

<b>Fiscal Year:</b>	FY 2013	<b>Task Last Updated:</b>	FY 01/11/2013
<b>PI Name:</b>	Phillips, Andrew J Ph.D.		
<b>Project Title:</b>	Physiologically-Based Modeling of Sleep-Wake Scheduling and the Effects of Pharmaceuticals (Postdoctoral Fellowship)		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>	NSBRI		
<b>Program/Discipline--Element/Subdiscipline:</b>	NSBRI--Human Factors and Performance Team		
<b>Joint Agency Name:</b>	<b>TechPort:</b>	No	
<b>Human Research Program Elements:</b>	(1) <b>BHP</b> :Behavioral Health & Performance (archival in 2017)		
<b>Human Research Program Risks:</b>	(1) <b>Sleep</b> :Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload (IRP Rev F)		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
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<b>Comments:</b>			
<b>Project Type:</b>	GROUND	<b>Solicitation / Funding Source:</b>	2009 NSBRI-RFA-09-01 Postdoctoral Fellowships
<b>Start Date:</b>	10/01/2009	<b>End Date:</b>	10/01/2012
<b>No. of Post Docs:</b>	1	<b>No. of PhD Degrees:</b>	0
<b>No. of PhD Candidates:</b>	0	<b>No. of Master' Degrees:</b>	0
<b>No. of Master's Candidates:</b>	0	<b>No. of Bachelor's Degrees:</b>	0
<b>No. of Bachelor's Candidates:</b>	0	<b>Monitoring Center:</b>	NSBRI
<b>Contact Monitor:</b>	<b>Contact Phone:</b>		
<b>Contact Email:</b>			
<b>Flight Program:</b>			
<b>Flight Assignment:</b>			
<b>Key Personnel Changes/Previous PI:</b>			
<b>COI Name (Institution):</b>	Klerman, Elizabeth ( MENTOR/Brigham and Women's Hospital )		
<b>Grant/Contract No.:</b>	NCC 9-58-PF02101		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			

**POSTDOCTORAL FELLOWSHIP**

NASA astronauts and ground crew must meet high-level cognitive and physical demands around-the-clock. These tasks place extreme stress on human physiology, which evolved under conditions of 24-h days with ample rest. The effects of sleep loss, circadian misalignment, and extended schedules on performance and subjective alertness pose serious risks to mission success. It is therefore crucial that countermeasures are developed for optimizing schedules and guiding pharmaceutical use.

Mathematical modeling provides a means of predicting performance and alertness under many different conditions, including untested conditions. Improved knowledge of sleep physiology has enabled development of more sophisticated models of sleep and wake. A physiologically based model of the sleep-wake switch has been developed and applied to sleep deprivation, shift work, pharmacologic stimuli, and fatigue. Meanwhile, a circadian model developed at the Brigham and Women's Hospital (BWH), has been applied to predicting performance and alertness, designing pre-mission countermeasures, and optimizing mission scheduling.

**Task Description:**

Our original aims were to combine the sleep-wake switch and circadian models, and incorporate pharmaceutical effects. We have successfully combined the sleep-wake switch and circadian models, including physiological interactions between these systems, thereby developing the most comprehensive model of human sleep/wake dynamics to date. This model has since been used to understand the physiological mechanisms underlying (1) interindividual differences in chronotype (i.e., morningness/eveningness preference) and (2) spontaneous desynchrony of the endogenous circadian rhythm from sleep/wake patterns during self-selected schedules. It has also been tested against data collected at the BWH research facilities during forced desynchrony experiments in which sleep/wake schedules are desynchronized from endogenous circadian rhythms using a non-24 h sleep/wake cycle. Results show that the model is capable of predicting the sleep/wake patterns observed during this imposed schedule, including difficulty initiating and maintaining sleep when scheduled at inappropriate circadian phases. The model has now been extended to include pharmaceutical effects, including both caffeine and melatonin. Recently, we showed that the model can be used to predict the effects of exogenous doses of melatonin on melatonin concentration in the blood and phase shifts of the circadian pacemaker. We are currently also testing the model against data for caffeine from experiments conducted at BWH. Development of our model has resulted in improved estimates of performance measures, and new diagnostics for assessing schedule suitability on an individual basis, including chronotype.

With much of the basic science completed, we have been developing a predictive software tool for optimizing the timing and use of pharmaceutical countermeasures for extended wake durations and circadian misalignment conditions. This tool will be usable by a non-specialist, and will allow the user to compare the efficacy of a user-inputted alternative countermeasure timing to the optimized solution so as to be flexible to the realities of schedule design. This tool will allow our findings to be deployed to the operational environment.

