Critical Research Issues in Development of Biomathematical Models of Fatigue and Performance

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This article reviews the scientific research needed to ensure the continued development, validation, and operational transition of biomathematical models of fatigue and performance. These models originated from the need to ascertain the formal underlying relationships among sleep and circadian dynamics in the control of alertness and neurobehavioral performance capability. Priority should be given to research that further establishes their basic validity, including the accuracy of the core mathematical formulae and parameters that instantiate the interactions of sleep/wake and circadian processes. Since individuals can differ markedly and reliably in their responses to sleep loss and to countermeasures for it, models must incorporate estimates of these inter-individual differences, and research should identify predictors of them. To ensure models accurately predict recovery of function with sleep of varying durations, dose-response curves for recovery of performance as a function of prior sleep homeostatic load and the number of days of recovery are needed. It is also necessary to establish whether the accuracy of models is affected by using work/rest schedules as surrogates for sleep/wake inputs to models. Given the importance of light as both a circadian entraining agent and an alerting agent, research should determine the extent to which light input could incrementally improve model predictions of performance, especially in persons exposed to night work, jet lag, and prolonged work. Models seek to estimate behavioral capability and/or the relative risk of adverse events in a fatigued state. Research is needed on how best to scale and interpret metrics of behavioral capability, and incorporate factors that amplify or diminish the relationship between model predictions of performance and risk outcomes.

Keywords: behavior, brain, cognitive functions, circadian rhythms, fatigue, biomathematical models, human factors, individual differences, jet lag, mathematical modeling, neurobehavioral functions, night work, performance, prediction, research gaps, shift work, sleep, sleep deprivation, sustained operations, two process model, wake, scheduling.

THE FATIGUE and Performance Modeling Workshop held in Seattle, WA, on June 13–14, 2002, reviewed seven biomathematical models of human performance based on sleep/wake and circadian dynamics (46). The development and application of these models had increased since the proceedings of the previous biomathematical workshop were published 3 yr earlier (34), and considerably so since the first mathematical models of processes underlying the regulation of sleep and circadian rhythms were published in the 1970's and early 1980's (33). The increasing number of biomathematical models of human performance and their applications to both experimental and operational contexts has fueled growing interest in the potential of these models as technologies for fatigue (or risk) management. This paper reviews the need for research on the continued development, validation and applications of such models. As such, it highlights the basic science questions that remain to be answered regarding the accuracy of models to predict aspects of human behavioral capability before such models can be tested in operational studies (27).

The models reviewed in the articles of this issue seek to predict human behavior or the biological state of fatigue. The focus in this article is on the need for refinement of the theoretical and experimental aspects of model development and validation, especially the importance of scientifically determining model inputs and outputs that are relevant for accurate model predictions in both scientific and applied settings. Mathematical approaches to model development are not discussed here, as these and the relevant scientific literature are presented throughout papers in this special issue. The highest priority research recommendations relative to advancing model development and utility are displayed in bolded italics. These selections reflect the author's views and evaluations, and not necessarily those of the Workshop participants, although many of them contributed to the ideas expressed below.

Validition of Models to Predict Fatigue and Performance

Scientific development of models of fatigue and performance originated from efforts to model the underlying relationships between sleep regulation and circadian dynamics (4,10,17,26,34). That is, progenitor models of sleep/wake dynamics were extrapolated to waking performance and fatigue, because considerable scientific evidence demonstrated that wakefulness was the product of neurobiological mechanisms underlying sleep and circadian processes and, therefore, the neu-

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rocognitive platform for performance. Before discussing the research needs posed by such extrapolation, it is important to recognize that modeling of sleep and circadian dynamics continues to have heuristic value even if it is not extrapolated to predictions of waking cognition and behavior. As the molecular, genetic, and neurobiological mechanisms of sleep and circadian processes become ever more elucidated (47,55), it will be increasingly possible to validate circadian and sleep-regulation models (and their interaction) against actual biological processes.

Demonstrating the validity of models of sleep/wake dynamics to predict human fatigue and performance brings an additional set of theoretical and scientific challenges that must be overcome. Most current models of fatigue and its effects on performance appear to be more descriptive curve-fitting, than theoretically driven, hypothesis-generating, data-organizing mathematical approaches, such as those used to guide the thinking (and predictions) of chronobiologists about the structure of circadian rhythms and the oscillatory systems producing them (13). What is needed is development (maturation) of theoretical models of the temporal dynamics of human neurobehavioral functions, which should include sleep and circadian components, but also extend to include individual differences in these parameters and cognitive vulnerability to them, as well as cognitive modeling components of performance changes likely during fatigue [e.g., state instability (23)], and perhaps also a computational model component for the behavioral and physical structure of the task to be performed (e.g., MIDAS models). This integrated approach to human performance modeling should be formalized to the point that it makes predictions about properties of the system not apparent from current data or experiments, in order to direct the design of future experiments for model validation. Much of what is discussed below regarding internal dynamics, inputs, and outputs reflects components of this overarching need for a more theoretically driven model that goes beyond current extrapolations of sleep regulation.

Validation of such a human performance model is essential if it is to be transitioned to real world operational settings (54). Therefore, research to establish both basic validity and ecological validity of models predicated on mathematical simulations of sleep/wake, circadian, and work/rest dynamics should be a high priority in each of the following areas. In addition, there should begin to be application of quantitative approaches for the selection of one model (or model subcomponents) over another (see 49,62).

