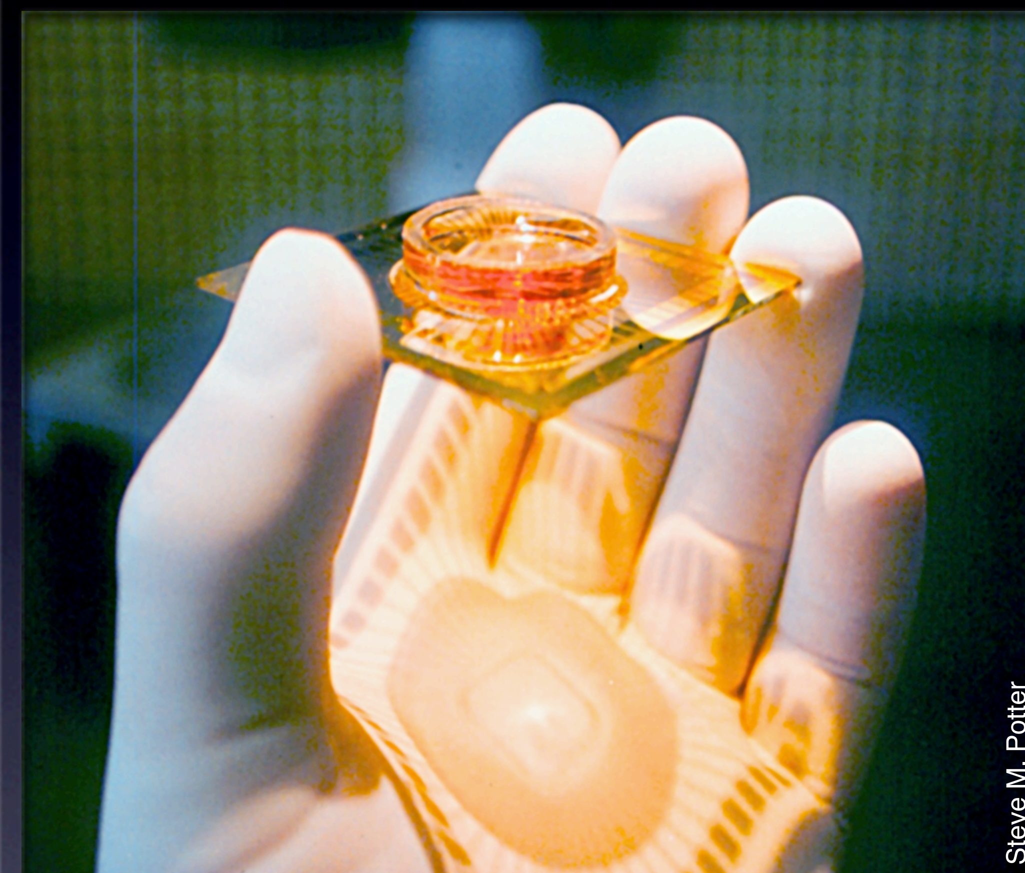
Closed-loop optical and electrical neural interfacing



Steve M. Potter, PhD

Adjunct Associate Professor and Consultant
Laboratory for NeuroEngineering
Department of Biomedical Engineering
Georgia Institute of Technology
and Emory University School of Medicine

NeuroTechX Webinar
2019-01-15

Closed-loop optical and electrical neural interfacing

- NeuroTechX webinar January 15, 2019   by: Steve M. Potter, PhD

ABSTRACT:
This webinar will introduce you to the future of neural interfacing: closed-loop optical interfaces. I will explain optogenetics and how it can be used to control neural activity with more specificity and precision than electrical interfaces can. In my lab at Georgia Tech, we developed a number of open-source solutions for neural interfaces, including MEAbench, NeuroRighter, and most recently the OptoClamp. We pioneered closed-loop interfaces to study learning and memory in cortical networks grown in vitro. Some of these comprised hybrid systems in which living neurons were embodied in robots or simulated animals. By using closed-loop feedback, network dynamics, learning and neural plasticity can be studied at a variety of time scales both in vitro and in vivo. We used closed-loop optical and electrical neural interfaces to control seizure activity and study homeostatic plasticity associated with epilepsy, chronic pain, tinnitus, and other deafferentation syndromes.

About the presenter, Steve M. Potter, PhD:

Professor Potter and his research group spent the past two decades developing new ways to study neural dynamics and plasticity at the networks-level using cortical networks of neurons and glia growing in Petri dishes instrumented with arrays of electrodes. They created the field of Embodied Cultured Networks, a new hybrid lab animal whose brain sits on the microscope stage while its robotic body behaves. Potter is a semi-retired Adjunct Associate Professor in the Department of Biomedical Engineering at the Georgia Institute of Technology and Emory University School of Medicine. From 1993-2002 he worked as Research Faculty at Caltech in the labs of Prof. Scott Fraser and Prof. Jerry Pine, building a 2-photon microscope, a high-speed neural activity imaging camera, and closed-loop multi-electrode array neural culture systems. He is currently a freelance consultant, writer, teacher and maker in Dundalk, Ireland. All of his research publications are available at http://potterlab.gatech.edu

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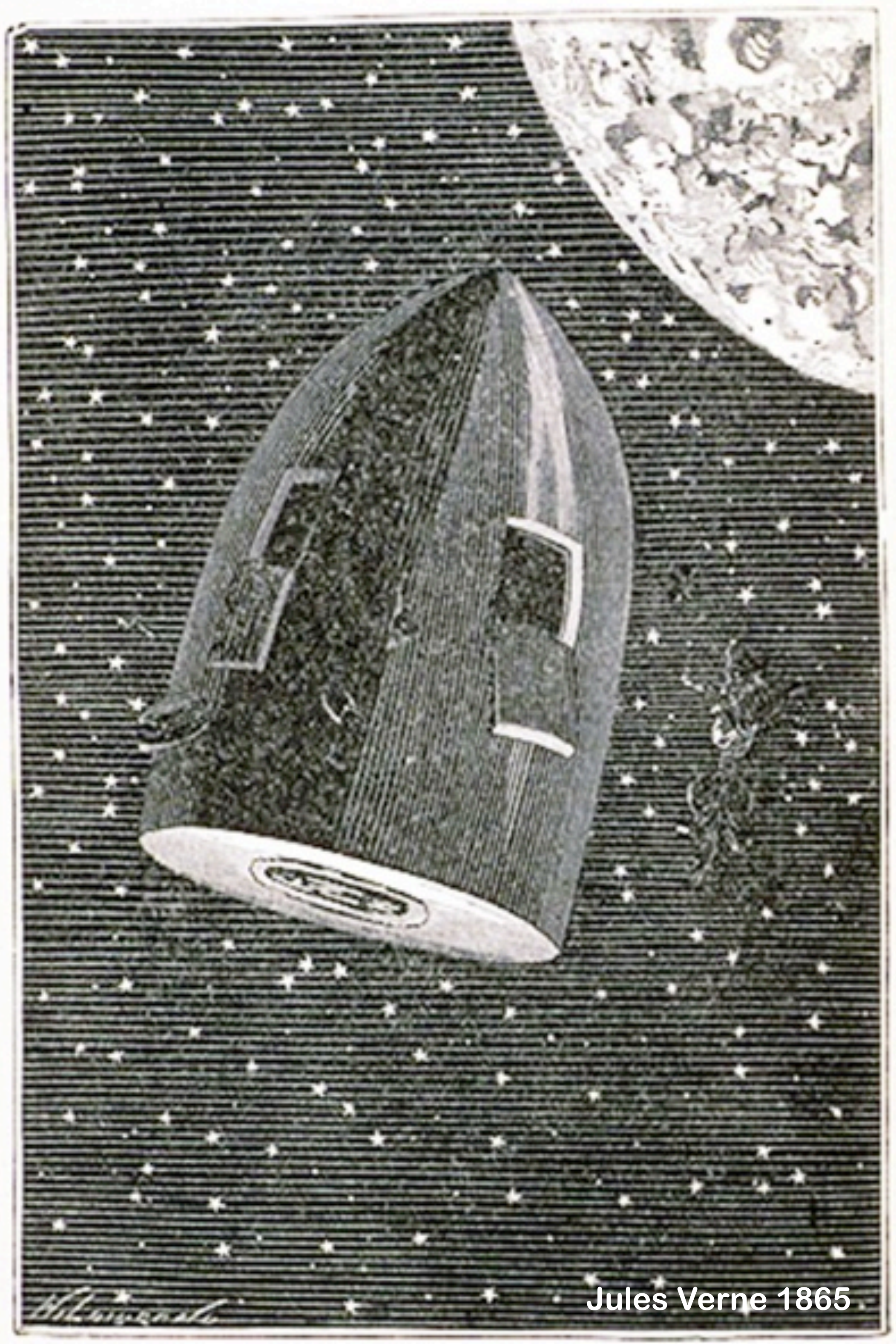
NeuroEngineering

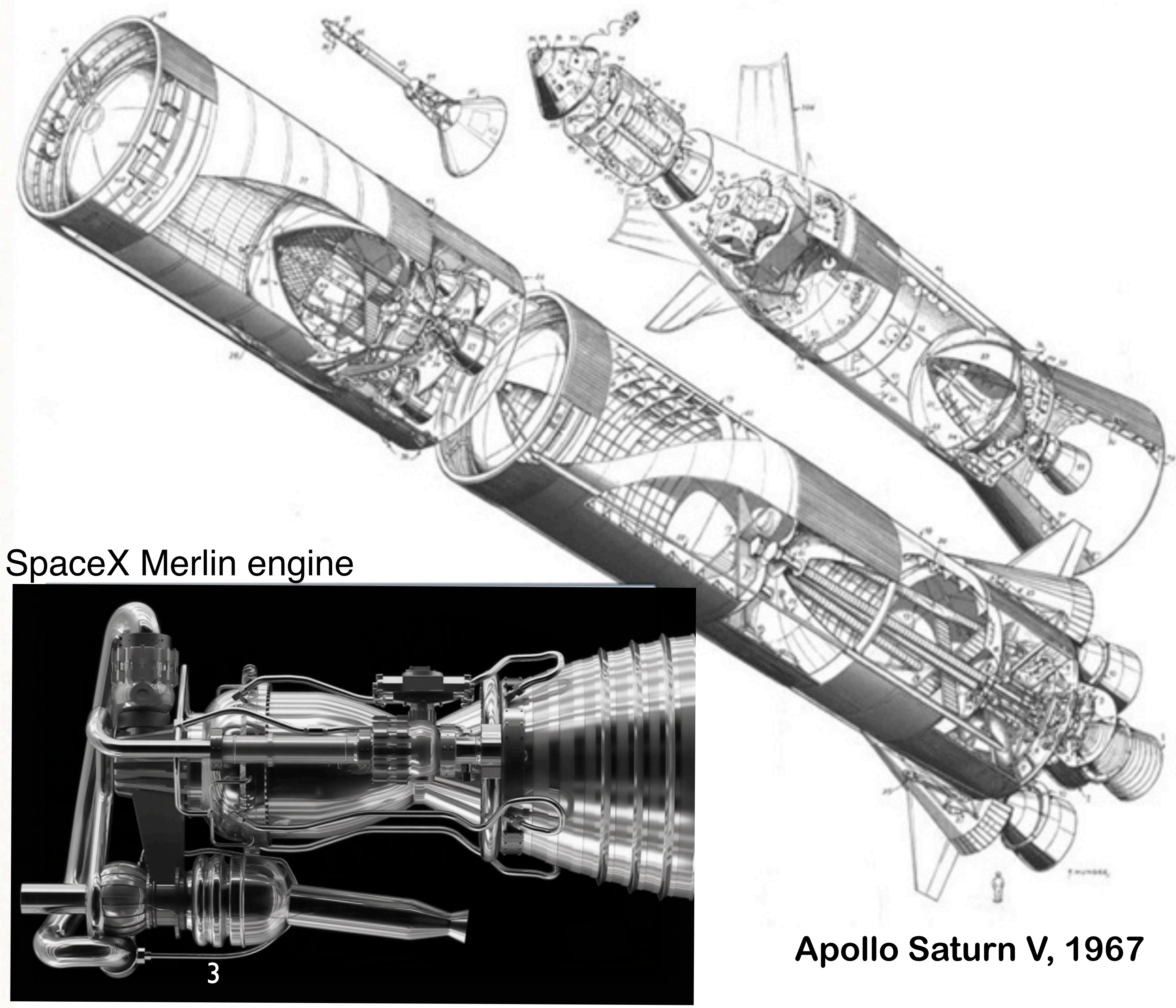
Current level of sophistication

Some time in the future....



