

Individualized Management of Fatigue and Cognitive Performance Impairment Through Biomathematical Modeling

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ABSTRACT

In this work, we present a method for developing individualized biomathematical models for predicting cognitive performance impairment of individuals subjected to total sleep loss. The proposed method uses the two-process model of sleep regulation as the underlying parametric model, whose parameters are systematically customized for an individual by optimally combining the performance information obtained from the individual's performance measurements with a priori performance information using a Bayesian framework. As a result, the models incrementally account for an individual's uncertain initial state and unknown trait characteristics as each new performance measurement from the individual becomes available, yielding improved performance predictions. Additionally, the proposed method enables the analytical computation of statistically based measures of reliability of the model predictions in the form of prediction intervals.

Results using data from subjects who participated in an 82-h total sleep loss laboratory study showed that the proposed method yielded individualized predictions that were up to 43% more accurate than group-average model predictions and better captured the circadian and homeostatic variations in the performance data.

1.0 INTRODUCTION

An effective strategy to better manage the detrimental effects of sleep loss on Soldier alertness and cognitive performance is to use biomathematical models. Biomathematical models can be used to forecast performance impairment levels, which can help in planning improved sleep/wake schedules and optimize timing and dosing of fatigue countermeasures to attain peak performance at the desired times of the day. As a result, there is a growing need to develop more accurate biomathematical models that better characterize an individual's level of fatigue and performance impairment.

In 2002, the U.S. Department of Defense (DoD) sponsored a Fatigue and Performance Modeling Workshop, which compared and contrasted the fatigue and performance modeling capabilities available at that time [1-3]. The workshop identified a number of capability gaps and found that, without exception, the existing biomathematical models of performance used the two-process model of sleep regulation [4, 5] as their underlying parametric modeling platform. One capability gap observed across all approaches was that the models were limited to the prediction of group, or population, averages, rather than accounting for and being customizable to an individual's cognitive performance variabilities. This

modeling strategy contradicts well-established findings that indicate significant and systematic differences in performance degradation due to sleep loss among individuals [6-9]. Hence, even if a group-average model could accurately predict mean-group performance, such a model would be of limited benefit without knowing how this translates into predictions at an individual level [10]. Another ubiquitous capability gap was the inability of the models to provide statistically based measures of reliability of the model predictions [11].

In this work, we present a biomathematical model of fatigue and performance impairment that addresses these two shortcomings of existing biomathematical models of performance impairment. First, it accounts for inter-individual variability in performance impairment, resulting in performance predictions of sleep-deprived individuals that are more accurate than those obtained with group-average models. Second, for the first time, the current model directly provides analytical expressions for computing statistically based error bounds around the model predictions in the form of prediction intervals (PIs).

We evaluated the proposed method on data consisting of psychomotor vigilance test (PVT) lapses obtained from a laboratory study of individuals subjected to 82 h of total sleep loss. The laboratory data allowed us to test the new approach under the context of inter- and intra-individual variability encountered in actual performance data and compare between individualized and group-averaged model predictions. In particular, we tested the proposed approach under two prediction mechanisms, where at each time step we used the most recent model-parameter estimates to: 1) make point predictions 10 h ahead and 2) make predictions over the next 24 h. The results show that the proposed method yields individualized predictions that are consistently more accurate than those of the group-average model, where the accuracy was measured in terms of the root mean squared error (RMSE).

2.0 METHODS

Here, we describe a recently developed method that uses the two-process model of sleep regulation as the underlying parametric modeling framework for predicting individualized performance impairment due to total sleep loss [12, 13]. Accordingly, to adapt the parameters and customize a model for a particular individual, we used a Bayesian approach, which combines performance information obtained from the individual's available performance measurements with the individual's *a priori* performance information. The *a priori* performance information was obtained from performance data generated from the two-process model, with its parameters set to *a-priori*-estimated values [13]. By transforming the entailing nonlinear programming problem (NLP) of finding the optimal estimates of the model parameters into a series of linear optimization problems [12], we guaranteed unique estimates of the model parameters. As each new performance measurement became available, it was augmented to the existing performance measurements and together used to adapt the model parameters for that individual. Based on the most recent parameter estimates, we made predictions according to a chosen prediction horizon. Using the linear representation of the two-process model [12], we reformulated it into an equivalent autoregressive (AR) model, which readily provides analytical expressions for computing measures of reliability of the model predictions in the form of PIs [14].

