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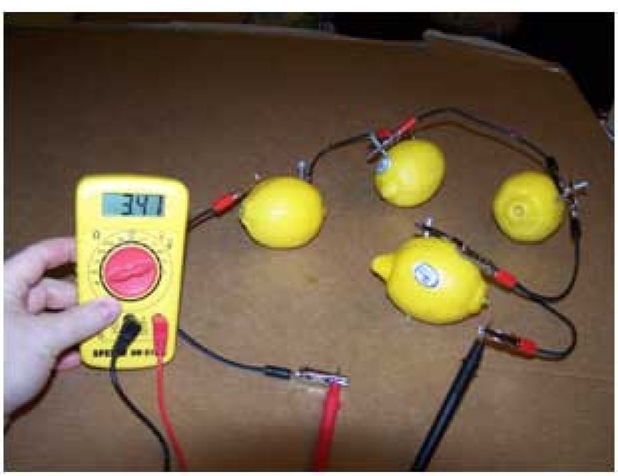
Mind over matter, light over mind

Imagine a remote controlled live mouse. Studies in optogenetics have done this! Researchers trying to understand the brain have found a way to rig neurons to fire when they shine light on them. The result? A lab mouse that will keep turning left when blue light illuminates its “left turn” neurons.[1] See for yourself by clicking on the link above! The hopes: to understand the brain and neural networks better and do some good along the way – like inhibiting the uncontrollable tremors in Parkinson’s disease.

Neurons

In a recent article,[2] the field of optogenetics is defined by one of its founders Karl Deisseroth as “[a combination of] optics with genetics to control the functioning of well-defined events within biological tissues.” One of the milestones of their work was finding a way to control the neuron firing.

To understand this better, consider the basics of what a neuron is and does. Neurons are cells within the nervous system that carry information to and from the brain. There are different types of neurons, but for all of them the information is carried through a process that involves chemical reactions and electrical signals (electric current) caused by charged particles moving into and out of the cell’s membrane.[3] Have you ever made a lemon battery? A lemon battery is an example of this. Two metals (copper and zinc) are inserted in a lemon and are connected by a wire outside of the lemon. A chemical reaction (zinc reacts with the lemon molecules) occurs to form ions (charged atoms), and free electrons that can easily be moved along the conducting wire. The result is an electric current. The charged particles are “pushed” by an electric force because one side of the battery is more positive than the other side of the battery.[4] Like charges repel and opposite charges attract. If an electric force is around then we can describe an electric field and electric potential energy stored in that field. In electric circuitry we describe the potential difference (energy per charge or voltage), which is needed for an electric current (movement of charge) to take place.



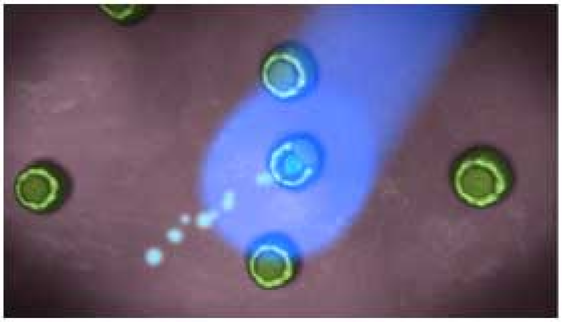
from the Wikimedia Commons. Because the potential difference for a lemon batter is small, four lemon batteries were connected in series here with a voltmeter placed in parallel to measure the potential difference they produce.

The neuron usually has a potential difference of -70 millivolts between the inside and outside of the neuron. When the potential difference reaches -55 millivolts the neuron fires – no matter what the cause of the potential difference. In the case of neurons, ions (electrically charged atoms with extra electrons or missing electrons) are responsible for the electric current that runs through us sending information. Ions are transferred from one neuron to another, through the cell membranes. Inside the cell are negatively charged protein molecules, positively charged potassium and sodium ions, and negatively charged chlorine ions. Outside the cell are positive potassium and sodium ions, and negatively charged chlorine ions. Potassium ions flow easily through the neuron's semipermeable membrane, but the chlorine and sodium ions do not. When the threshold potential is reached, a stimulus (chemical reaction) occurs that allows the neuron to open a channel for sodium ions to easily fit through. Because of the potential difference, sodium ions quickly enter the cell and potassium ions leave it. The sodium channels close after three sodium ions enter the neuron and two potassium ions leave. The neuron once fired equilibrates itself. To view this click here, and allow about thirty seconds for it to appear.[5]