Jules Verne 1865

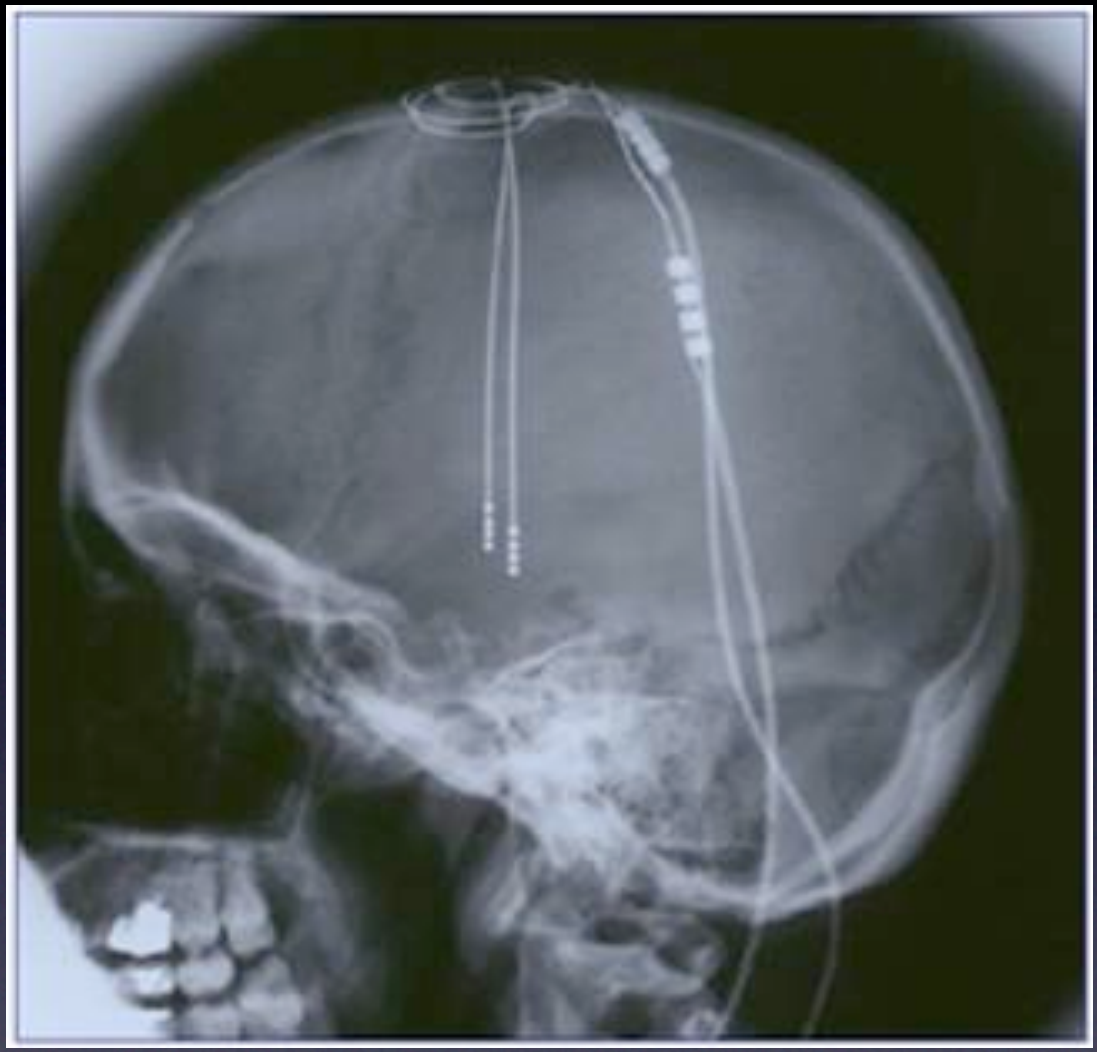
SpaceX Merlin engine



Apollo Saturn V, 1967

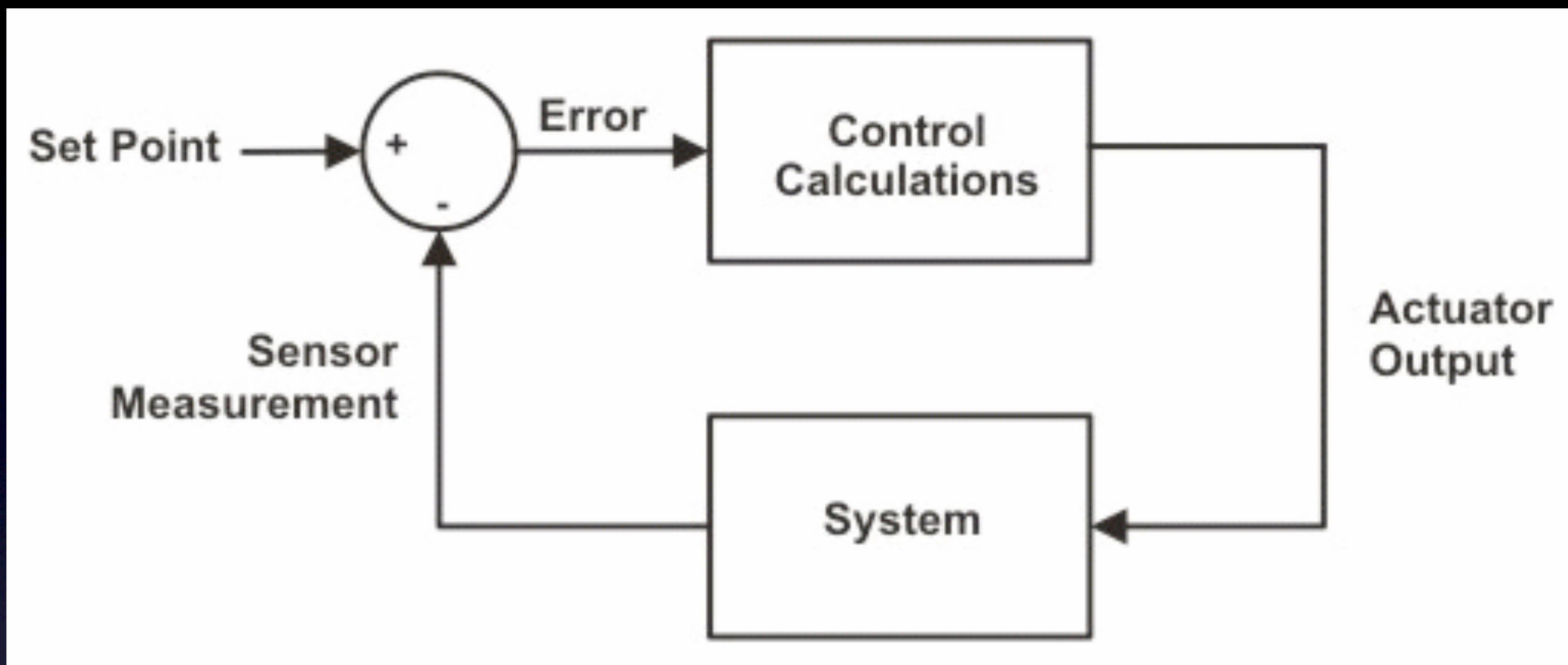
What's missing?

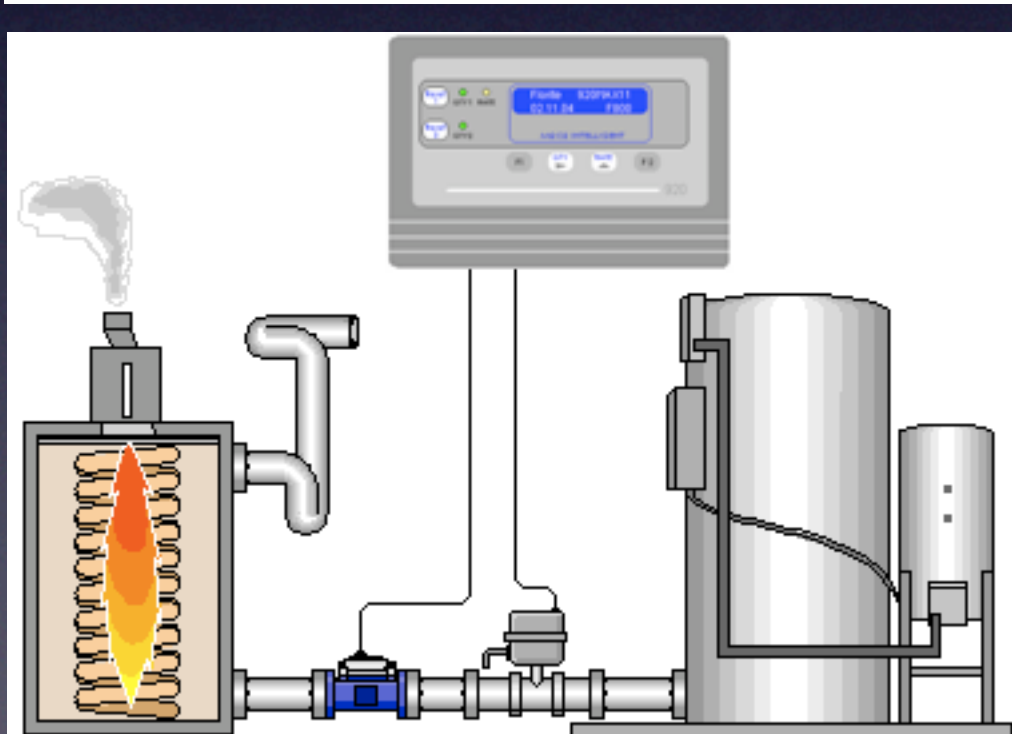
DBS: Deep Brain Stimulation



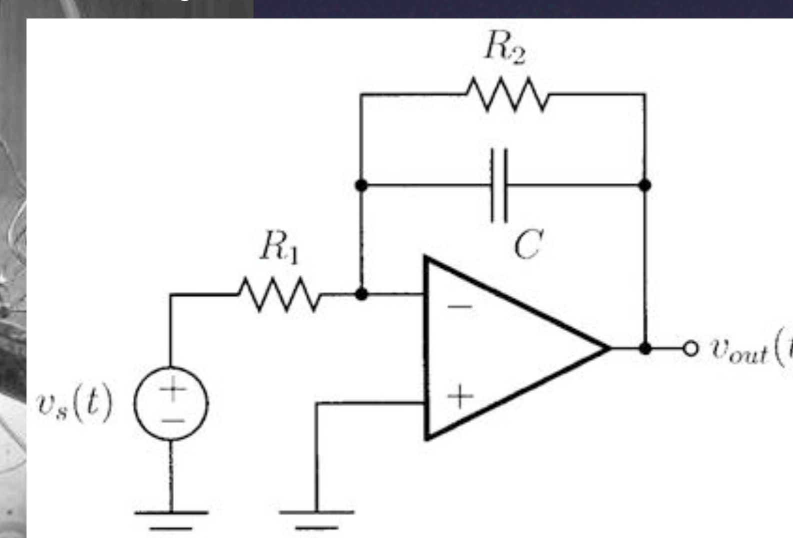
Feedback!

Closed-loop systems





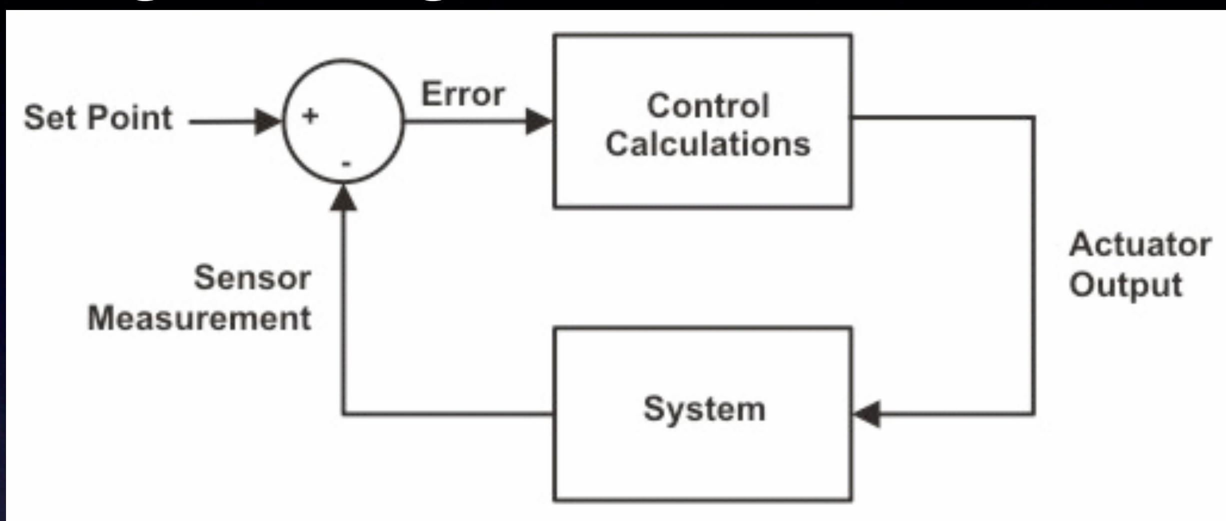
Operational amplifier circuit



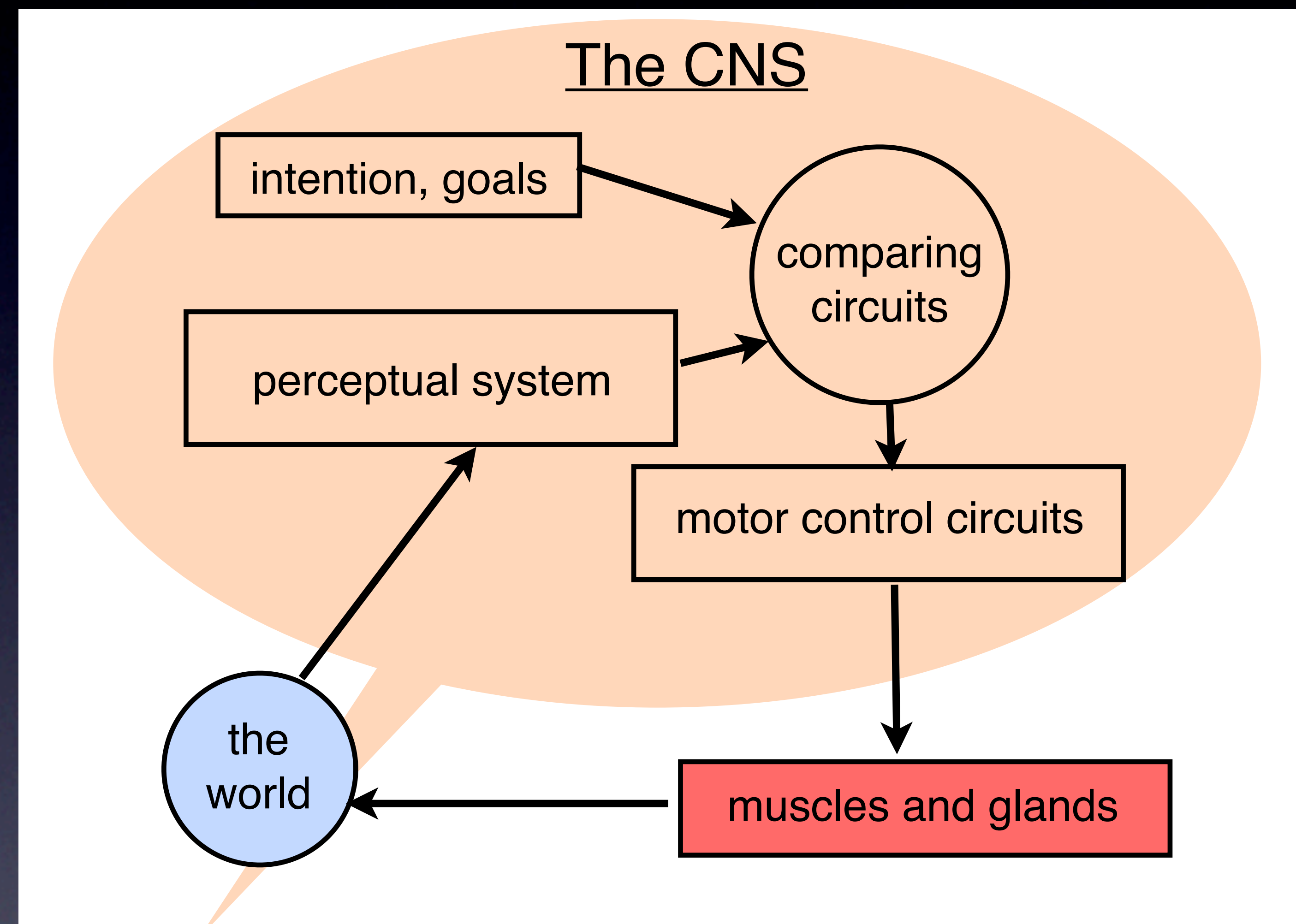
Feedback is ubiquitous in engineered systems

