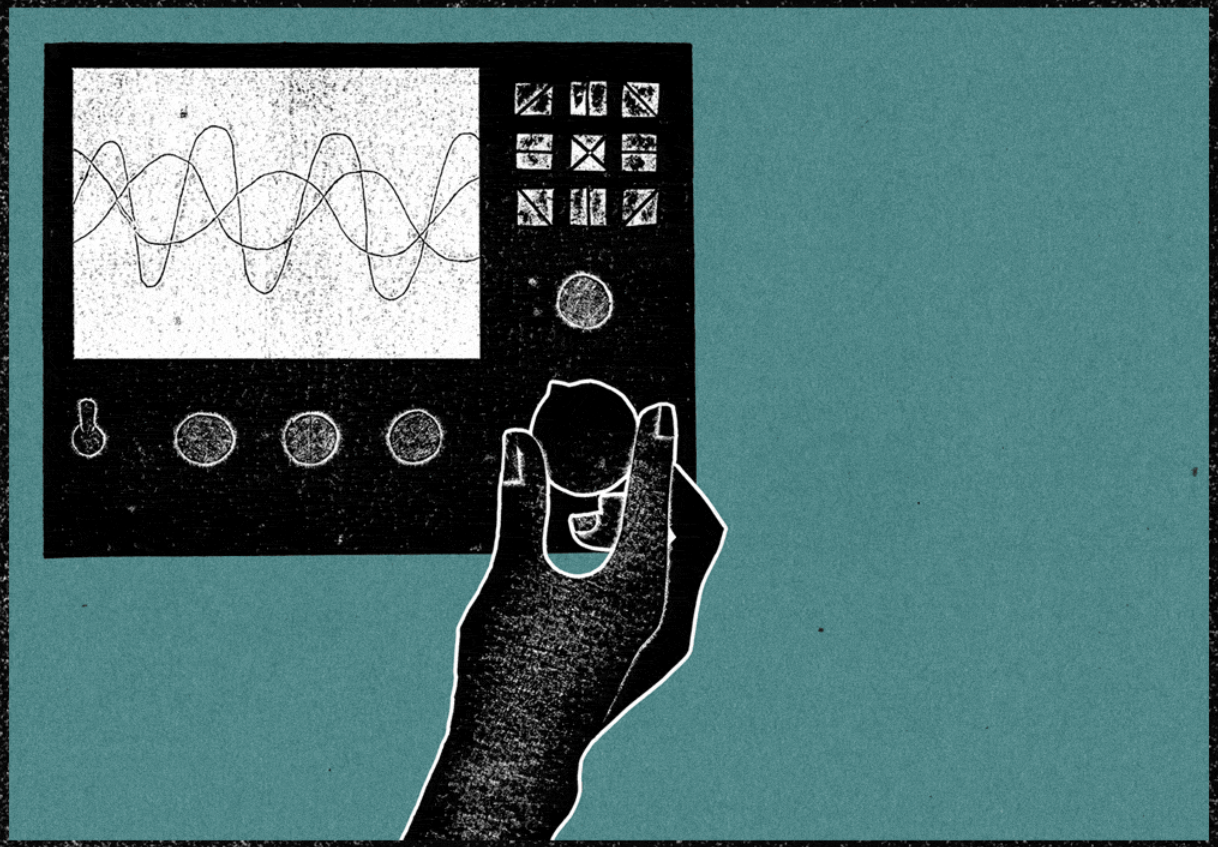
Applied Neuroscience

Columbia University Science Honors Program
Fall 2017



Course Evaluations

What were the best aspects of this course?

The teacher Naureen

I really enjoyed the class! The demos were great & Naureen is a fantastic teacher ☺.

What aspects of this course do you think should be changed?

I feel that the breaks should be shortened. It was usually intended for them to be 10 minutes, but they always ended up being longer.

General comments:

Best class ever

Fantastic course: would actually consider taking again.

Logistics

1. Maximum of **4 Absences**
2. For an excused absence, e-mail shpattendance@columbia.edu and ng2410@columbia.edu
3. Two 10 minute breaks at 11:00 AM and 12:00 PM
4. Joe's Coffee in Northwest Corner Building
5. Do not hesitate to ask questions
6. Do request topics of interest
7. No exams

- Name
- Grade
- Location
- What is something you would like to learn in this class?
- Share one interesting thing about yourself.

Why Applied Neuroscience?

19th Century Biology: Descriptive
20th Century Biology: Biochemical
21st Century Biology: Quantitative

"The 21st century biologist must be, at least in part, a mathematician."
-- Eric Lander, MIT

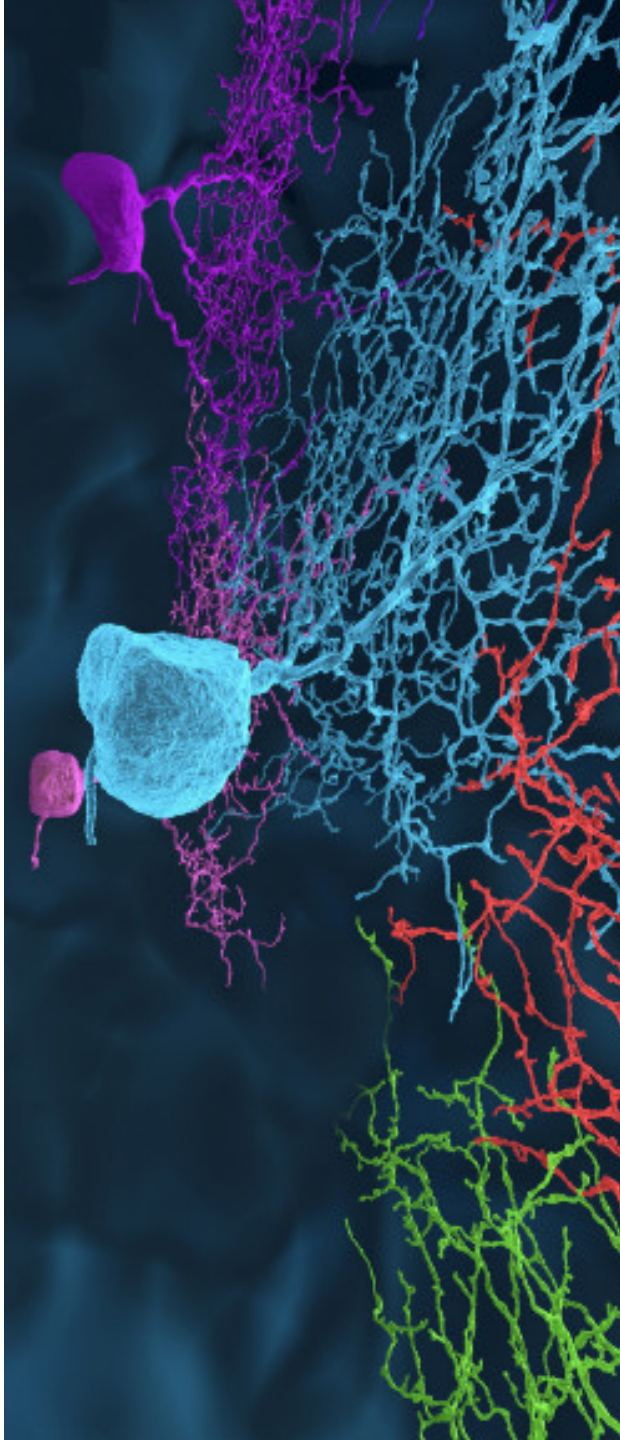
- NSF and NIH have expressed concern that there are not enough people trained to join hands across the disciplinary boundary between biology and math

Neural Circuits

Objective: Experimental Design in Neuroscience

Agenda:
Neural Circuits

- Anatomy
- Manipulations



Neural Circuits

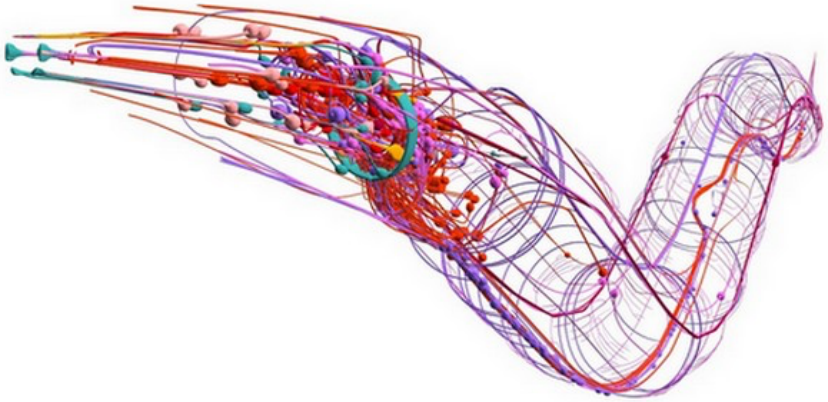
Neural Circuit: Functional entity of inter-connected neurons that is able to regulate its own activity using a feedback loop

