Fiscal Year:	FY 2008	**Task Last Updated:**	FY 12/16/2008
PI Name:	Klerman, Elizabeth B. M.D., Ph.D.		
Project Title:	Mathematical Modeling of Circadian/Performance Countermeasures		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Human Factors and Performance 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 Bachelor's Candidates:	0	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
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Task Description:	Manned space flight requires crewmembers and ground-based staff to function at a high level of performance, often for long durations of time and without adequate opportunity for sleep, while operating sophisticated instruments. In space, sleep and circadian rhythms are disrupted. 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 and slam-shifting of schedules present during missions. This mathematical model of light and the circadian system has been incorporated into our mathematical Circadian, Neurobehavioral Performance and Alertness (CPNA) Model so that we can now predict the effects of unusual light/dark and sleep/wake patterns on human performance and alertness at under any schedule on the ground or in space. This model is available in a user-friendly Circadian Performance Simulation Software (CPSS) 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 (CNPA) 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 includes: Specific Aim 1: We revised an existing mathematical model of the diurnal variations of plasma melatonin levels to include an effect of light suppression and a new compartment to model salivary melatonin levels. This revised model of melatonin has been incorporated into our CNPA model. CNPA can now provide an estimate of two melatonin phase markers, melatonin synthesis onset (Synon) and offset (Synoff), as well as melatonin amplitude and melatonin suppression by light. This revised model has been validated on several independent datasets to test predictions of circadian entrainment and phase-shift response. A manuscript of this work has been published. Specific Aim 3: We have revised the circadian model to include effects of different wavelengths of light. The revised model assumes circadian photoreception acts via two processes: a synaptic process via the rods and cones of the visual system and a second process via the photopigment melanopsin, which is found in intrinsically photosensitive retinal ganglion cells. This revised model can predict the circadian phase-shifting responses to monochromatic light exposures at wavelengths of 460nm and 555nm, based on fluence-response data collected under another NSBRI project (Brainard, P.I.). and the response under polychromatic light exposure. A manuscript of this work is in preparation. The revised equations can easily be incorporated into CNPA model. Specific Aim 4: We have developed a schedule/countermeasure program that allows a user to automatically design a mathematically optimal countermeasure schedule after a shift in sleep/wake schedule or during non-24-hour days. Our schedule building block technology is composed of two components: (1) building blocks as a flexible software technology that can be used to design any schedule, and (2) the Circadian Iterative Adjustment method that we developed to determine optimal countermeasure intensity and placement within a schedule. The work can be easily expanded to include other countermeasures, including pharmacologic agents. The software including this work has been demonstrated and taught to NASA and National Space Biomedical Research Institute (NSBRI) personnel so that they can use it to evaluate and design schedule alternatives for missions. Other work: We began work on quantifying inter-individual differences in response to circadian phase-shifting stimuli and extended wake durations. One approach of quantifying inter-individual differences not currently addressed in the circadian literature is to evaluate inter-individual differences using the appropriate model structure for analyzing circadian data. 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. Using this method, we have shown that optimal model structure can vary by individual and that simple adjustment of parameters may not suffice to accurately predict inter-individual differences in performance after circadian phase shifts or during extended wake durations. This work has been presented at scientific meetings and a manuscript of this work is in progress. We have also explored inter-individual differences in model parameters for extended wake durations without circadian disruption. We found a best-fit model to individual performance and alertness data using the CNPA model. We investigated inter-individual differences in parameter values of these best-fit models and the relationship of these values to individual subject characteristics, including age, gender, morningness-eveningness preference, habitual bedrest duration, and habitual sleep/wake times. Several important correlations between model parameters and subject characteristics have been found. These correlations indicate important trait-like differences in the underlying circadian and homeostatic processes represented by the model equations. This work has been presented at scientific meetings.