Our nervous system is embodied, situated, and operates closed-loop

Engineering



Biology

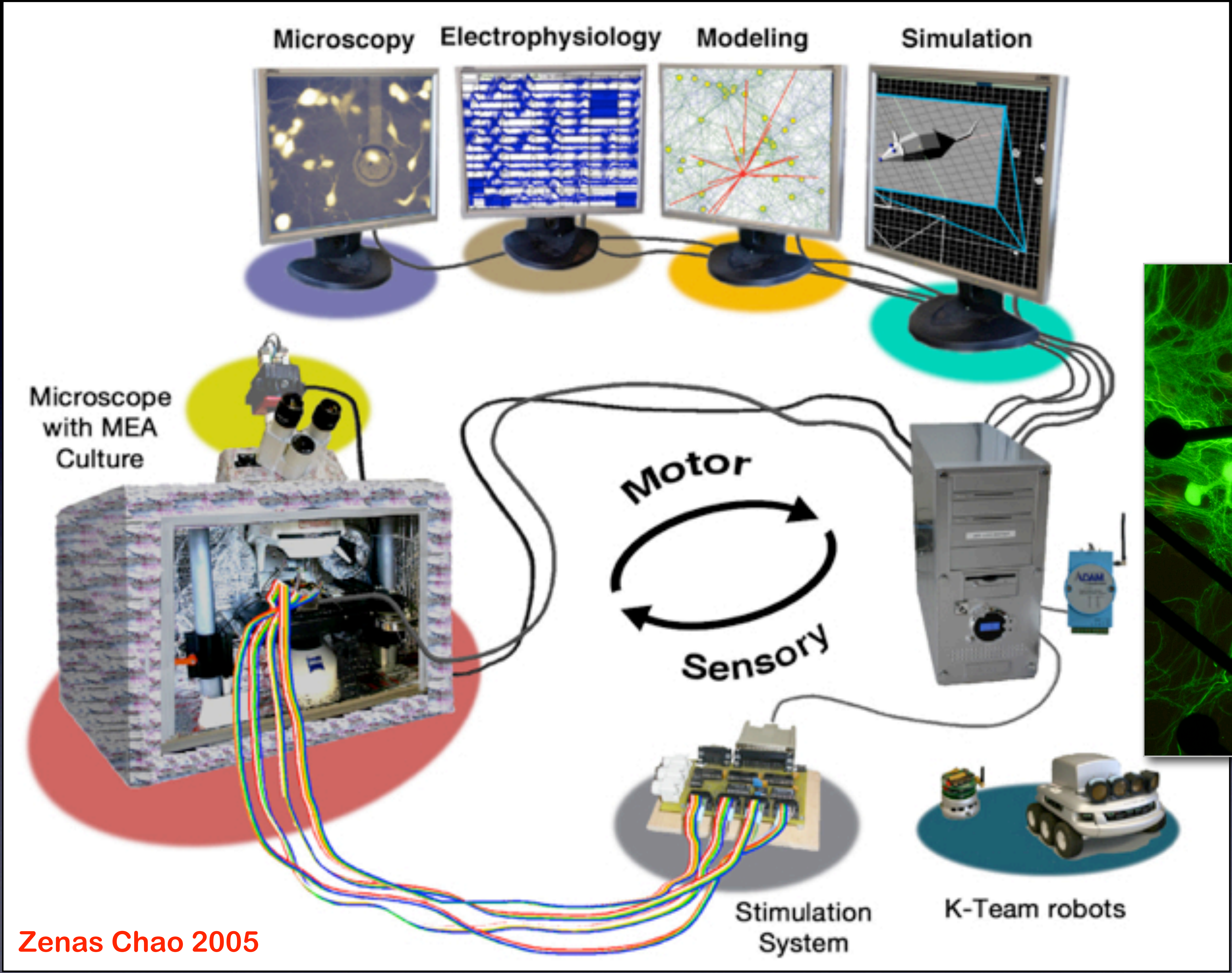


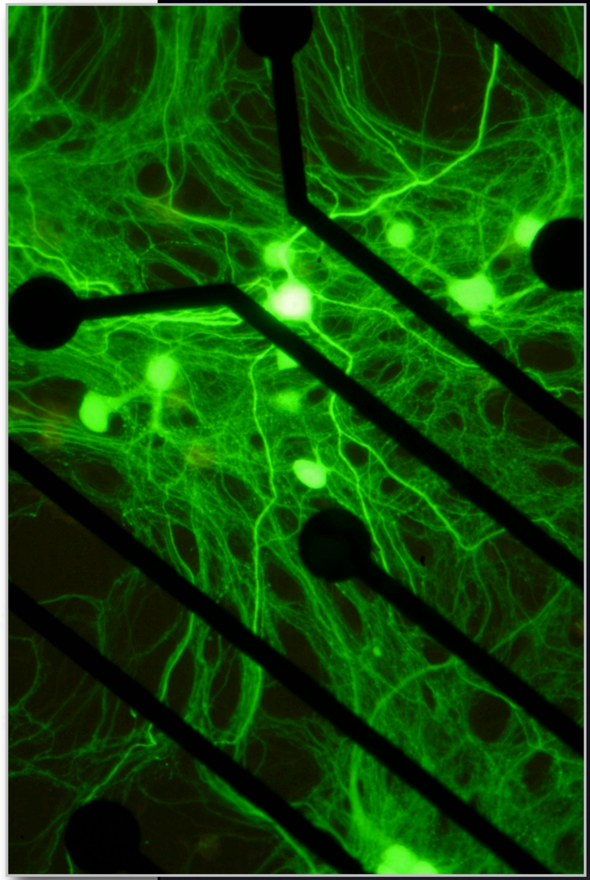
Lots of feedback control systems!

Get our free eBook on
Closed Loop Neuroscience

frontiersin.org

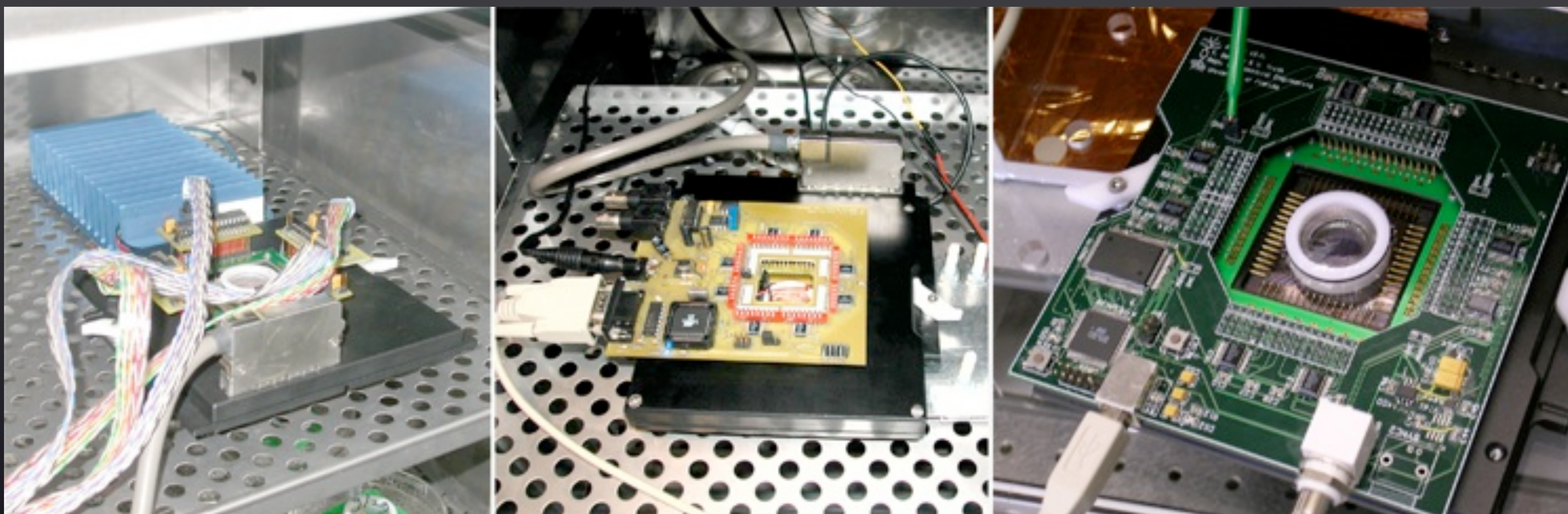
Closing the Loop with Embodied Cultured Networks





DeMarse, Wagenaar, Blau, & Potter (2001), “The neurally controlled animat: Biological brains acting with simulated bodies.” Autonomous Robots, 11, 305-310.

- MEA stimulators can provide complex multi-microelectrode stimuli.
- These can be used as artificial sensory input, modulatory or training signals.

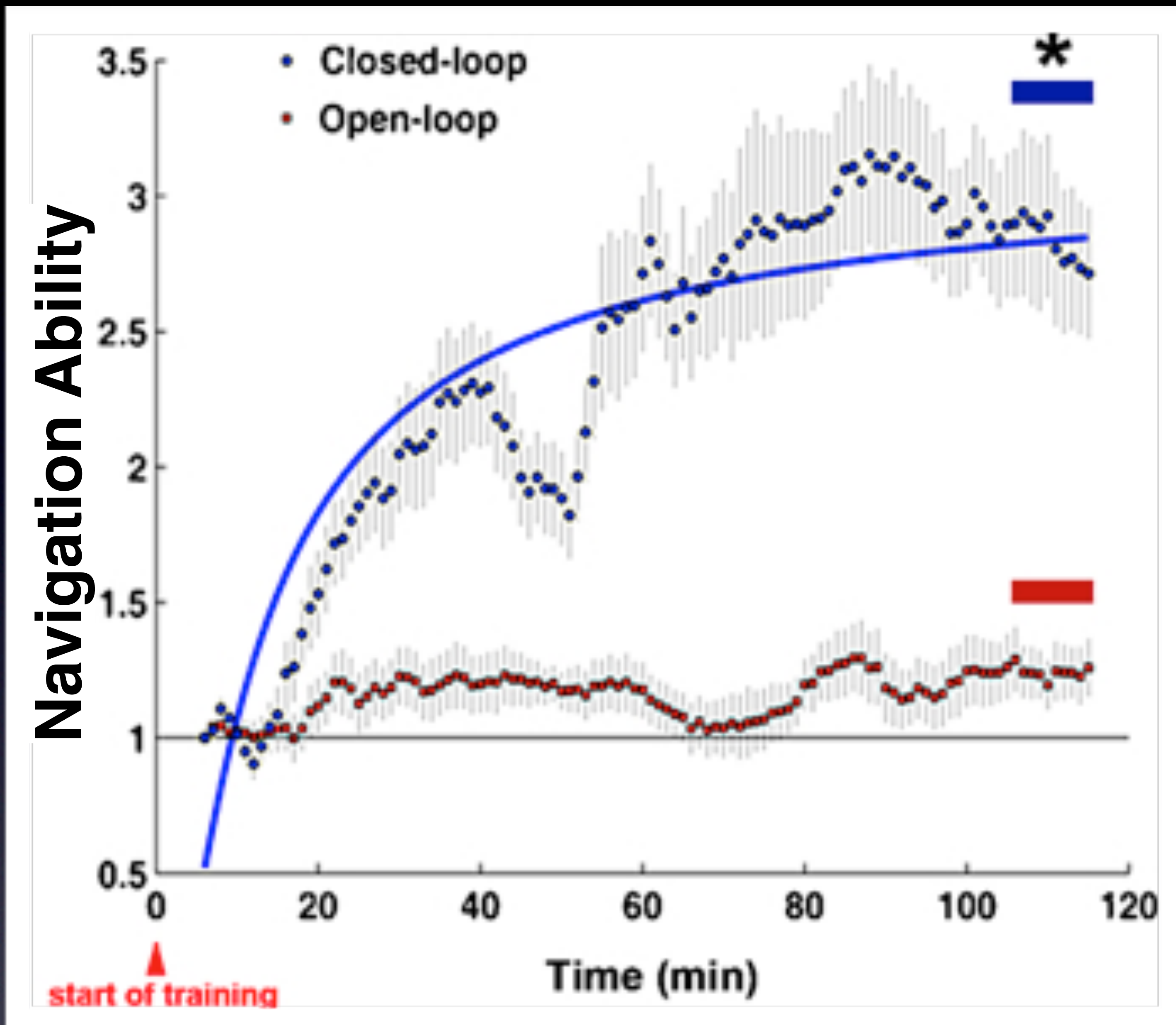


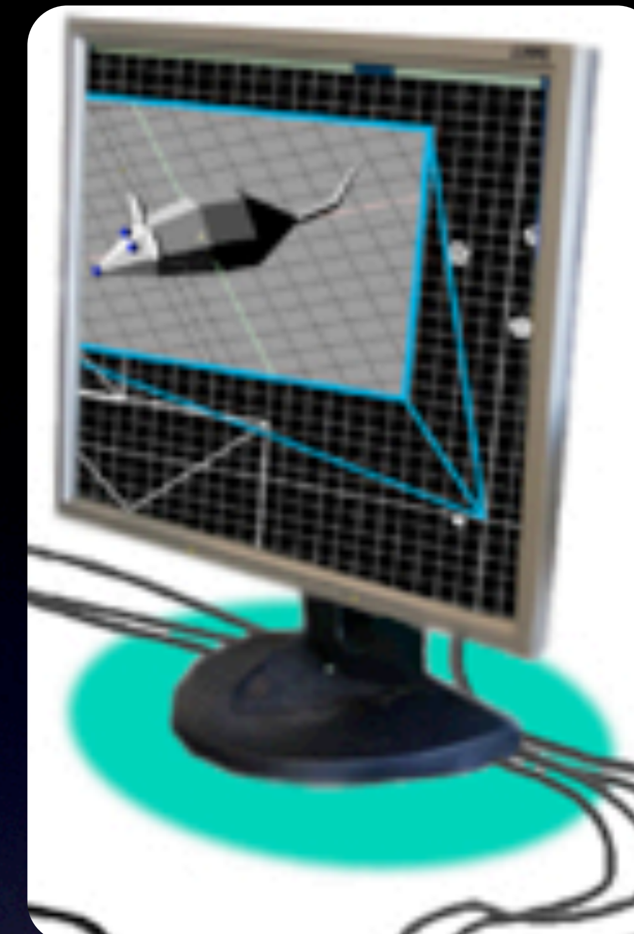
Wagenaar & Potter (2004). “A versatile all-channel stimulator for electrode arrays, with real-time control.” Journal of Neural Engineering, 1, 39-45.