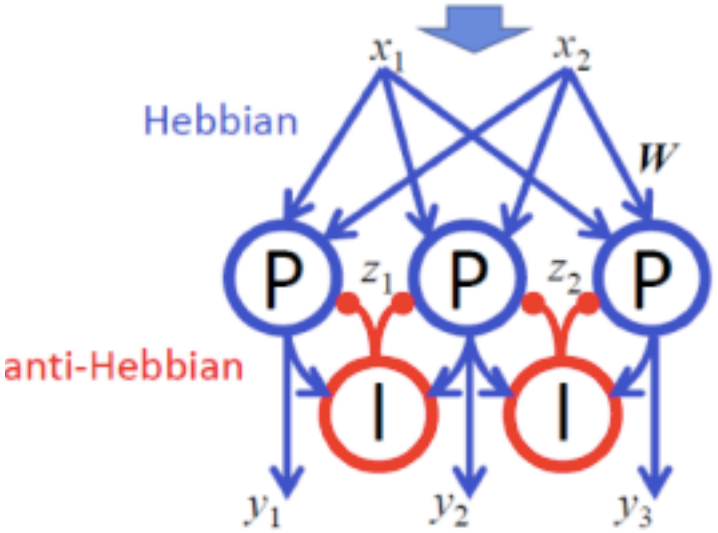
Features:

1. Neurons do not function in isolation
2. Neurons are grouped according to function
3. Synaptic connections define the circuit
    - Types of Connections
        1. Axon-Dendrite
        2. Neuron-Muscle
    - Types of Neurotransmitters Used
    - Location and Length of Connections

Reverse Engineering the Brain

Connectomics → **Theory**





Connectomes are brain wiring diagrams at the synapse level and requires serial electron microscopy.

Why Theory?
While we understand neuron physiology, there is no accepted algorithmic theory of neural computation.
With theory, we test hypotheses on neural connectivity.

Neuron
Review

CellPress

Neuroscience-Inspired Artificial Intelligence

Demis Hassabis,[1,2,*] Dharshan Kumaran,[1,3] Christopher Summerfield,[1,4] and Matthew Botvinick[1,2]
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[2]Gatsby Computational Neuroscience Unit, 25 Howland Street, London, UK
[3]Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London, UK
[4]Department of Experimental Psychology, University of Oxford, Oxford, UK
*Correspondence: dhcontact@google.com
http://dx.doi.org/10.1016/j.neuron.2017.06.011

The fields of neuroscience and artificial intelligence (AI) have a long and intertwined history. In more recent times, however, communication and collaboration between the two fields has become less commonplace. In this article, we argue that better understanding biological brains could play a vital role in building intelligent machines. We survey historical interactions between the AI and neuroscience fields and emphasize current advances in AI that have been inspired by the study of neural computation in humans and other animals. We conclude by highlighting shared themes that may be key for advancing future research in both fields.

Demis Hassabis

- Co-founder of DeepMind
- Computer game designer
- World-class games player

Well, hello Demis Hassabis, is that a cheque for £400m in your pocket, or are you just pleased to see us?

What... we're allowed to flirt with the guy. He may look like a 14-year-old who should stop playing Dungeons & Dragons and tidy his room immediately, but he's 37, cleverer than Brian Cox times Mark Zuckerberg squared, and the recent recipient of an eye-popping payout from Google, which has brought him in to build up the artificial intelligence behind its search systems and help it take over the world (mwah ha ha ha ha). So do forgive a little eyelash-fluttering. Demis is a baby-faced genius with Wolverine's eyebrows; a former child chess master who was made lead programmer for the video game Theme Park at just 17. He won the Mind Sports Olympiad (Sochi for brainiacs) a record five times and has a Double First in computer science and a PhD in cognitive neuroscience, all of which makes Crush's Tinder profile look pretty shoddy by comparison.

Source: London Evening Standard

Neural Circuits

Type	Examples	Neural Activity	Synaptic Signaling	Non-Synaptic Signaling
Acute (Fast)	Vision, Reflexes	Short window	Yes	No
Chronic (Slow)	Hunger, Mood	Long window	Yes	Yes

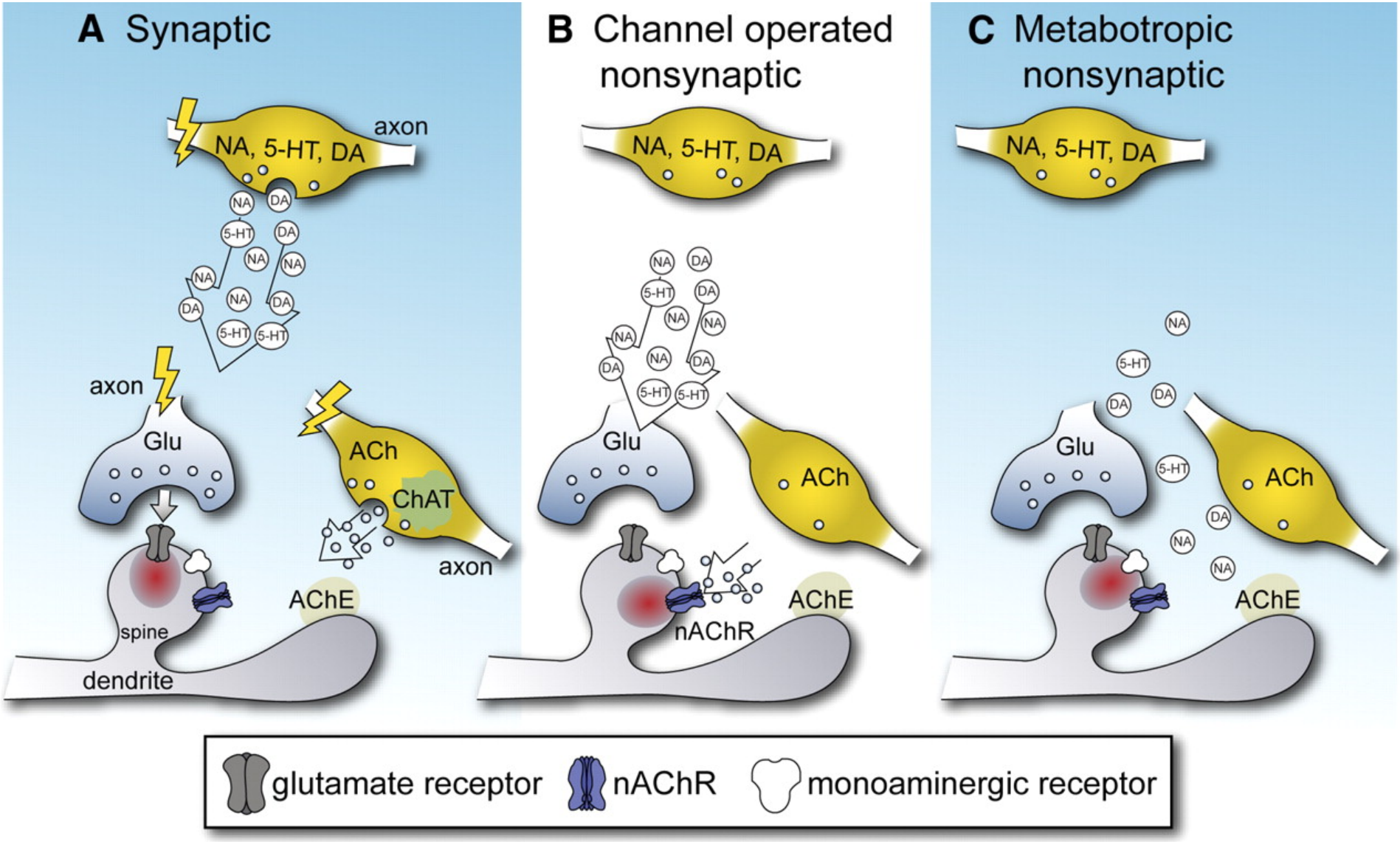
Acute Neural Circuits:

- Stimulus-dependent (clear causality)
- Fast responses require fast signaling, which implies anatomical synaptic connections

Chronic Neural Circuits:

- State-dependent (unclear causality as multiple stimuli may act together to elicit the behavior)
- Slow responses suggest non-synaptic signals

Non-Synaptic Signaling



Why Study Invertebrates?

Model	Correlated Neurons	Causal Neurons	Neural Circuit
Vertebrates	Yes	Sometimes	No— • Too many neurons • Neurons and connectivity varies
Invertebrates	Yes	Yes	Yes— • Fewer neurons • Stereotyped neurons and connectivity

Neural Circuits

Vertebrates	Invertebrates
1. Identify a stimulus-dependent behavior of interest (i.e. object attraction in mice). 2. Drop an electrode into a part of the brain, present the object to the mouse. See if neurons respond. 3. Inactivate neuron to show neuron is part of circuit. • By studying many parts of the brain, many neurons will be found. However, we will not know the gaps between neurons. • The same neuron is hard to identify across animals.	1. Identify a stimulus-dependent behavior of interest (i.e. heat avoidance in fly). 2. Active neuron of interest with optogenetics. See if behavior is produced. 3. Inactivate neuron with optogenetics to show neuron is part of circuit. • Neurons are countable (302 in *C. elegans* and 135,000 in *Drosophila melanogaster*) • Neurons are **stereotyped** across individuals and have **reproducible connectivity.**

Neural Circuits

Genes and molecules are conserved from invertebrates to vertebrates. Neuroscientists believe that neural circuit principles will be as well.