Research to Increase Accuracy of Estimated Sleep and Circadian Effects on Wakefulness

The hardware/software interface generally reveals the inputs and outputs of the model. Although these must be interpretable to a user, it is important to remember that an interface is not a model. The mathematical formulae and parameters that estimate the sleep, wake, circadian, work and other processes, and their interactions form the core of any model of fatigue and performance, but may be transparent to a user. Knowledge of these formulae and parameters is nevertheless critical to those who seek to validate models against experimental data. There are excellent presentations of the mathematical formulae and parameters used in the models presented in this special issue, along with the data these modelers used to validate aspects of their models (8,32).

The need for continued research to validate models and model components is of the highest priority. Lacking prospective validation, the formulae used to estimate the processes are prone to be biased or inaccurate, making a model invalid physiologically and/or ecologically, regardless of who sells it, endorses it, or uses it. Experimental validation is, therefore, a sine qua non for any model that professes to predict fatigue and the behavioral risks associated with it as a result of prolonged wakefulness, inadequate sleep, and circadian dynamics, or work schedules influenced by these factors. In addition, sensitivity analyses are needed to identify which parameters are most critical to a model's predictive accuracy and for which the precision of the estimates must, therefore, be greatest (2). Consequently, validation research should focus most on those parameters for which the greatest accuracy is needed.

The devil is in the details of mathematical functions, parameters and time constants: Regardless of the claims made by individual modelers regarding what their models predict (46), it appears that all seven of the biomathematical models of human performance reviewed in this issue (10) derived from the basic Two-Process Model of the regulation of sleep and wakefulness (1,4,11,17,26)—albeit with differences in inputs and outputs (46). The Two-Process Model of sleep regulation has been applied successfully to describe, predict, and understand sleep/wake regulation in a variety of experimental protocols such as total sleep deprivation and forced desynchrony (16), as well as irregular work schedules (4,26). It is understandable, therefore, that all seven models reviewed made comparably accurate predictions of the effects of acute total sleep loss on performance (where the Two-Process Model was validated), but inaccurate predictions of the effects of chronic sleep restriction (62) (where the Two-Process Model was not validated). The latter highlights the need for all models to develop much greater accuracy in predicting the effects of chronic sleep restriction (7,68). This is perhaps better achieved by mathematically instantiating a new theoretical construct for chronic effects (66) than by tweaking current parameters and formulae in the basic two-process model structure (38). Regardless, sensitivity analyses can help determine where more experimental research is needed to increase the precision of specific model parameters (2).

Also reflective of the seminal role of the Two-Process Model (1) is the fact that most of the other models have a similarity with regard to the mathematical assumptions they make about the decay of functional capability (i.e., performance or safety) with elevating sleep drive; the recovery of function with sleep; and the circadian modulation of sleep and waking (46). However, the models vary considerably in the detailed manner in which the underlying two processes (i.e., homeostatic drive for sleep and endogenous circadian timing) are mathematically represented. For example, the attenuation and replenishment curves for wake and sleep, respectively, are modeled in a variety of ways—linearly, exponentially, polynomially, and sigmoidally. Similarly, the circadian effect is modeled as a sinusoid, a skewed sinusoid, or modeled using a van der Pol oscillator—which is the only one readily capable of phase shifting. Research is needed to determine which of the mathematical assumptions for these basic processes is most accurate and physiologically valid for individuals and average data, or whether there are any substantial differences in the predictive accuracy of models when different functional formula are used. If there were no fundamental differences in the accuracy of prediction of these various mathematical approaches, then that would be equally valuable to demonstrate experimentally, and would suggest the simplest approach is optimal. This is an area of research where statistical modeling of experimental data (67) and formal model building approaches (13) must guide decisions about the mathematical nature of the derived curves.

There is a need to determine what effects repeated iterations over time (e.g., many days or weeks of specific work/rest schedules) have on the accuracy of mathematical formulae and their interactions (28). Such research needs make it essential that modelers specify in detail what assumptions, parameters, time constants, and mathematical interactions underlie the processes contained in their models. It is also obvious that, except for research purposes, a model interface should not contain an option to adjust a given process's time constant to a value for which the model was never validated. Even models that are customized to individual subjects should only offer parameter adjustments that reflect the range of individual responses.

Importance of the accuracy of estimates of recovery and interactions: Extant biomathematical models quantify fatigue by a balance between fatigue accumulated during wake and/or work periods and the amount of recovery obtained during sleep and/or time off from work (46). Issues of wake vs. work, and sleep vs. time off, are discussed in another section below. The important point here is that all models make mathematical assumptions both about the rate and shape of curves characterizing decay and recovery, and about whether and how decay and recovery functions interact additively or nonlinearly with related key processes (e.g., circadian phase; sleep inertia). Laboratory research is needed to precisely quantify the nature of these interactions (65) for accurate representations within models. There is also a need for evidence on the relationships between quantitative aspects of sleep (e.g., sleep duration, slow wave activity, physiological consolidation) and the rate of recovery of waking behavioral capability, since it appears the Two Process Model marker of sleep homeostasis—namely nonREM EEG slow wave activity—cannot account for performance in chronic conditions (68). This is not a limitation of the Two Process Model, which was initially conceptualized to reflect sleep regulation rather than performance (10), although it was extrapolated to performance in recent years (11). It does, however, highlight the need to determine what aspects of sleep predict performance during chronic conditions (68) and recovery from chronic conditions (7).

