Fiscal Year:	FY 2012	**Task Last Updated:**	FY 10/12/2011
PI Name:	Phillips, Andrew J Ph.D.		
Project Title:	Physiologically-Based Modeling of Sleep-Wake Scheduling and the Effects of Pharmaceuticals		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Human Factors and Performance Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **BHP**:Behavioral Health & Performance (archival in 2017)		
Human Research Program Risks:	(1) **Sleep**:Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	ajphillips@partners.org	**Fax:**	FY 617- 732-4015
PI Organization Type:	UNIVERSITY	**Phone:**	617-278-0057
Organization Name:	Brigham and Women's Hospital		
PI Address 1:	Division of Sleep Medicine		
PI Address 2:	221 Longwood Ave. Suite 438		
PI Web Page:			
City:	Boston	**State:**	MA
Zip Code:	02115	**Congressional District:**	8
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2009 NSBRI-RFA-09-01 Postdoctoral Fellowships
Start Date:	10/01/2009	**End Date:**	09/30/2012
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Klerman, Elizabeth (MENTOR/Brigham and Women's Hospital)		
Grant/Contract No.:	NCC 9-58-PF02101		
Performance Goal No.:			
Performance Goal Text:			

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

Task Description:	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. 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. Currently, the model is also being extended to include pharmaceutical effects, and we have already set the groundwork for incorporating the effects of caffeine, melatonin, and modafinil. 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 now also incorporating data for caffeine from experiments conducted at BWH. Further development of our model will result 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 now complete, we aim to develop 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:	
Research Impact/Earth Benefits:	Risks associated with fatigue due to circadian misalignment or extended wake are a serious danger in many work environments. Specifically, industries such as transportation, aviation, healthcare and defense often demand long and irregular working hours, with performance failures resulting in potentially fatal consequences. Developing effective countermeasures for fatigue is thus a problem with broad applicability on Earth. Our NSBRI research project addresses the issue of fatigue through the development of a mathematical model of human sleep and circadian rhythms that is also able to incorporate pharmaceutical effects. This approach provides three separate means of managing and reducing risks associated with fatigue: (1) The model can be used to guide the development of safe schedules; (2) The model can be used to predict times when fatigue-related risks will be greatest; (3) The model can be used to optimize the use and timing of fatigue countermeasures, including light, naps and pharmaceuticals. 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, given the large proportion of the US population involved in shift work. 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.
Task Progress:	In the past year, we have made substantial progress on this project's original specific aims. Specific Aim 1 (developing a combined model of sleep/wake and circadian rhythms): Our combined model of sleep/wake regulation and circadian rhythms is now fully implemented in MatLab. This model is based on physiology, and includes bidirectional interactions between the sleep and circadian systems. Our code has been developed in a modular structure, allowing it to be easily modified or extended for new applications, including the software tool we propose to develop in our third year. The model has now been validated against data from both human spontaneous and forced desynchrony experiments. This process has identified potential physiological mechanisms underlying spontaneous desynchrony (a phenomenon which remains poorly understood), and this work has been accepted for publication in the Journal of Biological Rhythms. The model has also been shown to reproduce inter-species and inter-individual differences in sleep/wake timing, and has provided new insights into the mechanisms that determine these timings, including the direct alerting effects of light (a new addition to the model). These findings demonstrate the translational value of this new mathematical model, and are critical to achieving effective countermeasures for fatigue due to circadian misalignment and/or extended wake on an individual basis.

	Specific Aim 2 (incorporating the effects of pharmaceuticals): Because our model is physiologically based, the effects of pharmaceuticals on the sleep/wake and circadian systems can be readily incorporated. In the past year, we have incorporated the effects of exogenous doses of melatonin. The model has been shown to reproduce experimental data for both blood melatonin concentration and circadian phase shifts. The groundwork has also been laid for including other sleep-promoting or wake-promoting pharmaceuticals, including caffeine and modafinil. We are currently using data from a forced desynchrony experiment where subjects were given caffeine to validate the model's predictions of the effects of caffeine on alertness at different times of day.
Bibliography Type:	Description: (Last Updated: 04/08/2019)
Abstracts for Journals and Proceedings	Gharibshahi S, Phillips AJK, Mietus JE, Thomas RJ. "Sleep fragmentation phenotypes in sleep apnea syndromes." 25th Annual Meeting of the Associated Professional Sleep Societies, LLC 2011, Minneapolis, MN, June 11-15, 2011. Sleep 2011;34 Suppl:A133. http://www.journalsleep.org/Resources/Documents/2011abstractsupplement.pdf , Jun-2011
Abstracts for Journals and Proceedings	Phillips AJK, Breslow E, Huang J, St Hilaire MA, Klerman EB. "Adding Melatonin Countermeasures to a Model of Human Sleep/Wake and Circadian Rhythms." 18th IAA Humans in Space Symposium, Houston, TX, April 11-15, 2011. 18th IAA Humans in Space Symposium, Houston, TX, April 11-15, 2011. , Apr-2011
Abstracts for Journals and Proceedings	Phillips AJK, Klerman EB, Bianchi MT. "Noise induced transitions reproduce realistic sleep/wake architecture in a mathematical model of human sleep." 25th Annual Meeting of the Associated Professional Sleep Societies, LLC 2011, Minneapolis, MN, June 11-15, 2011. Sleep 2011;34 Suppl:A36. http://www.journalsleep.org/Resources/Documents/2011abstractsupplement.pdf , Jun-2011
Articles in Peer-reviewed Journals	Duffy JF, Cain SW, Chang AM, Phillips AJ, Münch MY, Gronfier C, Wyatt JK, Dijk DJ, Wright KP Jr, Czeisler CA. "Sex difference in the near-24-hour intrinsic period of the human circadian timing system." Proc Natl Acad Sci U S A. 2011 Sep 13;108 Suppl 3:15602-8. Epub 2011 May 2. http://dx.doi.org/10.1073/pnas.1010666108 ; PubMed PMID: 21536890 , Sep-2011
Articles in Peer-reviewed Journals	Phillips AJK, Czeisler CA, Klerman EB. "Revisiting spontaneous internal desynchrony using a quantitative model of sleep physiology." J Biol Rhythms. In press, August 2011. , Aug-2011
Books/Book Chapters	Robinson PA, Phillips AJK, Fulcher BD, Puckeridge M, Roberts JA, Rennie CJ. "Quantitative modeling of sleep dynamics." in "Sleep and anesthesia: neural correlates in theory and experiment." Ed. A. Hutt. New York : Springer, 2011. p. 21-41., Jul-2011