> *"You have made your way from worm to man, and much within you is still worm."*
>
> *F. Nietzsche, Thus Spoke Zarathustra*

To Identify Neural Circuits

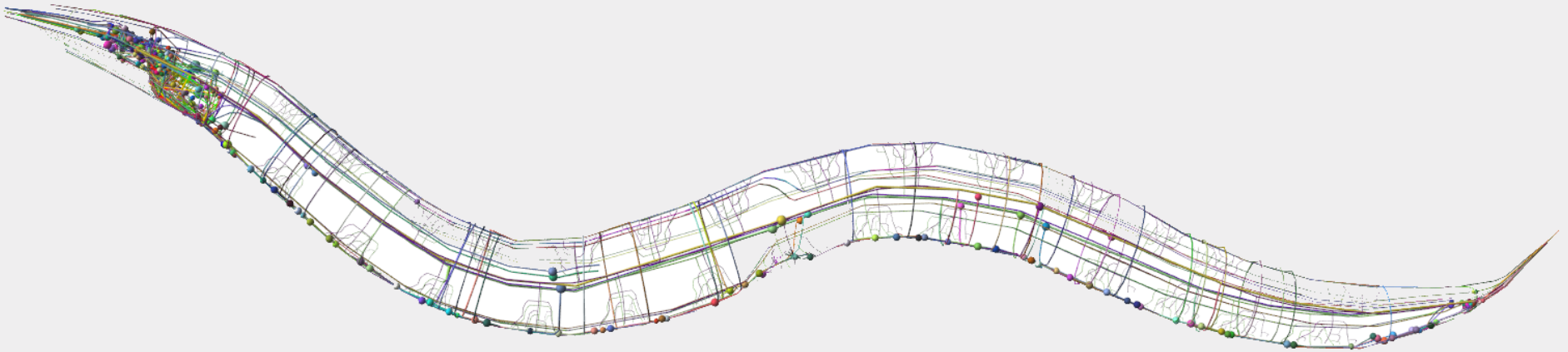
Step 1: Find one neuron involved in the circuit.

Step 2: Find additional functional neurons.

Step 3: Confirm role of all neurons in signal.

Step 4: Organize neurons by *epistasis analysis.*

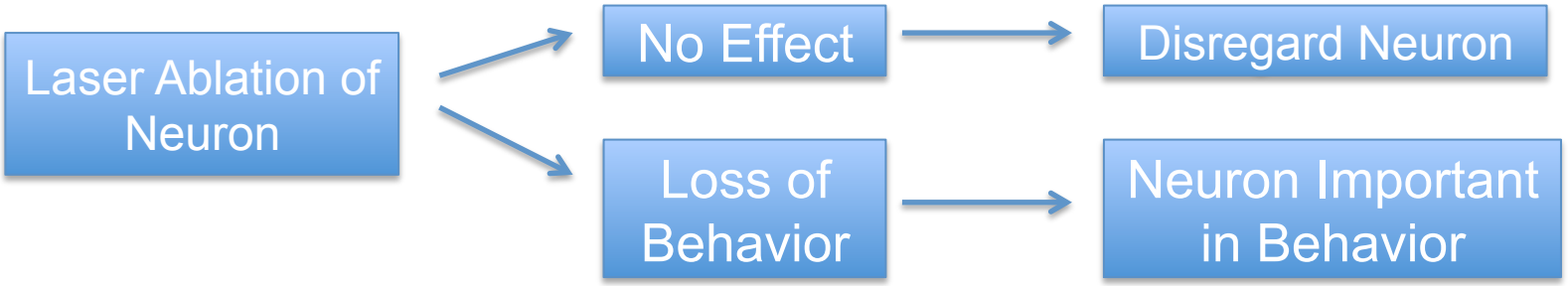
Step 5: Draw Circuit.



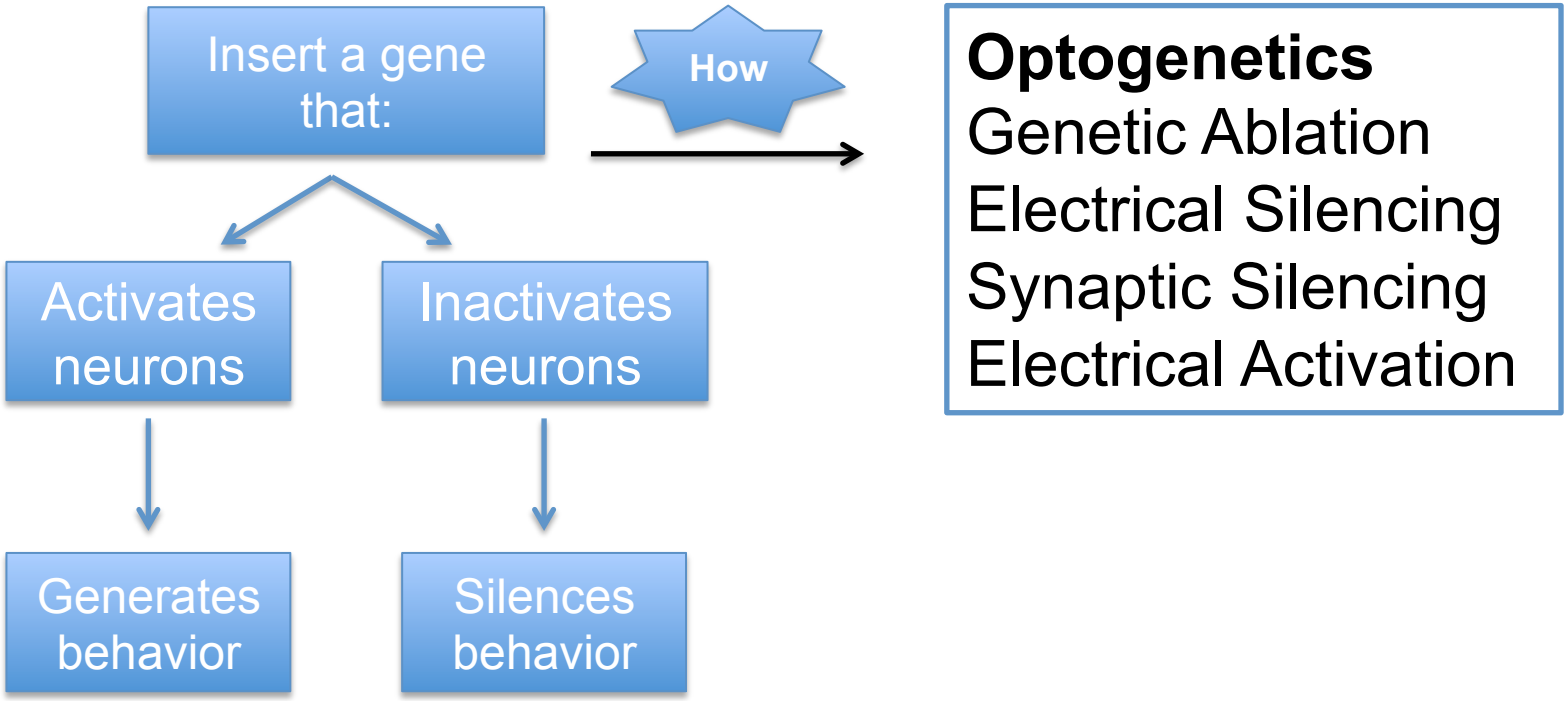
Step 1: Find one neuron involved in the circuit.