The fact that models instantiate in mathematical formulae functional recovery after sleep (46) is a testament to the overwhelming evidence that sleep is essential for waking behavioral capability to remain intact (23). However, very little is known about recovery of behavioral capability as a function of time off for sleep—a central issue for both proscriptive and non-proscriptive approaches to fatigue management. Other than assuming more sleep is better than less sleep, it is not clear how accurately any of the models estimate recovery of function following sleep of different durations over more than 1 or 2 d. There is only one published dose-response curve for sleep duration (35). ***Therefore, a research priority is the need for experimentally derived sleep duration dose-response curves for recovery of performance as a function of prior sleep homeostatic load and the number of days of recovery.***

The failure of all models to accurately predict the cumulative adverse effects of chronic sleep restriction (62), as observed in two independent laboratory studies (7,68), is a warning that cannot be ignored. It appears that representing recovery from fatigue during sleep by a relatively short exponential time constant, which derives from the notion that slow wave sleep subserves the bulk of recovery, may not be accurate when chronic sleep restriction occurs. All seven models—including the progenitor Two-Process Model applied to performance (1,11)—either have the wrong mathematical formulae for the recovery of function within and between days as a result of sleep duration, or the wrong time constant for the accumulation of functional deficits when sleep is restricted (32,38), or they may be missing an additional process [e.g., cumulative excess wakefulness (66,68)]. Further development of models of fatigue and performance must confront this basic issue, because many, if not most, real-life situations are characterized by chronic partial sleep deprivation rather than acute total sleep deprivation (18,32). ***More dose-response experimental data relating variations in chronic sleep duration to performance are needed at all circadian phases, to improve the models conceptually and in their quantitative validity.***

Importance of the accuracy of circadian estimates and interactions: Although models mathematically estimate the decline of behavioral capability as a function of time awake (or at work), and the recovery of behavioral capability following sleep (or time off for sleep), they do not all treat circadian phase with equivalent importance either as a required input and/or a necessary output (46). The failure to do so is contrary to extensive scientific evidence that circadian phase contributes substantially to the variance in waking performance (16,64). There are also ample data from operational environments in which night work, jet lag, and prolonged work occur, showing that loss of alertness and performance errors increase during (and for some hours after) the circadian nadir of endogenous core body temperature (64). Consequently, endogenous circadian processes combine with sleep homeostatic processes in the determination of sleep propensity and duration, as well as waking alertness and performance, regardless of the work context. For this reason, research is needed to establish how accurate different modeling approaches are in predicting circadian phase relative to precise physiological measures of phase (e.g., melatonin secretion) vs. the temporal pattern of performance, and precisely how circadian dynamics interact with sleep homeostatic dynamics to create a performance profile (65).

There is also a need to determine whether or not a 12-h circadian harmonic—which is included in some models—is valid or essential when predicting performance. A 12-h component has been added to the Two-Process Model (17) to create a skewed waveform. It has also been suggested it is needed to capture the mid-afternoon (or postprandial or siesta) increase in sleep propensity (12) and decrease in performance (48) sometimes present in data. But there is no reliable evidence from forced desynchrony studies for a 12-h component (42), and many sleep deprivation studies find no 12-h profile (23). Yet a mid-afternoon dip in performance is sometimes present in data. Research should resolve what the interaction is between homeostatic and circadian processes that can produce a midday dip in performance, and whether its presence constitutes a person-specific characteristic of the circadian profile.

Appropriately timed light exposure is well documented to have marked effects on not only circadian phase (9), but also on core alertness and performance during the circadian nadir (15,70). Yet only two models (1,37) include light exposure as required inputs (46). ***Research is needed to firmly establish the extent to which light input could incrementally improve model predictions of performance in persons exposed to simulated night work, jet lag, and prolonged work. If it is found that photic stimulation markedly enhances model accuracy, then research should shift to the development of better tools to measure exposure to light throughout the 24-h day for the testing of model predictions in field conditions (9). There is also a need to find ways to estimate circadian phase in operational environments, and to determine whether continuous exposure to light vs. light pulses has differential effects on endogenous circadian phase (6).***

Research on Prediction of Different Aspects of Neurobehavioral Functions and Risk

Extant models vary widely in the extent to which they purport to predict performance, subjective fatigue, physiology, and risk (46). Experimental studies demonstrate that these classes of outcome share common variance, but they also differ in important ways that require a prioritization in model validation.

Cognitive performance outcomes: The accuracy of model predictions for different aspects of neurobehavioral performance must be established. This information is essential to understanding whether some cognitive functions are affected by sleep and circadian perturbations more profoundly or with a different time course than other functions. For example, models should be based on experimental data on a range of cognitive functions relevant to attention, memory, executive functions, perception, sensory-motor skill, and problem solving. In addition, models should be validated on behavioral assays that are well documented to be affected by sleep/wake timing and circadian dynamics, which means that tasks that meet this criterion should be included in every experimental test of models (21).

Other aspects of performance should also be evaluated for the importance to models. Examples include the relevance of task novelty or its converse, overlearned tasks; time-on-task effects; and the impact of time pressure. It may turn out that such generic task factors markedly amplify or reduce vulnerability to the neurobehavioral effects of fatigue—in which case such factors should be included in model structure and formulae. There also may be compensatory neurobiological responses to fatigue that affect some functions more so than others (24). These possibilities need to be addressed in basic laboratory experiments in order to inform model development and to test model predictions prospectively. Even models that seek to predict risk require performance-based validation, although such validation may require field experiments and epidemiological data rather than laboratory studies.

