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14. ABSTRACT This young investigator award from the Air Force Office of Scientific Research to Daniel Forger played a pivotal role in his career. Many discoveries were made and are described in over 10 published papers or manuscripts in preparation. Some research highlights include: 1) discovering that timekeeping in mammals is more complex than originally thought, 2) discovering on how to optimially stimulate neuronal (and in particular the circadian) systems and 3) mathematical methods for studying biological clocks. Forger remains very grateful to the AFOSR for the opportunity to perform this work.						
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Air Force Office of Scientific Research Young Investigator Award to Daniel Forger

Project Summary:

The AFOSR Young Investigator Award was the most important grant I have received in my career. As a result, there were many scientific accomplishments and these are described below. In addition, as would be expected in a Young Investigator Award, this funding launched my independent career (including getting tenure), as well as played a major role in advancing the careers of members of my group. For example, a graduate student, Casey Diekman, now has a prestigious post-doc at the Mathematical Biosciences Institute, two of my post-docs have received faculty positions (Weihua Geng and Cecilia Diniz-Behn) and a third (Richard Yamada) received a prestigious American Mathematical Society Fellowship. My standing in the field has also increased, including invitations to be on editorial boards (even to start a new journal) and to give high profile talks and serve on advisory board memberships. Moreover, I continue to be committed to helping the scientific advantage of our military. High-ranking DoD officials have taken notice of my work (e.g. Major General Curtis Bedke). I was very pleased to learn that I will be receiving further support from AFOSR. For these reasons, I feel my AFOSR Young Investigator Award succeeded in its mission “to foster creative basic research in science and engineering; enhance early career development of outstanding young investigators; and increase opportunities for the young investigator to recognize the Air Force mission and related challenges in science and engineering.”

The scientific accomplishments of the Young Investigator Award are numerous and summarized below by topic. I also list any published or planned papers. Review papers are not listed.

Mammalian timekeeping is more complex than originally thought

Published Papers:

Ko CH, Yamada YR, Welsh DK, Buhr ED, Liu AC, Zhang EE, Ralph MR, Kay SA, Forger DB, Takahashi JS, Emergence of noise-induced oscillations in the central circadian pacemaker PLoS Biology **8** (2010) e1000513.

Belle M.D.C., Diekman C.O., Forger D.B. and Piggins H.D., Temporal Electrical Silencing in the Mammalian Circadian Clock Science **326** (2009) 281-4.

Paper in preparation:

Yamada YR, Ko CH, Takahashi JS, Forger DB Exploring Network Properties of a Detailed Mathematical Model of the Supra-Chiasmatic Nuclei

This set of papers is the highlight of the grant. They explain how mathematical models that I developed were used to make very unexpected predictions about daily timekeeping in mammals. These predictions were later verified by top experimental groups and

published in high profile journals. The first paper (Ko et al.) shows how the behavior of the whole timekeeping network of neurons in the brain can behave very differently than that of individual neurons in isolation. In particular, the network can exploit molecular noise, which is often thought of as detrimental, to allow for, albeit noisy, near 24-hour timekeeping. Further simulations and mathematical analysis is included in a manuscript we are preparing for submission (Yamada et al.). The second paper (Belle et al.) shows a very surprising result, that neurons within the central circadian pacemaker in the brain can be electrically silenced and highly depolarized through much of the day. This represents a novel signaling mechanism in mammalian neurons.

How to optimally stimulate a neuron a neuronal network, or the circadian system

Published Papers:

Forger DB Paydarfar D, Clay JR Optimal Stimulus Shapes for Neuronal Excitation Plos Computational Biology 7 (2011) e1002089.

Dean DA, Forger DB and Klerman EB Taking the Lag out of Jet Lag through Model Based Schedule Design. PLoS Computational Biology (2009) 5(6).

Paper in preparation:

Sergh K, Forger DB Novel mathematical methods in schedule design

The most recently published paper from the grant is a paper determining how to optimally excite a neuron (Forger et al.). We went in search of the signal which best stimulates a neuron. Surprisingly, we discovered that a neuron can be highly selective for more than one dissimilar shape. This work: 1) provides new methodology for determining how to optimally stimulate neurons, 2) demonstrates that computation in a single neuron is more complex than originally thought, and 3) shows how more effective control of neurons can be achieved. Although it is basic research, it could have many potential future applications, including better devices for deep brain stimulation and cardiac pacemakers.

With my Young Investigator Award, I finished a collaboration with the Division of Sleep Medicine at Harvard developing a computer program to predict optimal schedules for shift-workers or those traveling across time zones. Although this program finds a time of day when a countermeasure should be placed, it does not optimize the details of the countermeasure. Recently, a truly amazing undergraduate (Kirill Sergh) renewed my interest in the problem, and we are working on optimizing not only the time of the countermeasure, but also the light levels throughout the entire schedule. Moreover, we seem to be able to answer fundamental questions such as, "What is the maximal amount of phase shift that can be achieved in a set amount of time?"

Modeling the electrical activity of neurons

Published Papers:

Diekman CO, Forger DB Clustering Predicted by an Electrophysiological Model of the Suprachiasmatic Nucleus, *Journal of Biological Rhythms*, **24** (2009) 322-33.

Paper in preparation:

Bodova K, Paydarfar D and Forger DB Characterizing Spiking in Noisy Type II Neurons

This collection of papers studies the electrical activity of neurons. In the first, a graduate student, Casey Diekman, and myself showed how neurons in the central circadian pacemaker could “cluster” or self segregate into groups that fire in synchrony. This could be very important for how the central pacemaker processes information. Recent work with a collaborator, Katarina Bodova, explores how noise affects the firing of neurons. We have found a very simple mathematical characterization for spiking in noisy neurons, which can be used to understand experimental data from many neuronal systems.

Mathematical methods for understanding biochemical clocks

Published Paper:

Forger DB Signal Processing in Cellular Clocks *PNAS* (2011), **108** (2011) 4281-5.

Papers in preparation:

Geng W and Forger DB The role of combinatorial complexity in genetic networks

Kim, J and Forger DB Automatic model generation using time series data

I consider my recent *PNAS* paper the most important mathematical work of my career. It develops a general theory for understanding oscillations in biochemical clocks. This theory can predict when oscillations will occur in genetic feedback loops, or properties of these oscillations (e.g. their period). Two manuscripts in preparation continue these ideas. One explores the role of combinatorial complexity, and studies numerical methods for quick simulation of biochemical networks. The second uses techniques from the *PNAS* paper to automatically generate mathematical models of biological clocks from time series data. This greatly reduces the time needed to model a biological clock.

Modeling Sleep Regulation

Published Paper:

Fleshner M, Booth V, Forger DB, Diniz Behn CG Multiple Signals from the suprachiasmatic nucleus are required for circadian regulation of sleep-wake behavior in the nocturnal rat, Philosophical Transactions of the Royal Society A *Accepted*

Part of my work focused on modeling the circadian control of sleep regulation. Although this was mainly funded by another AFOSR grant, we used methods and results from my Young Investigator Award.

Summary

It has been a pleasure to work with AFOSR, and my program manager, Willard Larkin. I remain very grateful to AFOSR for helping my career, and hope I have significantly contributed to its mission.