Fiscal Year:	FY 2007	**Task Last Updated:**	FY 10/18/2007
PI Name:	Klerman, Elizabeth B. M.D., Ph.D.		
Project Title:	Mathematical Modeling of Circadian/Performance Countermeasures		
Division Name:	Human Research		
Program/Discipline:	NSBRI Teams		
Program/Discipline--Element/Subdiscipline:	NSBRI Teams--Human Performance Factors, Sleep, and Chronobiology Team		
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **BHP**:Behavioral Health & Performance (archival in 2017)		
Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (2) **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:	ebklerman@hms.harvard.edu	**Fax:**	FY 617-732-4015
PI Organization Type:	UNIVERSITY	**Phone:**	617-732-8145
Organization Name:	Brigham and Women's Hospital/Harvard Medical Center		
PI Address 1:	Department of Medicine		
PI Address 2:	Division of Sleep Medicine		
PI Web Page:			
City:	Boston	**State:**	MA
Zip Code:	02115-5804	**Congressional District:**	8
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2003 Biomedical Research & Countermeasures 03-OBPR-04
Start Date:	06/01/2004	**End Date:**	05/31/2008
No. of Post Docs:	0	**No. of PhD Degrees:**	2
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):			
Grant/Contract No.:	NCC 9-58-HPF00405		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Manned space flight requires crewmembers and ground-based staff to function at a high level of cognitive performance and vigilance, often for long durations of time and without opportunity for rest or sleep, while operating and monitoring sophisticated instrumentation. Due to the unusual light/dark patterns and sleep/wake schedules to which they are exposed, astronauts may frequently experience circadian misalignment, during which their circadian rhythms are not appropriately synchronized with their work schedules such that both their waketime performance and alertness and their ability to sleep can be severely compromised. We have developed a mathematical model of the effects of light on the human circadian pacemaker that has been used successfully to design a pre-flight light exposure regimen as a countermeasure to the circadian misalignment associated with early morning launch times often necessary for space shuttle flights. This mathematical model of light and the circadian system has been incorporated into our mathematical Circadian, Neurobehavioral Performance and Subjective Alertness Model so that we can now predict the effects of unusual light/dark and sleep/wake patterns on human performance at the time of launch. This model is available in a user-friendly Circadian Performance Simulation Software package for use by NASA personnel, scientists, engineers, teachers, and others. Our Specific Aims are: Specific Aim 1: Develop and refine the current circadian, neurobehavioral performance and subjective alertness model with melatonin as a marker rhythm to accurately predict phase and amplitude of the circadian pacemaker. Specific Aim 2: Refine and validate the current model by using data from chronic sleep restriction protocols. Specific Aim 3: Refine the current model to incorporate wavelength of light information. Specific Aim 4: Develop Schedule Assessment and Countermeasure Design Software using the amended CPNA model from Specific Aims 1, 2 and 3 to evaluate schedules and design and test appropriate countermeasures. Our progress on these aims includes: Specific Aim 1: We revised an existing mathematical model of the diurnal variations of plasma melatonin levels to include an effect of light and incorporated this into our model. This model provides an estimate of two melatonin phase markers, melatonin synthesis onset (Synon) and offset (Synoff), as well as melatonin amplitude and melatonin suppression by light. The phase relationships between Synon/Synoff and CBTmin have been determined and incorporated into our mathematical model. The revised model has been tested against experimental melatonin data in which subjects were exposed to 1-pulse of continuous bright light, continuous dim light or a pattern of intermittent bright and dim light. This model will be validated on several independent datasets to test predictions of circadian entrainment and phase-shift response. Specific Aim 3: We began to revise the light input to our model from lux to an irradiance measure of photons/cm2/sec for both polychromatic and monochromatic light exposures. We explored the physiological basis of a two-channel photoreceptor model, in which one channel is driven by rod/cone input and the other channel is driven by a melanopsin input with peak sensitivity at short wavelengths.~464nm. We also analyzed the effects of pupil diameter on circadian response. Specific Aim 4: Over the last year we have developed a schedule/countermeasure design prototype program that allows a user to interactively design a schedule and to automatically design a countermeasure regime. Mathematical optimization of schedule design has been added to the program. We have begun transitioning our previously developed schedule building blocks into prototype scheduling applications with the goal of building a tool that will facilitate the use of our models by NASA personnel to evaluate and design mission alternatives. As we reported previously our schedule building block technology is composed of two sections. The building blocks are a flexible software technology that can be used to design any schedule. The second component is the Circadian Iterative Adjustment method that we developed to determine optimal countermeasure placement within a schedule. Used together, we have shown that our methods can be used to design a variety of schedules relevant to NASA operations including shifting sleep-wake (slam shifting) and non-24 hour schedules. We have begun expanding our framework to include methods that determine the minimum amount of light required to maintain entrainment. Future work will involve expanding our prototype to evaluate a wider range of protocols and countermeasures, including pharmacologic agents. Other work: An aspect of individual difference not currently addressed in the circadian literature is to evaluate differences in the appropriate model structure for analyzing circadian data. Therefore, we have begun developing methodologies for determining how optimal model structure may differ by individual. To explore this line of research we used a Bayesian network framework. Within this framework, a model is defined as a graph where arrows designate an association and the strength of the association is defined by a corresponding probability distribution. The benefit of the framework is that models are easily understandable by non-mathematician and that the probability distributions can be approximated by existing data. Our initial results are promising and have shown that optimal model structure can vary by individual.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This research focuses on the further development of mathematical models and software that aid in schedule design to improve performance and thereby public safety for people who work at night, on rotating schedules, on non-24 h schedules or extended duty schedules (pilots, train and truck drivers, shift workers, health care workers, public safety officers). Attempting to work at adverse circadian phases and/or after long durations of time awake causes poor worker performance and productivity, increased accidents and decreased safety for workers and for others affected by the workers. For example, the Chernobyl, Three Mile Island, and the Exxon Valdez disasters were all were partially caused by workers attempting to perform at adverse circadian phases (~ 4 am). The mathematical modeling and the available Circadian Performance Simulation Software (CPSS) can be used to simulate different scenarios of sleep/wake schedules and light exposure to predict the resulting subjective alertness and neurobehavioral performance. CPSS has been used by members of academia, government and industry. We also examined the effect of light levels within cockpits and passenger cabins on circadian phase and performance during trans-meridian travel and polar flight paths for an article that appeared in The Wall Street Journal. The mathematical modeling has been used to design new research protocols. Using mathematical models to optimize measures to be studied in the protocol enables more efficient use of research resources. The modeling work can also

	direct new research in physiology. If the modeling of existing data is unsatisfactory, then the model assumptions need to be revised. This revision may include identification of physiological process not previously described. The mathematical modeling and CPSS have also been used in educational programs and in the popular press to teach students and teachers about circadian rhythms and sleep and their effects on alertness and performance.