2.1 Two-Process Model of Sleep Regulation

The two-process model of sleep regulation consists of two separate processes [4]: process S (sleep homeostasis), which is dependent on sleep/wake history, increases exponentially with wake time and decreases exponentially with sleep/recovery time to a basal value [5], whose rates of increase/decrease are individual specific and have unknown values; and process C (circadian), which is independent of

sleep/wake history and represents a self-sustaining oscillator with a 24-h period [15]. The equations comprising the two-process model at discrete sampling time index k can be expressed as [5, 16]

$$S(k) = 1 - \exp(-T_s / \tau_r) [1 - S(k-1)], \text{ during wakefulness,} \quad (1)$$

$$S(k) = \exp(-T_s / \tau_d) [S(k-1)], \text{ during sleep, and} \quad (2)$$

$$C(k) = \sum_{i=1}^5 a_i \sin\left(\frac{i2\pi}{\tau} ((k-1)T_s + \phi)\right), \quad (3)$$

where $S(k)$ denotes the value of the sleep homeostat at time k , usually scaled between 0 and 1 [16]; $C(k)$ denotes a five-harmonic sinusoidal equation that approximates the circadian oscillator under entrained conditions [17]; T_s represents the sampling period; τ_r and τ_d represent the time constants of process S during wakefulness and sleep, respectively; τ denotes the time period of the circadian oscillator (~ 24 h); a_i , where $i = 1, \dots, 5$, represents the amplitude of the five harmonics of the circadian process ($a_1 = 0.97$, $a_2 = 0.22$, $a_3 = 0.07$, $a_4 = 0.03$, and $a_5 = 0.001$); and ϕ denotes the initial circadian phase [15].

2.2 Individual-specific Biomathematical Model Development

We proposed that the temporal pattern of performance impairment can be represented as the additive interaction of processes S and C . Mathematically, performance $P(k)$ at some discrete time k was expressed as

$$P(k) = \alpha S(k) + \beta C(k), \quad (4)$$

where α and β denote real-valued positive parameters that control the relative effect of the two processes on performance. For total sleep deprivation, Eq. (4) can be rewritten as

$$P(k) = \alpha - \alpha S(0) \gamma^{k-1} + \sum_{i=1}^5 \bar{a}_i \sin[i\omega((k-1)T_s + \phi)], \quad (5)$$

where $\gamma = \exp(-\rho T_s)$, $\rho = 1/\tau_r$, $\omega = 2\pi/\tau$, $\bar{a}_i = \beta a_i$. To individualize the biomathematical model in Eq. (5), we estimated the model parameters using previous performance measurements collected from the individual we wish to predict along with *a priori* performance information. Such a Bayesian method allowed us to make predictions as soon as the first performance measurement became available and provided a theoretical approach to optimally balance prior information about an individual against recent performance measurements. As additional measurements became available, the proposed approach increased its trust in the measurements, deemphasizing the prior information, the rate of which became faster or slower as the amount of noise in the measurements decreased or increased, respectively.

The key challenge, however, is to correctly estimate the five unknown model parameters in Eq. (5), α , β , γ , $S(0)$, and ϕ , within the context of the Bayesian method. Figure 1 provides two possibilities. Figure 1, left, shows a conventional approach, which results in a NLP problem whose solution for model parameters may be suboptimal, i.e., may result in a local minimum [18]. Conversely, Fig. 1, right, shows our alternative approach, where instead of directly solving the nonlinear two-process model

representation in Eq. (5), we transformed it into a series of three linear optimization problems, whose solution, if it exists, is guaranteed to be unique [12]. Mathematically, to solve for one of the parameters, γ , the second approach was expressed as a two-step constrained linear least squares (LS) problem

