qquad \text{for } t \in [t_n + W_n,\, t_n + T_n]. \tag{26b}$$

Here u_n and v_n are the levels of the upper and lower asymptotes, respectively, in the n^{th} wake/sleep cycle. The non-homogeneities $\beta_1(t)$ and $\gamma_1(t)$ represent the circadian process, and may again be generalized to include other non-homeostatic influences on performance. Likewise, $\beta_2(t)$ and $\gamma_2(t)$ represent any circadian or other non-homeostatic effects there might be on the levels of the upper and lower asymptotes. Note that in this notation, $\beta_1(t)$ and $\beta_2(t)$ have absorbed the parameter μ_r (i.e., the slope of the linear rise of the upper asymptote during wakefulness). Analogous to Eqs. (23), Eqs. (26) are coupled as follows:

$$\begin{bmatrix} p_n(t_n + W_n) \\ u_n(t_n + W_n) \end{bmatrix} = \begin{bmatrix} q_n(t_n + W_n) \\ v_n(t_n + W_n) + \delta \end{bmatrix}, \tag{27a}$$

$$\begin{bmatrix} q_n(t_n + T_n) \\ v_n(t_n + T_n) \end{bmatrix} = \begin{bmatrix} p_{n+1}(t_{n+1}) \\ u_{n+1}(t_{n+1}) - \delta \end{bmatrix}, \tag{27b}$$

where $\delta > 0$ is the distance between the two asymptotes. For the extended two-process model, $\delta = 1$ (Avinash et al., 2005).

When we write Eqs. (26) in generalized form, it becomes clear that there is an asymmetry in the extended two-process model of Avinash et al. (2005):

$$\begin{bmatrix} \dot{p}_n \\ \dot{u}_n \end{bmatrix} = \begin{bmatrix} \alpha_{11} & \alpha_{12} \\ 0 & 0 \end{bmatrix} \begin{bmatrix} p_n \\ u_n \end{bmatrix} + \begin{bmatrix} \beta_1(t) \\ \beta_2(t) \end{bmatrix} \qquad \text{for } t \in [t_n,\, t_n + W_n], \tag{28a}$$

$$\begin{bmatrix} \dot{q}_n \\ \dot{v}_n \end{bmatrix} = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ 0 & \sigma_{22} \end{bmatrix} \begin{bmatrix} q_n \\ v_n \end{bmatrix} + \begin{bmatrix} \gamma_1(t) \\ \gamma_2(t) \end{bmatrix} \qquad \text{for } t \in [t_n + W_n,\, t_n + T_n]. \tag{28b}$$

Namely, Eq. (28b) for sleep has one more parameter than Eq. (28a) for wakefulness. Adding the corresponding coefficient α_{22} in Eq. (28a) generates a useful new model, as shown later in this report. Moreover, both equations have room for another parameter in the 2 by 2 coefficient matrices (i.e., α_{21} and σ_{21}, respectively).

We define our new class of models, formulated in terms of coupled non-homogeneous first-order ODEs, by the following generalized equations (which incorporate the original and extended two-process models):

$$\begin{bmatrix} \dot{p}_n \\ \dot{u}_n \end{bmatrix} = \begin{bmatrix} \alpha_{11} & \alpha_{12} \\ \alpha_{21} & \alpha_{22} \end{bmatrix} \begin{bmatrix} p_n \\ u_n \end{bmatrix} + \begin{bmatrix} \beta_1(t) \\ \beta_2(t) \end{bmatrix} \qquad \text{for } t \in [t_n,\, t_n + W_n], \tag{29a}$$

$$\begin{bmatrix} \dot{q}_n \\ \dot{v}_n \end{bmatrix} = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{bmatrix} \begin{bmatrix} q_n \\ v_n \end{bmatrix} + \begin{bmatrix} \gamma_1(t) \\ \gamma_2(t) \end{bmatrix} \qquad \text{for } t \in [t_n + W_n,\, t_n + T_n]. \tag{29b}$$

The coupling of these equations is given by Eqs. (27). Of the non-homogeneities $\beta_1(t)$, $\beta_2(t)$, $\gamma_1(t)$ and $\gamma_2(t)$ we require that they are bounded, oscillatory functions. They co-determine the profiles of performance changes *within* wake/sleep cycles, in part through the circadian process, but this

is beyond the focus of the present work. The α and σ coefficient matrices are of primary interest here, as they determine the dynamic behavior of the system *across* wake/sleep cycles.

For constant values of the α and σ coefficients, the general solution of the ODE system of Eqs. (29) is of the form (Derrick and Grossman, 1997):

$$\begin{bmatrix} p_n(t) \\ u_n(t) \end{bmatrix} = \psi_n(t)\psi_n^{-1}(t_n)\begin{bmatrix} p_n(t_n) \\ u_n(t_n) \end{bmatrix} + \int_{t_n}^{t} \psi_n(t)\psi_n^{-1}(s)\begin{bmatrix} \beta_1(s) \\ \beta_2(s) \end{bmatrix} ds, \tag{30a}$$

$$\begin{bmatrix} q_n(t) \\ v_n(t) \end{bmatrix} = \varphi_n(t)\varphi_n^{-1}(t_n + W_n)\begin{bmatrix} q_n(t_n + W_n) \\ v_n(t_n + W_n) \end{bmatrix} + \int_{t_n + W_n}^{t} \varphi_n(t)\varphi_n^{-1}(s)\begin{bmatrix} \gamma_1(s) \\ \gamma_2(s) \end{bmatrix} ds, \tag{30b}$$

where $\psi_n(t)$ and $\varphi_n(t)$ are the respective fundamental solutions of the homogeneous parts of Eqs. (29). These fundamental solutions depend on the eigenvalues λ_i and the corresponding eigenvectors $[k_{i1}\,;\,k_{i2}]$ of the α and σ coefficient matrices. The eigenvalues and eigenvectors of the α coefficient matrix are found by solving:

$$\det\left(\begin{bmatrix} \alpha_{11} - \lambda_i & \alpha_{12} \\ \alpha_{21} & \alpha_{22} - \lambda_i \end{bmatrix}\right) = 0; \tag{31a}$$

$$\begin{bmatrix} \alpha_{11} - \lambda_i & \alpha_{12} \\ \alpha_{21} & \alpha_{22} - \lambda_i \end{bmatrix}\begin{bmatrix} k_{i1} \\ k_{i2} \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}. \tag{31b}$$

The process is analogous for the σ coefficient matrix.

The fundamental solution $\psi_n(t)$ depends on the real and distinct eigenvalues λ_1 and λ_2 found by solving Eqs. (31); and the fundamental solution $\varphi_n(t)$ depends on the likewise derived real and distinct eigenvalues λ_3 and λ_4, as follows:

$$\psi_n(t) = \begin{bmatrix} k_{11}e^{\lambda_1 t} & k_{21}e^{\lambda_2 t} \\ k_{12}e^{\lambda_1 t} & k_{22}e^{\lambda_2 t} \end{bmatrix}, \tag{32a}$$

$$\varphi_n(t) = \begin{bmatrix} k_{31}e^{\lambda_3 t} & k_{41}e^{\lambda_4 t} \\ k_{32}e^{\lambda_3 t} & k_{42}e^{\lambda_4 t} \end{bmatrix}. \tag{32b}$$

Note that while Eqs. (32) are sensitive to shifting of the origin of the time variable t, the functions $\psi_n(t)$ and $\varphi_n(t)$ end up being used only in products with their respective inverses, and these so-called principal matrix solutions are invariant to time translation.

Having found the general solution of the ODE system of Eqs. (29), difference equations can be derived for the predicted level of performance at the onset of each wake period and at the onset of each sleep period. Although these predictions for wake onset do not account for transient effects of sleep inertia (e.g., Dinges, 1990), and the predictions for sleep onset are merely notional (since the person is asleep), they completely describe the model behavior across wake/sleep cycles. They therefore serve as useful anchor points to examine the pattern of cognitive performance changes across days.

