Fiscal Year:	FY 2006	**Task Last Updated:**	FY 01/08/2007
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		
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Zip Code:	02115-5804	**Congressional District:**	8
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2003 Biomedical Research & Countermeasures 03-OBPR-04
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No. of PhD Candidates:	1	**No. of Master' Degrees:**	3
No. of Master's Candidates:	3	**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):			
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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:

This work advances science and applications in other areas besides our specific aims.
This research focuses on 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, etc.). The mathematical modeling and the available CPSS software can be used to simulate different scenarios of sleep/wake schedules and light exposure and predict the resulting circadian phase and amplitude, subjective alertness and neurobehavioral performance. Attempting to sleep at adverse circadian phases is difficult and the sleep efficiency is poor. 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 accidents at Chernobyl and Three Mile Island nuclear reactors and the Exxon Valdez grounding all were partially caused by workers attempting to perform at adverse circadian phases (~ 4 am). CPSS has been requested by members of academia, government and industry. Its use could help produce improved schedules for working. The development of optimal and interactive scheduling tools will also be applicable to earth-based industry and government.

Research Impact/Earth Benefits:	We have completed systematic simulation studies of the effect of circadian shifting on phase re-entrainment and performance recovery. For example, we 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 can and has been used to design new research protocols. Inclusion of mathematical models in the process to optimize measures to be studied in the protocol enables more efficient use of research resources. The modeling work can also direct new research.If the modeling of existing data is unsatisfactory, then the model assumptions need to be revised. This revision may include identification of a new physiological process not previously described. As an example, Process L was added to our mathematical model to describe data collected in the BWH laboratory. Only recently has the anatomic and physiologic basis of Process L in our mathematical model been found. The mathematical modeling efforts and CPSS have 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 model to predict melatonin synthesis onset (Synon) and synthesis offset (Synoff) as two markers of melatonin phase. The phase relationships between Synon, Synoff and the fit minimum of Core Body Temperature CBTmin, another accepted marker of circadian rhythms, have been determined. The revised model can predict melatonin amplitude, melatonin suppression by light and phase-shifting of melatonin rhythms at bright light levels. Our model has been tested with 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. 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. This model has been tested with data from a 460nm fluence response curve and will be validated on future datasets. 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. 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 relevant to NASA operations including shifting sleep wake (slam shifting) and non-24 hour schedules. We have also begun expanding our framework to include methods that determine the minimum amount of light required to maintain entrainment. By request of the reviewers, we have began to explore inter-individual differences in performance. An aspect of individual difference not currently addressed in the circadian literature is to evaluate differences in the appropriate model structure. Consequently, 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 are promising and have shown that optimal model structure can vary by individual.
Bibliography Type:	Description: (Last Updated: 10/26/2023)
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