Performance on simulators and synthetic task environments: Laboratory experiments provide a high degree of control over the fundamental sleep/wake and circadian processes on which biomathematical models of fatigue and performance are built, but the neurobehavioral performance measures used in laboratory studies of model validation generally are behavioral assays for specific cognitive functions (e.g., vigilance, reaction time, cognitive throughput, working memory). Such cognitive functions are the basic building blocks of more complex real-world tasks. Performance on the latter, however, is what models are expected to predict by end users (27). ***There is a need to conduct research on model development and especially prospective validation of models of fatigue and performance, using more complex and ecologically valid performance measures, but with the full benefits of laboratory control and measurement.***

Simulators and synthetic task environments offer this possibility, as well as allowing much-needed study of the relationship between the individual performance components (vigilance, working memory, etc.) and overall complex performance outcomes.

Simulators range greatly in their fidelity to real-world work environments, from desktop PC-based tasks to expensive high-fidelity truck cabs, locomotives, cockpits, air traffic control towers, and fire control rooms. Although some modeling efforts have used data from (low-fidelity) laboratory driving simulation tasks (3,56), most have not, and the published literature does not show any attempts to validate model predictions using high-fidelity simulators. Although the effects of inadequate sleep and night work on cognitive performance can be modeled for any task environment, some models are being developed for specific types of work environments that are safety sensitive (e.g., aviation). In these cases, at some stage of model development, validation studies in high-fidelity simulators would be warranted.

High-fidelity simulators have distinct advantages in model evaluation. They offer ecological validity of performance measures, and the opportunity to use actual workers as subjects [e.g., commercial pilots operating a B747-400 simulator overnight on a long-haul flight (50)]. Studies consistently find that workers take high-fidelity simulators very seriously, and perform at high levels to prevent crashes and unsafe practices. However, one challenge posed when using high-fidelity simulators is identification and measurement of the types of deficits most likely to occur in fatigued subjects. Moreover, high-fidelity simulators are also relatively rare and expensive to operate, and consequently, thus far not used for studies of chronic work/rest schedules.

Synthetic task environments (STE) offer a laboratory alternative to high-fidelity simulators (30). They are designed to capture and measure fundamental elements of real-world tasks (e.g., Multi Attribute Task by NASA; Distributed Dynamic Decision-Making Team-in-the-Loop Simulation by Aptima; Predator Unmanned Aerial Vehicle Task by the U.S. Air Force Laboratory). They allow the experimenter to recreate abstract elements of workplace tasks while maintaining a high degree of control over potential confounding variables. As such, they provide a compromise between laboratory and field approaches to research, enabling a degree of face validity afforded by high-fidelity simulator or field studies, while maintaining the experimental control of laboratory work. Synthetic task environments also have an advantage over many laboratory performance evaluations in that they permit study of both individual and small group (team) performance. There is a need to understand how fatiguing work schedules affect not only the behavioral capability of an individual, but also the collective performance of a small group working toward common goals. There has been no development or validation of biomathematical models of fatigue using performance on STEs. As more STE scenarios become available, this approach affords an opportunity to test models of fatigue and performance in individuals and small groups.

Performance relative to risk as an outcome: Another reason that performance measures should form the bases for laboratory validation of biomathematical models of fatigue concerns the implicit and sometimes explicit goal of these models to predict the risk of adverse events in operational environments (25), or conversely, the safety of certain work/rest schedules. To the extent that risk and safety reflect behavioral capability of human operators—which they usually do when humans are involved—models of fatigue and performance based in the interactions of sleep/wake and circadian dynamics are relevant to risk and safety. On the other hand, so are many other factors (e.g., exposure; environmental factors; degree of automation), making it difficult to precisely match model predictions validated against performance with profiles of accidents (25). If these latter factors are known and their contribution quantified and accurately estimated (or corrected for), biomathematical models of fatigue and performance should be able to predict risk as defined prospectively by specific outcomes (e.g., near misses or crashes). This is the ecological validity required of models that seek to predict risk.

While reduction of serious adverse events such as accidents is a worthy goal for biomathematical models of performance, the models actually may be better suited to predicting the behavioral capability of human operators even when accidents are very rare (e.g., commercial aviation crashes). That is, many operational scenarios seek to have operators alert and capable of performing at a high level throughout the work shift (e.g., long-haul pilots) so they can handle any emergency (56). In such situations, the goal of applying a predictive model is to ensure an accurate estimate of performance capability, even if its utility for predicting crash risk directly is poor or unknown.

Validation of biomathematical models of fatigue using performance outcomes neither ensures nor fails to ensure their predictive utility for risk and safety. The latter requires further validation using risk/safety outcomes and incorporating information about other factors that influence these outcomes. Equations and parameters established through careful laboratory research should not be distorted to "fit" risk data from operational databases. ***Rather, studies should focus on understanding the additional factors that create risk and that modify the relationship between model predictions of performance and risk outcomes*** **(25).**

For models being sold to industry and government as risk-management tools (rather than as fatigue-management tools), some objective, ideally independent evidence should be proffered that the model was validated against actual risk outcomes (e.g., drowsy driving) and that the outcomes and context used in validation apply to the operational environment being considered.