A. Use systematic inactivation or activation

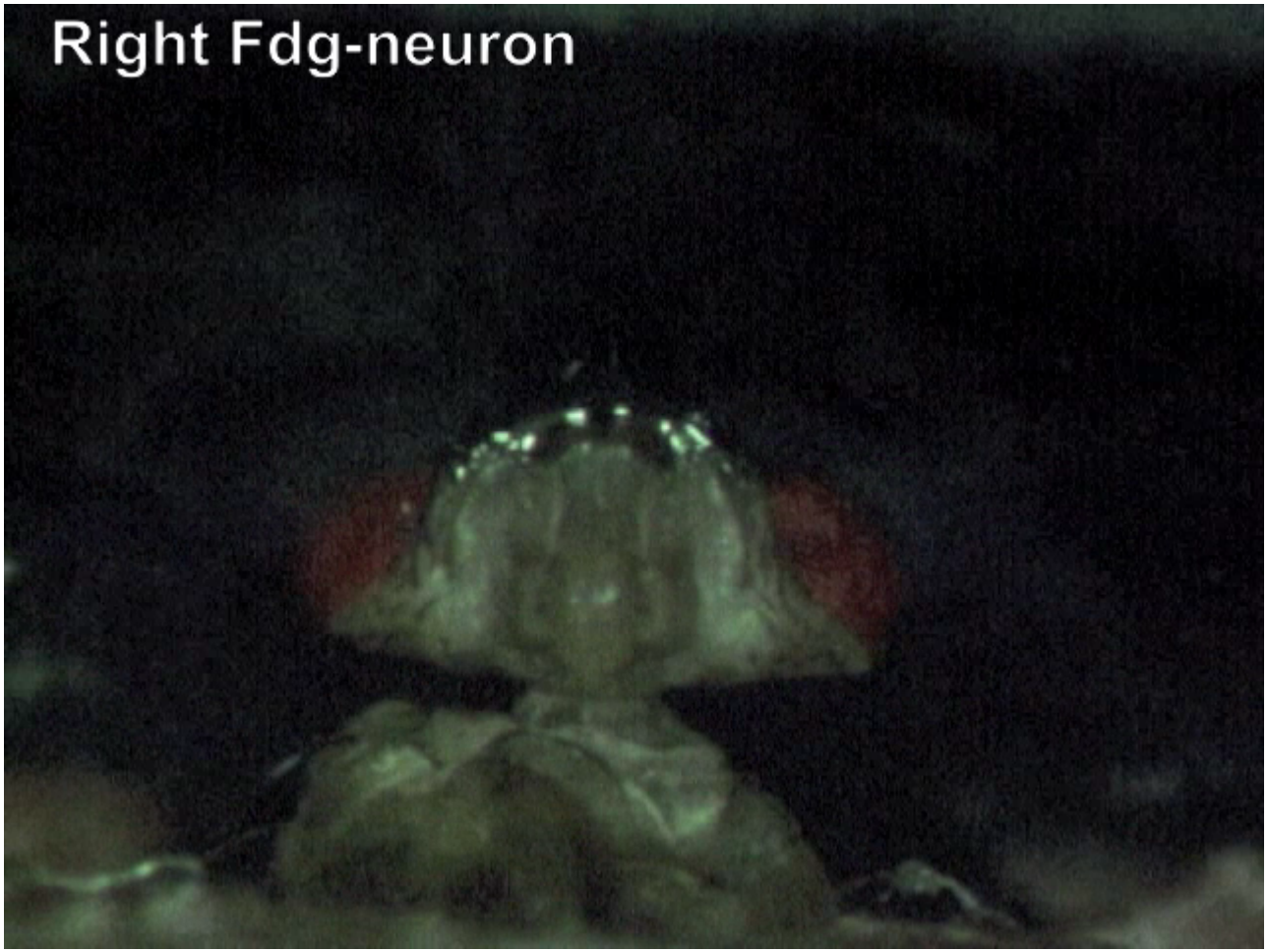
A. Use a laser to ablate neurons



B. Use a transgene to activate or inactivate neurons



Step 1: Optogenetic Activation of Neurons

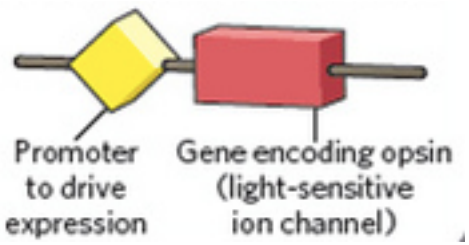


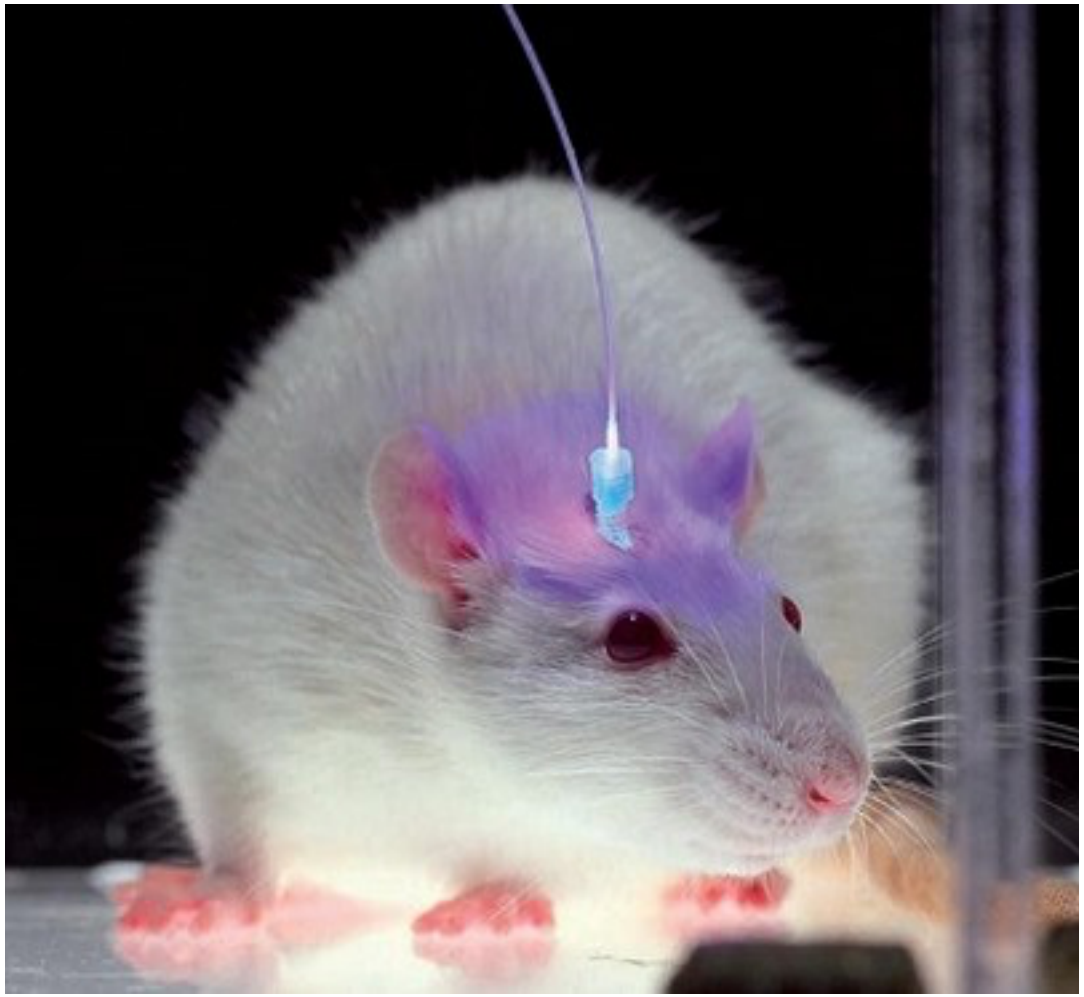
Proboscis

Optogenetic activation of an Fdg-neuron induces proboscis extension and pump movement in flies

Optogenetics

1. Piece together genetic construct.
2. Insert construct into virus.
3. Inject virus into animal brain. Opsin is expressed in targeted neurons.
4. Insert fiber-optic cable plus electrode.
5. Laser light of specific wavelength opens ion channel in neurons.





Laboratory of Karl Deisseroth, Stanford University

Optogenetics

Test Your Understanding

Select the statement that is false:

A.
Optogenetics is a technique that manipulates neural activity using light.

B.
Exogenous ligands are chemicals not made in the body that can bind to receptors in our nervous system.

C.
Ionotropic receptors are mechanically-gated.

D.
Influx of Ca^{2++} promotes exocytosis of neurotransmitters in the axon terminal.

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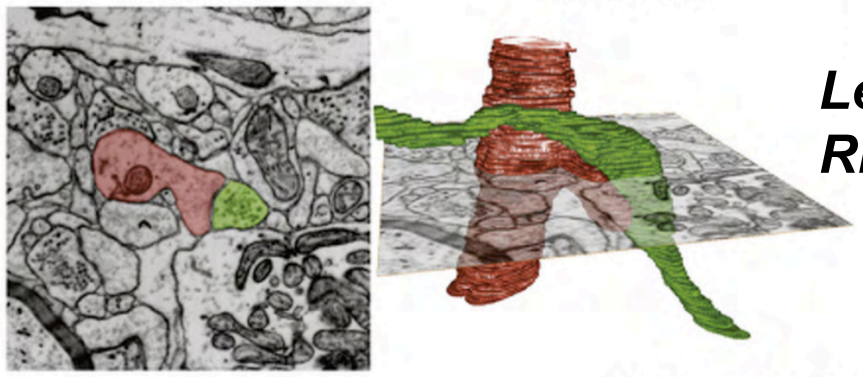
Explanation:

Ionotropic receptors are ligand-gated.

Step 2: Identify additional functional neurons.

A. Continue to use systematic inactivation or activation
B. Identify connectivity of neuron of interest. See if activation or inactivation illustrate function.
    1. Use serial electron microscopy to trace cell processes



Left: 2-D Cross-Section
Right: 3-D Reconstruction

    2. Use a transgene to map connections (trans-synaptic virus)

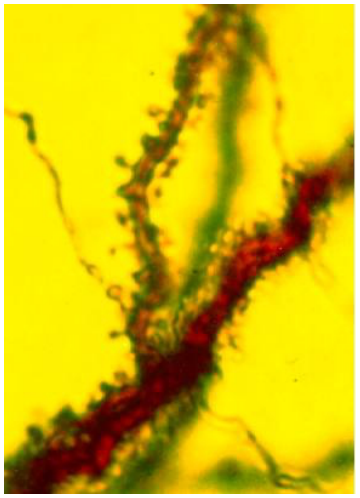
Caveat: This may not work. A functional connection may not act through an anatomical synapse. Instead, the circuit may rely on neuropeptides or hormones that are secreted and diffuse to the cells that they affect.