Using Eqs. (27) and (30), the difference equations for performance at wake onset, $p_n(t_n)$, and for performance at sleep onset, $q_n(t_n + W_n)$, can be shown to be given by:

$$\begin{bmatrix} p_{n+1}(t_{n+1}) \\ u_{n+1}(t_{n+1}) \end{bmatrix} = \varphi_n(t_n + T_n)\varphi_n^{-1}(t_n + W_n)\psi_n(t_n + W_n)\psi_n^{-1}(t_n)\begin{bmatrix} p_n(t_n) \\ u_n(t_n) \end{bmatrix} + F_n, \tag{33a}$$

$$\begin{bmatrix} q_{n+1}(t_{n+1} + W_{n+1}) \\ v_{n+1}(t_{n+1} + W_{n+1}) \end{bmatrix} = \psi_{n+1}(t_{n+1} + W_{n+1})\psi_{n+1}^{-1}(t_{n+1})\varphi_n(t_n + T_n)\varphi_n^{-1}(t_n + W_n)\begin{bmatrix} q_n(t_n + W_n) \\ v_n(t_n + W_n) \end{bmatrix} + G_n, \tag{33b}$$

$$F_n = \left(\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} - \varphi_n(t_n + T_n)\varphi_n^{-1}(t_n + W_n)\right)\begin{bmatrix} 0 \\ \delta \end{bmatrix} + \tag{33c}$$

$$\int_{t_n+W_n}^{t_n+T_n} \varphi_n(t_n + T_n)\varphi_n^{-1}(s)\begin{bmatrix} \gamma_1(s) \\ \gamma_2(s) \end{bmatrix} ds + \varphi_n(t_n + T_n)\varphi_n^{-1}(t_n + W_n)\int_{t_n}^{t_n+W_n} \psi_n(t_n + W_n)\psi_n^{-1}(s)\begin{bmatrix} \beta_1(s) \\ \beta_2(s) \end{bmatrix} ds.$$

$$G_n = -\left(\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} - \psi_{n+1}(t_{n+1} + W_{n+1})\psi_{n+1}^{-1}(t_{n+1})\right)\begin{bmatrix} 0 \\ \delta \end{bmatrix} + \tag{33d}$$

$$\int_{t_{n+1}}^{t_{n+1}+W_{n+1}} \psi_{n+1}(t_{n+1} + W_{n+1})\psi_{n+1}^{-1}(s)\begin{bmatrix} \beta_1(s) \\ \beta_2(s) \end{bmatrix} ds + \psi_{n+1}(t_{n+1} + W_{n+1})\psi_{n+1}^{-1}(t_{n+1})\int_{t_n+W_n}^{t_n+T_n} \varphi_n(t_n + T_n)\varphi_n^{-1}(s)\begin{bmatrix} \gamma_1(s) \\ \gamma_2(s) \end{bmatrix} ds.$$

Changes in cognitive performance *across* wake/sleep cycles depends entirely on this system of difference equations for performance at the onsets of wakefulness and sleep.

Of particular interest is whether the pattern of changes in cognitive performance across wake/sleep cycles can display a steady state or "fixed point"—that is, whether the performance profile within days can be found to repeat itself across days or across clusters of days when a particular wake/sleep schedule is maintained. This condition of fixed wake duration W and fixed wake/sleep cycle duration T is described by:

$$p_{n+m}(t_{n+m}) = p_n(t_n), \tag{34a}$$

$$q_{n+m}(t_{n+m} + W) = q_n(t_n + W), \tag{34b}$$

where $m = 1, 2, \ldots$ is the number of wake/sleep cycles after which the performance pattern repeats itself. If the oscillation period τ of the non-homogeneities $\beta_1(t)$, $\beta_2(t)$, $\gamma_1(t)$ and $\gamma_2(t)$ equals the wake/sleep cycle duration T, as is the case under conditions of circadian entrainment, then the fixed point performance pattern would be expected to repeat itself every day (i.e., $m = 1$). If $\tau \neq T$, then a beat phenomenon could occur in which the performance pattern repeats itself every m days. Forced desynchrony protocols (e.g., Dijk and Czeisler, 1994) are based on this supposition.

Indeed, for fixed wake duration W and fixed wake/sleep cycle duration T, and assuming that the non-homogeneities oscillate with period $\tau = T$, Eqs. (32), (33c) and (33d) may become repetitive across wake/sleep cycles n. Fixed points $[p(t_n) \;\; u(t_n)]$ and $[q(t_n + W) \;\; v(t_n + W)]$ can be derived by solving Eqs. (33), which results in:

$$\begin{bmatrix} p(t_n) \\ u(t_n) \end{bmatrix} = \left(\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} - \varphi(t_n + T)\varphi^{-1}(t_n + W)\psi(t_n + W)\psi^{-1}(t_n)\right)^{-1} F, \tag{35a}$$

$$\begin{bmatrix} q(t_n + W) \\ v(t_n + W) \end{bmatrix} = \left(\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} - \psi(t_n + W)\psi^{-1}(t_n)\varphi(t_n + T)\varphi^{-1}(t_n + W)\right)^{-1} G. \tag{35b}$$

Because of the matrix inversions embedded in Eqs. (35), fixed points can only exist if:

$$\det\left(\begin{bmatrix}1 & 0\\ 0 & 1\end{bmatrix} - \varphi(t_n+T)\varphi^{-1}(t_n+W)\psi(t_n+W)\psi^{-1}(t_n)\right) \neq 0, \quad \text{and} \tag{36a}$$

$$\det\left(\begin{bmatrix}1 & 0\\ 0 & 1\end{bmatrix} - \psi(t_n+W)\psi^{-1}(t_n)\varphi(t_n+T)\varphi^{-1}(t_n+W)\right) \neq 0. \tag{36b}$$

Below, we examine this condition for a specific case of the model defined by Eqs. (29).

Provided a fixed point is shown to exist, the question arises whether it is stable, that is, whether the model predictions would converge to this fixed point for a repetitive wake/sleep schedule. We can say that the model is asymptotically stable (for $m = 1$) or asymptotically periodic (for $m > 1$) if:

$$\lim_{n\to\infty}\begin{bmatrix}p_{n+m}(t_{n+m})\\ u_{n+m}(t_{n+m})\end{bmatrix} = \begin{bmatrix}p(t_n)\\ u(t_n)\end{bmatrix}, \tag{37a}$$

$$\lim_{n\to\infty}\begin{bmatrix}q_{n+m}(t_{n+m}+W)\\ v_{n+m}(t_{n+m}+W)\end{bmatrix} = \begin{bmatrix}q(t_n+W)\\ v(t_n+W)\end{bmatrix}, \tag{37b}$$

even if the starting values $[p_0(t_0)\ \ u_0(t_0)]$ and $[q_0(t_0)\ \ v_0(t_0)]$ are not already on the fixed point. Because Eqs. (33) are linear in $[p_n(t_n)\ \ u_n(t_n)]$ and $[q_n(t_n + W)\ \ v_n(t_n + W)]$, the stability of fixed points is determined by the eigenvalues of the following matrices:

$$\Psi_n(t_n) = \varphi(t_n)\varphi^{-1}(t_n+W)\psi(t_n+W)\psi^{-1}(t_n), \tag{38a}$$

$$\Phi_n(t_n+W) = \psi(t_n+W)\psi^{-1}(t_n)\varphi(t_n)\varphi^{-1}(t_n+W). \tag{38b}$$

It can be shown (Kelly and Peterson, 2001) that fixed points are asymptotically stable if all eigenvalues Λ_i of the system of Eqs. (33), whether real or complex, are inside the unit circle (i.e., $|\Lambda_i| < 1$). The eigenvalues are found by solving the characteristic equations:

$$\det\left(\Psi_n(t_n) - \Lambda_i\begin{bmatrix}1 & 0\\ 0 & 1\end{bmatrix}\right) = 0, \tag{39a}$$

$$\det\left(\Phi_n(t_n+W) - \Lambda_i\begin{bmatrix}1 & 0\\ 0 & 1\end{bmatrix}\right) = 0. \tag{39b}$$

Inspection of Eqs. (38), the results of which are mirrored, reveals that the eigenvalues derived from Eq. (39a) are identical to those derived from Eq. (39b). Thus, the fixed points $[p(t_n)\ \ u(t_n)]$ and $[q(t_n + W)\ \ v(t_n + W)]$ are either both asymptotically stable (or periodic), or both unstable. We now examine this property for a specific version of the model.

A Model with a Bifurcation

We consider a particular case of the model of Eqs. (29):

$$\begin{bmatrix}\dot{p}_n\\ \dot{u}_n\end{bmatrix} = \begin{bmatrix}\alpha_{11} & \alpha_{12}\\ 0 & \alpha_{22}\end{bmatrix}\begin{bmatrix}p_n\\ u_n\end{bmatrix} + \begin{bmatrix}\beta_1(t)\\ \beta_2(t)\end{bmatrix} \qquad \text{for } t \in [t_n,\, t_n + W_n], \tag{40a}$$

$$\begin{bmatrix} \dot{q}_n \\ \dot{v}_n \end{bmatrix} = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ 0 & \sigma_{22} \end{bmatrix} \begin{bmatrix} q_n \\ v_n \end{bmatrix} + \begin{bmatrix} \gamma_1(t) \\ \gamma_2(t) \end{bmatrix} \qquad \text{for } t \in [t_n + W_n,\, t_n + T_n], \tag{40b}$$

where $\alpha_{11} < 0$ and $\sigma_{11} < 0$, and where $\alpha_{11} \neq \alpha_{22}$ and $\sigma_{11} \neq \sigma_{22}$. The coupling of these equations is given by Eqs. (27). As before, we require that the non-homogeneities $\beta_1(t)$, $\beta_2(t)$, $\gamma_1(t)$ and $\gamma_2(t)$ are bounded, oscillatory functions.