Subjective outcomes: Some models specifically use subjective ratings of fatigue and alertness as surrogates for performance (46). Self-reports of fatigue (or sleepiness or alertness) relative to actual objective performance outcomes in experimental protocols should be studied to clearly establish if they should ever be used in model validation or prediction. Recent experimental reports show that subjective estimates of sleepiness and fatigue have a profile different than cognitive performance deficits during chronic sleep restriction (7,68). Although subjective ratings yield *average* profiles similar to performance in acute total sleep deprivation (68), even in acute paradigms there is little evidence that subjective reports track objective performance measures in individuals (43). Thus, despite their face validity and ease of acquisition, subjective ratings should not be the primary validation criteria for a model of performance until there is compelling evidence that in some contexts subjective ratings actually reflect neurobehavioral capability.

Physiological outcomes: Similar to subjective estimates of fatigue, physiological measures of sleep variables (e.g., nonREM EEG slow-wave activity) or specific waking physiology (e.g., alpha or theta power in the waking EEG) are inadequate as surrogates for performance in model validation, since they do not necessarily track performance responses to perturbed sleep/wake schedules (68). As suggested by Kronauer and Stone (42), accurate prediction of performance responses to unusual or perturbed sleep/wake schedules must be based directly on performance data and not inferred from sleep physiological measures. However, physiological measures can and do have theoretical importance for models designed to predict physiological outcomes from sleep and circadian dynamics [which is how the Two-Process Model began (10)]. Physiological measures of sleep in particular can be used as model inputs operationalizing the impact of sleep when predicting performance capability over time.

Research Needed on Modeling Inter-Individual Differences

For some time it has been recognized that all current biomathematical models of fatigue and performance need to quantify not only the prediction of average response to fatigue, but also provide estimates of the range of individual responses (19), or predict individual subjects' outcomes per se (67). Although sleep deprivation and night work produce large inter-individual differences among subjects in neurobehavioral performance responses (21,23,43,69), most experimental studies of sleep/wake and circadian dynamics ignore this fact by presenting average data analyzed as though all subjects had the same response to fatiguing work/rest schedules. Failure to take into account the differences among people in response to experimental perturbations of sleep/wake schedules can result in distorted estimates of the effects of fatigue on performance parameters, even for the population-average response. There are appropriate statistical techniques for incorporating the contribution of individual differences in response to fatigue (52,67). More research is needed in which these newer statistical techniques are applied to data sets used to develop (52) and/or validate (62) biomathematical models of fatigue. Incorporation of individual differences will ensure the latter accurately predict the range of responses to a given work/rest schedule.

There is another reason why it is important to use statistical analyses that take into account the true nature of individual differences in response to perturbations in work/rest schedules. Experiments not only show that some subjects are much more vulnerable to the adverse effects of fatigue on performance sooner and more dramatically than others, but also that these differential responses are relatively stable over repeated exposures to fatigue, which suggests they are trait-like and potentially predictable (69). Assumptions in current biomathematical models about what factors are most likely to potentiate vulnerability to perturbations of work/rest schedules may or may not be accurate. For example, it is commonly assumed that individual sleep need is the critical factor in the magnitude of the cognitive response to sleep loss (27). However, there is some evidence that individuals who were found to be consistently vulnerable to the adverse effects of sleep deprivation on performance neither required nor obtained more sleep on average than individuals who were resilient to sleep deprivation (67), which suggests that inter-individual differences in vulnerability to sleep loss are not just determined by differences in sleep need as defined by habitual sleep obtained (69).

Consequently, it is not yet known what biological and/or behavioral factor(s) may eventually prove to be important in predicting individual differences in response to sleep/wake schedule perturbations, but models of fatigue and performance could include such predictors. To ensure that models accurately predict key portions of variance due to individual differences in behavioral capability, research must resolve what contributions (if any) age, gender, diurnal preference (18), work experience (60), and other demographic factors have in vulnerability to fatigue and performance deficits following scheduled changes in sleep/wake and circadian dynamics. There may be multiple vulnerability factors, adding precision to model predictions if these factors are known ahead of time. In addition, as noted by Balkin and colleagues (5), it is equally important to account for individual differences in terms of the effects of countermeasures for fatigue (e.g., naps, caffeine)—an achievable goal as well, if the appropriate statistical analyses are used in research on countermeasure efficacy and effectiveness. ***Thus, a key research need exists to quantify the naturally occurring inter-individual variability in responses to experimental interventions and countermeasures, and then to find biological and/or behavioral predictors for the factors that contribute most to these individual differences. Such research should provide critical information about how to fine-tune model parameters for individuals not studied before (52).***

There is also a very practical reason for giving research priority to the prediction of individual differences in response to fatiguing work schedules. There are instances in which a biomathematical model may be applied to selected individuals whose fatigue at work could pose grave risks to life or property (e.g., in aircraft operations). In such instances, optimization of model parameters to the individuals involved will ultimately prove more useful than application of a generic model (63). Maislin (44) nicely summarized additional reasons why incorporation of estimates of individual variability should become a research priority.