Daniel Wagenaar

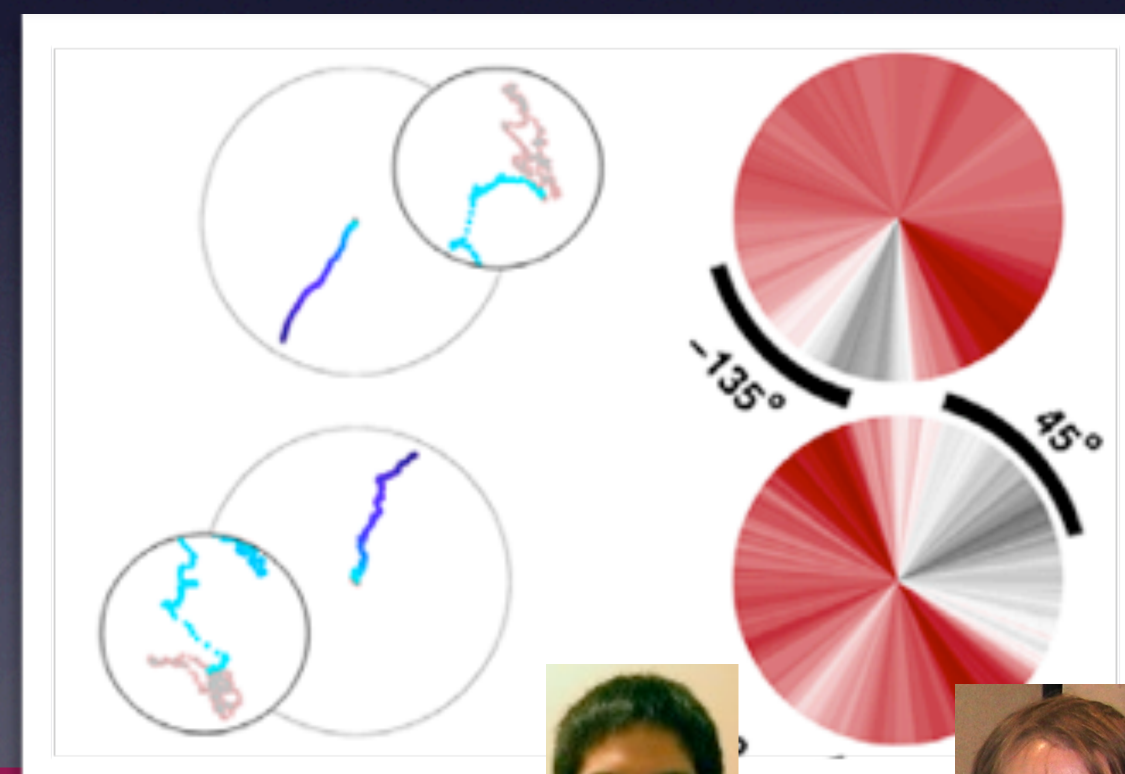
Tom DeMarse

With closed-loop electrical stimulation we trained a neurally-controlled animat



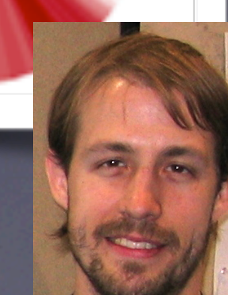


learning curve



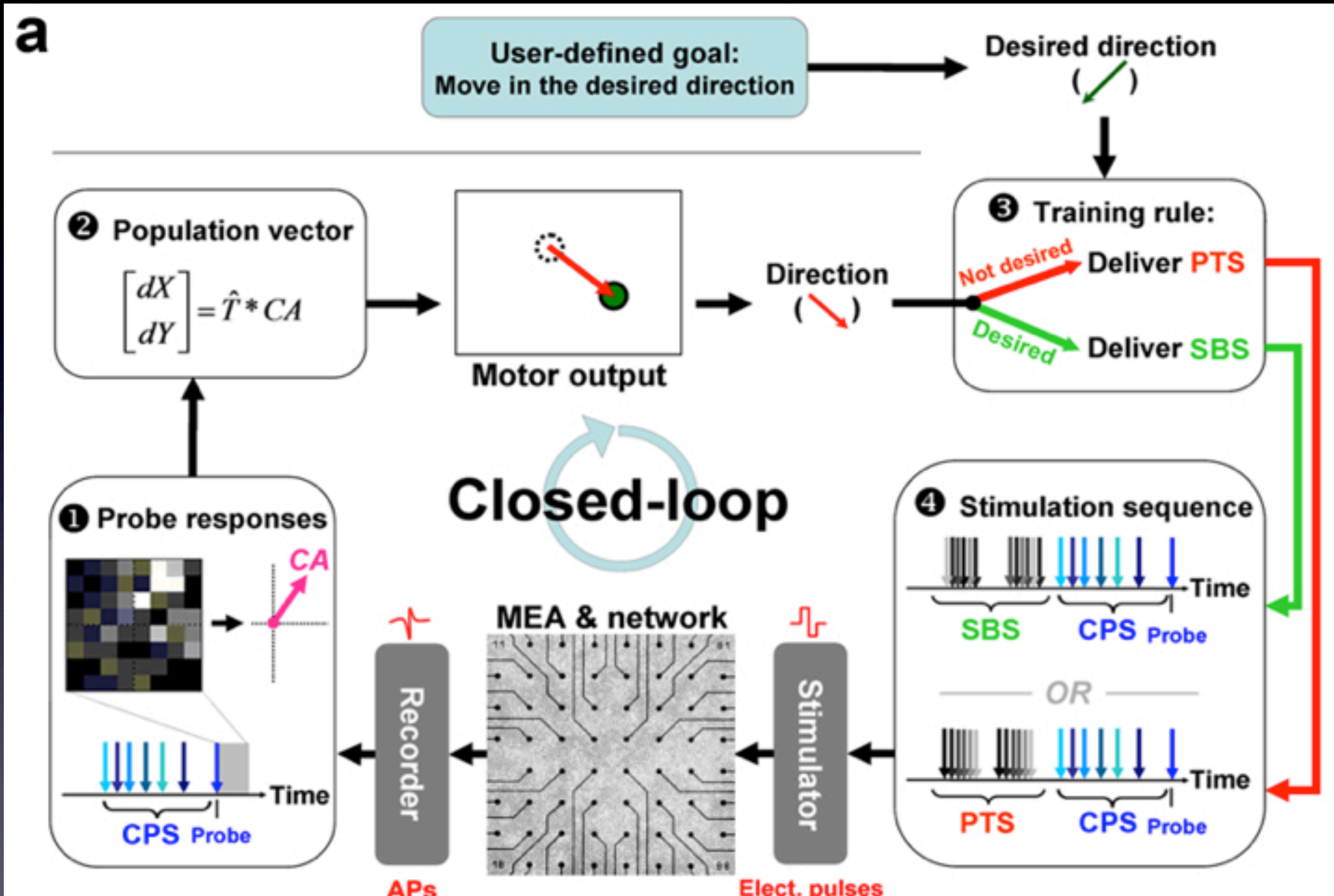
Chao, Bakkum & Potter (2008).
"Spatio-temporal electrical stimuli shape behavior of an embodied cortical network in a goal-directed learning task."
Journal of Neural Engineering, 5, 310-323.

Zenas Chao



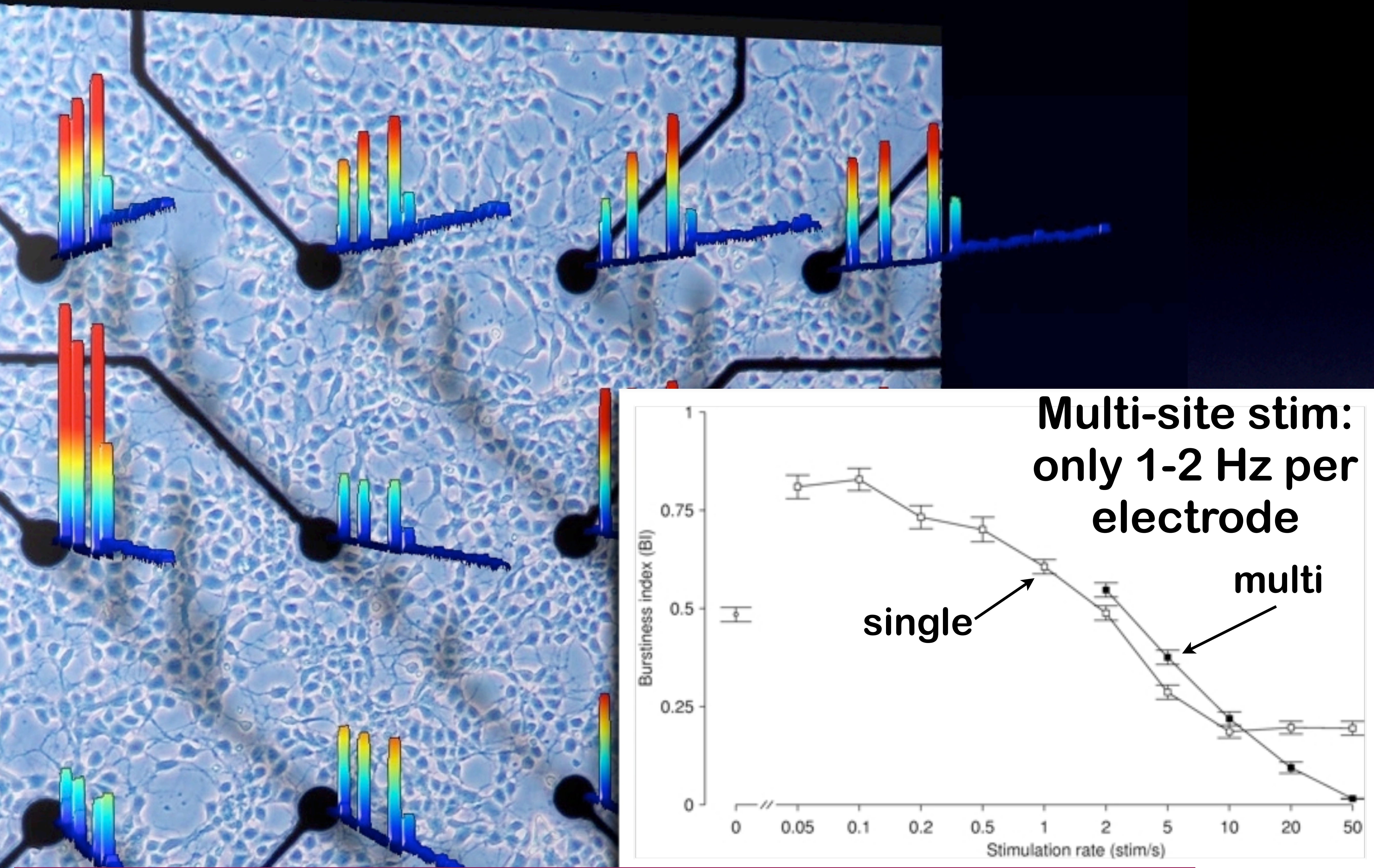
Doug Bakkum

Electric training protocol



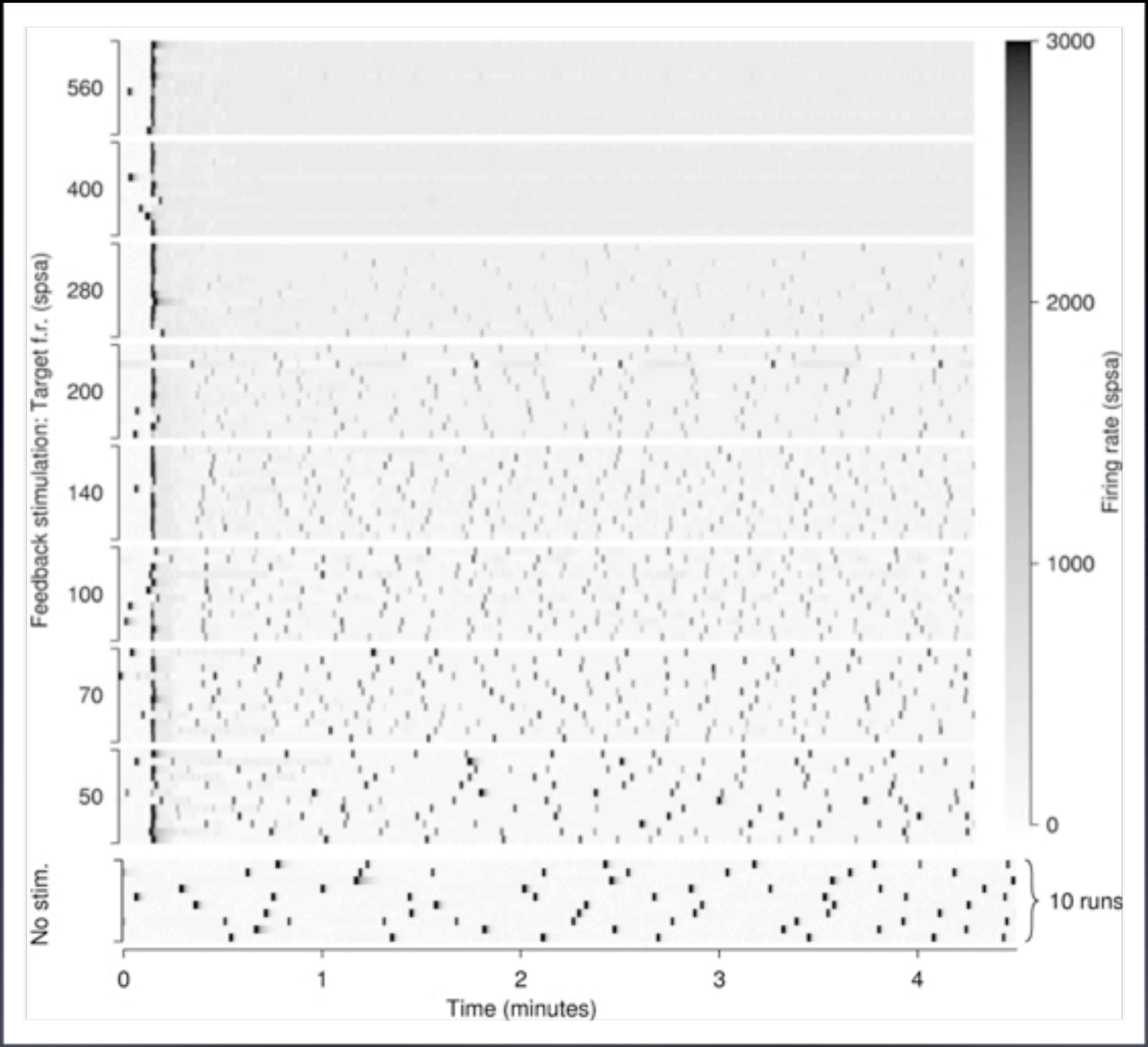
Bakkum, Chao & Potter (2008) “Spatio-temporal electrical stimuli shape behavior of an embodied cortical network in a goal-directed learning task.” Journal of Neural Engineering, 5, 310-323.

Burst quieting with distributed electrical stimulation



Wagenaar, Madhavan, Pine, & Potter (2005). "Controlling bursting in cortical cultures with closed-loop multi-electrode stimulation" J. Neuroscience, 25, 680-688.