Per Eqs. (31), the (real and distinct) eigenvalues of the α and σ coefficient matrices are: $\lambda_1 = \alpha_{11} < 0$; $\lambda_2 = \alpha_{22}$; $\lambda_3 = \sigma_{11} < 0$; and $\lambda_4 = \sigma_{22}$. Through Eqs. (32), these eigenvalues determine the existence of fixed points as assessed using Eqs. (36). Under conditions of fixed wake duration W and fixed wake/sleep cycle duration T, Eqs. (36) reduce to the following sole inequality: $(1 - e^{\alpha_{11} W} e^{\sigma_{11}(T-W)})(1 - e^{\alpha_{22} W} e^{\sigma_{22}(T-W)}) \neq 0$. If both α parameters and both σ parameters are negative, this inequality is satisfied and thus fixed points exist for all $0 < W \leq T$ (both for performance at wake onset and for performance at sleep onset). If either $\alpha_{22} \geq 0$ or $\sigma_{22} \geq 0$, however, there may be a critical amount of daily wakefulness W_c, with $0 < W_c \leq T$, for which no fixed point exists:

$$W_c = \frac{-\sigma_{22}}{\alpha_{22} - \sigma_{22}} T. \tag{41}$$

To assess the stability of the fixed points when they do exist, we solve Eqs. (39), which results in the following eigenvalues:

$$\Lambda_1 = e^{\alpha_{11} W} e^{\sigma_{11}(T-W)}, \tag{42a}$$

$$\Lambda_2 = e^{\alpha_{22} W} e^{\sigma_{22}(T-W)}. \tag{42b}$$

If all α and σ parameters in Eqs. (42) are negative, then $0 < \Lambda_i < 1$ for both eigenvalues, meaning that the fixed points (which then exist for all $0 < W \leq T$) are always asymptotically stable. Since the difference equation system considered here is linear, this stability is global (i.e., the predictions converge to the fixed point regardless of initial conditions).

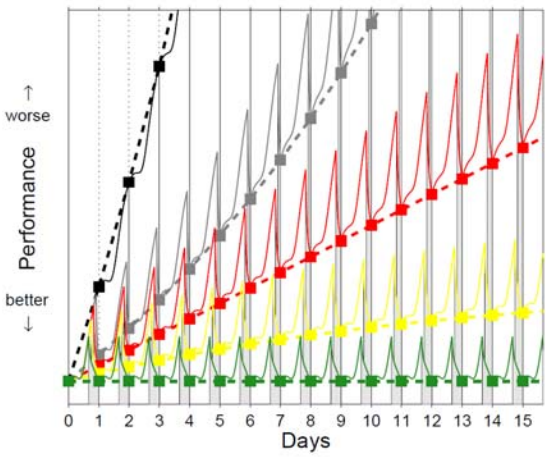

Figure 9: Dynamic behavior of the bifurcating model given by Eqs. (40). The figure shows performance predictions (PVT lapses of attention) at wake onset (boxes) for 16 days ($n = 0, 1, \ldots, 15$) of fixed duration $T = 24$h, assuming a constant period $\tau = 24$h for the non-homogeneities. The thin curves represent the predictions within days using the non-homogeneities given by Eqs. (45)—but the profile of changes across days (dashed lines) as determined by the α and σ coefficient matrices is of primary interest here. Each prediction curve corresponds to a different amount of daily wakefulness: $W = 16$h (green), $W = 18$h (yellow), $W = 20$h (red), $W = 22$h (dark gray), and $W = 24$h (i.e., total sleep deprivation; black). Light gray areas indicate nocturnal sleep periods. In this illustration, the bifurcation point is set to occur at $W_c = 20$h. For daily wake durations below the bifurcation point (green and yellow), the model thus converges to an asymptotically stable fixed point, that is, performance impairment ultimately levels off. For daily wake durations beyond the bifurcation point (gray and black), the model diverges from an unstable fixed point, meaning that performance impairment tends to escalate. At exactly the bifurcation point $W = W_c$ (red), there is no fixed point, resulting in an asymptotically linear build-up of performance impairment across days.

If α_{22} (the key parameter distinguishing the model given by Eqs. (40) from the extended two-process model) is positive, there are three possibilities for Λ_2. In order of increasing amount of sleep loss, these possibilities are:

- For $W < W_c$, we find that $0 < \Lambda_2 < 1$, implying globally asymptotically stable fixed points;
- For $W = W_c$, no fixed point exists (see above);
- For $W > W_c$, we find that $\Lambda_2 > 1$, implying that the fixed points are unstable.

Thus, for $\alpha_{22} > 0$, the model behavior is such that if the amount of wakefulness W in each wake/sleep cycle exceeds a critical threshold W_c, the model flips from a state in which performance predictions converge toward an asymptotically stable fixed point, to a state in which performance predictions diverge away from an unstable fixed point. This qualitative change in dynamic behavior constitutes a bifurcation—see Fig. 9.

It is instructive to study the model behavior when daily wakefulness is kept constant at the bifurcation value: $W = W_c$. Here, the generalized iterative system of Eqs. (33) assumes the following specific form:

$$\begin{bmatrix} p_{n+1}(t_{n+1}) \\ u_{n+1}(t_{n+1}) \end{bmatrix} = \begin{bmatrix} e^{\frac{\alpha_{22}\sigma_{11}-\alpha_{11}\sigma_{22}}{\alpha_{22}-\sigma_{22}}T} & f \\ 0 & 1 \end{bmatrix} \begin{bmatrix} p_n(t_n) \\ u_n(t_n) \end{bmatrix} + F, \tag{43a}$$

$$\begin{bmatrix} q_{n+1}(t_{n+1}+W_c) \\ v_{n+1}(t_{n+1}+W_c) \end{bmatrix} = \begin{bmatrix} e^{\frac{\alpha_{22}\sigma_{11}-\alpha_{11}\sigma_{22}}{\alpha_{22}-\sigma_{22}}T} & g \\ 0 & 1 \end{bmatrix} \begin{bmatrix} q_n(t_n+W_c) \\ v_n(t_n+W_c) \end{bmatrix} + G, \tag{43b}$$

$$f = \frac{\sigma_{12}(e^{\sigma_{11}(T-W_c)} - e^{\sigma_{22}(T-W_c)})e^{\alpha_{22}W_c}}{\sigma_{11}-\sigma_{22}} + \frac{\alpha_{12}(e^{\alpha_{11}W_c} - e^{\alpha_{22}W_c})e^{\sigma_{11}(T-W_c)}}{\alpha_{11}-\alpha_{22}}, \tag{43c}$$

$$g = \frac{\sigma_{12}(e^{\sigma_{11}(T-W_c)} - e^{\sigma_{22}(T-W_c)})e^{\alpha_{11}W_c}}{\sigma_{11}-\sigma_{22}} + \frac{\alpha_{12}(e^{\alpha_{11}W_c} - e^{\alpha_{22}W_c})e^{\sigma_{22}(T-W_c)}}{\alpha_{11}-\alpha_{22}}. \tag{43d}$$

The solution of this system tends to a straight line as $n \to \infty$. The change across days for performance at wake onset and sleep onset is defined, respectively, by slopes M_p and M_q:

$$M_p = \frac{f \cdot F_2}{1 - e^{\frac{\alpha_{22}\sigma_{11}-\alpha_{11}\sigma_{22}}{\alpha_{22}-\sigma_{22}}T}}, \tag{44a}$$

$$M_q = \frac{g \cdot G_2}{1 - e^{\frac{\alpha_{22}\sigma_{11}-\alpha_{11}\sigma_{22}}{\alpha_{22}-\sigma_{22}}T}}, \tag{44b}$$

where F_2 and G_2 are the second element of vectors F and G in Eqs. (33). From Eqs. (44) it follows that the slopes of change across days are not necessarily the same for performance at wake onset and performance at sleep onset.

Model Simulations

To compare the model given by Eqs. (40) to actual performance observations under conditions of sleep loss, we fit it to group-average data of performance lapses on a psychomotor vigilance test (PVT; Dinges and Powell, 1985; Dorrian et al., 2005) from a study of healthy young adults

subjected to chronic sleep restriction or total sleep deprivation—with W = 16h, 18h, 20h, or 24h (Van Dongen et al., 2003). These data are shown in Fig. 8a.

For the non-homogeneities, we make use of the circadian process $c(t)$ defined by Borbély and Achermann (1999), applied to the performance predictions p_n and q_n (but not the asymptotes u_n and v_n):

$$\begin{bmatrix}\beta_1(t)\\ \beta_2(t)\end{bmatrix}=\begin{bmatrix}\gamma\, c(t-\theta)+\mu\\ 0\end{bmatrix} \qquad \text{for } t\in[t_n,\, t_n+W_n], \tag{45a}$$

$$\begin{bmatrix}\gamma_1(t)\\ \gamma_2(t)\end{bmatrix}=\begin{bmatrix}\gamma\, c(t-\theta)+\mu\\ 0\end{bmatrix} \qquad \text{for } t\in[t_n+W_n,\, t_n+T_n]. \tag{45b}$$

Here γ and μ are parameters scaling the circadian process, and θ is a phase parameter shifting it in time. For the initial conditions $[p_0(t_0)\ \ u_0(t_0)]$ we estimate the values corresponding to the fixed point at W = 16h, which characterizes the baseline condition in the study. Further, t_0 = 7.5h (i.e., 07:30), and T and τ are fixed at 24h.