Estimating Normative Behavioral Capability

Predictive modeling of changes over time within an individual requires valid and reliable knowledge of the individual's normative behavioral capability in a non-fatigued state, or the use of relative scaling based on average performance for a population. The latter is problematic since people vary greatly in their aptitude and mastery at certain tasks. Current biomathematical models necessarily assume that at some specific time (usually after a period off duty), performance is "normalized." But research suggests that this will depend on prior sleep debt, circadian phase, and their interaction, as well as differences among subjects in vulnerability to sleep loss, etc. The problem of assuming normative function at the start of a duty period is intimately tied up with the challenge of accurately estimating both acute (fast) and chronic (slow) processes [e.g., recovery (fast) from sleep debt (slow) (7,69)].

Moreover, without some way of interpreting the "normative" value relative to an objectively established standard, such as minimally acceptable performance or risk, the model output is strictly a relative scale that allows users to assign meaning where none may exist (e.g., the use of arbitrary thresholds of acceptable performance and/or the representation of these thresholds in the form of colored lights—green, yellow, red).

This issue is especially problematic when a model is used retrospectively to "predict" that work/rest schedules or fatigue were likely to *not* have contributed to a serious adverse event (e.g., truck crash). Such negative predictability applications are at best dubious when a model is being used to analyze an individual for which no preexisting normative performance, sleep, or circadian data are available. If such normative data exist ahead of time and have been included in the model for that individual, then such retrospective uses of biomathematical models may have merit, assuming the model is validated to be reasonably accurate in the first place. However, absent such normative data, retrospective "prediction" with a model is not likely to be accurate and, as importantly, cannot be verified.

One way in which performance estimates from models of fatigue might be "calibrated" for accuracy is by online, real-time input to the models of information on performance or a biobehavioral measure validated to reflect fatigue and relevant to performance [e.g., slow eyelid closures relative to driving performance and drowsiness (45)] (27). Assuming an accurate performance or biobehavioral measure is fed into a model online, algorithms could be developed for updating the model's "knowledge" about the operator's behavioral capability (52). The model could then predict performance over the coming period of time, and if necessary, direct the individual to engage in a countermeasure. Such online technologies are being developed for specific work environments, and could prove a useful addition to biomathematical modeling.

In summary, more extensive basic research is needed on the best ways to estimate normative behavioral capability in a non-fatigued state, and/or to calibrate models to individuals. In addition, research is needed on how to best represent, scale and interpret metrics of behavioral capability. Models that are to be used to make specific predictions on specific individuals—prospectively or retrospectively—should be evaluated in research for the accuracy of both their positive predictability (i.e., validly identifying when an individual is likely to be affected by fatigue) and negative predictability (i.e., validly identifying when an individual is not affected by fatigue). Research should determine whether online, real-time monitors of individual performance or fatigue provide sufficient improvement of the accuracy of model estimates of performance to warrant the cost of monitoring.

Estimating Countermeasure Effects

Biomathematical models of fatigue and performance based on sleep/wake and circadian dynamics generally incorporate estimates of decay of functional capability with elevating sleep drive and the recovery of this capability with sleep. Thus, estimates of major daily sleep episodes and naps, as *preventative countermeasures* (59) for fatigue, are necessarily included in models, although as Balkin and colleagues observe, "prediction accuracy of any such model would be enhanced if the model was informed of the actual, objectively measured amounts of sleep obtained, instead of relying on self-generated predictions of sleep duration." (5) Similar issues arise relative to light exposure and the estimation of circadian phase (9).

In order to ensure optimal prediction of functional capability relative to sleep/wake and circadian dynamics, models must also incorporate estimates of the effects of *operational countermeasures* for fatigue (19). Commonly used operational countermeasures include behavioral rest breaks (i.e., time-off-task and/or work pauses without sleep); naps (i.e., physiological sleep in the workplace averaging less than habitual sleep at home); and widely available unregulated stimulants (i.e., caffeine, nicotine) (59). [There are also special situations in which even more potent pharmacological agents are used, but these will not be discussed here. Light as a countermeasure (9,16) is discussed below, under environmental variables.]

More scientific evidence is needed for the effectiveness of commonly used operational countermeasures (i.e., their positive and negative effects; magnitude of these effects; time courses of the effects; their interactions with sleep and circadian dynamics and with other countermeasures; and inter-individual differences in responses). Little is known about countermeasure effectiveness when used chronically vs. acutely. Even naps and caffeine, which have been heavily investigated in acute-duration laboratory studies, have rarely been evaluated for habituation, tolerance, etc., under controlled conditions of chronic use, which is what occurs in operational environments. Such research is needed, along with studies of common operational fatigue countermeasures [e.g., wake rest breaks (50) with and without food consumption] for which there are sparse experimental data. There is also a need to determine experimentally whether the social structure of performance (e.g., individual vs. small group problem solving) has large enough effects on performance or underlying sleep/wake, circadian, and performance dynamics to warrant their inclusion in biomathematical models.

To the extent that biomathematical models are considered to be "quantitative tools for online monitoring of the state of alertness and fatigue-related error risk" (3), the most effective fatigue countermeasures routinely used in operational environments will need to be taken into account on-line in model predictions—assuming their use can be determined. This will not be possible without basic research to identify which if any operational countermeasures are potent enough to warrant mathematical instantiation in models.

