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14. ABSTRACT

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RPPR Final Report
as of 24-Feb-2022

Agency Code: 21XD

Proposal Number: 70978MA **Agreement Number: W911NF-17-1-0562**
INVESTIGATOR(S):

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Report Date: 24-Nov-2021 Date Received: 15-Feb-2022
Final Report for Period Beginning 25-Sep-2017 and Ending 24-Aug-2021
Title: A Quantitative Approach to the Biochronicity of Circadian Rhythm, Sleep, and Neurobehavioral Performance
Begin Performance Period: 25-Sep-2017 **End Performance Period:** 24-Aug-2021
Report Term: 0-Other
Submitted By: John Wen Email: wenj@rpi.edu
Phone: (518) 276-6156
Distribution Statement: 1-Approved for public release; distribution is unlimited.

STEM Degrees: 1 **STEM Participants:**

Major Goals: Analyze mathematical models that include both circadian and sleep processes for key properties, such as the stability of periodic solutions. Periodic solutions of such models correspond to stable entrainment of joint circadian-sleep-lighting processes. 2. Develop optimal algorithms for entrainment, such as entrainment in minimal time. 3. Develop optimal strategies for maximizing mental alertness during critical missions. The subjects of the optimal strategies include scheduling of sleep, lighting, and tasks. 4. Developing state estimation algorithms that will allow for the implementation of the optimal strategies above in a closed-loop, using biometric data from the mission performers. This will also enable us to adapt and personalize the mathematical model during runtime.

Accomplishments: 1. Optimization of lighting and sleep schedules for fastest circadian rhythm entrainment: We solved an optimal control problem for time optimal entrainment (quickest entrainment) for a mathematical model that involves the circadian rhythms and sleep process dynamics. Such a model is typically referred to as the two-process model. The model is inherently hybrid, as its dynamics (in the sense of differential equation) is affected by the discrete sleep state of the subject (i.e., asleep or awake). The challenge in solving the quickest entrainment problem for such model is in finding both the optimal light signal and the optimal sleep schedule that result in the quickest entrainment while maintaining a level of sleep comfort for the subject. We considered two cases: one where the sleep schedule is autonomous, i.e., a constraint but not optimized, and one where we jointly optimize the lighting and sleep schedules [R1, R4]. We have found that it is possible to gradually trade off sleep comfort with entrainment expedience [R5]. To date, as far as we know, we are the only group that has published time optimal results for joint circadian and sleep rhythms entrainment.
2. Characterization of the impact of model reduction on the optimization: Our optimization approach is based on the calculus of variations and relies on having a model of the system to compute the optimal lighting and sleep schedules. As models for circadian rhythm are available in various complexities (i.e., model orders), we studied the impact of model complexities on the optimization results. In particular, we looked at reduced-order variants of the well-accepted Jewett-Forger-Kronauer circadian rhythm model. We found that, generally, optimization results obtained using a reduced-order model cannot be applied directly on the original model without a significant loss in performance. This discrepancy is directly linked to the amplitude quenching in the circadian oscillation. We also found that optimization results obtained using a reduced-order model can be used effectively to (1) warm start the optimization for the original model [R2, R3], and (2) train a feedback controller that can be used on the original model [R1, R5] (see #3 below).
3. Learning of optimal feedback control laws: The optimization results described in the previous paragraphs are in the form of optimal schedules, which can be implemented in an open-loop fashion. That is, lighting and sleep are pre-scheduled according to the circadian rhythm and sleep states at the beginning of the entrainment period. Expectedly, such approach is not robust to disturbances and modeling uncertainties that may impact the system

during the execution. We have developed a method for learning optimal feedback control laws based on the computed optimal schedules. Our method is based on the nearest neighbor algorithm. It computes the feedback control law that implements lighting and sleep schedules based on the current circadian rhythm and sleep states of the subject, which we assume to be known (see #4 below), and those of the reference. We showed that this approach leads to a more robust solution. For example, optimal feedback control laws that are learned from optimization results of the reduced-order models can be applied effectively on higher-order models without a significant loss of performance [R1, R5].