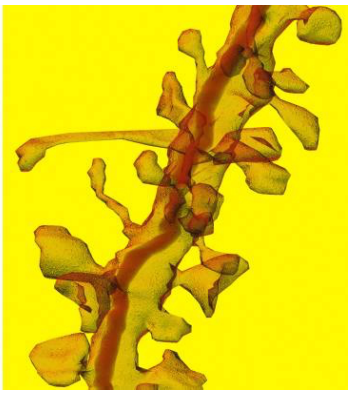
Tools for Anatomy

Anatomy provides information on the **structure and connectivity of the nervous system.**

Electron Microscopy	Light Microscopy
• Best technique for determining synaptic connectivity • High spatial resolution • *Caveat:* No ability to see changes over time as sample must be fixated.	• Simpler than EM • Can be done with dye injection or transgene (i.e. GFP) • If a pre-synaptic protein is tagged with GFP, then synapses can be visualized. • *Caveat:* No way to know what synapse is connected to.

Dendrite Morphology





Tools for Anatomy

Anatomy (connectomes) do not provide information about function:

Anatomy enables neuroscientists to generate hypotheses for circuit function.

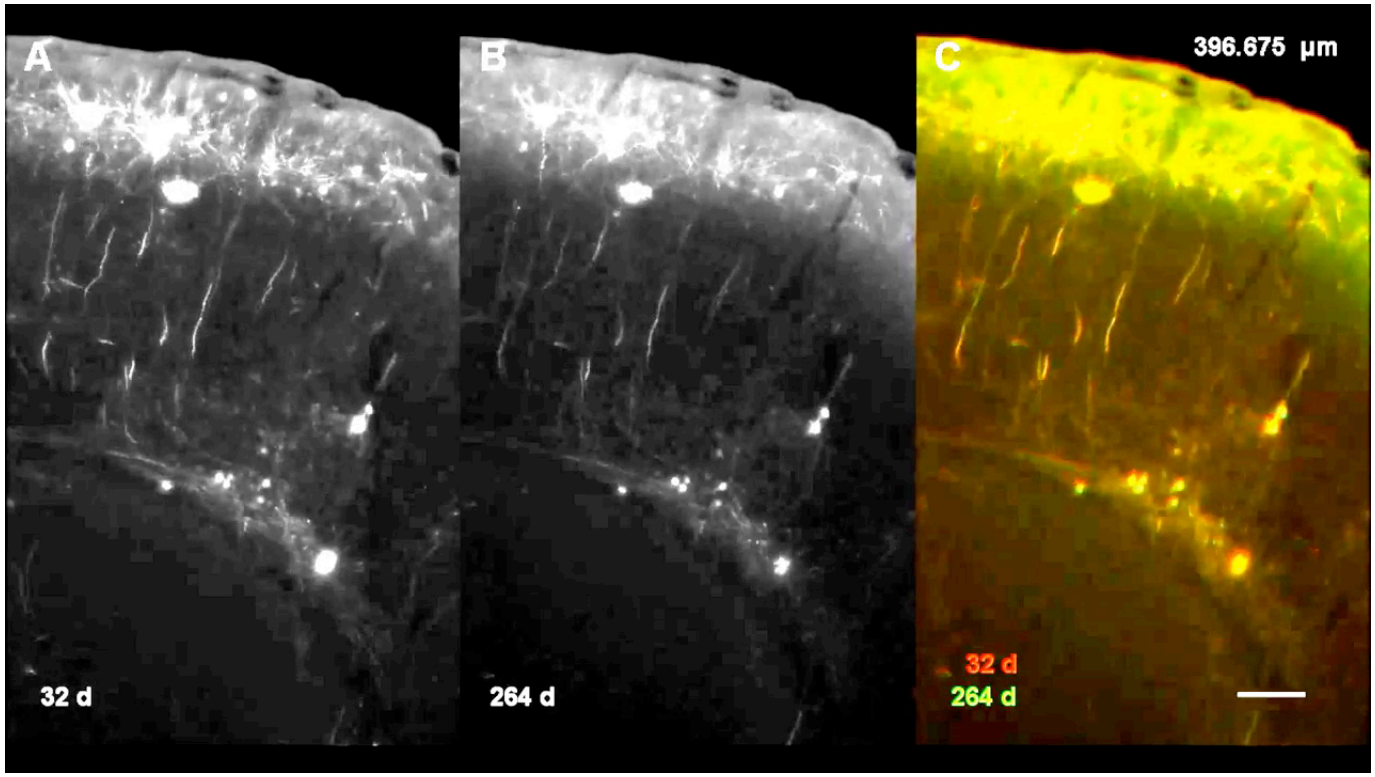
Caveats:

- Even if two neurons synapse, it doesn't mean these two neurons **act together** to perform a function.
- Even if two neurons are **not** anatomically connected, it doesn't mean they're not **functionally connected.**
  - A form of non-synaptic signaling may exist, implying a chronic circuit (slower signal).

Even though the connectome for C. elegans was determined in 1970, its nervous system was not well understood for the reasons above.

- Researchers need to determine the **functional routes.**

Step 2: Viral Tracing

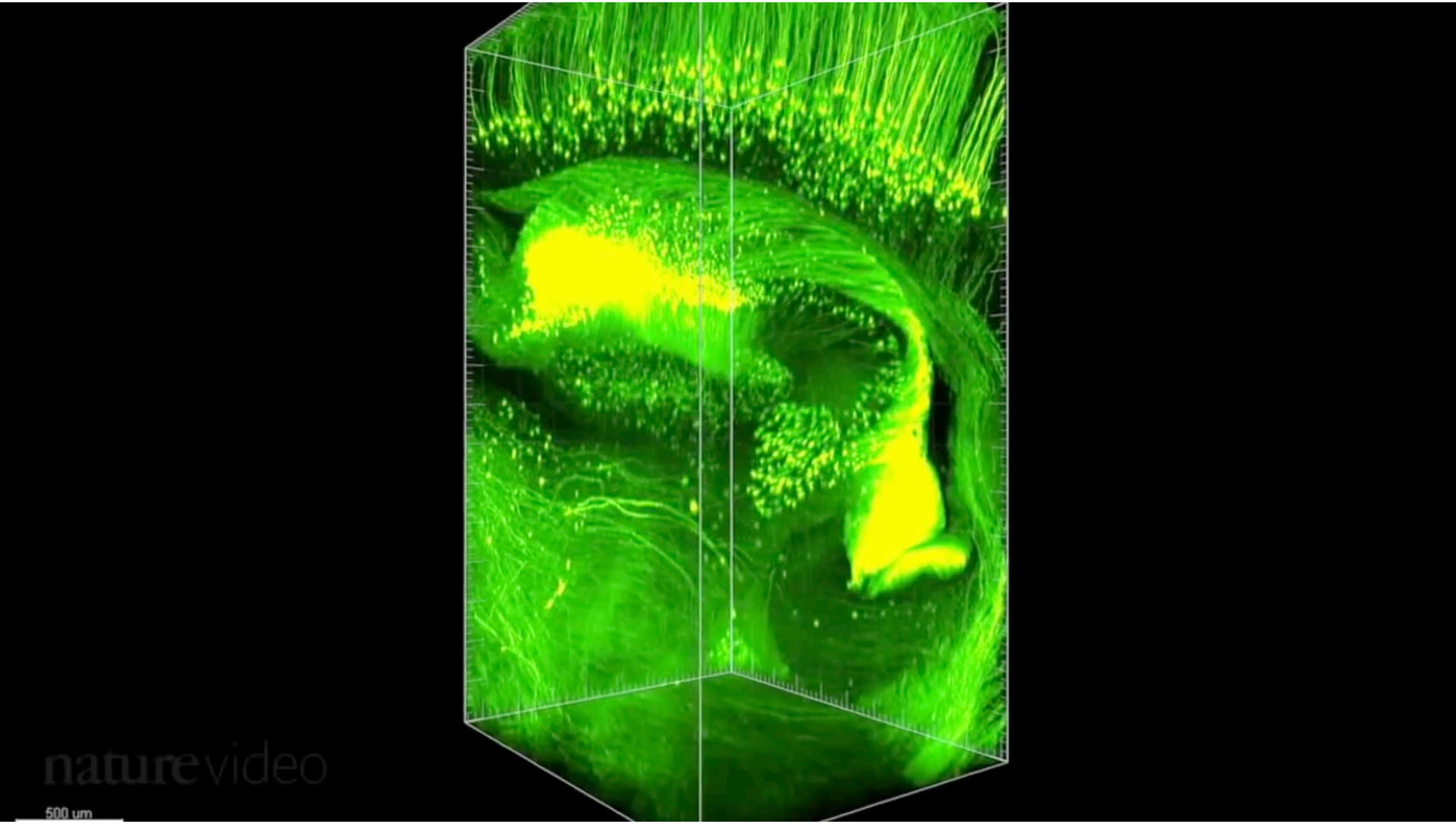


Anterograde Transport: tracer moves from soma to synapse, uses **kinesin** to move viruses along axon in anterograde direction