$$\arg \min_{0 \leq \gamma < 1} \left\{ \arg \min_{\mathbf{P}} \left[\|\mathbf{P} - \mathbf{y}\|_2^2 + \mu^2 \|\tilde{\mathbf{P}} - \tilde{\mathbf{y}}\|_2^2 + \lambda^2 \|\mathbf{L}_\gamma \mathbf{P}\|_2^2 \right] \right\}, \quad (6)$$

where \mathbf{y} denotes the $N \times 1$ vector of performance measurements $y(k)$; $\tilde{\mathbf{y}}$ denotes the $M \times 1$ vector of prior performance data $\tilde{y}(k)$; μ^2 and λ^2 are positive real numbers; and \mathbf{P} represents the $(N + M) \times 1$ vector of the performance fit $\bar{P}(k)$, with $k = 1-M, 2-M, \dots, N$, whose first M elements are represented by $\tilde{\mathbf{P}}$ and the remaining N elements are represented by \mathbf{P} (see Ref. 12 for additional information). The prior performance data $\tilde{\mathbf{y}}$ was generated from the two-process model in Eq. (5), with its parameters set to *a priori* values, reflective of those of an “average” individual.

Once the optimal γ was obtained by solving Eq. (6), we obtained the other four parameters by solving the associated constrained LS problems (see Refs. 12 and 13 for additional information). Based on the most recent parameter estimate obtained by solving Eq. (6) and related equations, we made predictions for a chosen prediction horizon, and as soon as a new performance measurement became available we updated \mathbf{y} and repeated the process to adjust the five model parameters.

Figure 1: Two potential approaches to estimate the five parameters of the two-process model for a specific individual based on performance measurements from that individual. Left: conventional approach; right: our alternative approach. See the text for descriptions of the parameters.

We obtained analytical expressions for computing PIs around the model predictions using the linear representation of the two-process model in Eq. (5). This was achieved by using the property that $P(k)$ in

Eq. (5) can be considered as a 12th-order AR process [13], in which, at any time k , $P(k)$ is expressed as a linear combination of previous measurements [14, 19], such that

$$P(k) = \sum_{i=1}^{12} b_i P(k-i), \quad (7)$$

where b_i (where $i = 1, \dots, 12$) denotes the AR model coefficients (see Ref. 12, Appendix B for additional information). Finally, by using the analytical expression to compute statistically based error bounds for AR model predictions [14], we obtained the following expression for computing PIs with a coverage probability of $100(1-\theta)\%$

$$PI_{100(1-\theta)\%}(k) = P(k) \pm Z_{\theta/2} \sqrt{\mathbf{b}\Sigma\mathbf{b}^T + \hat{\sigma}^2}, \quad (8)$$

where θ represents the significance level; $Z_{\theta/2}$ represents the percentage point of a standard normal distribution with a proportion $\theta/2$ above it; \mathbf{b} denotes the 1×12 vector of coefficients b_i (with $i = 1, \dots, 12$); $P(k)$ denotes the performance prediction at time k given previous measurements $y(k-1)$, $y(k-2)$, \dots ; Σ denotes the covariance matrix of $\bar{P}(k-1), \dots, \bar{P}(k-12)$ obtained by solving Eq. (6); and $\hat{\sigma}^2$ denotes the user-provided noise-level estimate of the performance measurements y (see Ref. 12 for additional information).

3.0 RESULTS

We used data collected from a laboratory study in which 48 healthy adults were kept continuously awake for 85 h to determine the effects of fatigue countermeasures on performance sustenance during prolonged sleep loss [20]. Here, we chose a subset of 11 subjects who were not administered fatigue countermeasures, and for whom PVT measures were collected every 2 h for a total of 42 measurements. Figure 2 shows the mean performance profile (solid circles) and the standard deviation of the 11 subjects over the 82 h of PVT data collection along with group-average model predictions (solid lines).

The profile of the mean group PVT lapses shows a trend that supported the two-process model framework, combining homeostatic and circadian variations with time awake. As previously observed, the inter-individual PVT lapse variations increased over time [12]. Figure 2 also shows that the group-average model predictions did not accurately forecast the performance profile of the group.