This research program will not only significantly reduce risks on future NASA missions, but also has broad applications to optimizing shift work and other work schedules on Earth. The tool we develop will be easily generalizable to managing extended wake and circadian misalignment conditions in industries such as defense, healthcare, transport, and shift workers. Furthermore, we anticipate that our research will lead to better understanding and regulation of pharmaceuticals for use in treating sleep disorders.

**Rationale for HRP Directed Research:**

Our project is not only important to the space program, but also has broad applicability on Earth. Mathematical models of sleep/wake and circadian rhythms can be used to optimize performance and improve worker schedules in a wide range of environments. They are thus of potential use to all industries that require humans to operate at a high level at adverse times or after long periods awake. Chiefly, this includes the medical, military, aviation, and ground transportation industries, as well as shift workers. Recently, shift work and circadian disruption have been identified as significant risk factors for cancer, cardiovascular disease, diabetes, and suppressed immune function. The need for mathematical tools to circumvent – or at least minimize – occupational risks is thus a growing requirement. Ultimately, the development of tools that can be used to improve performance in the workplace would have a large potential impact across many industries.

**Research Impact/Earth Benefits:**

Providing a framework for better understanding and predicting the effects of pharmaceuticals that interact with the circadian and sleep/wake systems is also of wide importance. With the explosion in use of over-the-counter products such as caffeine and melatonin, it is important to develop models that can aid in understanding the physiological and performance impacts of self-medication. Furthermore, since our model is physiologically based, it could be used to help identify target pathways for future pharmaceuticals, and to better understand drugs of known efficacy but unknown mode of action (e.g., modafinil).

Developing mathematical models of sleep/wake and circadian rhythms is also a problem of basic scientific value. Such models serve multiple roles, including: (1) Improving our understanding of how the underlying physiology gives rise to the observed dynamics; (2) Making predictions about how the system will respond under untested conditions; and (3) Aiding the design of experimental protocols by predicting which conditions will provide the most informative results, thus making better use of available resources. The two-way dialogue between experimentalists and theorists is proving to be highly valuable to the sleep/wake and circadian scientific communities. New experimental findings inform the design and refinement of mathematical models, while models provide insight into the observed phenomena. In our case, the unexpected finding that our model can reproduce the sleep of other species is an excellent example of how modeling provides us with the tools to expand our scientific horizons.

Specific Aim 1 (developing a combined model of sleep/wake and circadian rhythms): We have successfully combined our physiologically based models of the systems underlying sleep/wake regulation and circadian rhythms, and developed a flexible software implementation to facilitate the incorporation of future modifications. The new integrated model includes bidirectional interactions between the sleep/wake and circadian systems, and is able to dynamically predict sleep/wake behaviors in response to imposed schedules. This includes insomnia when sleep is scheduled at inappropriate circadian phases, which is known to be a significant risk in the space environment. We have simulated data from spontaneous desynchrony protocols as a first stage of validation, and the model has provided insights into the physiological mechanisms underlying this phenomenon. We have also simulated forced desynchrony protocols and are now extending the model to include the effects of caffeine and/or chronic sleep restriction under these conditions. We

<b>Task Progress:</b>	<p>have also improved the utility of the model by developing linked models of the ultradian REM/NREM cycle and entrainment of circadian rhythms by food.</p> <p>Specific Aim 2 (incorporating the effects of pharmaceuticals): We have successfully included the effects of melatonin on the circadian pacemaker and the effects of caffeine on the sleep homeostat. We are now investigating interactions between the circadian pacemaker and the sleep homeostat, as well as the effects of caffeine under forced desynchrony.</p> <p>Specific Aim 3 (developing user-friendly software): Over the past 12 months, we have continued to improve the modular structure and functions of our MATLAB implementation of the model. These changes have made the model easier to implement in different settings. We have also successfully implemented software that can be used to simulate the effects of sleep, light, and pharmaceutical countermeasures on a single schedule. We are currently still working toward completing our implementation of a GUI (graphical user interface) system.</p>
<b>Bibliography Type:</b>	Description: (Last Updated: 04/08/2019)
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<b>Articles in Peer-reviewed Journals</b>	Breslow ER, Phillips AJ, Huang JM, St Hilaire MA, Klerman EB. "A mathematical model of the circadian phase-shifting effects of exogenous melatonin." J Biol Rhythms. 2013 Feb;28(1):79-89. <a href="http://dx.doi.org/">http://dx.doi.org/</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/23382594/">PMID: 23382594</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC3733227/">PMCID: PMC3733227</a> , Feb-2013
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