Retrograde Transport: tracer moves from synapse to soma, uses **dynein** to move viruses along axon in retrograde direction

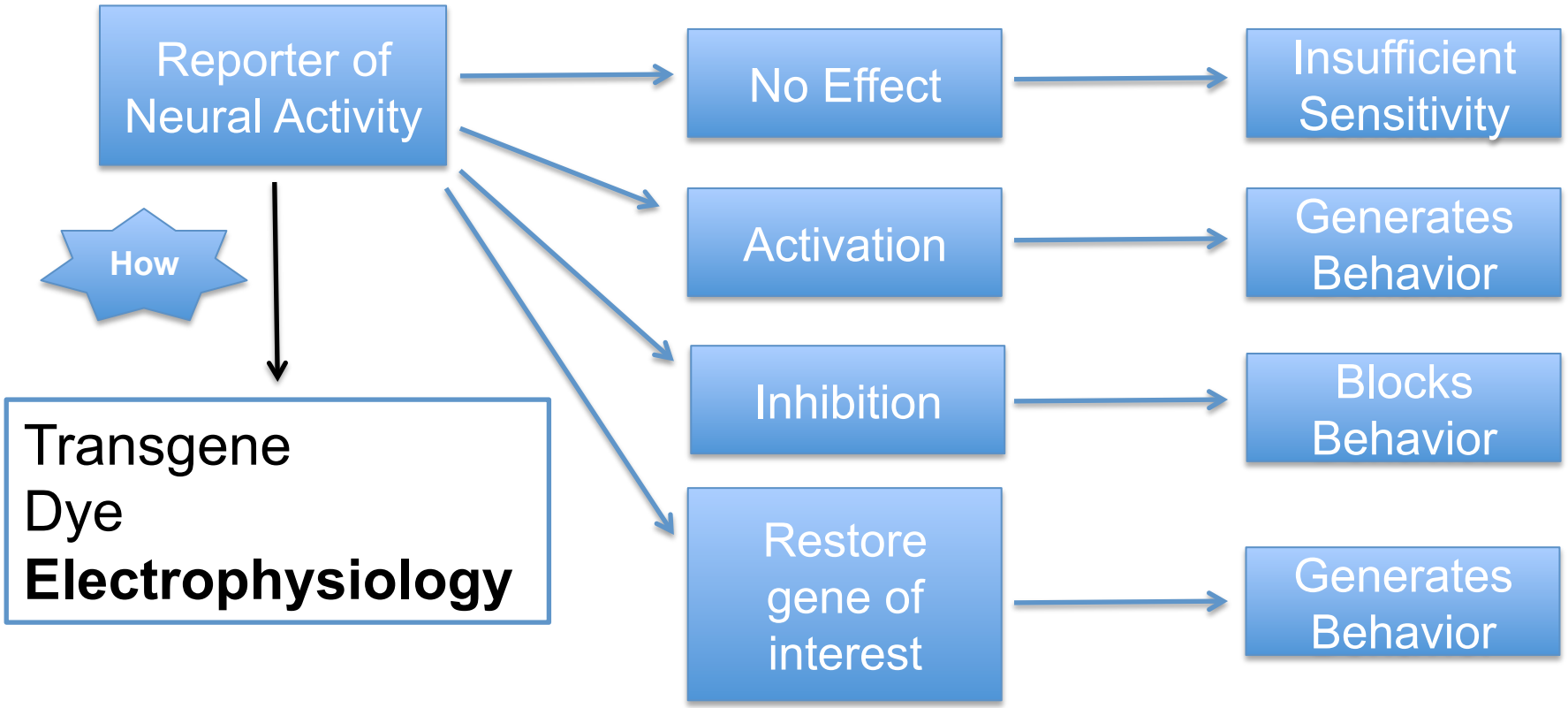
Dual Transport: combines above methods to determine both the inputs and outputs of neuronal circuitry

Step 2: CLARITY

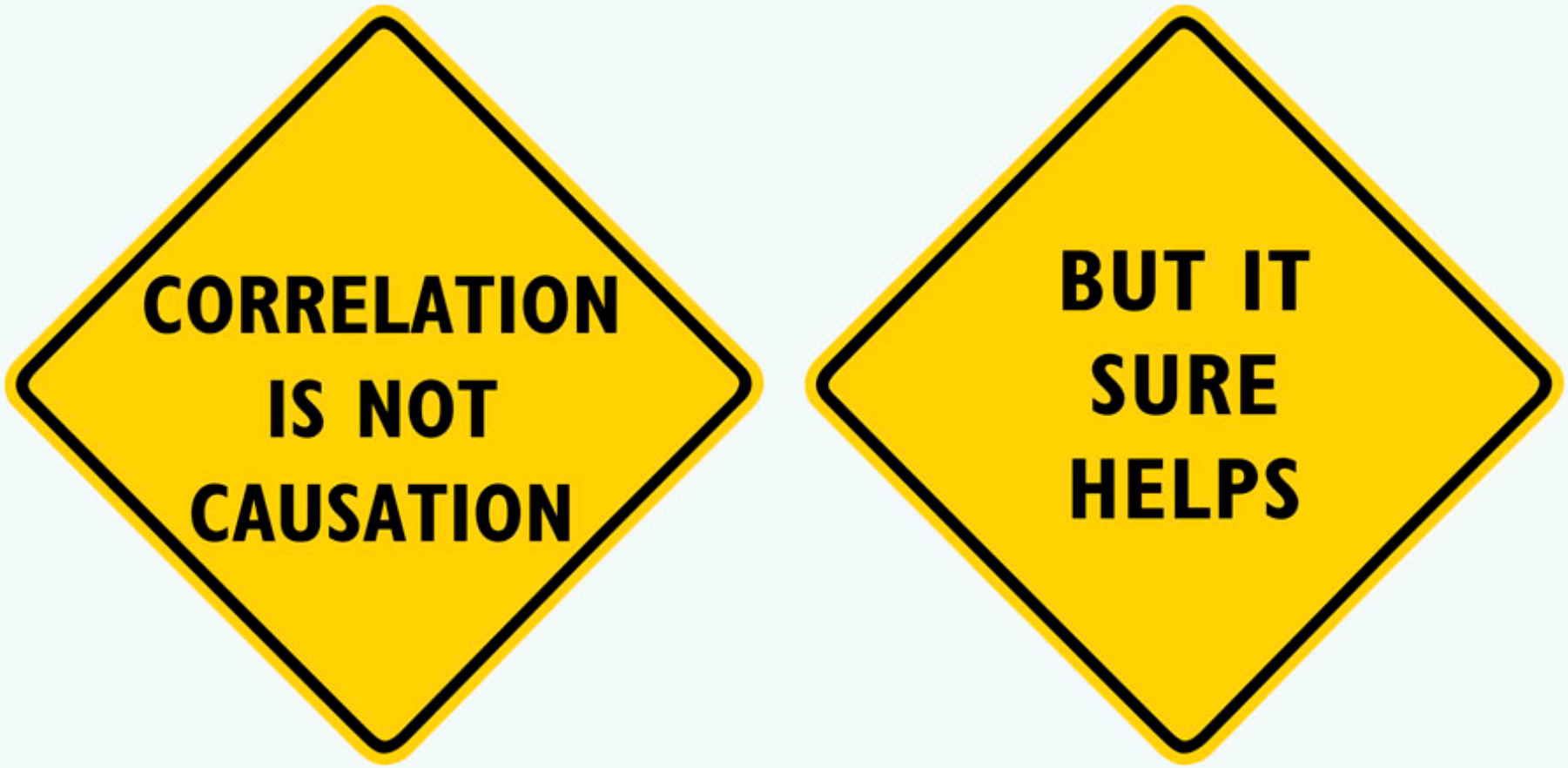


Step 3: Confirm the role of identified neurons in generation of behavior

A. Use a reporter of neural activity in response to stimulus



Correlation v. Causation



How can we manipulate physiology to show causal function in neural circuits?