4. Biometric Signal Processing for Circadian Rhythm and Sleep State Estimation: A key ingredient in an effective control algorithm for regulating and optimizing the circadian rhythm and neurobehavioral processes is the ability to estimate the state of the system. We focus on state estimation algorithms that use biometric signals as indirect markers of circadian rhythms and sleep. In particular, we focus on biometric signals that are practical to measure, e.g., using wearable sensors. Actigraphy is one of them. We recently found that our signal processing algorithm, which involves a self-tuning mechanism to account for individual differences, can be applied on actigraphy signals to obtain accurate estimations of circadian phase shifts [R6]. This result is validated against the standard clinical procedure that requires measurements of melatonin hormone level. This work was done in collaboration with researchers at the University of New Mexico who conducted the human subject experiments. We have also found that actigraphy signals can be used effectively to estimate the sleep state and the timing of sleep. This result has led to the possibility of using actigraphy to identify mild Traumatic Brain Injury (TBI) based on irregularities in the subject's sleep pattern [R7]. This work was in collaboration with researchers at the Thomas Jefferson University who conducted the human subject experiment.

5. Optimization of lighting and sleep schedules for neurobehavioral performance: We use alertness as a measure of neurobehavioral performance. Alertness is affected by both the circadian rhythm and sleep process. There are well accepted models that quantify alertness based on the three-process model which also includes sleep inertia. We have recently started to work on the optimal control problem related to optimizing alertness during mission performance. We can use some of the variational techniques that we have developed for time optimal entrainment in this problem. We have studied this problem in two settings. First, we look at a rotating-shift worker who has a periodic weekly schedule that involves day- and night-shifts (i.e., three night-shifts and two day-shifts every week). We compute the optimal weekly lighting and sleep schedules that optimize the total alertness during the work shifts. Second, we look at a mission performer who is assigned to perform a night-time mission (11 pm – 7 am). We compute the optimal lighting and sleep schedules that optimize the total alertness during the mission for different amounts of lead time. That is, we assume that the optimization begins on day D-1 up to D-7 of the mission and assess the gain in alertness resulting from the gain in lead time. Both results are currently in preparation for publication.

[R1] A.A. Julius, J. Yin, J. T. Wen, Time-Optimal Control for Circadian Entrainment for a Model with Circadian and Sleep Dynamics, in Proc. IEEE Conf. Decision and Control, Melbourne, Australia, 2017
[R2] A.A. Julius, J. Yin, J.T. Wen, Time Optimal Entrainment Control for Circadian Rhythm, PLoS ONE, vol. 14(12): e0225988, 2019.
[R3] J. Yin, A.A. Julius, J.T. Wen, Rapid Circadian Entrainment in Models of Circadian Genes Regulation, in Proc. IEEE Conf. Decision and Control, Nice, France, 2019.
[R4] A.A. Julius, J. Yin, J.T. Wen, Optimization of Lighting and Sleep Schedules, in Journal of the Homeland Defense & Security Information Analysis Center, vol. 6(3), pp. 44 – 47, 2019.
[R5] J. Yin, A.A. Julius, J.T. Wen, Optimization of Light Exposure and Sleep Schedule for Circadian Rhythm Entrainment, PLoS ONE, 16(6): e0251478, June 2021.
[R6] J. Yin, A.A. Julius, J.T. Wen, M. M. K. Oishi, L. Brown, Actigraphy-based Parameter Tuning Process for Adaptive Notch Filter and Circadian Phase Shift Estimation, Chronobiology International, August 2020.
[R7] J. Yin, A.A. Julius, J.T. Wen, J. P. Hanifin, B. Warfield, G. C. Brainard, Automatic Sleeping Time Estimation and Mild Traumatic Brain Injury (mTBI) Detection Using Actigraphy Data, Journal of Biomedical Signal Processing and Control, January 2021.