Task Progress:	Specific Aim 1 is to develop and refine our current model to incorporate melatonin as a marker rhythm. We have incorporated an existing physiologically-based mathematical model of the diurnal variations in plasma melatonin levels into our mathematical circadian rhythms model. The revised model can predict melatonin amplitude, markers of melatonin phase (melatonin synthesis onset and synthesis offset), melatonin suppression by light, and salivary melatonin concentrations. Our model has been validated on several independent data sets. This work has been presented at scientific meetings. A manuscript has been submitted for publication and is under review. Specific Aim 3 is to incorporate wavelength sensitivity into our current model. We have begun to revise the light input to our model from lux to an irradiance measure (photons/cm2/sec) for both polychromatic and monochromatic light exposures. We explored the physiological basis of a two-channel photoreceptor model, in which one channel is driven by rod/cone input and the other channel is driven by a melanopsin input with peak sensitivity in the short wavelength range. We have also analyzed the effects of pupil diameter on circadian response. We started to analyze the effects of the aging of the lens of light transmission and we have begun to incorporate new 460nm and 555nm fluence response data. This work has been presented at a scientific meeting. Specific Aim 4 is to develop Schedule Assessment and Countermeasure Design Software. Over the last year we have developed a schedule/countermeasure design prototype program that allows a user to interactively design a schedule and to automatically design a countermeasure regime (intensity, duration and placement). We have begun transitioning our previously developed schedule building blocks into prototype scheduling applications to build a tool that will facilitate the use of our models by NASA personnel. Used together we have shown that our methods can be used to design a variety of schedules and countermeasures relevant to NASA operations including shifting sleep wake (slam shifting) and non-24 hour schedules. This work has been presented at scientific meetings. A manuscript is in progress. By request of the reviewers, we have begun to explore inter-individual differences in performance. (1) We have begun developing methodologies for determining how optimal model structure may differ by individual. The benefit of the framework is that models are easily understandable by non-mathematicians and that the probability distributions can be approximated by existing data. Our initial results have shown that optimal model structure can vary by individual. (2) We have begun data analysis to quantify differences in model parameter values and correlate these with differences between individuals such as age, gender, morningness-eveningness, habitual bedrest duration and habitual sleep/wake times. This work has been presented at a scientific meeting.
Bibliography Type:	Description: (Last Updated: 06/25/2025)
Abstracts for Journals and Proceedings	St Hilarie M, Klerman EB. "A tool to analyze melatonin phase and amplitude using a physiologically based model of melatonin." Sleep 2006, 20th Anniversary Meeting of the Association of Professional Sleep Societies, Salt Lake City, UT, June 17-22, 2006. Sleep. 2006;29(Suppl):A53-4. , Jun-2006
Abstracts for Journals and Proceedings	St Hilaire MA, Klerman EB. "Inter-individual variability in the parameters of a mathematical model of neurobehavioral performance and alertness." Sleep 2007, Annual Meeting, Minneapolis, MN, June 9-14, 2007. Sleep 2007;30(Suppl):A52. , Jun-2007
Articles in Peer-reviewed Journals	Dean DA 2nd, Fletcher A, Hursh SR, Klerman EB. "Developing mathematical models of neurobehavioral performance for the “real world“." J Biol Rhythms. 2007 Jun;22(3):246-58. Review. PMID: 17517914 , Jun-2007
Articles in Peer-reviewed Journals	Kronauer RE, Gunzelmann G, Van Dongen HP, Doyle FJ 3rd, Klerman EB. "Uncovering physiologic mechanisms of circadian rhythms and sleep/wake regulation through mathematical modeling." J Biol Rhythms. 2007 Jun;22(3):233-45. Review. PMID: 17517913 , Jun-2007
Articles in Peer-reviewed Journals	Klerman EB, Hilaire MS. "On mathematical modeling of circadian rhythms, performance, and alertness." J Biol Rhythms. 2007 Apr;22(2):91-102. Review. http://dx.doi.org/10.1177/0748730407299200 ; PMID: 17440211 , Apr-2007
Articles in Peer-reviewed Journals	Indic P, Gurdziel K, Kronauer RE, Klerman EB. "Development of a two-dimension manifold to represent high dimension mathematical models of the intracellular Mammalian circadian clock." J Biol Rhythms. 2006 Jun;21(3):222-32. PMID: 16731662 , Jun-2006