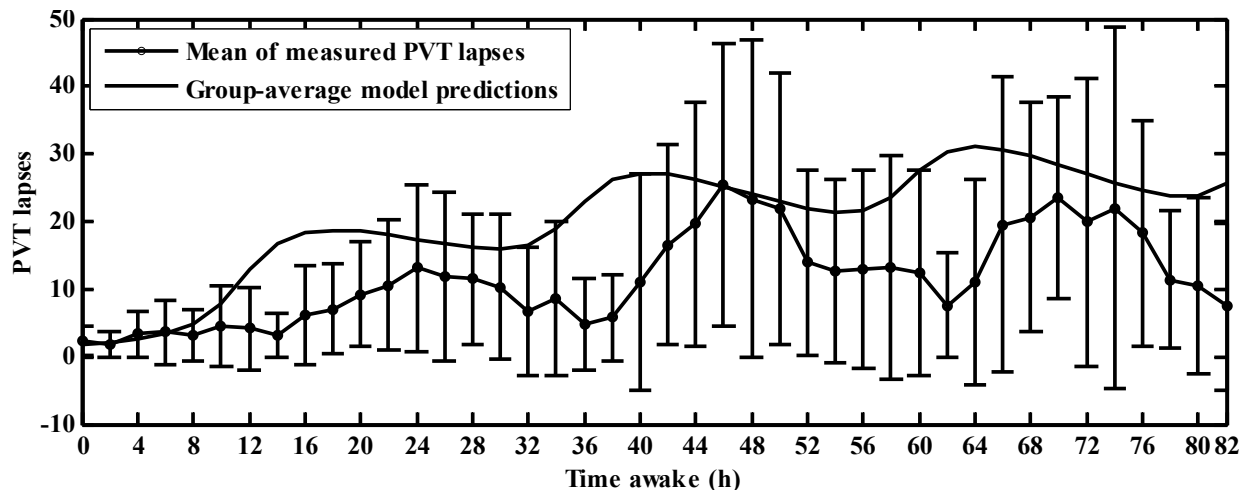


Figure 2: Mean and standard deviation of psychomotor vigilance task (PVT) lapse measurements collected every 2 h for 11 individuals during 82 h of total sleep loss. The solid line shows the performance predictions obtained with a group-average model.

We evaluated the prediction capability of the proposed approach under two predictions mechanisms, where, based on the most recent parameter estimates, we made: 1) point predictions 10 h ahead and 2) predictions up to 24 h ahead. For illustration purposes, we selected 3 of the 11 individuals in the study, each representing one of three different sleep-loss phenotypes: relatively vulnerable to sleep loss, relatively average sensitivity to sleep loss, and relatively resilient to sleep loss. In each simulation, we set the *a priori* values of the five parameters in Eq. (5) to those used by Rajaraman et al. [13] and used the equation to generate prior performance data. These same parameters were used for the group-average model predictions in all simulations. In the simulations, we set the noise level estimate $\hat{\sigma}^2$ in Eq. (8) to 77.60, representing a typical noise level observed in PVT lapse data [21].

Figure 3 shows the measured PVT lapses (solid circles) for the average (*top*), vulnerable (*middle*), and resilient (*bottom*) subjects along with the group-averaged model predictions (solid lines) and the 10-h-ahead individualized predictions (dashed lines) and their corresponding 95% PIs (dotted lines). We used the RMSE, defined as the squared root of the mean of the square of the differences between predicted and measured PVT lapses, as a metric to quantify the accuracy of the predictions (the smaller the RMSE, the better is the resulting prediction) [14]. For the 10-h-ahead predictions, the RMSEs suggested that the individualized predictions were up to 43% more accurate than the group-averaged model predictions. Initially, the individualized predictions for all three individuals were close to the group-averaged predictions, as the Bayesian approach placed more trust in the *a priori* performance information (i.e., the group-average model) compared with the individual's measurements. However, as more of the individual's measurements became available, the individualized predictions were closer to the performance data and captured its circadian and homeostatic variation better than the group-averaged model predictions. Moreover, the corresponding analytically computed 95% PIs almost entirely covered the future performance measurements, reflecting the accuracy of our method for computing reliability of the model predictions.