Step 4: Organize Neurons by Epistasis Analysis

A. Inactivate a pair of neurons together and observe whether the behavioral defect is enhanced.

1. If enhanced, neurons likely function in parallel.
2. If not enhanced, neurons function in series.

B. Activate a pair of neurons together and observe if behavior is enhanced over a single activation.

1. If enhanced, neurons likely function in parallel.
2. If not enhanced, neurons likely function in series.

C. Activate neuron X and see if neuron Y responds.

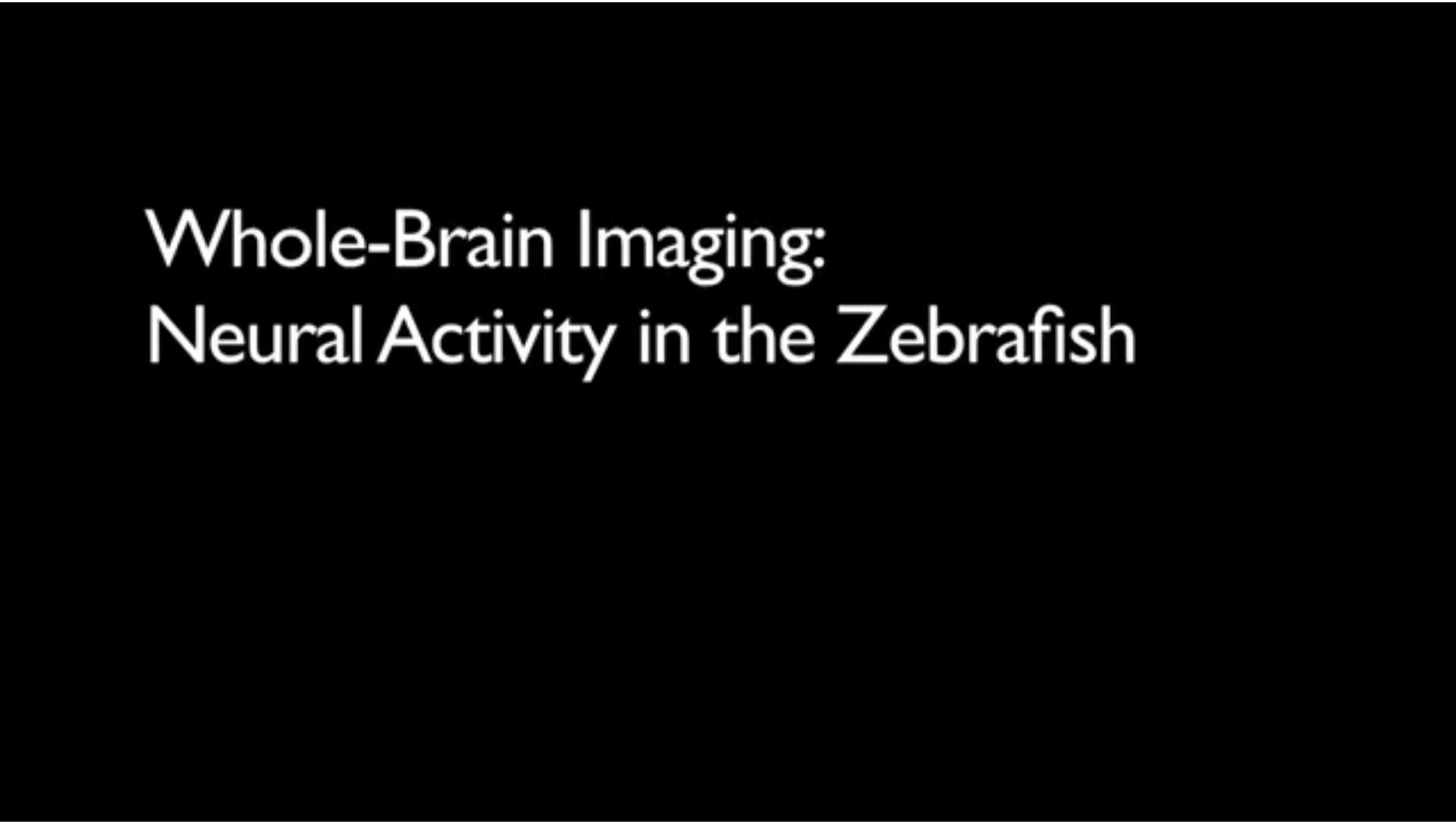
1. If it does, neuron Y is downstream of X.
2. If it does not, neuron Y is upstream of or in parallel with X.

D. Activate neuron Y and see if neuron X responds.

1. If it does, neuron Y is upstream of or in parallel with X.
2. If it does not, neuron Y is downstream of X.

Inactivation experiments show necessity.
Activation expressions show sufficiency.

Neural Activity Imaging



Inactivation Experiments

To show a neuron is *necessary* for a behavior, one needs to illustrate that the loss of that neuron results in *partial or complete loss of behavior*.

Techniques

A. Laser Ablation
B. Synaptic Silencing
   - Transgenic method where protein blocks chemical synaptic transmission in neuron
     (i.e. tetanus toxin, genetic mutants)
   - If synaptic silencing doesn't result in loss of behavior, neuron may receive input directly from environment or gap junctions.
C. Electrical Silencing
   - Hyper-polarize the neuron through current injection
   - Halo-rhodopsin and Archae-rhodopsin (Arch)

Activation Experiments

In some cases, inactivation won't show any effect because there is *redundancy* in the circuit. An activation experiment will overcome this problem.

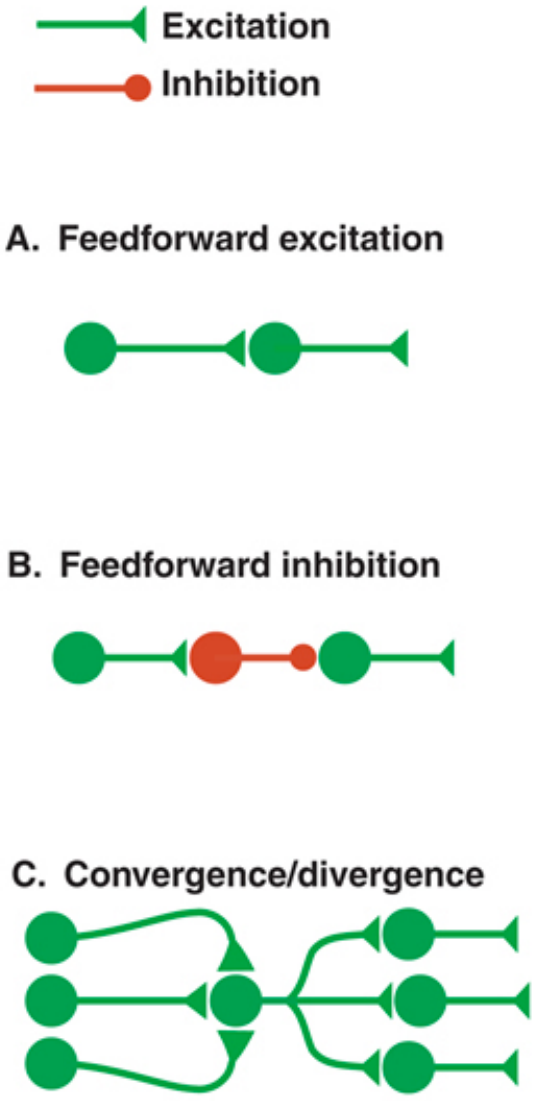
Techniques

A. Restore genetic function in neuron
   - Rescue experiment (i.e. NT synthesis)

B. Electrical Activation
   - De-polarize the neuron through current injection
   - Channel-rhodopsin 2 (ChR2)

If both activation and inactivation experiments are done and result in the expected effect on behavior, ***and*** *a physiological response is observed, it is reasonable to conclude that neuron of interest acts in neural circuit.*

Neural Circuit Motifs



A. Feed-forward Excitation

Allows one neuron to relay information to its neighbor. Long chains of these can be used to propagate information through the nervous system

B. Feed-forward Inhibition

A pre-synaptic cell excited an inhibitory interneuron, which then inhibits the next follower cell. This is a way of limiting excitation.