Using least-squares regression, we find the following parameter estimates:

$$\begin{cases}\begin{bmatrix}\alpha_{11} & \alpha_{12}\\ 0 & \alpha_{22}\end{bmatrix}=\begin{bmatrix}-0.0135 & 0.000929\\ 0 & 0.00743\end{bmatrix}\\ \begin{bmatrix}\sigma_{11} & \sigma_{12}\\ 0 & \sigma_{22}\end{bmatrix}=\begin{bmatrix}-2.17 & 0.872\\ 0 & -0.0397\end{bmatrix}\\ \delta=19.8\\ \gamma=5.86\\ \mu=0.472\\ \theta=13.8\\ p_0(t_0)=4.49\\ u_0(t_0)=29.9\end{cases} \tag{46}$$

The resulting PVT performance predictions are shown in Fig. 8d, and the predictions for the total sleep deprivation condition (W = 24h) are explored in more detail in Fig. 10. With the parameter estimates of Eqs. (46), the model explains 72.4% of the variance in the group-average data of Fig. 8a. It fits substantially better to the data than the original two-process model (Fig. 8b, explained variance 22.6%) and the extended two-process model (Fig. 8c, explained variance 38.4%).

Evaluation of Eq. (41) given the parameter estimates in Eqs. (46) indicates that there must be a bifurcation at W_c = 20.2h. That is, the model should flip from a state of convergence to a state of divergence when daily sleep is reduced to less than 3.8h.

This property can be verified by comparing model predictions to the group-average observations of PVT performance in another study of chronic sleep restriction, with W = 15h, 17h, 19h or 21h (Belenky et al., 2003). These data are shown in Fig. 11a. We use the non-homogeneities defined in Eqs. (45) again, set t_0 = 7.0h (i.e., 07:00) in accordance with the study design, and fix all model parameters at their previously estimated values given in Eqs. (46).

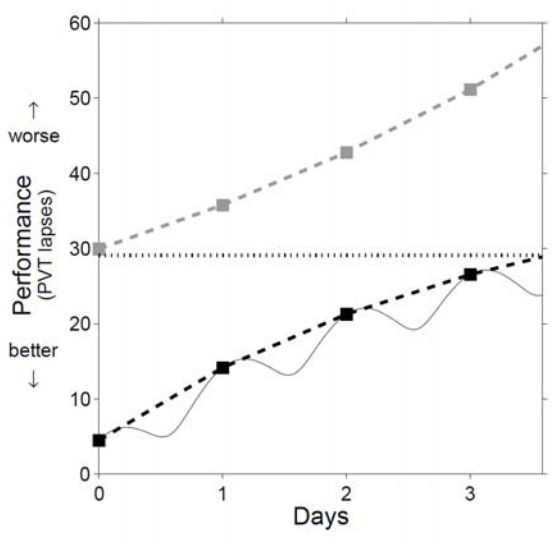

Figure 10: Examination of the performance predictions under conditions of total sleep deprivation. The new model defined by Eqs. (40) and (45) with the parameter estimates given by Eqs. (46) has a bifurcation at $W_c = 20.2$h, implying that predictions for performance in the total sleep deprivation condition (i.e., $W = 24\text{h} > W_c$) of Fig. 8a (top left panel) should exhibit diverging (i.e., escalating) performance impairment across days. However, the actual predictions displayed in Fig. 8d (bottom left panel) would seem to suggest a converging pattern. This can be explained by simultaneously considering the performance predictions p_n (black dashed curve), the fixed point p (dotted horizontal line), and the upper asymptote u_n (gray dashed curve). Since $\alpha_{22} > 0$, the upper asymptote u_n increases exponentially across days. Thus, within waking episodes, performance p_n is increasingly drawn upwards. On the other hand, the fixed point p is located above the initial performance value $p_0(t_0)$. Thus, divergence from the fixed point would entail a drive downwards. Here, the net result is that performance impairment is predicted to increase across days, but in a decelerating manner (cf. Van Dongen et al., 2003). If wakefulness were maintained for additional days, though, the performance predictions would cross the fixed point and then diverge from it upwards, exposing the typical escalating behavior for $W > W_c$ in this model (see the illustration in Fig. 9).

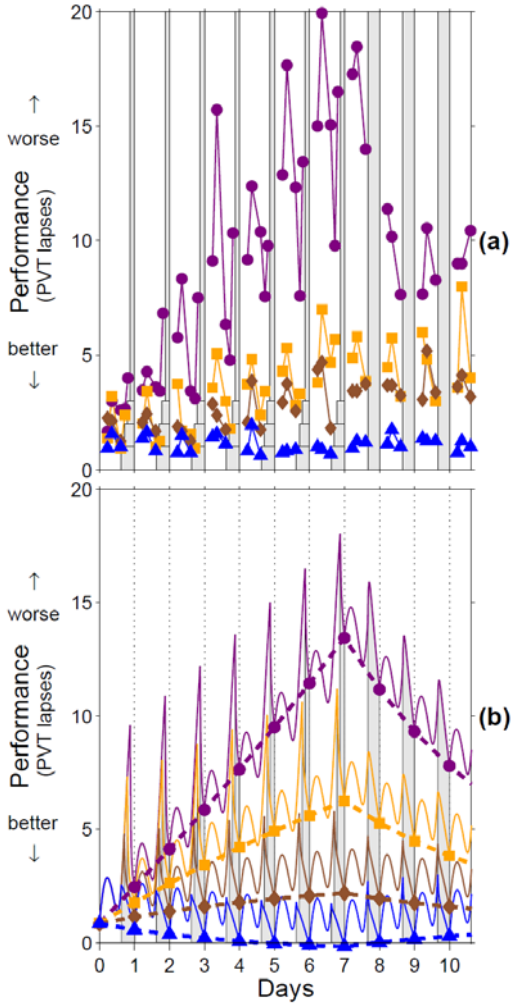

Figure 11: Experimental observations and predictions by our new model for performance impairment. A total of 66 healthy young adults were subjected to one of four laboratory sleep deprivation protocols (Belenky et al., 2003). Each protocol began with several baseline days involving 8h time in bed (TIB), the last of which is labeled here as day 0. Subsequently, the subjects underwent various doses of sleep restriction for 7 consecutive days, followed by 3 days with recovery sleep at 8h TIB. The sleep restriction doses were 3h TIB per day for 13 subjects (blue); 5h TIB per day for 13 subjects (brown); 7h TIB per day for 14 subjects (orange); and 9h TIB per day for 16 subjects (purple). Awakening was scheduled at 07:00 each day. Cognitive performance was tested every day at 09:00, 12:00, 15:00 and 21:00 using the PVT. In the 5h TIB condition an additional test bout occurred at midnight, and in the 3h TIB condition another one took place two hours after midnight.
(a) Observed performance (PVT lapses) for each test bout (dots represent group averages). The first test bout of each waking period is omitted in order to avoid confounds from sleep inertia. Gray bars indicate scheduled sleep periods.
(b) Corresponding performance predictions according to the new model defined by Eqs. (40) and (45). Parameter estimates are fixed at the values of Eqs. (46), as previously estimated with the data in Fig. 8a. Boxes represent predictions at wake onset; thin curves represent predictions within days. The focus here is on changes across days (dashed lines). Note that the model predictions across the 7 days of sleep restriction accurately capture the qualitative change from convergence (i.e., leveling off of performance impairment) in the 9h, 7h and 5h TIB conditions, to divergence (disproportionately rapid escalation of performance impairment) in the 3h TIB condition.

Applying linear scaling to account for any irrelevant differences in absolute performance outcomes (e.g., due to variations in population characteristics or performance testing conditions), we find the scaling factor to be 1.17—suitably close to 1. The corresponding performance predictions are shown in Fig. 11b. They explain 72.2% of the variance in the data, and fit well to the observed performance changes across days.

Note that the $W = 21$h condition shows a divergent profile in both observations and predictions (Figs. 11a and 11b), which is not seen in the $W \leq 19$h conditions in this study. This qualitative difference indicates the presence of a bifurcation. Indeed, on the basis of fitting the model to the data in Fig. 8a, we had predicted that a bifurcation should occur at $W_c = 20.2$h (see above). The goodness-of-fit of our model to the data in Fig. 11a is consistent with this prediction, and provides a first validation of the model.

New Theoretical Predictions

The value of a new model is determined, in part, by any falsifiable new predictions it makes. Here we present two specific predictions that can be tested in future work, and that will have considerable theoretical impact if confirmed. The first new prediction pits the new model defined by Eqs. (40) against the only other quantitative, sleep/wake physiology-based model of the effects of chronic sleep restriction on cognitive performance: the excess wakefulness model (Van Dongen et al., 2003). In that model, performance impairment across days is posited to be proportional to the cumulative amount of wakefulness exceeding a maximum period of stable wakefulness (of ~16h if prior sleep duration exceeds ~4h). This is conceptually distinct from the modeling framework introduced in the present report.

Our first prediction involves the important question of how much sleep is needed to recover from performance impairment induced by prior chronic sleep restriction (e.g., Lamond et al., 2007). The excess wakefulness model would predict that as long as wake duration exceeds the maximum period of stable wakefulness, performance continues to deteriorate. On the contrary, the model defined by Eqs. (40) with the parameter values given by Eqs. (46) would predict that when wake duration is less than the bifurcation point W_c, performance levels should converge to a fixed point, and thus some recovery could occur if wake duration is shorter than what was maintained in the prior days of chronic sleep loss.