Training Opportunities: This project supports the training of one One Ph.D. student (Jiawei Yin) who graduated in August 2020.

Results Dissemination: The project outcome has been disseminated in the following venues:
[1] A.A. Julius, J. Yin, J. T. Wen, Time-Optimal Control for Circadian Entrainment for a Model with Circadian and Sleep Dynamics, in Proc. IEEE Conf. Decision and Control, Melbourne, Australia, 2017
[2] A.A. Julius, J. Yin, J.T. Wen, Time Optimal Entrainment Control for Circadian Rhythm, PLoS ONE, vol. 14(12): e0225988, 2019.
[3] J. Yin, A.A. Julius, J.T. Wen, Rapid Circadian Entrainment in Models of Circadian Genes Regulation, in Proc. IEEE Conf. Decision and Control, Nice, France, 2019.
[4] A.A. Julius, J. Yin, J.T. Wen, Optimization of Lighting and Sleep Schedules, in Journal of the Homeland Defense & Security Information Analysis Center, vol. 6(3), pp. 44 – 47, 2019.
[5] J. Yin, A.A. Julius, J.T. Wen, Optimization of Light Exposure and Sleep Schedule for Circadian Rhythm Entrainment, PLoS ONE, 16(6): e0251478, June 2021.
[6] J. Yin, A.A. Julius, J.T. Wen, M. M. K. Oishi, L. Brown, Actigraphy-based Parameter Tuning Process for Adaptive Notch Filter and Circadian Phase Shift Estimation, Chronobiology International, August 2020.
[7] J. Yin, A.A. Julius, J.T. Wen, J. P. Hanifin, B. Warfield, G. C. Brainard, Automatic Sleeping Time Estimation and Mild Traumatic Brain Injury (mTBI) Detection Using Actigraphy Data, Journal of Biomedical Signal Processing and Control, January 2021.
[8] J. Yin, Light-based Rapid Circadian and Sleep Entrainment, Doctoral Dissertation, Rensselaer Polytechnic Institute, August 2020.

Honors and Awards: Nothing to Report

Protocol Activity Status:

Technology Transfer: A related patent was issued in 2021:

Jiaxiang Zhang, John T. Wen, Agung Julius. Circadian Phase Estimation, Modeling and Control. U.S. Patent 10,896,739B2 (January 19, 2021) 10,529,440 (January 6, 2020).

PARTICIPANTS:

Participant Type: PD/PI
Participant: John Wen
Person Months Worked: 12.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Co PD/PI
Participant: Agung Julius
Person Months Worked: 12.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Graduate Student (research assistant)
Participant: Jiawei Yin
Person Months Worked: 12.00 **Funding Support:**
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Date Submitted: 8/28/18 12:00AM Date Published: 6/25/18 9:02PM
Publication Location:
Article Title: Asymptotic Synchronization of Phase Oscillators with a Single Input
Authors: He Bai, John T. Wen
Keywords: Oscillators, Synchronization, Numerical models, Asymptotic stability, Lyapunov methods, Clustering algorithms
Abstract: We consider asymptotic synchronization of multiple phase oscillators represented by first order reduced dynamics with a phase response curve (PRC) function. A single control input is employed to synchronize the oscillators. We design a feedback control that achieves asymptotic synchronization of the oscillators. We also show that the undesired equilibria of the closed-loop system are unstable, thereby guaranteeing almost global synchronization. We extend the design to address the scenarios where the control is symmetrically or asymmetrically bounded and where the coefficients in the PRC function are unknown constants. Simulation results are presented to validate the proposed control algorithms.
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Article Title: Time optimal entrainment control for circadian rhythm
Authors: A. Agung Julius, Jiawei Yin, John T. Wen, Tjeerd olde Scheper
Keywords: Circadian Rhythm, time optimality, optimal entrainment
Abstract: The time-optimal circadian entrainment problem has been previously solved in settings that involve either a reduced-order JFK model or open-loop optimal solutions. In this paper, we present (1) a general solution for the time-optimal control problem of fastest entrainment that can be applied to the full order JFK model (2) an evaluation of the impacts of model reduction on the solutions of the time-optimal control problem, and (3) optimal feedback control laws for fastest entrainment for the full order Kronauer model and evaluate their robustness under some modeling errors.
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Date Submitted: 11/10/20 12:00AM Date Published: 9/1/19 12:00PM
Publication Location:
Article Title: Assessing circadian rhythms and entrainment via intracranial temperature after severe head trauma
Authors: Joseph D. Gleason, Meeko M.K. Oishi, John T. Wen, Agung Julius, Suguna Pappu, Howard Yonas
Keywords: Nonlinear estimationCircadian rhythmsTraumatic brain injury
Abstract: The health effects of circadian regulation are profound, yet assessments of circadian processes are often infeasible in the neurotrauma intensive care unit (ICU). We assess circadian periodicity through the energy density spectrum, applying model-based and model-free methods: an extended Kalman filter (using the Kronauer model) in conjunction with a fast Fourier transform (FFT), and the Lomb–Scargle periodogram, respectively. We compute the change in relative energy in a narrow band of the spectrum, corresponding to a period of 23-25?h, over the first 48 and last 48?h of each subject's stay in the ICU. The change in relative energy in the spectrum increases in subjects with Good outcomes, and decreases in subjects with Poor outcomes, with statistical significance. For those subjects with Good outcome, we show evidence of regulation in circadian phase using an adaptive notch filter.
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Publication Type: Journal Article Peer Reviewed: Y **Publication Status:** 1-Published
Journal: Chronobiology International
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Volume: Issue: First Page #:
Date Submitted: 11/9/20 12:00AM Date Published: 8/31/20 4:00AM
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Article Title: Actigraphy-based Parameter Tuning Process for Adaptive Notch Filter and Circadian Phase Shift Estimation
Authors: Jiawei Yin, Agung Julius, John T. Wen, Meeko M. K. Oishi, Lee K. Brown
Keywords: Adaptive notch filter (ANF); circadian rhythms; actigraphy; circadian phase estimation; melatonin
Abstract: We report herein the application of an adaptive notch filter (ANF) algorithm to minute-by-minute actigraphy data to estimate the continuous circadian phase of 8 healthy adults. As the adaptation rates and damping factor in the ANF algorithm have large impacts on the ANF states and circadian phase estimation results, we propose a method for optimizing these parameters. The ANF with optimal parameters is further used to estimate the circadian phase shift from the actigraphy data. Dim light melatonin onset (DLMO), considered the "gold standard" method for identification of circadian phase, was determined by a serial collection of salivary melatonin per standard protocol simultaneously with the collection of actigraphic data. We were able to demonstrate that the ANF algorithm, when applied to the actigraphy data, was able to estimate the circadian phase as determined by DLMO.
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Article Title: Optimization of Lighting and Sleep Schedules
Authors: Agung Julius, Jiawei Yin, John T. Wen,
Keywords: Circadian Rhythm, Sleep, Optimization, Lighting
Abstract: We report herein the application of an adaptive notch filter (ANF) algorithm to minute-by-minute actigraphy data to estimate the continuous circadian phase of 8 healthy adults. As the adaptation rates and damping factor in the ANF algorithm have large impacts on the ANF states and circadian phase estimation results, we propose a method for optimizing these parameters. The ANF with optimal parameters is further used to estimate the circadian phase shift from the actigraphy data. Dim light melatonin onset (DLMO), considered the "gold standard" method for identification of circadian phase, was determined by a serial collection of salivary melatonin per standard protocol simultaneously with the collection of actigraphic data. We were able to demonstrate that the ANF algorithm, when applied to the actigraphy data, was able to estimate the circadian phase as determined by DLMO.
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Publication Location: United States
Article Title: Optimization of Light Exposure and Sleep Schedule for Circadian Rhythm Entrainment
Authors: Jiawei Yin, A. Agung Julius, John T. Wen
Keywords: Light Optimization, Sleep Scheduling, Circadian Rhythm, Entrainment
Abstract: This paper addresses the regulation of both Process C and Process S by scheduling light exposure and sleep. This is a significant step beyond the existing literature that only considers the entrainment of Process C. Regulation of the two-process model poses several unique features and challenges: 1. Process S is non-smooth, i.e., the homeostatic dynamics are different in the sleep and wake regimes; 2. Light only indirectly affects Process S, through Process C; 3. Light does not affect Process C during sleep. We consider two scenarios: light intensity as the control input with spontaneous (i.e., unscheduled) sleep/wake times and light input with controllable sleep/wake times which allows limited delayed sleep and early waking as part of the control input. We solve the time-optimal entrainment problem for the two-process model for both scenarios using an extension of the gradient descent algorithm to non-smooth systems.
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Article Title: Automatic Sleeping Time Estimation and Mild Traumatic Brain Injury (mTBI) Detection Using Actigraphy Data
Authors: Jiawei Yin, A. Agung Julius, John T. Wen, John P. Hanifin, Benjamin Warfield, George C. Brainard
Keywords: Actigraphy Circadian Rhythm, Sleep, Traumatic Brain Injury (TBI), Concussion Detection
Abstract: Sleep schedule and circadian phase irregularity are associated with some health problems and diseases, e.g., narcolepsy, circadian disorder, and concussion. Actigraphy has been widely used in the study of sleep and circadian rhythms. This paper presents a method for estimating the sleep/wake state based on the minute-by-minute actigraphy data measured by wrist actigraphy and its associated scoring software. The circadian phase shift is estimated from actigraphy data using an adaptive notch filter algorithm. Compared with the scoring methods used in wrist actigraphy, the estimated wake-onset time from our method is more consistent with the sleep logs reported by the subjects. Concussion detection based on the sleep-related features calculated from actigraphy data is also presented, with detection accuracy up to about 90%. This result implies that the concussion is closely related to sleep and circadian disruption.
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Paper Title: Time-Optimal Control for Circadian Entrainment for a Model with Circadian and Sleep Dynamics
Authors: Agung Julius, Jiawei Yin, John T. Wen
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Paper Title: Rapid Circadian Entrainment in Models of Circadian Genes Regulation
Authors: Jiawei Yin, Agung Julius, John T. Wen
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Authors: Jiawei Yin
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Partners