Rationale for HRP Directed Research:	
	The development (1) of mathematical models of circadian rhythms, sleep, alertness, and performance and (2) of software based on these models that aid in schedule design can improve performance and alertness and thereby effectiveness and public safety for people who work at night, on rotating schedules, on non-24-hr schedules or extended duty schedules (pilots, train and truck drivers, shift workers, health care workers, public safety officers, etc.). Attempting to sleep at adverse circadian phases is difficult and sleep efficiency is poor. Attempting to work at adverse circadian phases and/or after long durations of time awake results in poor worker performance and productivity, increased accidents, and decreased safety for workers and for others affected by the workers. For example, the accidents at the Chernobyl and Three Mile Island nuclear reactors and the Exxon Valdez grounding all were partially caused by workers working at adverse circadian phases (~ 4 am). The mathematical modeling and the available Circadian Performance Simulation Software (CPSS) can be used to simulate and quantitatively evaluate different scenarios of sleep/wake schedules and light exposure to predict the resulting circadian phase and amplitude, subjective alertness, and performance. CPSS has been requested by members of academia, government, and industry (transportation (especially airline personnel), safety, medical, military). Its use could help produce improved schedules for working for people in space and on Earth.

	The software also now includes optimal countermeasure design, so that countermeasures can be planned for times of predicted poor performance and alertness. The schedule/countermeasure design program allows a user to interactively design a schedule and to automatically design a mathematically optimal countermeasure regime (intensity, duration, and placement). This will be valuable to those who schedule people who work at night, on rotating schedules, on non-24-hr schedules, or extended duty schedules. Individuals can design countermeasures for their assigned work schedules so that their sleep and wake rhythms will be adjusted for optimal performance at desired times. Using these tools, 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 in 2004. The mathematical modeling has been used for basic scientific research. Inclusion of mathematical models in the planning process to optimize measures to be studied in experimental protocols enables more efficient use of research resources and directs 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, an additional component (non-linear response to ocular light stimuli) was added to the circadian rhythms component of our mathematical model to describe data collected in our clinical research facilities, even before the anatomic and physiologic basis of this component of the mathematical model was found. Later experiments validated this mathematical finding. The mathematical model had demonstrated that previously unknown additional physiological processes were involved. The modeling work on the differential effects of different wavelength of light on circadian rhythms and alertness can be used for designing artificial (indoor) lighting systems that can maximize circadian or alerting response. The mathematical modeling efforts 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.
Research Impact/Earth Benefits:	(see above)
Task Progress:	We developed and refined our current mathematical model of circadian rhythms to incorporate melatonin as a marker rhythm. We used an existing physiologically based mathematical model of the diurnal variations in plasma melatonin levels. The revised model can predict melatonin amplitude, markers of melatonin phase (melatonin synthesis onset (Synon) and synthesis offset (Synoff)), melatonin suppression by light, and salivary melatonin concentrations. Our model has been validated on several independent data sets. A manuscript of this work has been published. We incorporated wavelength sensitivity into our current mathematical model. We have revised the light input to our model from lux to an irradiance measure (microW/cm2) for both polychromatic and monochromatic light exposures. We have developed 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 (~480nm). Our model can predict the response of the circadian pacemaker to 1-pulse light exposures of 460nm and 555nm at different irradiances to generate fluence-response curves of circadian phase-shifts to polychromatic light. This work has been presented at scientific meetings. A manuscript of this work is in preparation. We developed schedule assessment and countermeasure design software. We have developed a schedule/countermeasure design program that allows a user to interactively design a schedule and to automatically design a mathematically optimal countermeasure regime (intensity, duration, and placement). We have demonstrated this tool to NASA personnel. We have substantially redesigned the user interface for CPSS, the software implementation of our mathematical model, based on feedback from NASA users and operational requirements. 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), sleep deprivation, and non-24 hour schedules. This work has been presented at scientific meetings. A manuscript is in progress. 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. (2) We have conducted data analysis to quantify differences in model parameter values and we have correlated these model parameter differences with individual characteristics such as age, gender, morningness-eveningness, habitual bedrest duration, and habitual sleep/wake times. We have demonstrated the trait-like characteristics in the robustness of parameters associated with the homeostatic process under experimental light interventions. This work has been presented at scientific meetings.
Bibliography Type:	Description: (Last Updated: 06/25/2025)
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