As a specific example, consider a scenario involving 5 days of sleep restriction to 4h per day (i.e., $W = 20$h), followed by a day with 6h time for sleep (i.e., $W = 18$h). The opposing model predictions are illustrated in Fig. 12. The excess wakefulness model predicts that performance deteriorates progressively across the 5 days with 4h sleep, and continues to deteriorate—albeit at a slower rate—following the 6h sleep. Our new model also predicts progressive performance degradation across the 5 days with 4h sleep. However, the fixed point for 6h sleep ($W = 18$h) is lower than the level of performance degradation reached after 5 days with 4h sleep. Therefore, the new model forecasts some degree of recovery after the subsequent 6h sleep. This prediction may seem counterintuitive considering that 6h sleep following multiple days with 8h sleep actually leads to performance degradation (Van Dongen et al., 2003). Yet, preliminary evidence from an ongoing laboratory study (Banks et al., 2005) suggests that some recovery does occur

with 6h sleep in this chronic sleep restriction scenario, supporting the new model over the excess wakefulness model.

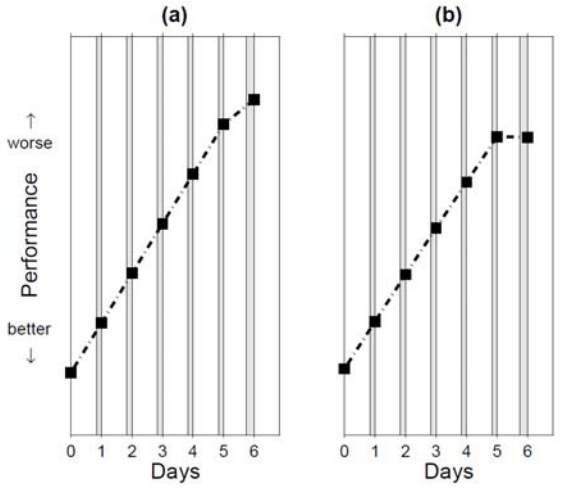

Figure 12: Opposing predictions from two models regarding recovery following chronic sleep restriction. The figure shows performance predictions at wake onset (boxes) for five 24h days with sleep restriction to 4h per day (W = 20h) followed by one 24h day with 6h recovery sleep (W = 18h). Gray areas indicate nocturnal sleep periods. (a) Predictions for performance changes across days according to the excess wakefulness model (Van Dongen et al., 2003). This model predicts that performance deteriorates progressively across the 5 days with 4h sleep, and continues to deteriorate at a slower rate following the 6h sleep period. (b) Predictions for performance changes across days according to the model given by Eqs. (40), (45) and (46). This new model also predicts that performance deteriorates progressively across the 5 days with 4h sleep, but forecasts a modest relative performance improvement following the 6h recovery sleep.

The second new prediction concerns the "recycle" issue, which derives from the question of whether or not there is any carry-over of performance impairment from past sleep restriction when beginning a new period of sleep restriction following limited time for recovery. We consider a laboratory study currently underway (Banks et al., 2007b), which involves a period of 5 days with sleep restriction to 4h per day (i.e., W = 20h), followed by a day with 10h time for recovery sleep (i.e., W = 14h), followed by another period of 5 days with sleep restriction to 4h per day (W = 20h). Initial experimental evidence would suggest that the intervening 10h sleep period should be enough for (near-)complete recovery to baseline performance (Banks et al., 2007a), effectively undoing the impairment incurred by the prior sleep loss. Thus, the performance profile seen during the second 5-day period of sleep restriction might be expected to be similar to that seen during the first 5-day period of sleep restriction.

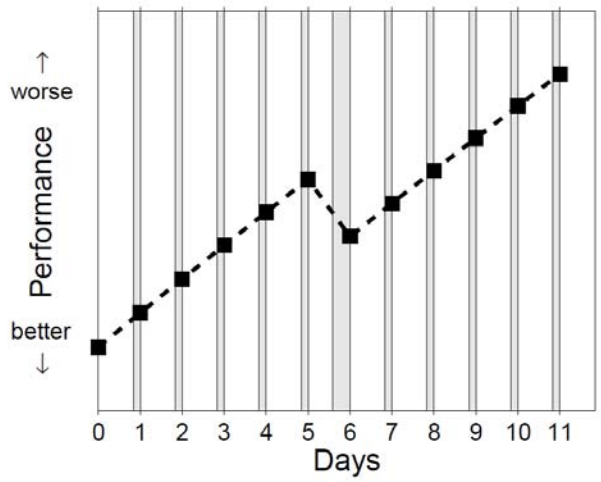

Figure 13: New prediction for rapid recycling after a period of chronic sleep restriction. The figure shows predicted performance at wake onset (boxes) over days, during a period of five 24h days with sleep restriction to 4h per day (W = 20h), followed by one 24h day with 10h recovery sleep (W = 14h), followed by recycling into a second period of five 24h days with sleep restriction to 4h per day (W = 20h). Gray areas indicate nocturnal sleep periods. The performance predictions, derived from the new model given by Eqs. (40), (45) and (46), indicate that the intermittent recovery sleep should confer only a short-lasting benefit—in the second period of sleep restriction, performance is predicted to further deteriorate (while converging towards the asymptotically stable fixed point for W = 20h with a time constant extending far beyond the period displayed in the graph).

The dynamics of the new model, however, would imply that the single 10h recovery sleep should be seen as an intermittent perturbation in an extended series of days with sleep restriction to 4h per day. Thus, the model predicts that the recovery sleep confers only a short-lasting performance improvement, after which performance further deteriorates as it continues to converge to the asymptotically stable fixed point associated with W = 20h. This prediction is illustrated in Fig. 13. Preliminary evidence from the laboratory study examining the scenario at hand suggests that indeed there is substantial carry-over of performance impairment from the first 5-day sleep restriction period to the second (Banks et al., 2007b), providing tentative support for the new model.

Discussion

The regulation of sleep, wakefulness and performance is not fully understood, and involves an array of possible neurobiological mechanisms (e.g., Porkka-Heiskanen et al., 1997; Krueger and Obál, 2003; Fuller et al., 2006). Nonetheless, at the behavioral level, the circadian component has been captured by models with relatively few degrees of freedom (see Indic et al., 2006). We believe the same may be possible for the sleep homeostatic component. Using evidence from laboratory studies with multiple days of sleep loss (Figs. 8a and 11a), we showed that the homeostatic regulation of cognitive performance can be described by means of a system of coupled non-homogeneous first-order ODEs with only a few additional degrees of freedom relative to the homeostatic process postulated in the original two-process model (Borbély and Achermann, 1994, 1999).

Our new model does include an additional component, modulating the homeostatic process across days and weeks, as prompted by findings from chronic sleep restriction experiments demonstrated to be incongruent with the original two-process model (Van Dongen et al., 2003; Van Dongen, 2004). Yet, the model structure introduced here is essentially still composed of a homeostatic process and a circadian process. Conceptually, therefore, the new model remains compatible with the principles of sleep regulation instantiated in the original two-process model (Borbély, 1982). The dynamics of the new model *across* days are principally governed by the α and σ coefficient matrices in the homogeneous part of the differential equations (the homeostatic process), while the changes *within* days are primarily governed by the non-homogeneities (the circadian process). These model components also interact, in agreement with laboratory observations of a nonlinear interaction between the homeostatic and circadian processes (Dijk et al., 1992; Van Dongen and Dinges, 2003a).

Two seminal laboratory studies first highlighted the need for fundamentally new model development beyond the two-process model in order to account for the waking cognitive consequences of chronic sleep loss (Belenky et al., 2003; Van Dongen et al., 2003). However, these two studies previously drew markedly different conclusions about the dynamics of cognitive impairment across days of sleep restriction. In their study with 7 days of systematic sleep restriction, Belenky et al. (2003) reported a plateau of cognitive impairment when sleep was restricted to 7h or 5h per day, as well as incomplete recuperation at the end of the study after 3 days with 8h time in bed for recovery sleep. They hypothesized that chronic sleep loss induces long-lasting adaptive changes in the brain's response to sleep loss, leading to stabilized reduced

performance under conditions of sleep loss at the cost of transiently diminished maximal performance capacity following recovery sleep. In contrast, in their study with 14 days of sleep restriction, Van Dongen et al. (2003) noted that performance continued to degrade when sleep was restricted to 6h or 4h per day, with no evidence of adaptation across the study period.

In the present project, the two data sets (Figs. 8a and 11a) were examined in a single analytical framework. Using PVT performance lapses as a well-validated outcome measure (Dorrian et al., 2005) for both studies, no convincing evidence of an impairment plateau is found in either data set. Yet, our modeling results indicate that stabilization of performance impairment would occur eventually, beyond the duration of the two experiments. Furthermore, the modeling outcomes suggest that several days with recovery sleep would be needed to restore performance to baseline levels. Experiments currently underway (Banks et al., 2007a, 2007b) will shed further light on the time course of post-deprivation recovery.

Our mathematical examination of the dynamics of the new model defined by Eqs. (40) revealed an unanticipated emergent model property: a bifurcation involving a critical amount of wakefulness which, if exceeded, changes the model behavior from a state of convergence toward an asymptotically stable fixed point, to a state of divergence away from an unstable fixed point (as illustrated in Fig. 9). This feature, previously alluded to (Belenky et al., 2003; Van Dongen and Dinges, 2003b) but as yet never explicitly considered, turned out to capture an essential aspect of the nature of performance impairment due to sleep loss. Using data from the chronic sleep restriction and total sleep deprivation experiments documented by Van Dongen et al. (2003) (Fig. 8a), we estimated the critical wakefulness threshold to occur at 20.2h, that is, at 3.8h sleep per 24h. This estimate was supported by data from the chronic sleep restriction study of Belenky et al. (2003), who observed escalating performance impairment when sleep was reduced to just 3h per day (Fig. 11a).