,

I certify that the information in the report is complete and accurate:
Signature: John Wen
Signature Date: 2/15/22 11:21PM

Objective

- Analyze mathematical models that include circadian, sleep and alertness processes, and their interaction with light and sleep schedule.
- Develop algorithms for optimal lighting and sleep scheduling to achieve, e.g., minimum time circadian phase entrainment and maximum alertness at specified time.
- Develop state estimation algorithms for circadian, sleep, and alertness states based on biometric data.

Approach

- We use functional gradient method with a comprehensive model that integrates the circadian, sleep, and alertness processes in our computation.
- We use adaptive notch algorithm with parameter tuning algorithm to extract periodic signals from noisy biometric measurements. We also develop a method to tune the filter parameters automatically.

Accomplishments

- Algorithm for computing the optimal lighting and sleep schedule for fastest circadian and sleep entrainment.
- Algorithm for optimizing alertness during a specified time interval, which can be used to prepare mission performers.
- Biometric signal processing algorithm for circadian phase shift estimation and mild TBI detection.

Conclusions

- Functional gradient-based approach is effective in computing the optimal lighting and sleep schedules. For high-dimensional models, we can deal with the local optimality of this method by choosing initial guesses based on optimizing the reduced-order models.
- Biometric signals can be used for circadian phase shift estimation and mild TBI detection. The latter is based on variations in sleep metrics.