Figure 4 shows the individualized predictions up to 24 h ahead for the average (*left*), vulnerable (*middle*), and resilient (*right*) subjects in snapshots taken at 6-h intervals. The first snapshot (Fig. 4, *top* row) was taken after collecting the 12th measurement (i.e., 22 h of time awake). Thereafter, the following snapshots were taken after every 6 h, with the final snapshot (Fig. 4, *bottom* row) taken after 58 h of time awake.

The results indicated that initially, when only a few performance measurements (solid circles) were available for model individualization, the individualized predictions (solid lines) up to 24 h head did not accurately capture the performance trend in the future measurements (solid squares). However, as more PVT lapse measurements became available and the model parameters were better customized to each subject (after ~34 h), the individualized predictions better captured the circadian and homeostatic variations in the future performance data for each of the individuals.

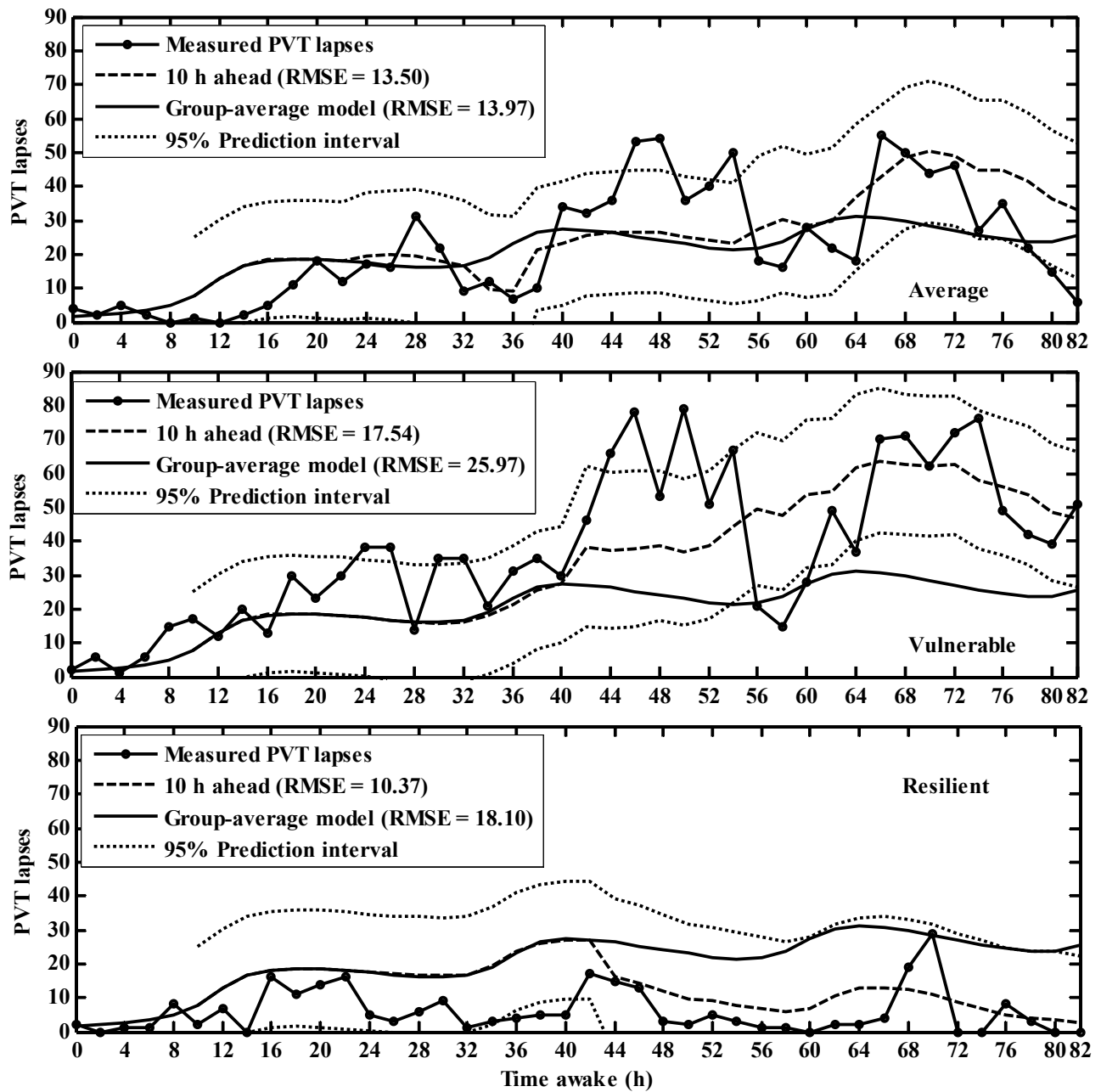


Figure 3: Individualized model predictions for three subjects with different sleep-loss phenotypes [average sensitivity to sleep loss (*top*), vulnerable to sleep loss (*middle*), and resilient to sleep loss (*bottom*)]. The solid circles in each panel represent the measured psychomotor vigilance task (PVT) lapses, which were measured every 2 h. The dashed lines represent the 10-h-ahead predictions, whereas the dotted lines

represent the corresponding analytically computed 95% prediction intervals. The solid line in each panel represents group-average model predictions. The smaller the root mean squared error (RMSE), the better is the prediction.