The importance of the bifurcation in the new model implies that other two-process-based models of performance impairment due to chronic sleep loss (Hursh et al., 2004; Johnson et al., 2004; Avinash et al., 2005), which do not possess the bifurcation property, must have a more limited range of applicability than the new model. The excess wakefulness model (Van Dongen et al., 2003), which is based on the fundamentally different conjecture that performance impairment across days is proportional to the cumulative amount of wakefulness in excess of a ration determined by the preceding sleep period, does not a priori have this same limitation of scope (Van Dongen and Dinges, 2003b). However, the excess wakefulness model and the model introduced in the present report make opposite predictions for performance impairment after a period of chronic sleep restriction followed by a limited amount of recovery sleep (Fig. 12). This juxtaposition entails the first of two testable new predictions by which our present model can be validated.

The other new prediction, which has real-life relevance, concerns the longevity of the performance improvement conferred by a single prolonged recovery night (“sleeping in”) preceded and followed by periods of chronic sleep restriction (Fig. 13). Our model predicts that a single recovery night intervening a series of consecutive sleep opportunities of, say, 4h per day constitutes a mere temporary perturbation, after which performance levels continue to decline and converge to an asymptotically stable fixed point. Confirmation of this prediction by

experimental evidence currently being obtained (Banks et al., 2007b) will have significant implications—both theoretically, for our understanding of sleep and performance regulation, and practically, with regard to sleep/wake/work scheduling in operational settings.

The dynamics of the model defined by Eqs. (40) may provide insight into the nature of the underlying neurobiological mechanisms. Conceptually, the model resembles a system of two connected compartments containing interacting substances with time-varying concentrations—one with longer time constants than the other. In this regard, our model could be a mathematical representation of the interaction between a neurotransmitter or neuromodulator and its receptor, with the density of both changing dynamically across time awake and time asleep. However, the model's dynamic behavior and the parameter estimates we obtained (notably the finding that $\alpha_{12} > 0$ and $\sigma_{12} > 0$) point to positive feedback regulation in the system, which is not typical in neurotransmitter/neuromodulator mechanisms. Yet, such a regulatory process may be taking place in the adenosinergic system.

Adenosine is a (by)product of brain energy metabolism (Porkka-Heiskanen et al., 2002), and has been reported to induce sleepiness and impair waking functions, particularly through the cholinergic system in the basal forebrain (Basheer et al., 2000). Hence, the adenosinergic system might be a final pathway in the homeostatic regulation of sleep and waking cognitive functions (Benington and Heller, 1995), and could be the temporal bottleneck that determines the time constants across days in our model. In accordance with the dynamic structure of the model, it has been observed that both extracellular adenosine level and adenosine A_1 receptor density change dynamically in response to sleep loss (Yanik and Radulovacki, 1987; Basheer et al., 2004, 2007; Elmenhorst et al., 2007; Porkka-Heiskanen et al., 2000). Moreover, sleep deprivation-induced increases in extracellular adenosine lead to concomitant increases in A_1 receptor expression, implicating positive feedback regulation (Basheer et al., 2007) in agreement with the model.

Based on these considerations, we propose an explanation for the effects of sleep loss on PVT performance lapses in particular, and on cognitive performance in general, in terms of adenosine binding to receptors that are up- and downregulated dynamically across wake/sleep cycles. We postulate that periods of wakefulness and sleep induce adenosine receptor upregulation and downregulation, respectively, as represented in the model by increases and decreases of the asymptotes u and v. Thus, increased adenosine production during extended wakefulness would cause both increased sleep homeostatic pressure inducing waking cognitive impairment, and receptor upregulation. This would effectively enhance sensitivity to sleep loss on subsequent days (Basheer et al., 2007), which would serve a protective function by restraining further sleep restriction. Should additional sleep loss occur anyway, a shifted physiologic balance would establish as the rates of adenosine receptor upregulation during wakefulness and downregulation during sleep reach a new equilibrium.

However, if wakefulness is extended to more than the critical amount W_c, which we have estimated to be 20.2h, then a physiologic balance may no longer be achievable. This bifurcation, observed in both the model predictions and the experimental observations, may suggest a role for slow wave activity (SWA; ~0.5–4.5 Hz) in the EEG of non-REM sleep. SWA is substantially preserved when sleep duration is reduced down to 4h per day (Brunner et al., 1993; Van Dongen et al., 2003). However, when daily sleep is restricted below approximately 4h, then insufficient

time remains to fully express SWA (see Van Dongen and Dinges, 2003b). This reduction in SWA could be related to the qualitative change in the effects of sleep loss on cognitive performance when sleep duration is reduced to below ~4h per day.

Also, a connection between SWA and adenosinergic mechanisms has been noted. For instance, stimulation of adenosine A_1 receptors affects SWA expression in the same manner as does acute total sleep deprivation (e.g., Benington et al., 1995).

Here, we hypothesize more specifically that SWA is a physiological correlate of adenosine receptor downregulation during sleep. This could explain why homeostatic balance can be achieved when wake duration is no more than approximately 20h per 24h day, as it allows enough time for sleep (at least ~4h) to preserve SWA. However, if daily wakefulness is extended beyond the bifurcation threshold, then despite SWA intensification, the overall expression of SWA is curtailed. The hypothesized adenosine receptor downregulation may thus no longer be sufficient to counter the upregulation during prior wakefulness, and a homeostatic balance may not be reached anymore. As a result, adenosinergic sensitivity to sleep loss would escalate, which in turn would cause the accelerating cognitive impairment that has been observed under such extreme sleep restriction conditions (Belenky et al., 2003; Van Dongen et al., 2003; Van Dongen and Dinges, 2003b).

Our proposed account of the waking cognitive effects of sleep deprivation across days, postulated to be governed by dynamic changes in both adenosine production and adenosine receptor expression, may have noteworthy implications for the role of caffeine as a countermeasure for cognitive impairment due to sleep loss. Caffeine's main mode of action is as an adenosine receptor antagonist (e.g., Biaggioni et al., 1991). As such, in addition to mitigating the cognitive consequences of sleep loss (e.g., Penetar et al., 1993), it might also block the sleep deprivation-mediated adenosine receptor upregulation.

It may thus be hypothesized that regular consumption of moderate amounts of caffeine could help to prevent increasing sensitivity to sleep loss across days of sleep restriction, which would offer a strategy for managing chronic sleep loss. Although this may already be practiced by millions of individuals around the world, how this could be effective had not really been understood mechanistically as yet (and still needs to be confirmed by experimental evidence).

At higher doses, caffeine may interfere with the expression of SWA (e.g., LaJambe et al., 2005), which by extension of our hypothesis would block the sleep-related downregulation of adenosine receptors. Thus, depending on dose, caffeine may also be counterproductive in mitigating the waking cognitive consequences of sleep loss. In that sense, effective use of caffeine as a countermeasure for sleep loss may not be straightforward. In safety-critical scenarios, therefore, it may be advisable to target caffeine administration with the help of a biology-based model of its physiological effects. Such a model could be developed using the new mathematical framework introduced in the present report.

In conclusion, we have put forth a new model formulated in terms of coupled non-homogeneous first-order ODEs, with a dynamic repertoire capturing sleep homeostatic changes in waking cognitive functions across a wide range of wake/sleep schedules. Further work is needed to

integrate our model with a state-of-the-art mathematical model of the circadian component (e.g., Jewett et al., 1999; St. Hilaire, 2007), and to deal with sleep inertia (e.g., Åkerstedt and Folkard, 1997; Jewett and Kronauer, 1999). In addition, trait-like inter-individual differences in vulnerability to sleep loss (Van Dongen et al., 2004a) have yet to be accounted for in our new model. This will be resolved in a follow-up project using modern statistical modeling tools (e.g., Van Dongen et al., 2004b, 2004c), which can also yield improved model parameter estimates (and their standard errors) as well as confidence intervals for the model predictions (see Van Dongen et al., 2007a).

Finally, it should be recognized that the effects of sleep loss on waking cognitive performance depend in part on which aspects of cognitive functioning are considered (Durmer and Dinges, 2005). Our present focus on PVT performance lapses entails a well-validated (Dorrian et al., 2005) but incomplete account of cognitive responses to sleep loss (e.g., see Van Dongen et al., 2004a). Ongoing efforts to connect fatigue and performance models with computational models of cognition (Gunzelmann et al., 2007) represent a promising strategy to address this issue.

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Van Dongen H. P. A., Mott C. G., Huang J.-K., Mollicone D. J., McKenzie F. D., Dinges D. F. Optimization of biomathematical model predictions for cognitive performance impairment in individuals: Accounting for unknown traits and uncertain states in homeostatic and circadian processes. Sleep 30, 1129–1143, 2007a.

Van Dongen H. P. A., Mott C. G., Huang J.-K., Mollicone D. J., McKenzie F. D., Dinges D. F. Confidence intervals for individualized performance models. Sleep 30, 1083, 2007b.