Closed-loop burst quieting requires fewer electrodes or lower voltages



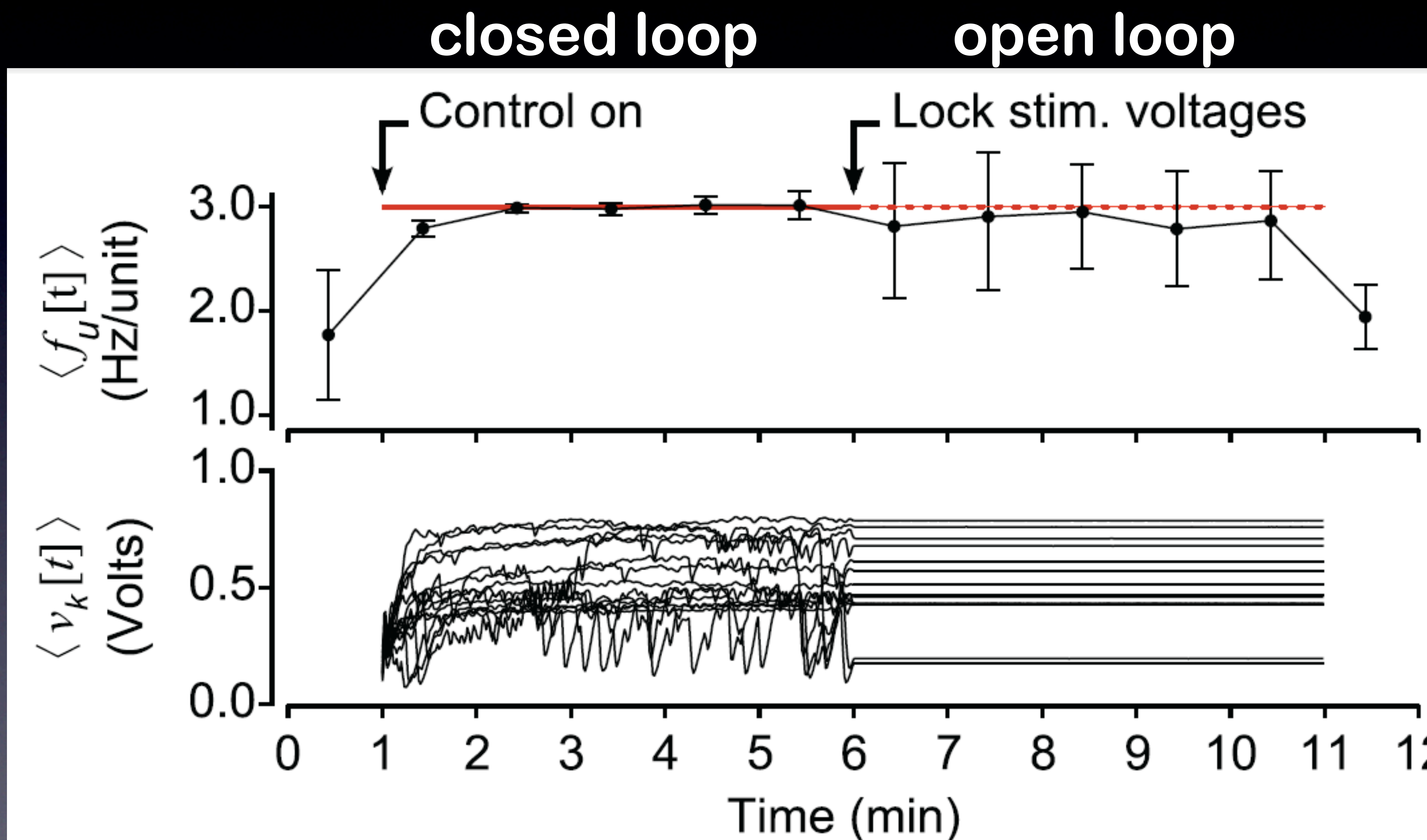
Application: drug-free electrical treatment of epilepsy

Sharanya Arcot Desai now at NeuroPace

Wagenaar, Madhavan, Pine, & Potter (2005). "Controlling bursting in cortical cultures with closed-loop multi-electrode stimulation" J. Neuroscience, 25, 680-688.

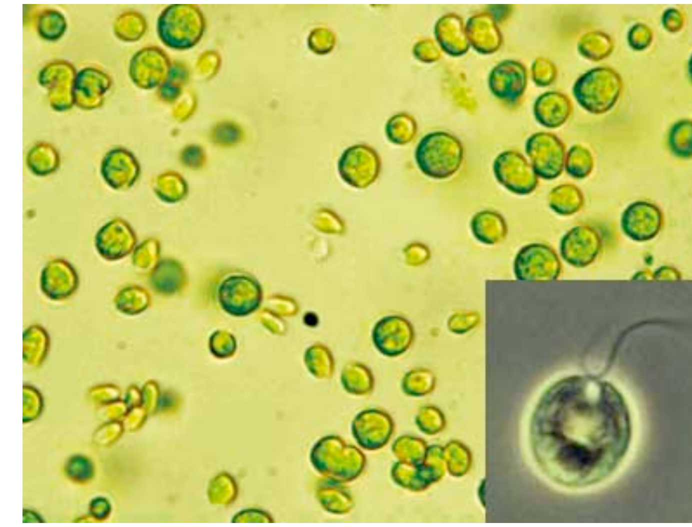
Dr. Robert Gross
Emory Neurosurgery

Electrical clamping of network firing rate using NeuroRighter



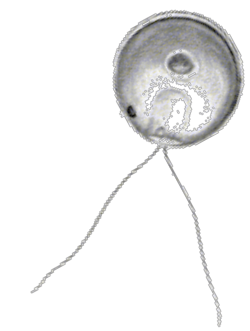
Newman et al. (2013) "Closed-loop, multichannel experimentation using the open-source NeuroRighter electrophysiology platform," Frontiers in Neural Circuits 6:98

Optogenetics!

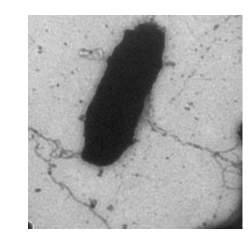


Stimulate or inhibit neural firing with light

- Light-sensitive ion channel from algae, Chlamydomonas reinhardtii: Channelrhodopsin-2 (ChR2). Lets Na in.



- Light-sensitive inward chloride *pump* from halophilic bacteria, Natromonas pharaonis "Halo" (NpHR)



Karl Deisseroth, Stanford U.

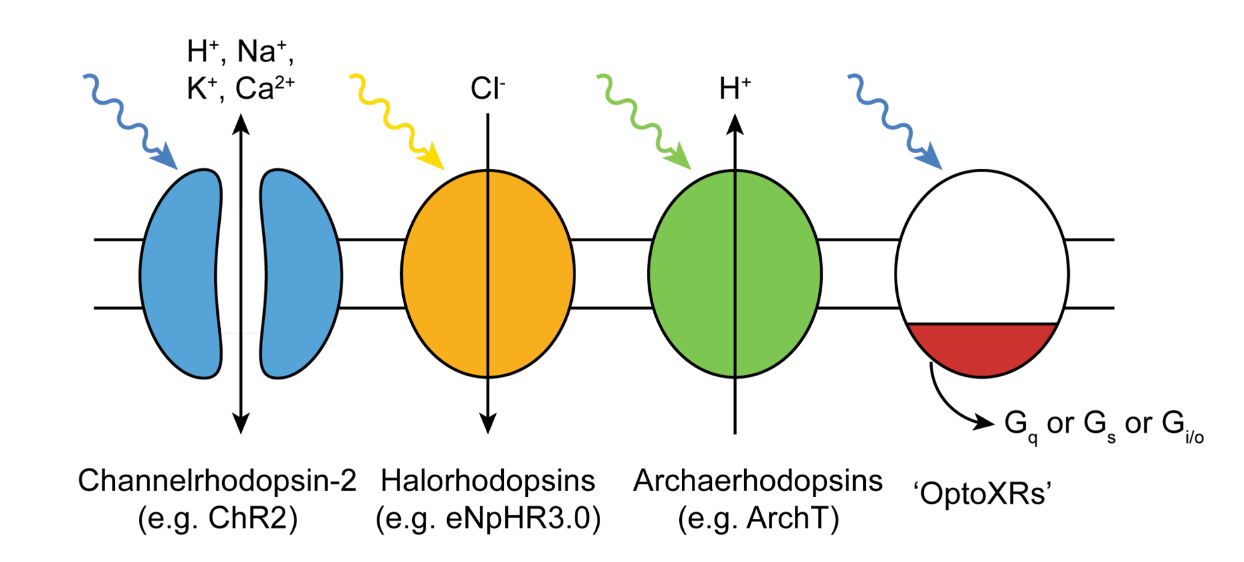
Ed Boyden, MIT

Potential Applications

- Anything that DBS can do, or might be able to do
- Neuromodulation (e.g., DA release, hunger)
- Sensory prostheses
- Sensory-motor prostheses (limbs with sensors)
- Circuitry studies, trans-synaptic labeling
- Basic science research into neural coding

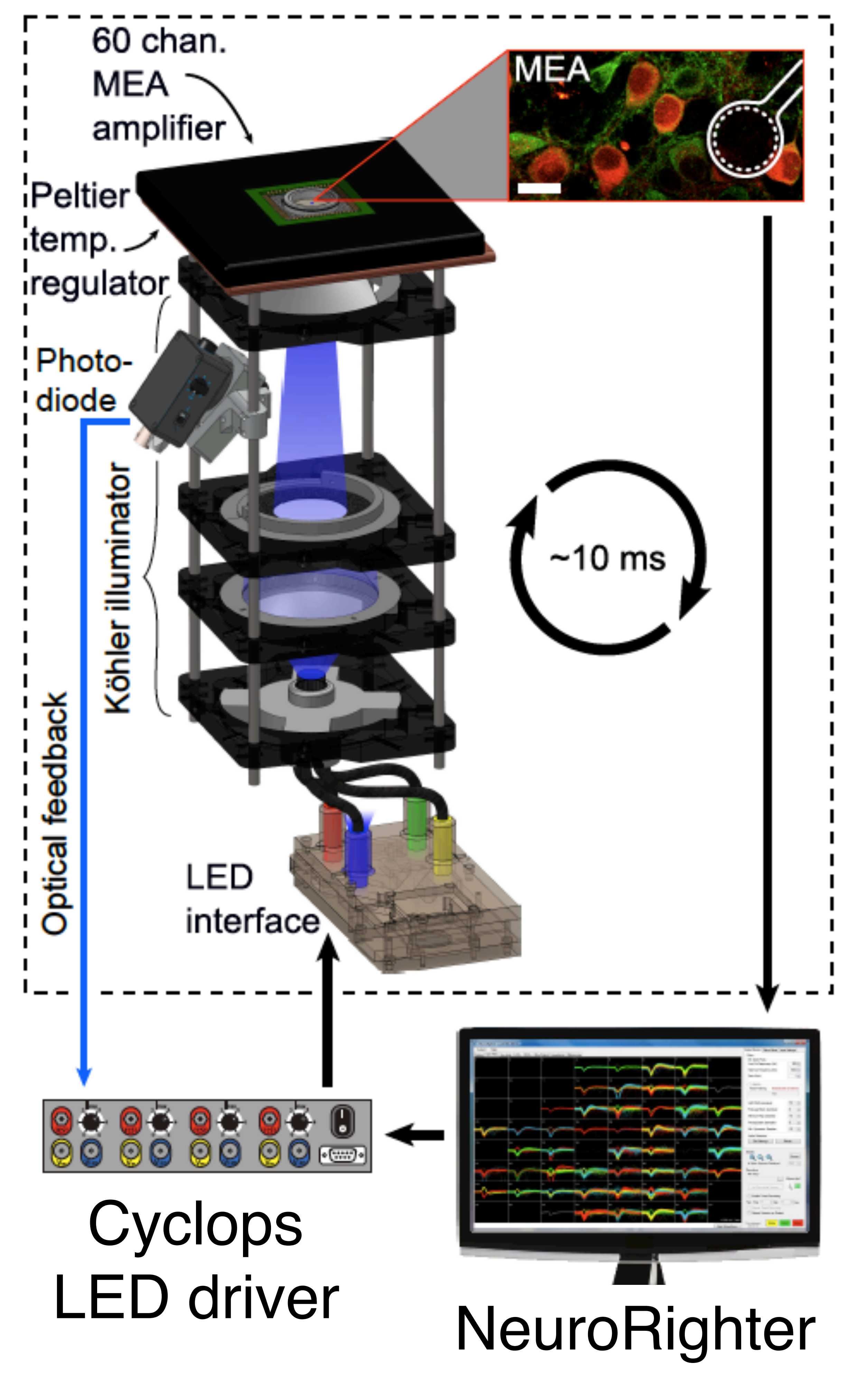
Optogenetic tools are particularly well suited for use in feedback neural control with MEAs

- Minimal electrical recording artifact
- Relatively narrow excitation spectra
- Bi-directional actuation: excitation and inhibition
- Cell-type specificity with various promoters
- Millisecond temporal resolution
- Can be improved with genetic engineering
- Co-express with fluorescent proteins
- Create reversible lesions
- Mammals have the needed cofactor



Packaging and Delivery

- Lentivirus (10kb limit); integrates into chromosome
- Adeno-associated virus (5kb limit)
- ChR2: 737 AAs (2.2kb)
- NpHR: ~300 AAs (0.9kb for gene, 7kb for construct with promoter, XFP)
- Mammalian codon optimization by Deisseroth's group
- Trans-synaptic labeling possible with rabies virus
- Transgenic mice, flies, and worms with ChR2 have been made
- Fiber optics are more biocompatible than wires

