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Daniel Evanko, PhD
Chief Editor
Nature Methods

Dear Dr. Evanko,

We submit our manuscript entitled "Optogenetic Feedback Control of Neuronal Firing" for consideration as a full Article in Nature Methods.

The ability to finely control activity in various neural circuits opens the possibility of controlling sensation, perception, behavior, and even memory formation. As you know, the advent of optogenetic tools has opened up enormous possibilities in the field of Neuroscience. However, current techniques that employ optogenetic tools for modulating neural activity, including "closed-loop" methods (Leifer et al., Nat. Methods, 2011; Stirman et al., Nat. Methods, 2011; Paz et al., Nat. Neurosci., 2013; O'Conner et al., Nat. Neurosci., 2013), do not update stimulus parameters based on stimulus efficacy. Here we present a method for precisely controlling neural activity using true real-time optogenetic feedback. We have long embraced the idea of sharing our blueprints (e.g., our *NeuroRighter* platform, Newman et al., Frontiers in Neural Circuits, 2013), with web sites for open source code and hardware, including the tools and techniques described here.

Using our novel technique, neural spiking activity levels are continuously assessed using electrode recordings and used to update optical stimulus parameters in real time. This allows us to precisely specify, and rapidly switch between, neural activity levels over a wide range of firing levels and time scales (seconds to days). We demonstrate the technique both in vitro, using dissociated cortical networks grown on microelectrode arrays, and in vivo, in somatosensory thalamus of rats. In both preparations we show how real-time feedback can be used to control neural activity in spite of pharmacological or sensory perturbations that affect neural excitability, allowing causally related variables of circuit activation to be studied independently.

There is a growing recognition by the community that there is an immediate need for technology that can precisely control neural populations, allowing us to move from merely reading the neural code to also *writing* the neural code (Stanley, Nat. Neurosci., 2013). This will be increasingly important with prosthetics and neuromodulatory therapies. Given the highly nonlinear and nonstationary nature of neural dynamics, and the heterogeneity of neural circuits across preparations and across development, real-time feedback will be required to meet this goal. This manuscript and our associated websites present a foundational technology that that allows precise control of single-cell and network firing levels across preparations and time scales. The ability of our technique to finely control neural activity in precisely defined sensory circuits is likely to accelerate the design of closed-loop prosthetic devices, both sensory and motor. For this reason, we feel this manuscript is of great interest to the general readership of Nature Methods.

Georgia Institute of Technology

The Wallace H. Coulter
Department of Biomedical Engineering
at Georgia Tech and Emory University

EMORY UNIVERSITY
SCHOOL OF MEDICINE

We suggest the following reviewers, who are familiar with closed-loop neurophysiological systems and optogenetics:

Eberhard Fetz, University of Washington, fetz@uw.edu, 206-543-4839
Christopher Moore, Brown University, Christopher_Moore@brown.edu, 401-863-1054
Edward Boyden, Massachusetts Institute of Technology, esb@media, 617-324-3085

We request the exclusion of the following as a reviewer, due to direct competition between our lines of study:

Karel Svoboda, Janelia Farm Research Campus

We thank you for your consideration, and look forward to sharing our work in Nature Methods.

Sincerely,

Steve Potter

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