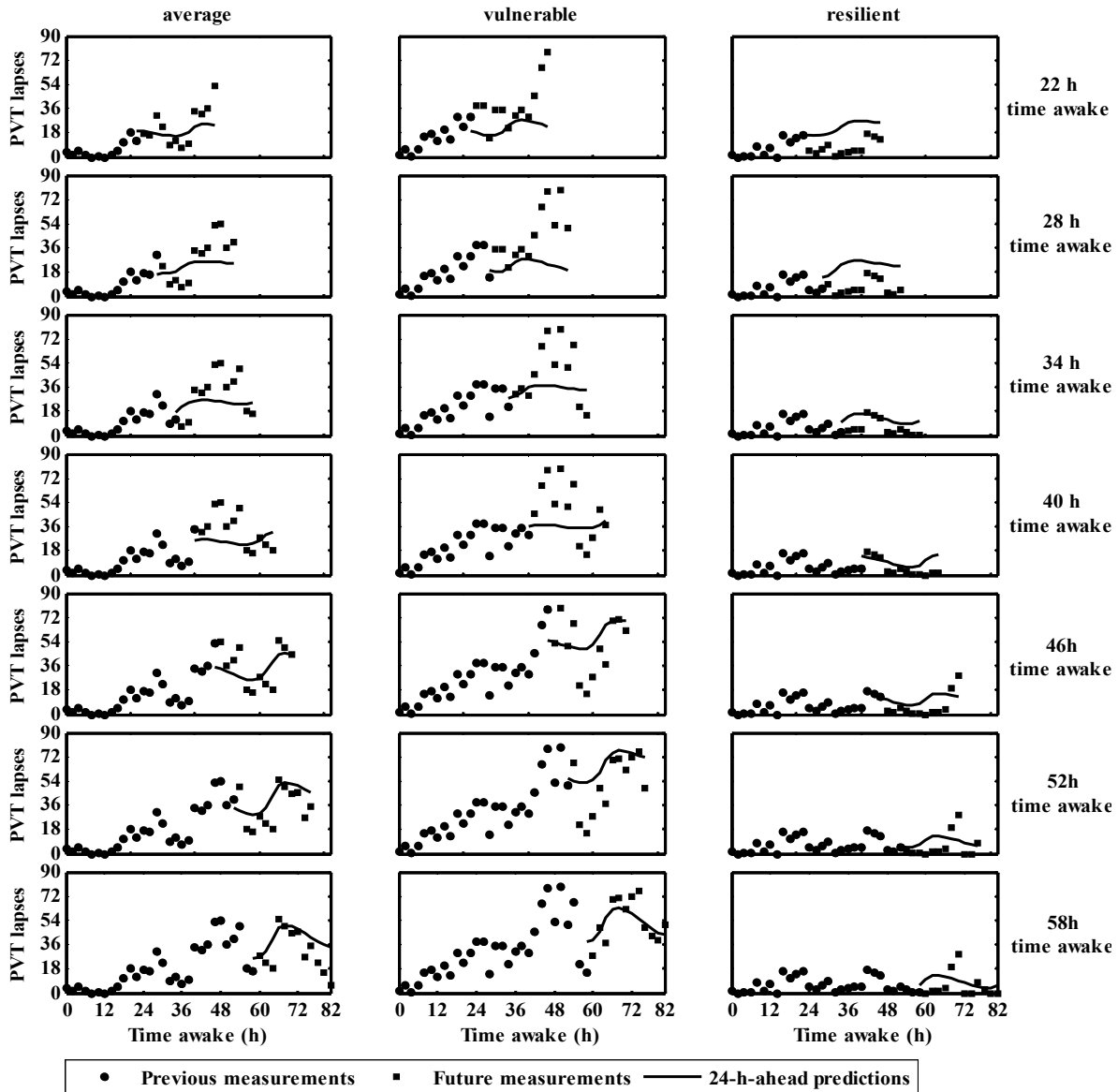


Figure 4: Individualized model predictions up to 24 h ahead for the three subjects [average (*left*), vulnerable (*middle*), and resilient (*right*)] shown in Fig. 3. In each panel, the solid circles represent previous PVT lapse measurements, the solid squares represent future PVT lapse measurements, and the solid lines represent predictions up to 24 h ahead.

4.0 CONCLUSIONS

In this work, we presented a new method for individualized performance prediction for sleep-deprived individuals based on the two-process model of sleep regulation. This method combined an individual's current and past performance measures and *a priori* performance information in a Bayesian formalism to

customize the models and individualize the predictions. As a result, model individualization and prediction could commence as soon as the first performance measurement from an individual became available. However, unlike other methods, which require solving a NLP problem for finding the optimal parameter estimates, the proposed method, using the linear representation of the two-process model [12], transformed the NLP problem into a series of linear optimization problems, which guarantee unique estimates of the five parameters of the two-process model parameters, avoiding brute-force, grid-search procedures [21].

Additionally, the current work, for the first time, provided statistically based error bounds around the model predictions in the form of PIs. This was achieved by taking advantage of the linear representation of the two-process model [12], which allowed for reformulating the two-process model into an equivalent AR model. The AR model formulation of the two-process model provided an analytical expression for computing PIs, bypassing the need to first compute confidence intervals around the model parameter estimates before extrapolating these uncertainties about the model predictions [21].

