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| **Fiscal Year:** | FY 2011 | **Task Last Updated:** | FY 11/09/2010 |
| **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 | | |
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| **Organization Name:** | Brigham and Women's Hospital | | |
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| **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:** | 09/30/2011 |
| **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:** | 0 | **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, including untested, conditions. Improved knowledge of sleep physiology has enabled development of more sophisticated models

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| **Task Description:** | 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.<br><br>By combining the sleep-wake switch and circadian models, including physiological interactions between these systems, we have developed 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. Currently, the model is being tested against data collected at the BWH research facilities during forced desynchrony experiments in which the sleep/wake schedule is desynchronized from endogenous circadian rhythms using a non-24 h sleep/wake cycle outside the range of entrainment. Preliminary 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. Once this validation procedure is complete, the model will be ready to predict sleep/wake patterns and incidence of insomnia during imposed schedules in both space and Earth environments. Further development of this model will result in improved estimates of performance measures, and new diagnostics for assessing schedule suitability on an individual basis, including chronotype. Alloying our complementary expertise in sleep-wake switch and circadian modeling will thus provide a significant step forward in assessment and design of mission schedules.<br><br>Since the model is physiological it is also readily extended to include pharmaceuticals that target sleep/wake physiology. We have set the groundwork for incorporating the effects of caffeine, melatonin, and modafinil on the sleep/wake and circadian systems; data for this work are available from studies already conducted at the BWH research facilities. Preliminary results indicate that the model captures the key effects of these drugs, and future work will allow us to calibrate the model to other experimental data obtained at the BWH. Our goal is to thus incorporate into our models predictions of the efficacy of pharmaceuticals as countermeasures for reducing fatigue and combating insomnia. These models will facilitate recommendations for administration of pharmaceuticals before, during and after missions.<br><br>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. Furthermore, we anticipate it will lead to better understanding and regulation of pharmaceuticals for use in treating sleep disorders. |
| **Rationale for HRP Directed Research:** | |
| **Research Impact/Earth Benefits:** | Our current funded 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.<br>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).<br><br>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:** | 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 are currently simulating data from forced desynchrony protocols as a second stage of validation.<br>We have also shown that the combined model is able to identify the physiological sources of interindividual and interspecies differences in sleep/wake timings. These findings are of significant translational value in terms of designing individualized countermeasures, and in using animal experiments to gain additional information about the underlying sleep/wake physiology.<br><br>Specific Aim 2 (incorporating the effects of pharmaceuticals): With model validation now nearing completion, we are well poised to incorporate pharmaceuticals into the model. We are presently incorporating the effects of melatonin by extending a previous model of endogenous melatonin output to include the effects of exogenous doses. To date, we have achieved a working model of the phase-shifting effects of melatonin, and intend to next include the hypnotic effects of melatonin. Once this is complete, the model will be validated against forced desynchrony data in which subjects were administered melatonin or placebo. Similar methodologies can then be used to model the effects of other drugs, |

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| | including caffeine and modafinil (since BWH also has forced desynchrony data for both of these). |
| **Bibliography Type:** | Description: (Last Updated: 04/08/2019) |
| **Abstracts for Journals and Proceedings** | Phillips AJ, Chen PY, Robinson PA, Czeisler CA, Klerman EB. "Using physiologically-based modeling to determine the mechanisms underlying complex sleep/wake dynamics." SIAM Conference on the Life Sciences, Pittsburgh, PA, July 12-15, 2010.<br>SIAM Conference on the Life Sciences, Abstract Book, July 2010. p. 176.<br>http://www.siam.org/meetings/ls10/LS10_abstracts.pdf , Jul-2010 |
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| **Abstracts for Journals and Proceedings** | Phillips AJ, Czeisler CA, Klerman EB. "Predicting sleep/wake schedule compliance using a physiologically based model of sleep." SLEEP 2010 24th Annual Meeting of the Associated Professional Sleep Societies, San Antonio, Texas, June 5-9, 2010.<br>Sleep 2010;33 Suppl:A71-2. http://www.journalsleep.org/PDF/AbstractBook2010.pdf , Jun-2010 |
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| **Articles in Peer-reviewed Journals** | Phillips AJ, Chen PY, Robinson PA. "Probing the mechanisms of chronotype using quantitative modeling." J Biol Rhythms. 2010 Jun;25(3):217-27. http://dx.doi.org/10.1177/0748730410369208 ; PMID: 20484693 , Jun-2010 |
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| **Awards** | Phillips AJK. "Richard E. Kronauer Award, July 2010." Jul-2010 |
| **Awards** | Phillips AJK. "School of Physics Postgraduate Alumni Prize, May 2010." May-2010 |
| **Awards** | Phillips AJK. "Sleep Research Society First Time Travel Award, June 2010." Jun-2010 |