Scientific Barriers

- Analysis and optimization of the circadian-sleep-alertness system is challenging because the dynamics is non-smooth.
- Biometric data are noisy. Filtering algorithms need parameter tuning for good performance.

Scientific Opportunities

- New algorithms for optimal control of switched systems allowed us to deal with the non-smooth dynamics.
- Leveraging collaborators outside of this project to obtain human biometric data for our biometric signal processing algorithms.

Significance

- We enable more practical solutions to jetlag and other circadian entrainment problems by taking sleep needs into account.
- Our biometric signal processing results validate the use of actigraphy data for circadian phase shift estimation and mild TBI detection.

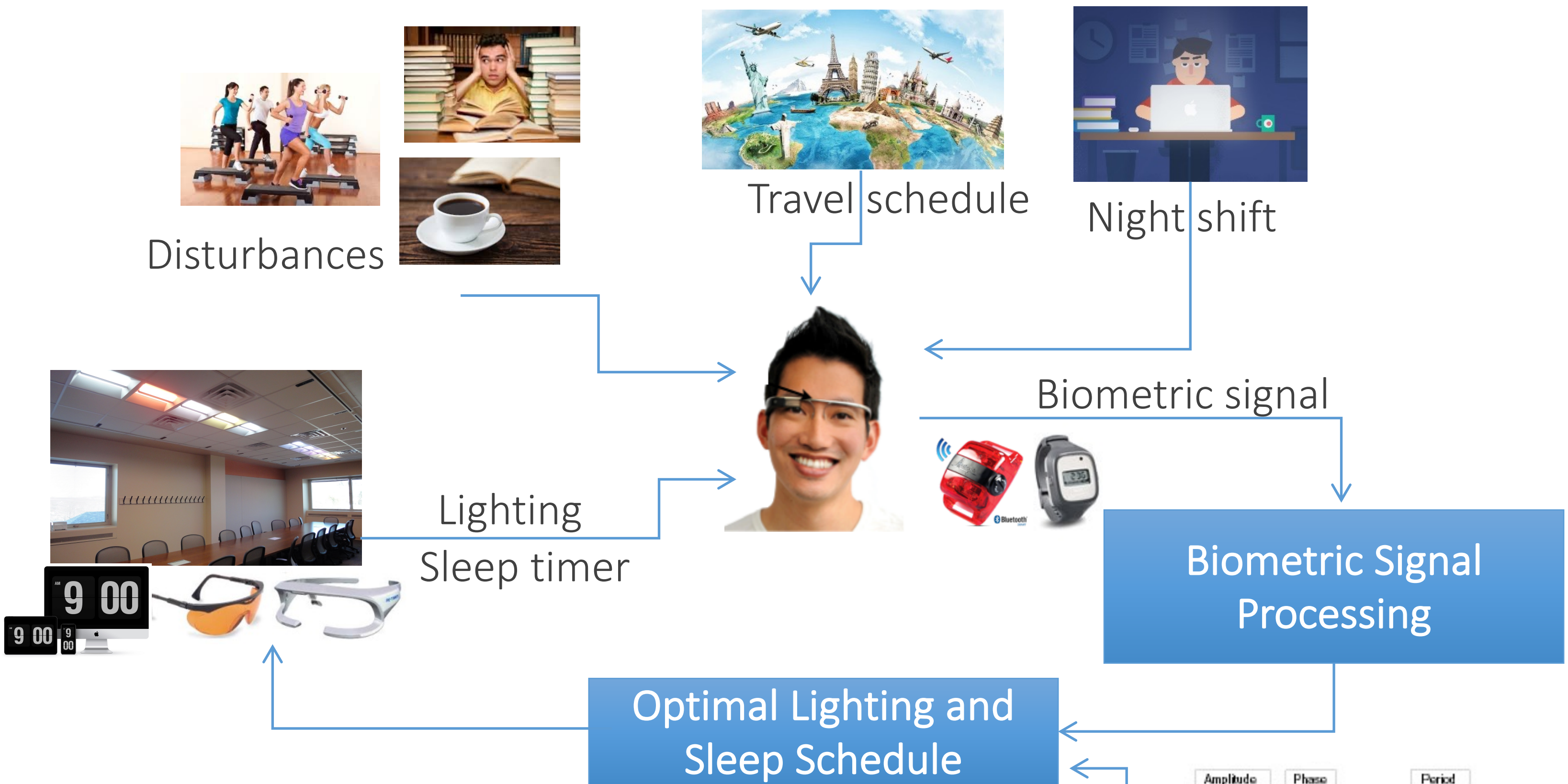
Collaborations, Partnerships, and Leveraged Funding