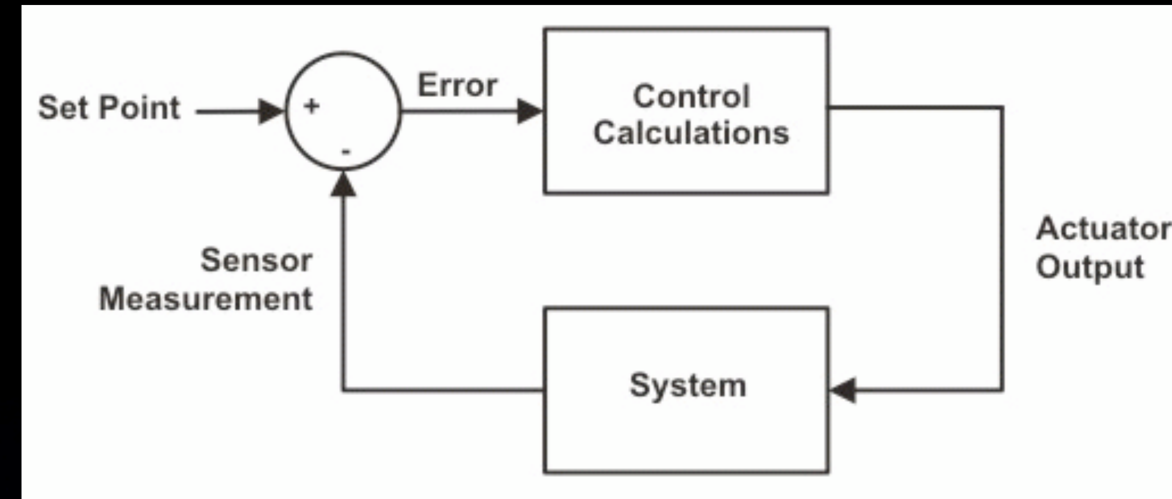


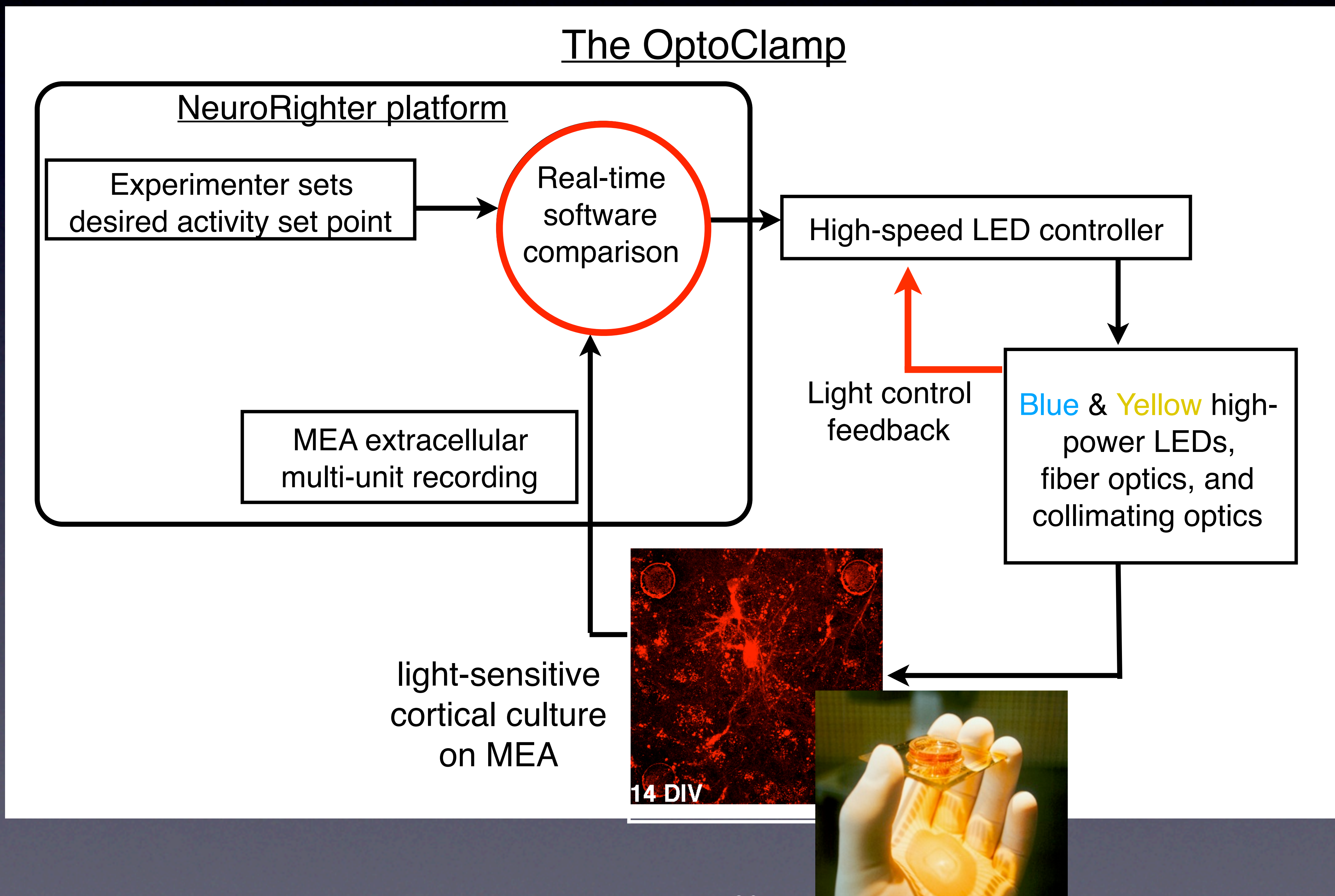
The OptoClamp

Closed-loop Optogenetic rig for controlling neural activity with light

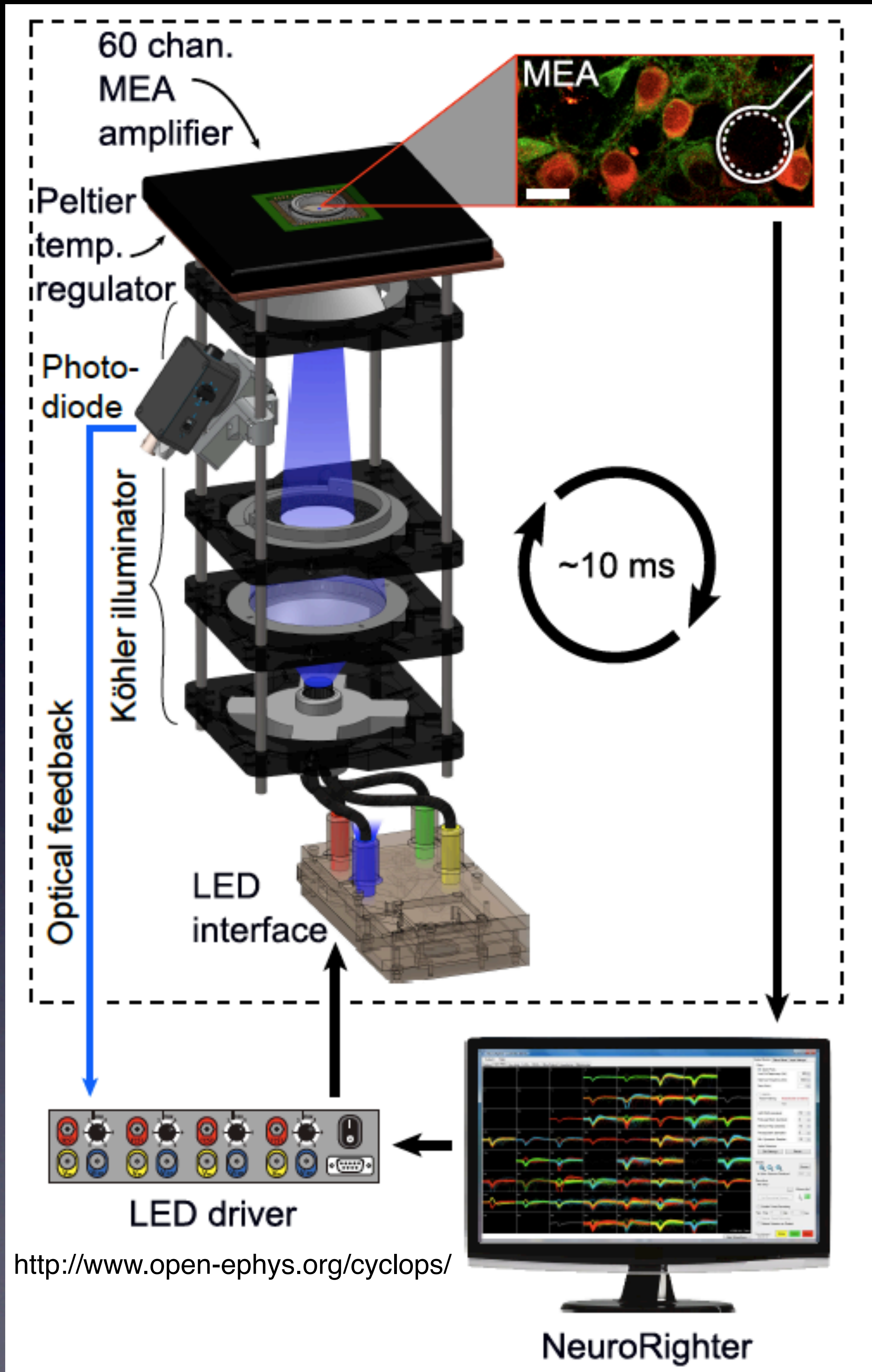
- AAV vector
- Excitation with Blue light
- Inhibition withYellow light
- CaMKIIa promoter: expressed in excitatory neurons only.

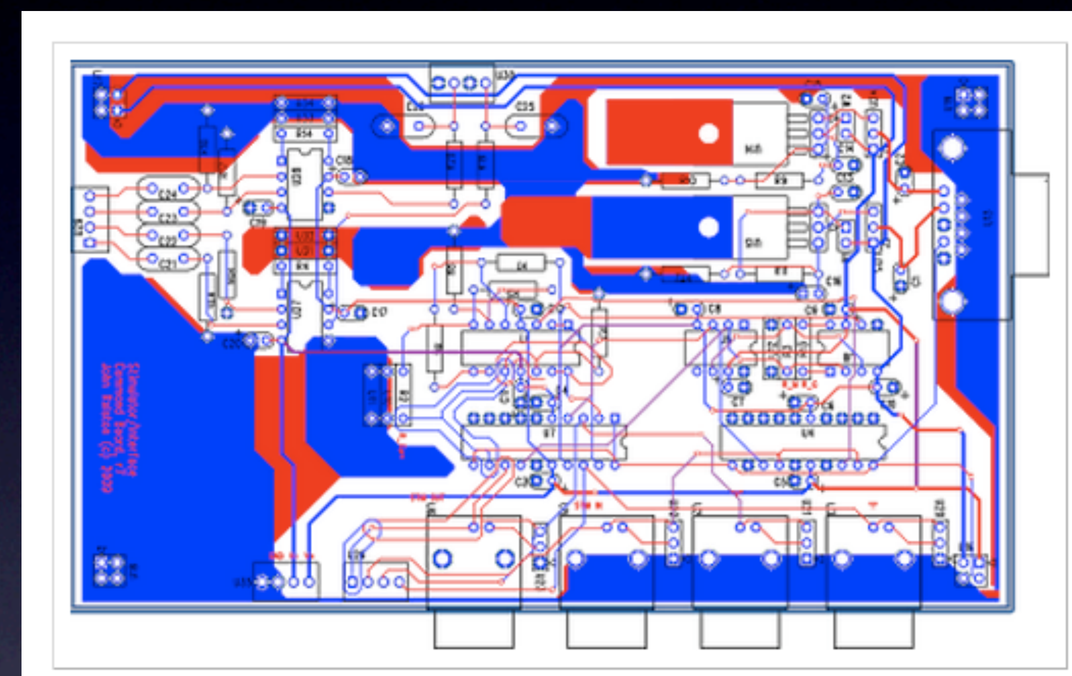
Jon Newman


Set Point
+
-
Error
Control Calculations
Actuator Output
Sensor Measurement
System


The OptoClamp
NeuroRighter platform
Experimenter sets desired activity set point
Real-time software comparison
High-speed LED controller
MEA extracellular multi-unit recording
Light control feedback
Blue & Yellow high-power LEDs, fiber optics, and collimating optics
light-sensitive cortical culture on MEA
14 DIV

Potter lab's Open Hardware and software





https://sites.google.com/site/neurorighter/

open source hardware

NeuroRighter:

Newman, Zeller-Townson, Fong, Desai, Gross, & Potter, (2012). "Closed-loop, multichannel experimentation using the open-source NeuroRighter electrophysiology platform." *Frontiers in Neural Circuits*, *6*, 98.

http://www.open-ephys.org/

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We are a team of neuroscientists who want to change the way our tools are developed and shared

Why do we need Open Ephys?

In the field of systems neuroscience, **there is a huge amount of technical development happening inside each and every lab**. Whether they're designing equipment for measuring behavior, constructing implants for extracting signals from the brain, or writing code for analyzing their data, neuroscientists are constantly building new tools for their research. We want to embrace these efforts and foster collaborations that produce tools that are transparent enough, flexible enough, and affordable enough to help everyone do great science.

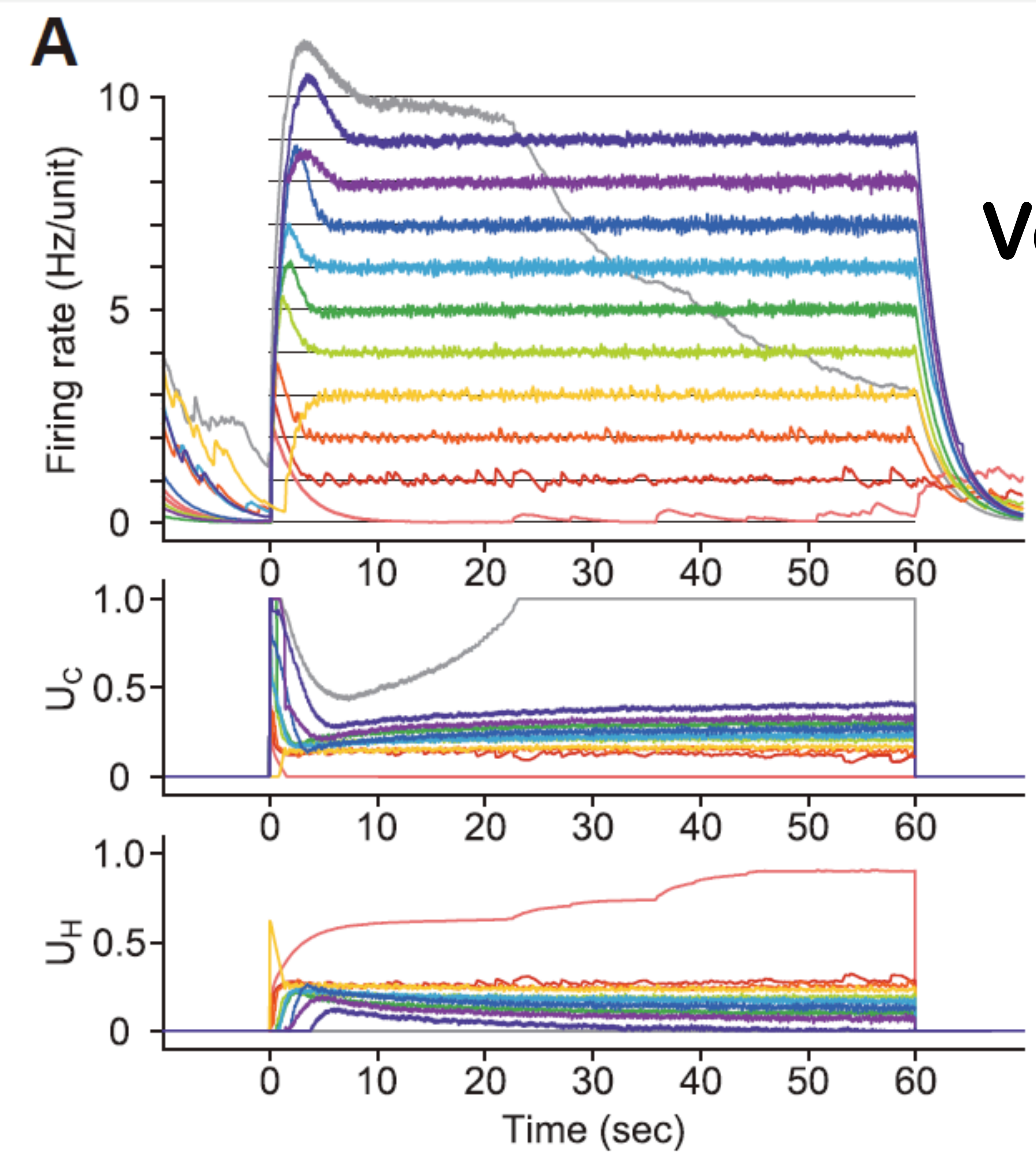
We see four main advantages to using open-source tools: **flexibility** to modify features to fit the needs of your research, ability to run experiments at a **lower cost**, the scientific and educational benefits of the tools' **transparency**, and the **reduced redundancy** that results from shared development efforts.

What does Open Ephys do?

We showcase and distribute tools for electrophysiology research that are open-source, thoroughly documented, and field-tested. We've had tremendous success using open-source tools for our own research, and we want to share the benefits with everyone. We also want to dispel the myth that tools built by researchers cannot be plug-and-play. We hate wasting time debugging as much as anyone, so we only promote tools that are easy to use and easy to maintain.

Whenever possible, we'd like to sell finished versions of the tools we've developed. As a first step, we've started selling some of our tools and the components needed to build the tools through our store. As Open Ephys continues to grow, you can expect to see more products available from us. If you're interested in helping out with manufacturing and distribution, please get in touch through our contact page.