Work

In operational settings, fatigue is commonly attributed to work hours; to aspects of the work itself (e.g., workload, monotony, repetitive motion); to the work environment (e.g., noise, postural comfort); and to perceived stressors in the workplace (e.g., time pressure, social friction). Currently, such factors are not represented in biomathematical models of performance (46), and may not need to be, if none of these factors have a prominent role interacting with sleep/wake and circadian dynamics in ways that either potentiate the effects of fatigue and performance deficits, or substantially mitigate these effects over time. To the extent that research on these factors is available in other areas (e.g., psychology, human factors), it could help identify those work-related components that may interact with sleep and circadian regulation of performance. If such components exist, more laboratory-based research may be needed on the specific work-related factor(s), to determine if it merits inclusion in models of fatigue and performance. Whether or not they prove to be important in model development, the manner in which work requirements affect sleep/wake and circadian dynamics may require that performance models be adapted to optimize prediction in specific work environments. Indeed, some of the current biomathematical models have been developed for specific types of work contexts (8,32).

Work-Rest Times vs. Sleep/Wake Times

It is has been repeatedly demonstrated in studies in operational environments that work time is only a subset of wake time, and conversely that sleep time is only a subset of off-duty (rest) time. In other words, work/rest times often underestimate wake time and overestimate sleep time. Although work/rest times are what many government and industry initiatives use to "manage fatigue" proscriptively and non-proscriptively, research has demonstrated that obtaining normal physiological sleep is much more essential to daily recovery from fatigue and maintenance of performance than is rest (i.e., awake but not working). Regardless of the work hours, if daily sleep is inadequate, fatigue will increase and performance will suffer. Moreover, when work/rest patterns violate circadian dynamics, difficulty sleeping is a common problem [e.g., Navy submarine personnel on the non-circadian 6-h on/12-h off watch-standing cycle (31)]. This is the reason that experts in sleep and circadian rhythms have recommended an increase in off-duty time (rather than a decrease in work hours) and maintaining a circadian work/rest schedule, as new duty hour changes in various industries in the United States (20,61).

As shown in Table III of Mallis et al.(46), four of the current biomathematical models require *only* work hours (not sleep/wake times) as inputs to the models. These models have an operational focus, and assume that work hours are easily known, and that sleep times are easily estimated or inferred from work hours. In contrast, three other models require information on sleep/wake times as inputs, but not work hours. The implication is that work hours contribute little to fatigue or can be estimated from wake time. The issues that must be resolved to determine if these two approaches to modeling are equivalent include: 1) whether work/rest times are as important (or, less or more important) as sleep/wake times in predicting fatigue and performance; and 2) whether work/rest times can serve as a valid surrogate for sleep/wake times or vice versa. ***Resolving the relative importance of work/rest vs. sleep/wake inputs in the predictive accuracy of models is one of the more important research issues facing continued development of models.*** It may be that for modeling fatigue and performance in some operational contexts involving highly stable work/rest schedules, work/rest times are sufficient to estimate sleep/wake times; but that in other operational contexts in which work/rest schedules are highly variable, information on sleep/wake times is critical to maintaining a high degree of model accuracy (62).

Work-Related Factors

In general, the biomathematical models of fatigue and performance do not have parameterized inputs for type of work (e.g., sedentary vs. physically demanding tasks); or workload (high vs. low cognitive demands); or task difficulty; or task duration; or chronic work schedule history (work schedule tenure); or work experience. Many of the articles by modelers and by commentators in this special issue point out the need for research to determine whether one or more of these work-related factors are important alone or in interaction with sleep/wake and/or circadian dynamics, especially for models focused on risk (25).

Time on task appears to be the one work-related factor most represented in current biomathematical models (46). Research has shown that when sleep-deprived or working at night, subjects tend to show greater rates of deterioration (relative to baseline) on certain cognitive performance as time on task progresses (39). Relative to time on task, *workload* is less well represented in current biomathematical models. Some have been developed for application primarily to common sedentary work (3) or low workload conditions (8). These modelers intend to use data in which the type of work and workload were systematically varied to extend their models to other work contexts. *Type of work* or the extent to which work requires physical activity has not yet been evaluated for model parameterization. Rosa (57) points out that it is unclear what applicability extant models have to more physically demanding performance, since model validation has largely been based on more cognitively demanding performance. It has also been suggested that models should be designed to take into account waking activity levels from off-duty as well as on-duty periods (63). As with *time on task* and *workload*, it is unknown whether information on *type of work* and *waking activity levels* will markedly enhance predictions of fatigue and performance. Basic laboratory studies can help resolve these issues.

Light

Environmental conditions can vary greatly in work contexts, yet it is not known what effect environmental differences may have on the neurobehavioral expression of fatigue based in sleep/wake and circadian dynamics (60). Since laboratory experiments on sleep/wake and circadian perturbations often involve near-constant environmental conditions, the influence of environmental factors on fatigue responses is rarely assessed, except for the effects of light, for which there are known neurobiological receptors that transmit light information to the endogenous biological clock (29).

Despite strong scientific evidence for the biological importance of light to processes regulating circadian phase and alertness (9,16), only the progenitor Two-Process Model (1) and the Interactive Neurobehavioral Model (37) include light exposure as critical inputs (46). Light information is relatively easily determined in a workplace, and/or acquired online with miniaturized technology. Such information may be especially important when models are used to predict performance capability of persons exposed occupationally to different lighting intensities and spectra (e.g., long-haul transmeridian flight crew), or when models are used to predict performance during (simulated) night work, jet lag and prolonged work.