Van Dongen H. P. A., Mullington J. M., Dinges D. F. Circadian phase delay during 88-hour sleep deprivation in dim light: Differences among body temperature, plasma melatonin and plasma cortisol. In: Beersma D. G. M., Van Bemmel A. L., Folgering H., Hofman W. F., Ruigt G. S. F. (Eds.), Sleep-Wake Research in the Netherlands, vol. 8. Dutch Society for Sleep-Wake Research, The Netherlands, 33–36, 1998.

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Van Dongen H. P. A., Vitellaro K. M., Dinges D. F. Individual differences in adult human sleep and wakefulness: Leitmotif for a research agenda. Sleep 28, 479–496, 2005b.

Vonesh E. F., Chinchilli V. M. Linear and Nonlinear Models for the Analysis of Repeated Measurements. Marcel Dekker, New York, 1997.

Yanik G., Radulovacki M. REM sleep deprivation up-regulates adenosine A_1 receptors. Brain Res. 402, 362–364, 1987.

THESIS RESULTING FROM THE PROJECT

Deepa Avinash, M.S. successfully defended her Master's thesis on a portion of the work performed for this project, on 23 August 2005, at Drexel University in Philadelphia, Pennsylvania. The executive summary of her thesis (Avinash, 2005) is as follows. Results are integrated in this final report.

Laboratory experiments have demonstrated that cognitive performance deteriorates due to sleep deprivation and sleep restriction (even if sleep is reduced only a few hours per day on a chronic basis). Various biomathematical models have been developed to predict performance deficits resulting from sleep deprivation. One influential model is the "two-process model" of sleep regulation, which predicts sleep and performance on the basis of two interacting processes. The first process, referred to as the "sleep homeostat" or Process S, which seeks to balance time spent awake and time spent asleep. The second process, known as the "circadian rhythm" or Process C, is driven by the biological clock in the brain, which keeps track of the time of day. The two-process model properly predicts the performance degradation associated with multiple days of total sleep deprivation, but does not accurately predict performance under conditions of chronic partial sleep restriction. The model predicts that chronic sleep restriction leads to relatively little cognitive impairment, whereas laboratory experiments have shown that performance deteriorates progressively across days of sleep restriction. This thesis describes the development of an expansion of the two-process model to accurately predict the performance impairment resulting from chronic sleep loss, by integrating a novel Process U along with the original two processes S and C. The parameters of Process U were estimated using statistical analysis. The parameter assessment was performed by maximum likelihood estimation using nonlinear mixed effects modeling (NONMEM) software. The predictions of the expanded two-process model were compared to psychomotor vigilance task (PVT) performance data from a laboratory experiment involving 14 days of sleep restriction to 4h, 6h or 8h time in bed (TIB) or 3 days of total sleep deprivation. Model predictions were fitted to experimental observations of PVT lapses (reaction times $\geq$ 500ms), as measured every 2h during scheduled wakefulness in the laboratory study. We used the observations from two baseline days (8h TIB per day) and all experimental sleep loss days, for a total of $n = 47$ subjects; as well as data from one recovery day (8h TIB) for the subset of 34 subjects exposed to chronic sleep restriction. The expanded two-process model may prove useful in operational environments faced with sleep loss, such as hospitals, emergency services, and transportation. The model could be used for improved scheduling of work hours for people working in such sleep-deprived environments, or to signal the need to employ fatigue countermeasures to maintain optimal performance. Thus the expanded model may help optimize safety and performance.

PERSONNEL, PUBLICATIONS, TRANSITIONS, AND INVENTIONS

Personnel Supported and/or Associated with the Project

Faculty
Hans P.A. Van Dongen, Ph.D. (PI, supported)
David F. Dinges, Ph.D. (co-investigator, University of Pennsylvania, supported)
Gregory Belenky, M.D. (co-investigator, Washington State University, supported)

Support staff
Claire G. Fox, RPSGT (polysomnographic technologist, University of Pennsylvania, supported)
Michele M. Carlin, B.S. (data manager, University of Pennsylvania, supported)
Oliver Crenshaw (IT specialist, University of Pennsylvania, supported)

Trainees
Deepa Avinash (M.S. graduate trainee, Drexel University, supported)
Amber D. Smith, M.S. (Ph.D. graduate trainee, Washington State University, supported)
Peter McCauley, M.S. (postgraduate trainee, Washington State University, supported)
Darshil D. Amin (undergraduate trainee, University of Pennsylvania, supported)
Blair M. Robinson (undergraduate trainee, University of Pennsylvania, supported)

Associated investigators
Alan D. Genz, Ph.D. (Washington State University, not supported on grant)
Jen-Kuang Huang, Ph.D. (Old Dominion University, not supported on grant)
Leonid V. Kalachev, Ph.D. (University of Montana, not supported on grant)
Frederic D. McKenzie, Ph.D. (Old Dominion University, not supported on grant)
Daniel J. Mollicone, Ph.D. (Pulsar Informatics, Inc., not supported on grant)
Christopher G. Mott, M.S. (Pulsar Informatics, Inc., not supported on grant)
Erik Olofsen, M.S. (Leiden University, the Netherlands, not supported on grant)

Publications

Peer-reviewed papers

G. Gunzelmann, K. A. Gluck, J. Kershner, H. P. A. Van Dongen, D. F. Dinges. Understanding decrements in knowledge access resulting from increased fatigue. In D. S. McNamara, J. G. Trafton (Eds.), Proceedings of the twenty-ninth annual meeting of the Cognitive Science Society. Lawrence Erlbaum Associates, Mahwah, 2007: 329–334.

G. Gunzelmann, L. R Moore Jr., K. A. Gluck, H. P. A. Van Dongen, D. F. Dinges. Individual differences in sustained vigilant attention: Insights from computational cognitive modeling. In D. S. McNamara, J. G. Trafton (Eds.), Proceedings of the thirtieth annual meeting of the Cognitive Science Society. Lawrence Erlbaum Associates, Mahwah, in press.

R. E. Kronauer, G. Gunzelmann, H. P. A. Van Dongen, F. J. Doyle III, E. B. Klerman. Uncovering physiologic mechanisms of circadian rhythms and sleep/wake regulation through mathematical modeling. Journal of Biological Rhythms 2007; 22: 233–245.

D. J. Mollicone, H. P. A. Van Dongen, N. L. Rogers, D. F. Dinges. Response surface mapping of neurobehavioral performance: Testing the feasibility of split sleep schedules for space operations. Acta Astronautica, in press.

H. P. A. Van Dongen, J. A. Caldwell Jr., J. L. Caldwell. Investigating systematic individual differences in sleep-deprived performance on a high-fidelity flight simulator. Behavior Research Methods 2006; 38: 333–343.

H. P. A. Van Dongen, C. G. Mott, J.-K. Huang, D. J. Mollicone, F. D. McKenzie, D. F. Dinges. Optimization of biomathematical model predictions for cognitive performance impairment in individuals: Accounting for unknown traits and uncertain states in homeostatic and circadian processes. Sleep 2007; 30: 1129–1143.

Peer-reviewed conference abstracts

P. McCauley, A. Smith, G. Belenky, H. Van Dongen. Adapting to sleep loss: Dynamic properties of cognitive performance predictions based on the two-process model. Sleep 2007; 30: A123.

A. D. Smith, A. C. Genz, G. Belenky, H. Van Dongen. An efficient procedure for finding the 95% confidence interval of performance predictions based on the Two-Process Model. Sleep, in press.

A. Smith, P. McCauley, G. Belenky, H. Van Dongen. Efficient computational procedure for individualization of sleep/wake model parameters. Sleep 2007; 30: A352.

H. P. A. Van Dongen, D. Avinash, B. M. Robinson, D. F. Dinges, M. M. Mallis. Development of an Astronaut Scheduling Assistant. Habitation 2006; 10: 210–211.

H. Van Dongen, C. Mott, J. Huang, D. Mollicone, F. McKenzie, D. Dinges. Biomathematical fatigue modeling: Individualized prediction of cognitive performance. Sleep 2007; 30: A149.

H. Van Dongen, C. Mott, J.-K. Huang, D. J. Mollicone, F. McKenzie, D. F. Dinges. Individualized biomathematical modeling of cognitive performance impairment. Sleep and Biological Rhythms 2007; 5: A36.

Miscellaneous

D. Avinash. Modeling performance impairment due to chronic sleep restriction. Master's thesis. Drexel University, Philadelphia, 2005.

D. Avinash, C. P. Crudele, D. D. Amin, B. M. Robinson, D. F. Dinges, H. P. A. Van Dongen. Parameter estimation for a biomathematical model of psychomotor vigilance performance under laboratory conditions of chronic sleep restriction. Sleep-Wake Research in the Netherlands, 2005; 16: 39–42.

H. P. A. Van Dongen, C. G. Mott, J.-K. Huang, D. J. Mollicone, F. D. McKenzie, D. F. Dinges. Confidence intervals for individualized performance models. Sleep 2007; 30: 1083.

Interactions and Transitions

Participation/presentations at meetings, conferences, seminars, etc.

March 2005 (Van Dongen): Lecture "Investigating the neurobehavioral consequences of sleep deprivation," Washington State University: Pullman, Washington.

May 2005 (Van Dongen): Lecture "Mathematical models of neurobehavioral performance changes over time: Challenges and potential for use in scheduling tools," Aerospace Medical Association 76th Annual Scientific Meeting; Kansas City, Missouri.