OptoClamp using a Proportional-Integral (PI) controller

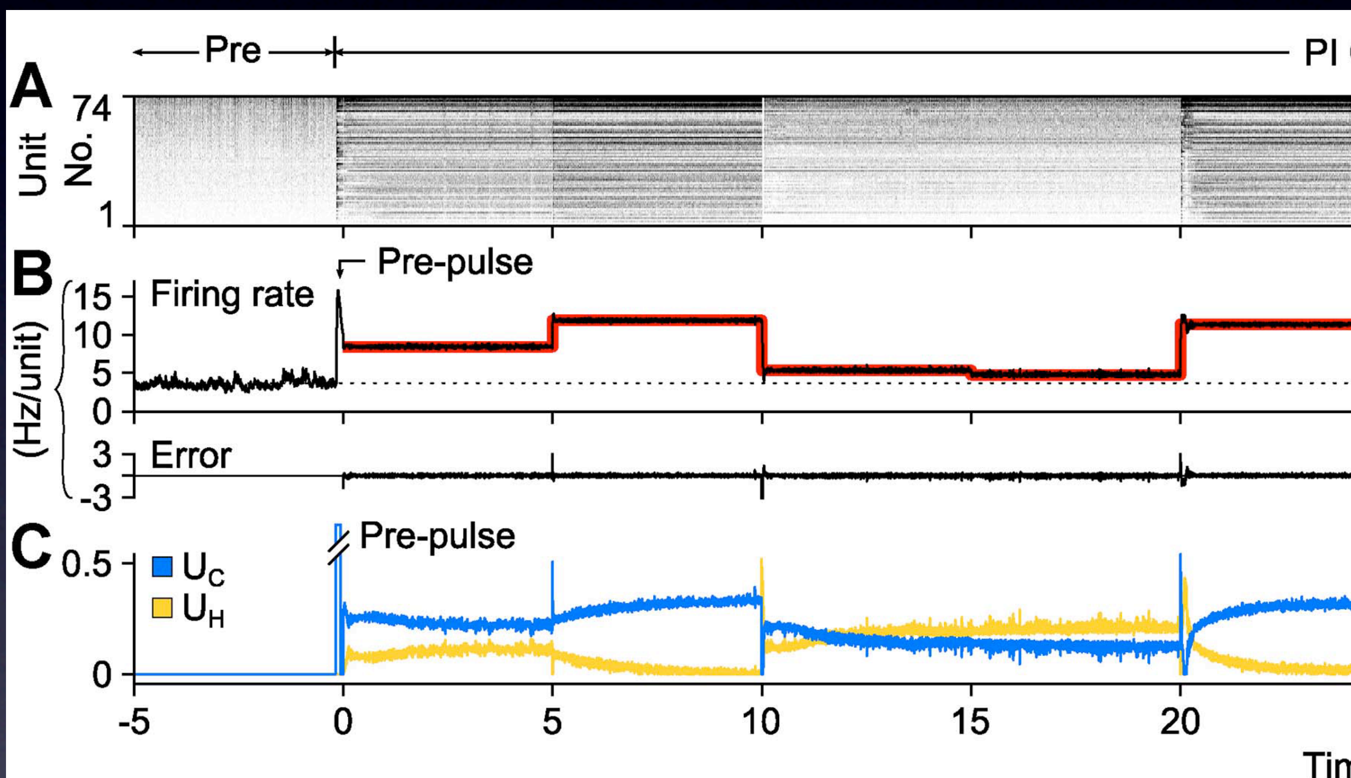


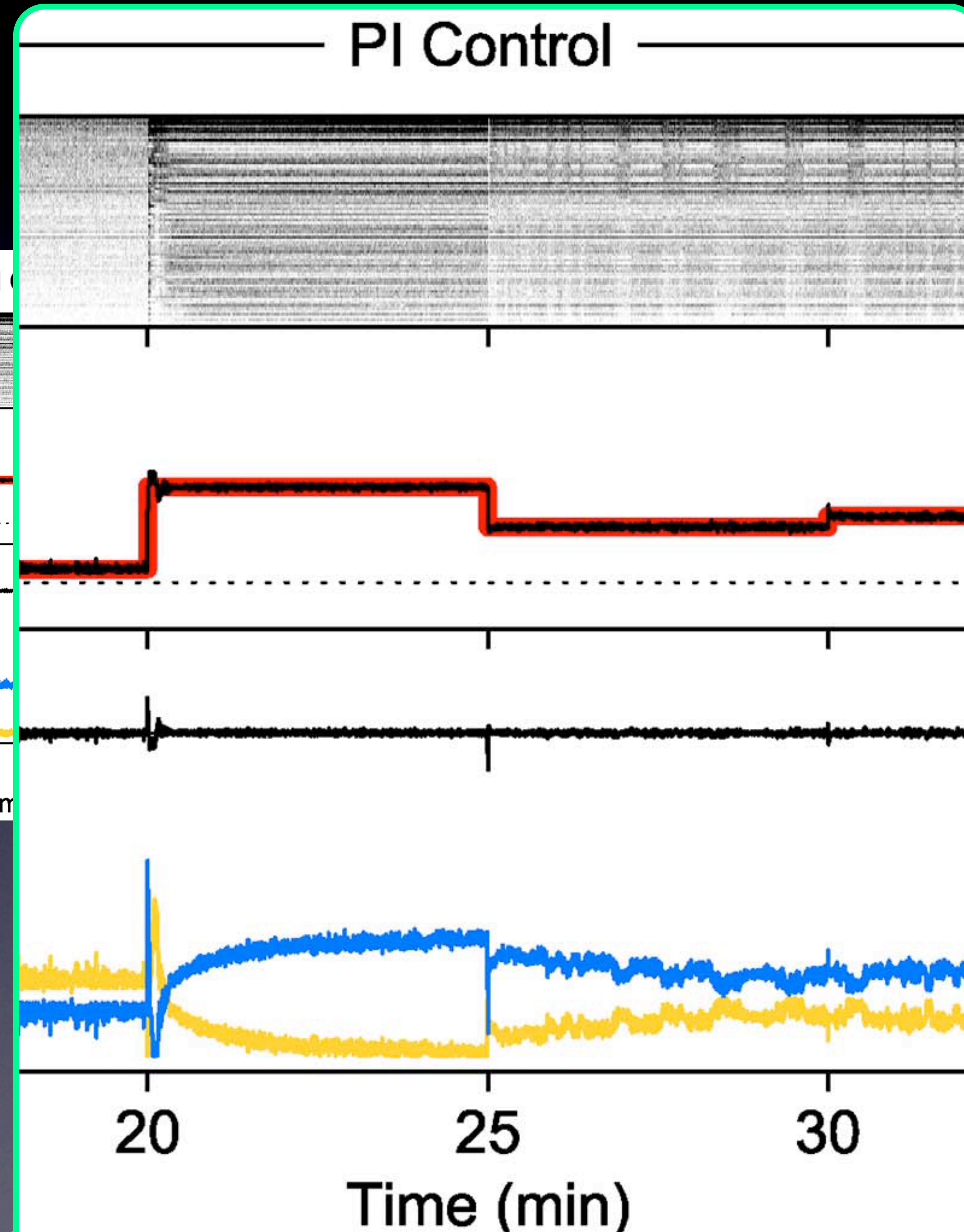
Very good clamp at 2-9 Hz/neuron

Blue light signal

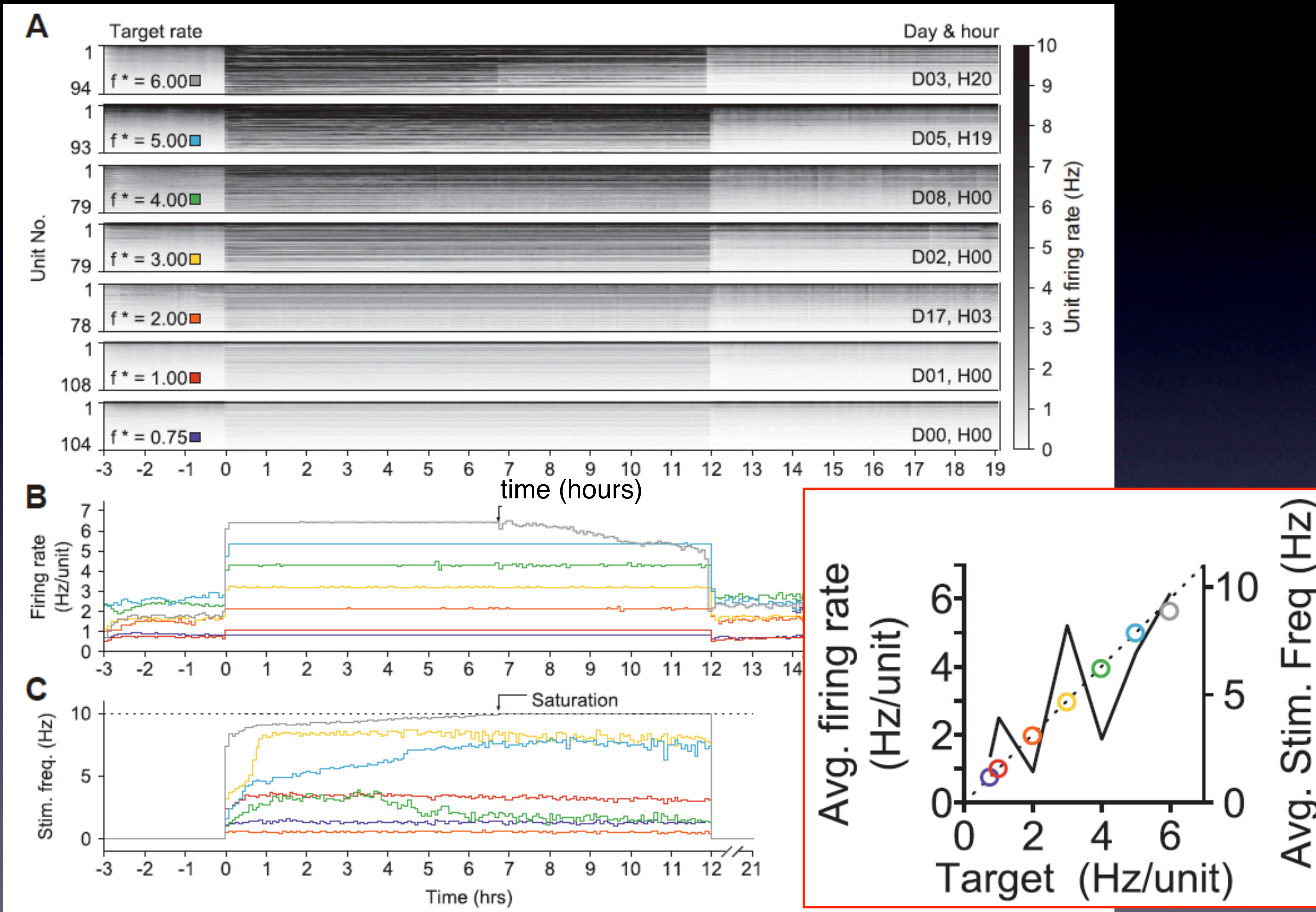
Yellow light signal

50-min Proportional-Integral (PI) feedback control





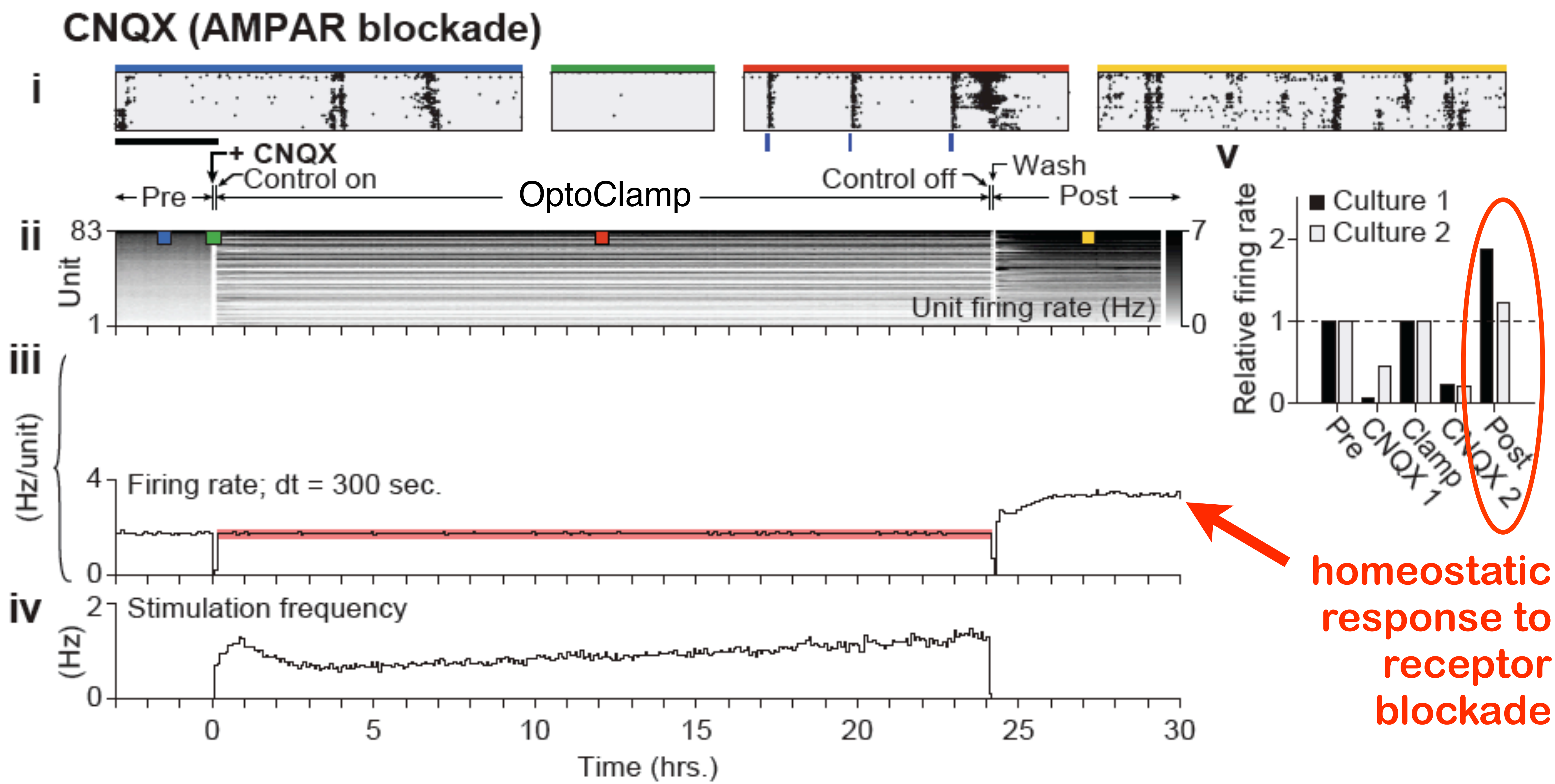
Firing rate can be can be controlled with OptoClamp for many hours