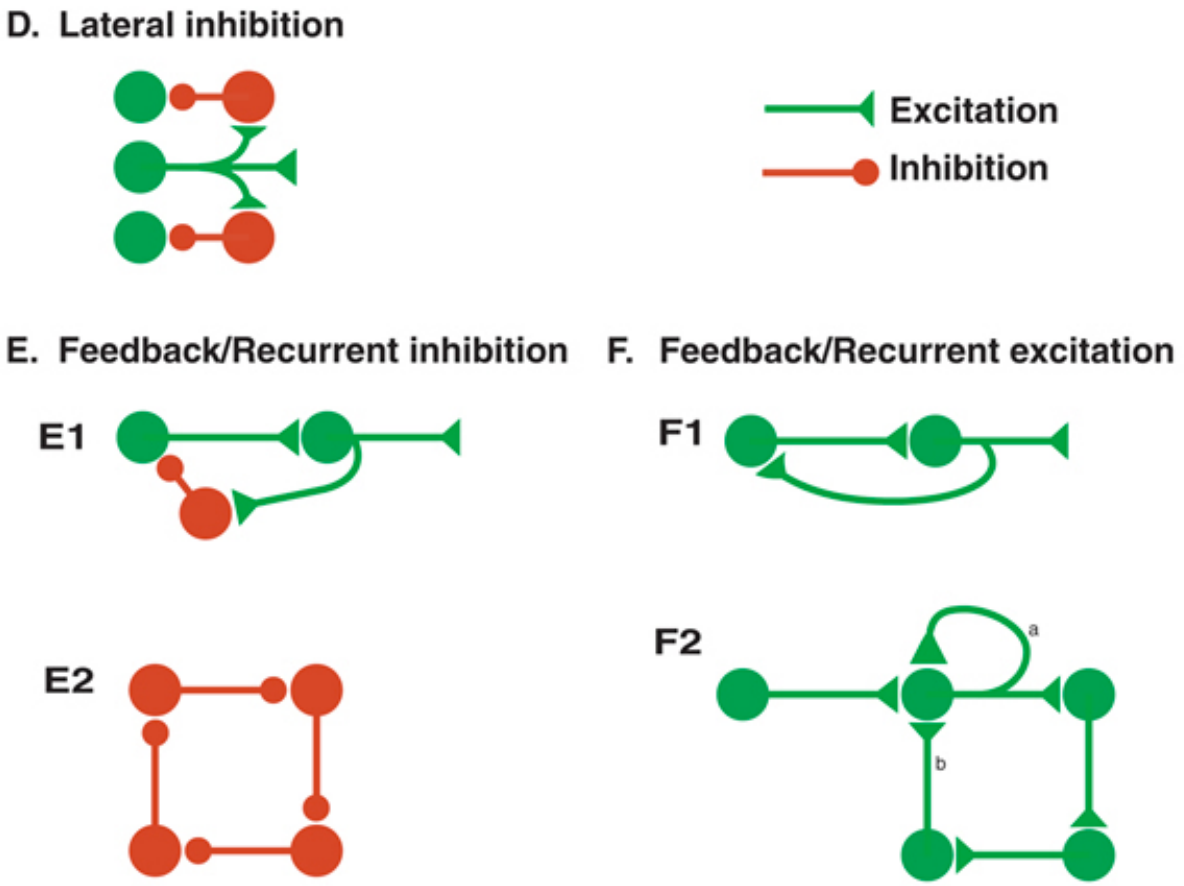
C. Convergence/ Divergence

One post-synaptic cell receives convergent input from a number of different pre-synaptic cells and any individual neuron can make divergent connections to different post-synaptic cells.

Divergence *allows one neuron to communicate with many neurons in a network.*

Convergence *allows a neuron to receive input from many neurons in a network.*

Neural Circuit Motifs



D. Lateral Inhibition
A pre-synaptic cell excites inhibitory interneurons, which inhibit neighboring cells in the network.

E. Feedback/ Recurrent Inhibition

F. Feedback/ Recurrent Excitation

Test Your Understanding

This term best represents a neural circuit where one pre-synaptic neuron synapses with several post-synaptic neurons in order to amplify a sensory signal:

A. Feed-Forward Excitation
B. Convergence
C. Divergence
D. Lateral Inhibition

Test Your Understanding

This term best represents a neural circuit where one pre-synaptic neuron synapses with several post-synaptic neurons in order to amplify a sensory signal:

A. Feed-Forward Excitation
B. Convergence
C. Divergence
D. Lateral Inhibition

Explanation:

Diverging circuits allows one neuron to communicate with many neurons (i.e. skeletal muscle contractions). On the other hand, converging circuits allows one neuron to receive many inputs (i.e. spinal cord to brain).

Properties of Neural Circuits

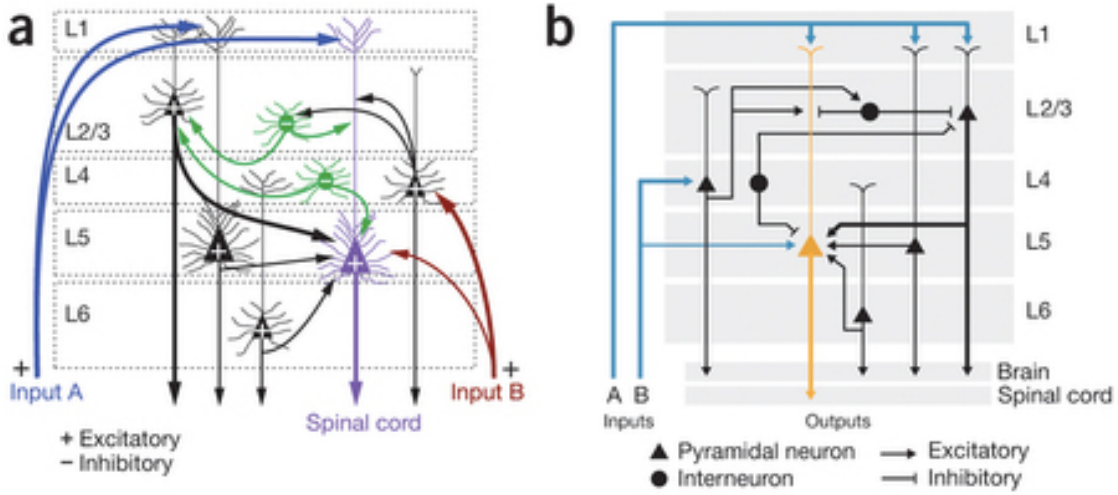
1. Feedback
2. Degeneracy
3. Competition
4. Modularity

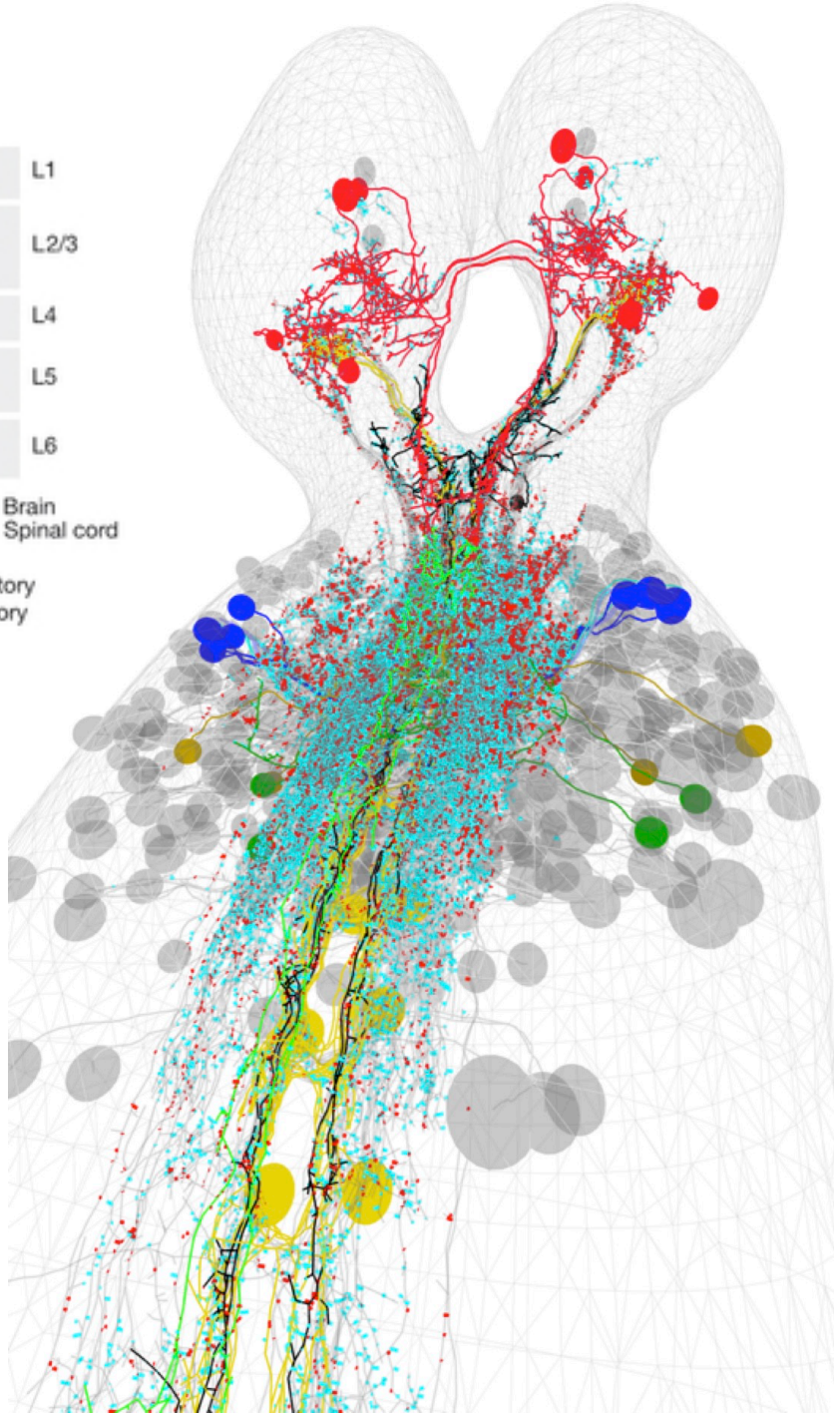
Degeneracy: the ability of multiple different configurations or mechanisms to produce the same outcome or serve the same function

Competition: small-scale axon elimination during development of nervous system

Modularity: permits an organism to process a new input without evolving an entirely novel circuit from scratch (i.e. building diverse objects using existing building-blocks)

Step 5: Circuit is Complete





Multi-Sensory Circuits

Crayfish Escape Response

Crayfish Escape Response

Step 1: Find one neuron involved in the circuit.

Step 2: Find additional functional neurons.

Step 3: Confirm role of all neurons in signal.

Step 4: Organize neurons by *epistasis analysis.*

Step 5: Draw Circuit.

Use systemic activation or **inactivation**

Electrical Silencing

THE CRAYFISH LATERAL GIANTS AS COMMAND NEURONS FOR ESCAPE BEHAVIOR

GENE C. OLSON and FRANKLIN B. KRASNE*