June 2005 (Van Dongen): Lecture "Modeling human cognitive performance with the two-process model and beyond," American Professional Sleep Societies 19th Annual Meeting; Denver, Colorado.
June 2005 (Van Dongen): Lecture "Sleep loss: Individual differences and effects on routine life," 10th Annual Trainee Symposium, American Professional Sleep Societies 19th Annual Meeting; Denver, Colorado.
September 2005 (Van Dongen): Keynote lecture "Sleep loss and circadian stressors in shiftwork: On inter-individual differences," 17th International Symposium on Shiftwork and Working Time; Hoofddorp, The Netherlands.
September 2005 (Van Dongen): Lecture "Theoretical and mathematical predictions of the two-process model relative to sleep debt and excess wakefulness," World Federation of Sleep Research and Sleep Medicine Societies Conference; New Delhi, India.
November 2005 (Van Dongen): Program committee member for the "2005 Sleep and Circadian DataBlitz," Society for Neuroscience Annual Meeting; Washington, D.C.
January 2006 (Van Dongen): Lecture "Managing sleep to sustain performance," Washington State University; Spokane, Washington.
February 2006 (Van Dongen): Lecture "Consequences of insufficient sleep," in the Advanced Sleep Medicine Course; La Jolla, California.
April 2006 (Van Dongen): Lecture "Inter-individual differences in cognitive impairment from sleep loss," Washington State University; Pullman, Washington.
May 2006 (Belenky): Lecture "Managing sleep to sustain performance," Boeing Flight Operations Symposium 2006; Seattle, Washington.
June 2006 (Van Dongen): Lecture "Sleep, sleep deprivation, cognitive impairment & inter-individual differences," in the Advances in Sleep Medicine Course: Moving the Frontier Forward; Salt Lake City, Utah.
June 2006 (Van Dongen): Lecture "Measuring cognitive performance during sleep deprivation—catching the brain asleep," in the postgraduate course What Is It That Sleeps? Salt Lake City, Utah.
July 2006 (Van Dongen): Lecture "Managing sleep to sustain performance," Airline Pilots Association Air Safety Forum; Washington, D.C.
August 2006 (Van Dongen): Lecture "Modeling individual differences," Joint SIAM-SMB Conference on the Life Sciences; Raleigh, North Carolina.
September 2006 (Van Dongen): Organizer of the symposium "Inter-individual differences in sleep and sleep regulation: states and traits," Eighteenth Congress of the European Sleep Research Society; Innsbruck, Austria.
September 2006 (Van Dongen): Lecture "Trait and state individual differences in sleep structure," Eighteenth Congress of the European Sleep Research Society; Innsbruck, Austria.
September 2006 (Van Dongen): Lecture "Individual differences in sleep and sleep deprivation," Max Planck Institute of Psychiatry; Munich, Germany.
October 2006 (Van Dongen): Co-organizers of the workshop "New approaches to modeling sleep/wake dynamics and cognitive performance," Mathematical Biosciences Institute, Ohio State University; Columbus, Ohio.
October 2006 (Van Dongen): Lecture "Sleep and sleep deprivation: trait inter-individual differences," University of Chicago; Chicago, Illinois.
November 2006 (Van Dongen): Lecture "Cognitive impairment from sleep loss: individual differences and prediction," Washington State University; Spokane, Washington.

November 2006 (Van Dongen): Lecture "Sleep, sleep deprivation, and cognitive performance," Idaho Sleep Disorders Association 2006 Meeting; Coeur d'Alene, Idaho.
November 2006 (Van Dongen, Belenky): Organization of the international symposium "Sleeping, waking, working," Sleep and Performance Research Center, Washington State University; Spokane, Washington.
March 2007 (Smith): Lecture "Predicting performance impairment under conditions of sleep deprivation: Individualization and confidence intervals," Eastern Washington University; Cheney, Washington.
March 2007 (Van Dongen): Lecture "Sleep and sleep deprivation," Spokane Chapter of the National Rehabilitation Association; Spokane, Washington.
May 2007 (Van Dongen, Belenky): Lecture "Sleep deprivation," Naval Postgraduate School; Monterey, California.
May 2007 (Van Dongen): Lecture "Neurobiology and chronobiology of sleep," American Thoracic Society 2007 Conference; San Francisco, California.
June 2007 (Van Dongen): Organization of the symposium "Individual differences in sleep: basic research and clinical relevance," SLEEP 2007 Conference; Minneapolis, Minnesota.
June 2007 (Van Dongen): Lecture "Trait individual differences in the sleep structure of healthy young adults," SLEEP 2007 Conference; Minneapolis, Minnesota.
June 2007 (Van Dongen): Meet the Professor session "Cumulative sleep loss: consequences for wakefulness and sleep," SLEEP 2007 Conference; Minneapolis, Minnesota.
July 2007 (Van Dongen): Briefing on "Sleep deprivation, cognitive performance, and biomathematical modeling," JASON 2007 Summer Study; La Jolla, California.
September 2007 (Van Dongen): Lecture "Individual differences in neurobehavioral impairment from sleep loss," WorldSleep07; Cairns, Australia.
September 2007 (Van Dongen): Lecture :Status and perspectives of the 2-process model: Neurobehavioral functions," International Symposium on 25 Years with the Two-Process Model of Sleep Regulation; Ittingen, Switzerland.
October 2007 (Van Dongen): Lecture "Sleep deprivation and circadian rhythms," Washington State Department of Services for the Blind; Tacoma, Washington.
November 2007 (Van Dongen): Lecture "Fatigue and performance models in 24-hour operations: Potential and challenges," National Center for Intermodal Transportation; Washington, D.C.
November 2007 (Van Dongen): Lecture "Cognitive performance impairment: Contribution of homeostatic, circadian, and individual variability factors," University of Surrey; Guildford, United Kingdom.
February 2008 (Van Dongen): Lecture "Bayesian forecasting for predicting individual performance: Foundational information," Individual Differences Workshop; Baltimore, Maryland.

Consultative and advisory functions to other laboratories and agencies

January 2005–present (Van Dongen): Member of steering committee for Core Capability in Fatigue and Performance Modeling and Interventions Research, Military Operational Medicine Research Program, Walter Reed Army Institute of Research; Washington, D.C.
March 2005–present (Van Dongen): Member of Editorial Advisory Board, *Journal of Sleep Research*.

April 2005–present (Van Dongen): Consultation for NIH K23 Career Development Award of Dr. Peter Franzen, Ph.D., University of Pittsburgh School of Medicine; Pittsburgh, Pennsylvania.
June 2005–March 2006 (Van Dongen): Consultation on individual differences modeling to Dr. Adam Fletcher, Walter Reed Army Institute of Research; Washington, D.C.
July 2005 (Van Dongen): Academic liaison for pharmacologic countermeasures panel at military operational medicine workshop "Cognitive performance: Force multiplication through human-in-the-loop augmentation," U.S. Army Medical Research and Materiel Command & Defense Advanced Research Projects Agency; Las Vegas, Nevada.
October 2005 (Van Dongen): Member of National Institutes of Health program project grant review panel; Washington, D.C.
November 2005 (Belenky): Consultation on fatigue risk management to Union Pacific Railroad; Omaha, Nebraska.
January 2006 (Belenky): Consultation on managing sleep to sustain performance to U.S. Air Force human factors researchers; Spokane, Washington.
June 2006–present (Van Dongen): Associate Editor, journal *SLEEP*.
September 2006 (Belenky): Consultation on fatigue risk management to United Airlines; Denver, Colorado.
September 2006–March 2008 (Van Dongen): Member of dissertation committee for Daniel Mollicone, B.S., Drexel University; Philadelphia, Pennsylvania.
April 2007–present (Van Dongen): Member of Editorial Board, *The Open Sleep Journal*.
February 2008–present (Van Dongen): Member of advisory group for Warfighter Rapid Awareness Processing Technology program, Archinoetics, LLC; Honolulu, Hawaii.

Transitions

- We transitioned the Bayesian forecasting framework developed as part of this project to help industry develop a state/trait optimization tool deployable by the military for the prediction of cognitive performance in the face of both unknown individual traits and uncertain prior states (key individuals involved: Daniel Mollicone, Ph.D. and Christopher Mott, M.S. of Pulsar Informatics, Inc.).
- We transitioned an earlier version of the chronic modulating process developed as part of this project to the Institute of Experimental Psychiatry in Philadelphia, Pennsylvania, so as to contribute to the development of an Astronaut Scheduling Assistant for NASA (key individuals involved: Melissa Mallis, Ph.D. and John Caldwell, Ph.D. of the Fatigue Countermeasures Group at NASA Ames Research Center).

New Discoveries, Inventions, or Patent Disclosures

A provisional patent application for individualized performance prediction by means of state/trait optimization has been submitted. This application covers a range of individualization algorithms developed in a project initiated after and building on the present project, and funded through other mechanisms (USAMRMC awards W81XWH-04-1-0923 and W81XWH-05-C-0155). The provisional patent application also covers the Bayesian forecasting procedure outlined in this report, as applied to individualized prediction of fatigue and performance, owing to the fact that the other individualization algorithms fundamentally employ the same mathematical and statistical principles.