Using PVT measurements from a laboratory study, the proposed method yielded 10-h-ahead individualized predictions for three sleep-loss phenotypes that were up to 43% more accurate than the group-average predictions. Also, the corresponding 95% PIs almost entirely covered the entire set of measurements. Using the same data set, we showed that the ability to capture circadian and homeostatic variations in future measurements (up to 24 h ahead) by the individualized predictions increased as the number of performance measurements for model individualization increased, reflecting the adaptive nature of the proposed model.

Despite the advances made by the proposed method in individualized performance predictions for sleep-deprived individuals, there exist some limitations. As with any approach using Bayesian inference, a “good” choice of the prior performance information, i.e., the prior parameter values, is key for obtaining optimal results [22]. Another limitation lies in the assumption that measures of performance, such as PVT lapses, would be available on a frequent basis, which may not be possible in real-world settings, where it is infeasible to discontinue work-related tasks for administering performance tests. Also, we note that, although PVT is arguably one of the most sensitive measures to sleep loss and one of the most practical for operational use [23], it may not accurately reflect the real, work-related performance of individuals.

Our future modeling efforts will focus on developing models for individualized performance predictions for individuals exposed to chronic/partial sleep restriction. Also, we will focus on developing models that can predict the effect of stimulants, such as caffeine, on performance sustenance at an individual level. In addition, we will evaluate the performance of the proposed method on other outcome measures of performance, such as the Karolinska sleepiness scale [24], the Stanford sleepiness scale [25], the serial addition/subtraction task [26], and the digit symbol substitution task [27].

An extensive effort is still required to fully address the capability gaps in biomathematical models of fatigue and performance identified at the DoD-sponsored Fatigue and Modeling Workshop [2, 3, 28]. Nonetheless, the work described here is a significant step toward closing these research gaps and developing models that accurately predict cognitive performance impairments due to sleep deprivation at an individual level.

5.0 REFERENCES

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