Homeostatic plasticity

- A form of slow learning or adaptation
- Neural circuits tend toward preferred level of activity
- Perturbations cause compensatory mechanisms to kick in, to bring activity back to normal. (Homeostasis)
- Homeostatic mechanisms can be harmful:
  - epilepsy after head injury
  - chronic pain after amputation
  - tinnitus resulting from deafness

We saw enduring upscaling after blocking AMPAergic transmission for many hours, while restoring spiking



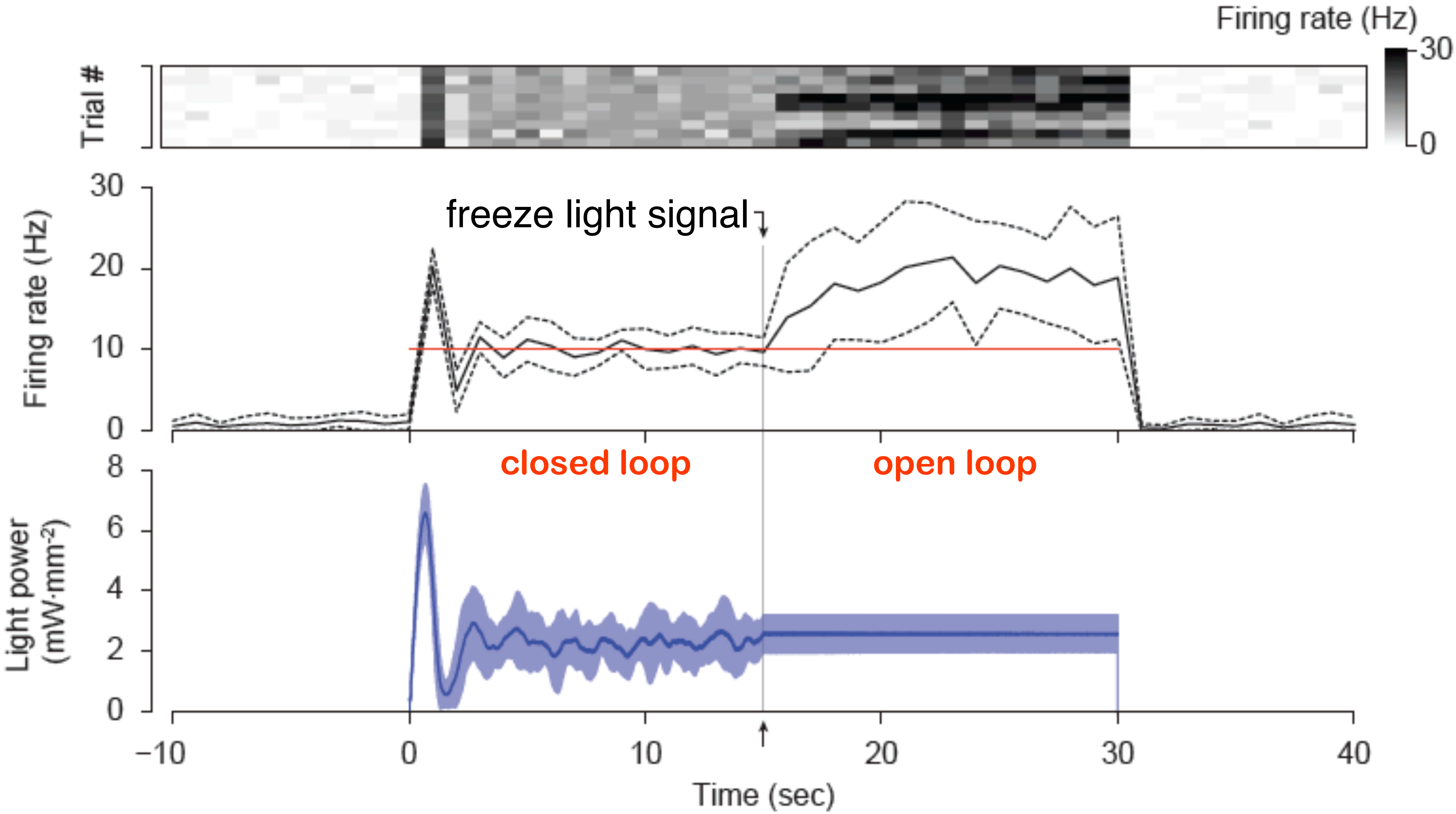
Ming-fai Fong
Jon Newman

Fong, Newman, Potter & Wenner "*Upward synaptic scaling is dependent on neurotransmission rather than spiking*", Nature Communications, 2015

Homeostatic synaptic scaling

- Block activity for many hours: cortical circuits compensate by increasing synaptic strength.
- Reduced spiking was thought to be the signal to provoke the homeostatic upscaling.
- We saw upscaling as a result of NT blockade, even when spiking was restored using the OptoClamp.
- So the reduction in NT signaling is the trigger for upscaling. Spiking is NOT the trigger, as previously believed.

in vivo: Maintain thalamic firing at a set point with OptoClamp



Counteract anesthesia with light

Garrett Stanley Lab:
Clarissa Whitmire and Daniel Millard

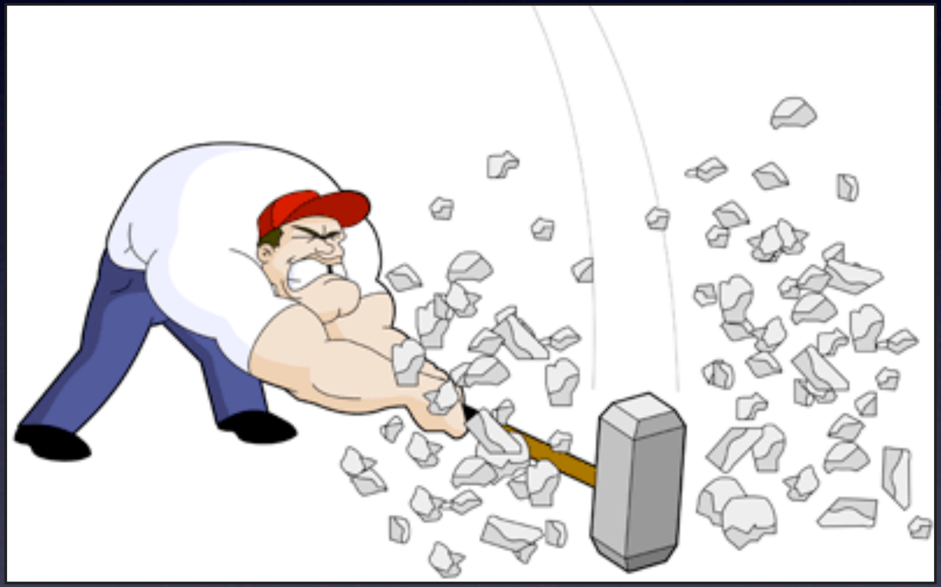
Summary

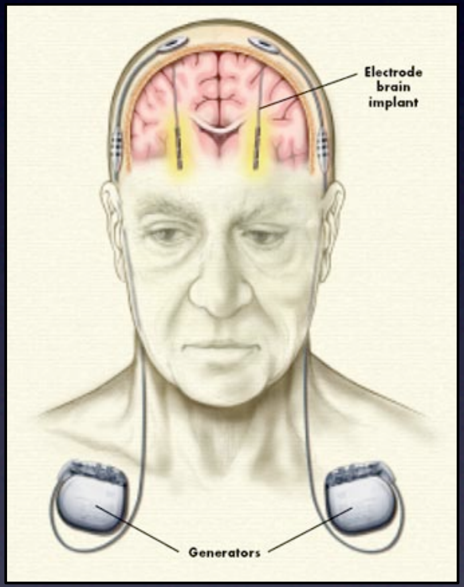
- Closed-loop tools like NeuroRighter and the OptoClamp enable neuroscientists to study neural systems with exquisite control.
- We answered a long-standing question about synaptic scaling: neurotransmitter release matters more than spiking itself.
- Closed-loop optical neural control also works well in vivo – Artificial sensory input.
- The rest of engineering has been using feedback to enhance control for decades.
- It is time neuroengineering caught up.

Close the Loop!

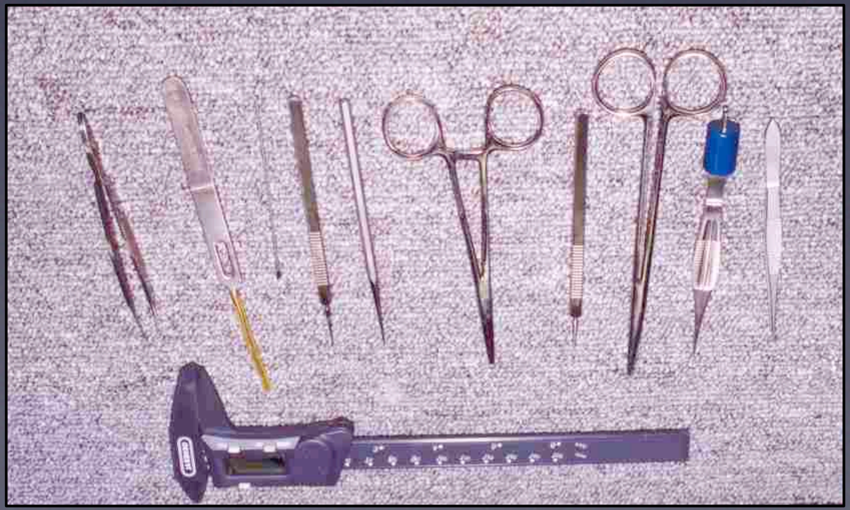
- Some day all brain stimulation, whether electrical or optical, will be controlled in real time by recordings.
- Open-loop stimulation will be considered barbaric.

Open Loop



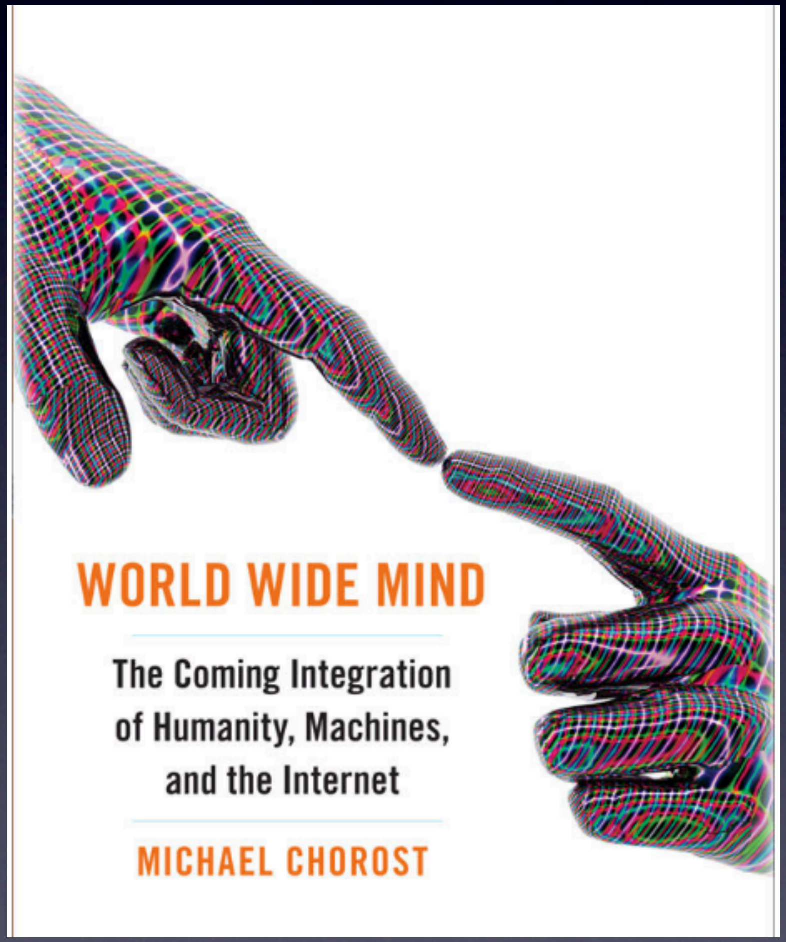


Closed Loop



Fiber-optic implants for therapy and enhancement

They will all be CLOSED-LOOP!



See "Powered by Photons" in Wired Nov. 2009, and book "World-wide Mind" by Michael Chorost

Thanks!

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Epilepsy Research Foundation

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Sharanya Arcot Desai, Ethan Craig, Eric Eisner, Candace Law, Ushnik Ghosh, Silvia Vaca, Nathan Killian, Alex Calhoun, **Jon Newman**, Riley Zeller-Townson, **Ming-fai Fong**, Marc Powell, Michelle Kuykendal

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Mark Booth

Chad Hales

Axel Blau

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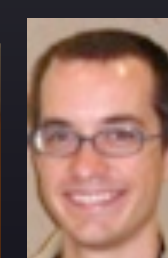
Daniel Wagenaar

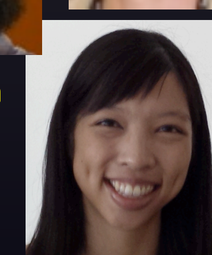
Komal Rambani

Zenas Chao

John Rolston



Jon Newman

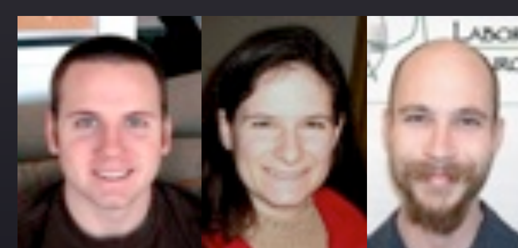


Ming-fai Fong

Radhika Madhavan

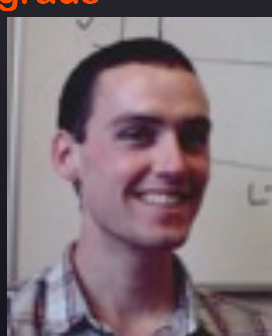
Doug Bakkum

Former Technicians

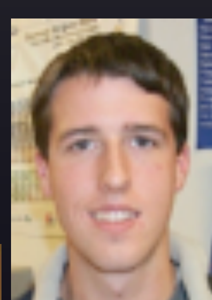


Alex Kohl
Sarah Davis
Douglas Swehla

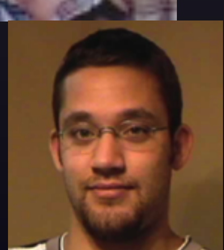
Former Georgia Tech and Emory Undergrads



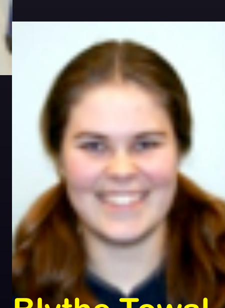
Matthew MacDougall



John Brumfield

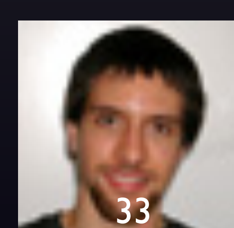


Alec Shkolnik

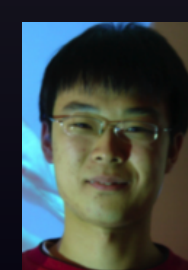


Blythe Towal

Bhavesh Mehta



Ryan Haynes



Yixiao Zou