A fruitful line of investigation underway by Jewett and colleagues (36,40,41) concerns the possibility of using light exposure history to calculate circadian phase. If it is found that light information enhances model accuracy for individuals—providing significantly better circadian phase estimates than might be derived from sleep/wake times (8)—then research should focus on the development of even better tools to measure exposure to light throughout the 24-h day during tests of model predictions in field conditions (9), as well as determine how often light information needs to be sampled to enhance model performance. Finally, both the phase-shifting (9) and evoked alerting (53) effects of light make it a potentially important countermeasure for fatigue in the workplace.

Other Factors

Posture also has been reported to influence both the consolidation of sleep (51), and the level of alertness and performance after a night without sleep (14). Although sleep-deprived subjects can fall asleep sitting up and standing, and non-sleep deprived alert subjects can stay awake lying supine, sleep is more consolidated when the body is supine, and alertness is heightened by standing. Brief postural breaks during simulated night work have been shown to have a transient alerting effect in airline pilots (50). Biomathematical models of fatigue and performance generally do not include as an input posture while working. Laboratory studies could help resolve whether posture during work (e.g., sitting vs. standing while performing), and/or posture during sleep (i.e., supine vs. non-supine) have sufficiently large or long-lasting effects on performance to warrant the inclusion of sleep/wake postures in models.

There has been no systematic work on the role that other factors (e.g., sound, vibration, temperature, humidity, altitude, hypoxia) may have in altering performance relative to changes in sleep/wake dynamics. The most relevant area for research for biomathematical models concerns the potential impact any of these factors may have on model estimates of recovery from sleep (58). To the extent that environmental factors can (like posture) interfere with and fragment sleep, they may reduce the recovery potential of sleep obtained in certain work environments where sleeping quarters are exposed to disruptive types and intensities of acoustic and vibrotactile stimuli (e.g., sleeper berths and bunks).

Finally, some high-profile operational environments in which biomathematical models might eventually be used can involve additional *work stressors* that affect performance. These include intense time pressure (e.g., rescue teams); performance with extremely serious consequences for an error (e.g., extravehicular activity in space); and/or performance in life-threatening circumstances (e.g., military conflict). There are common, often contradictory beliefs about fatigue in interaction with evoked physiological arousal, relative to performance capability during sleep loss, but there is little data to falsify any particular belief, and individual differences may be considerable. For models that are targeted for these types of operational scenarios, scientific data will ultimately be needed on the extent to which *work stressors* warrant inclusion to enhance ecological validity of performance models.

Conclusions

The emphasis on predicting dynamic change associated with endogenous (biological) shifts in functional capability sets biomathematical models of fatigue and performance apart from temporally static models of human factors, which traditionally focus on task-based or machine-based limits on human operator performance. The growing demand for biomathematical models of performance to help manage fatigue is a direct result of the way modern humans live in the 21st century in industrialized societies—more people awake more of the time managing ever more technologically sophisticated machines (27). As it has become clear that older models of fatigue management based in training, incentive pay, professionalism, and "right stuff" constructs were limited relative to the ubiquitous biological control of waking performance, attention has turned toward technologies to mitigate fatigue and ensure high levels of cognitive performance around the clock. Biomathematical models of fatigue and performance are one class of these technologies.

Models of fatigue and performance have considerable potential. As this article suggests, continued basic science can help validate models and bring them closer to transition to operational environments. Although some models are already being used operationally and touted for their ability to predict which work/rest schedules will produce fatigue and which will not, there are virtually no systematic, objective, independent studies of the accuracy of predictions of any model relative to operational outcomes. Clearly, models should not be rushed to practical use without prospective outcome studies replicated by independent multiple investigators, to ensure the strength of the findings. Modelers that have freely provided their models to others for research of this kind are to be commended. This article highlights research needed to move biomathematical modeling closer to the goal of accurately predicting human behavioral capability across many days of changing sleep/wake schedules. The effort to validate models for such use will require resources, but the investment is likely to yield benefits by reducing errors and accidents, and improving productivity for the millions of people involved in 24/7 operations.

When applied to practical problems in operational environments, biomathematical models of fatigue and performance are appropriately considered to be technologies for "fatigue management" (i.e., reduction of the performance-impairing and risk-enhancing consequences of fatigue), through the implementation of ostensibly safer work/rest schedules; and/or the timely delivery of countermeasures that promote alertness and performance capability (27). No one really knows how such models actually will be used, and studies will eventually be needed on how managers make use of models and modeling information for different goals (e.g., safety vs. productivity). This is analogous to testing how any safety-enhancing technology is used to optimize its benefits and mitigate its side effects.

Like any technology designed to safely and effectively enhance the predictability of human performance, models must meet a range of criteria involving scientific validity and reliability, practical utility, and legal and ethical standards (22). Given the lethal consequences of errors in certain civilian and military contexts, the potential for harm, wasted resources, and false security is substantial if invalid models are deployed. However, if biomathematical models can generate work schedules that are safe but also meet the needs of specific industries, much good could be accomplished.

In conclusion, biomathematical models have potential, but research must be carried out to clearly establish their basic scientific validity relative to laboratory data, and after that step, research on their ecological validity relative to different real-world scenarios is essential. Models should not be used beyond their range of validity, and they should provide estimates of prediction error. Regardless of how biomathematical models of fatigue and performance may ultimately prove useful, there is widespread agreement on the merits of developing such quantitative technologies to predict the impact on performance and safety of acute sleep loss, cumulative sleep loss, circadian desynchrony, recovery during sleep periods, the effects of fatigue countermeasures, and related aspects of work/rest schedules.

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