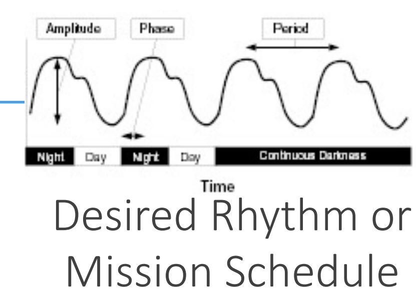
- We partner with researchers from Thomas Jefferson University and University of New Mexico, who are affiliated with the Center for Lighting Enabled Systems and Applications (LESA).
- We recently obtained NSF funding to work on developing hardware and software for multimodal biometric signal processing.

Future Plans

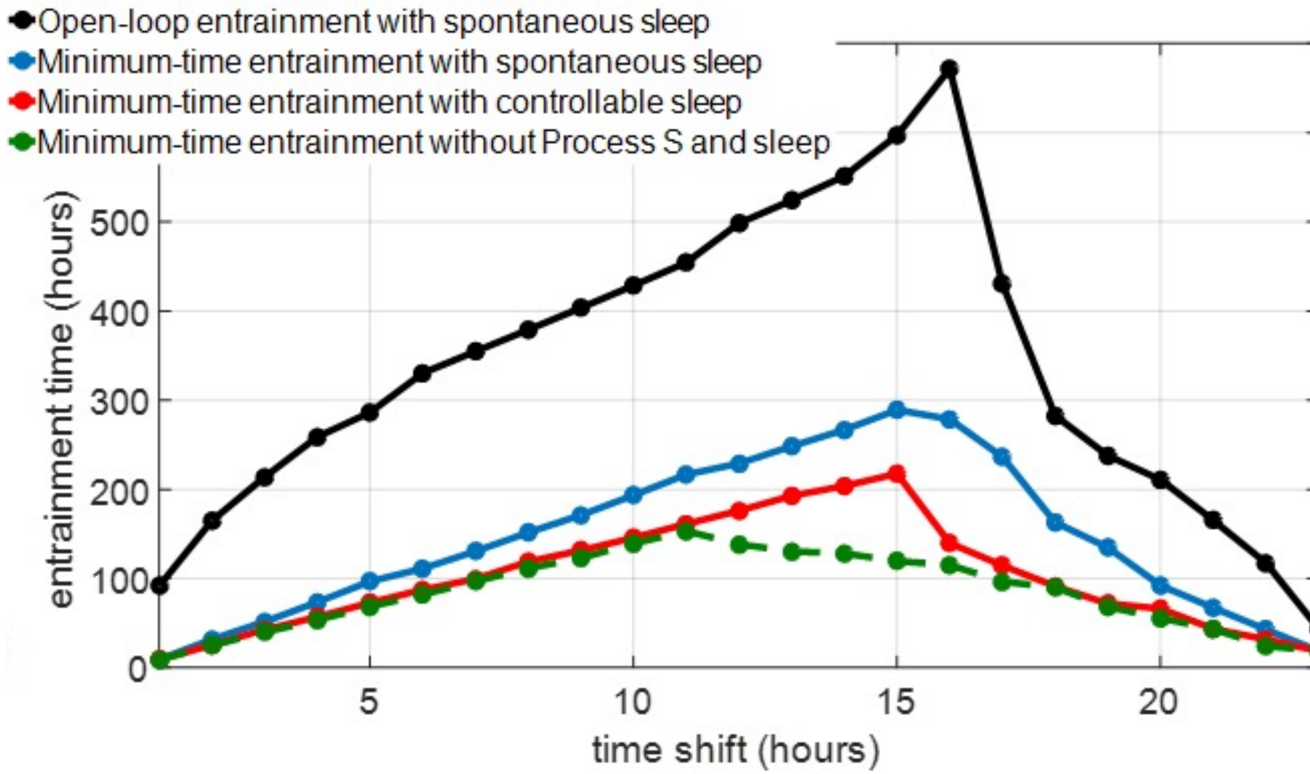
We have discussed a plan for follow-on work which includes:

- Assessing the robustness of optimal circadian regulation under model uncertainties.
- Developing algorithms for learning and adaptation in optimal regulation of circadian rhythms and neurocognitive processes.
- Modeling of the circadian rhythms and sleep aspects of mild Traumatic Brain Injuries (TBI).

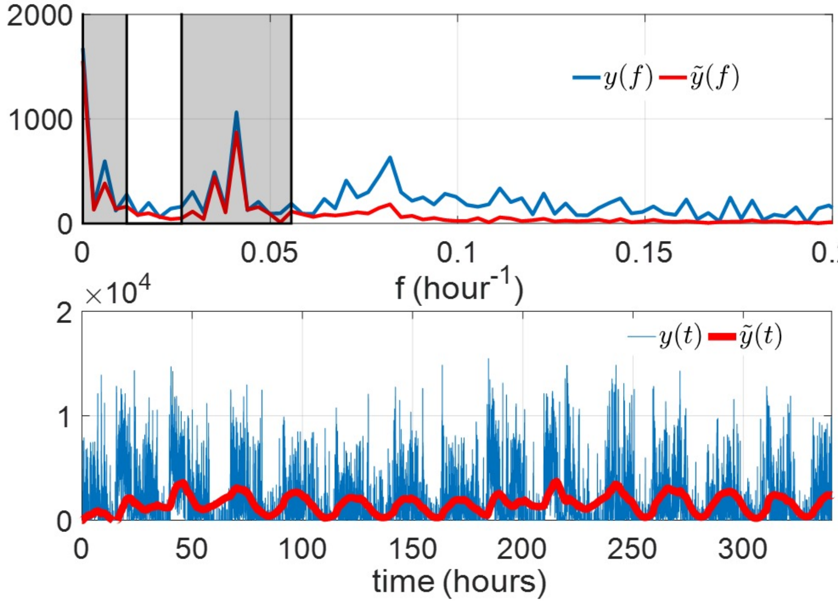




An overview showing how two parts of our research: *Optimal Lighting and Sleep Schedule* and *Biometric Signal Processing* contribute to promoting circadian health and productivity.



The y-axis shows the time needed to recover from jetlag. The x-axis shows the amount of jetlag. The black curve is baseline (without optimization). Other curves show the results of our algorithm that allow us to balance entrainment expediency with sleep need (green: quickest with most sleep deficiency, blue: slow with no sleep deficiency, red: quick with bounded sleep deficiency).



Our Adaptive Notch Filter (ANF) algorithm is self-tuned based on the biometric data (in this case, actigraphy) from the subject. Blue and red curves show the raw actigraphy signal and the filter output, respectively, in the frequency domain (top panel) and time domain (bottom panel). The output of the filter is used to compute the amount of circadian phase shift in the subject. The result has been validated with clinical standard method (using dim-light melatonin onset measurement).

We developed algorithms for quantifying sleep quality features based on actigraphy data (shown above for 7 days from one subject). Time variation of such features can be used for mild TBI detection, with false positive and false negative rates of below 10%. We also rank ordered the importance of the features used in the detection.