This threshold potential is like an on/off switch for an electric circuit. Imagine a nightlight with a little photodetector on it. When there is not enough light hitting the photodetector the nightlight turns on. The photodetector creates a potential difference or voltage across the circuit causing an electric current to flow through the circuit. For the neural cells one of the ground-breaking innovations was figuring out a way to create an on/off switch to the cell that the researcher could control.

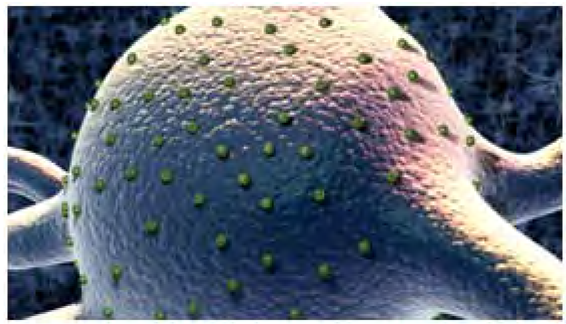
Light – the on/off switch

Researchers had to figure out a way to control the potential difference between the inside and outside of the neuron. To do this they looked into molecules that could act as a photodetector, and could switch on the neuron. The researchers (Ed Boyden and Karl Deisseroth) knew that all plants have molecules that respond to light resulting in the electrochemical process of photosynthesis. They looked for a light sensitive molecule that could do more than convert light to energy, they needed molecules that cause ions to flow through cell membranes. They found such photosynthetic molecules in algae, archaea, and fungi.

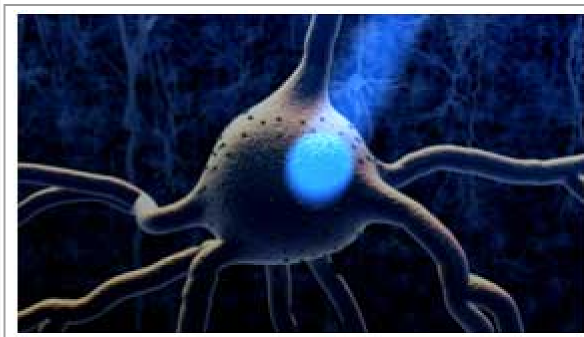
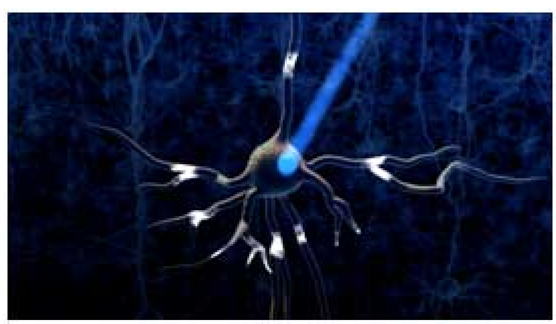
	
(a)Algae that have an eyespot within them made	(b)In the eyespot, opsins respond to light by

of photosynthetic cells that help them to navigate toward light.	moving charge across a membrane. Image courtesy of Ed Boyden, MIT

These photosynthetic molecules do not directly drive energy production; instead they act as a sensor for the organism to navigate toward light. After years of searching they found a light sensitive molecule from an algae called opsin that was compatible with neurons in brain cells. Then they figured out a way to introduce one of these light sensitive molecules into the neuron cell. To introduce opsin into neurons they developed a virus, which when introduced into the neuron, uses the genetic code in the virus to create its own opsin.

	
(a) DNA encoding for the opsin is taken and transplanted into a neuron.	(b) Neurons express the opsin and install it in the membrane. Image courtesy of Ed Boyden, MIT

The result – a light sensitive neuron. Furthermore, by creating a virus to introduce opsin, the researchers are able to control, which type of neuron it enters or allow it to infect all neurons but only become active in certain types of cells based on the genetic code of the virus.[2]

	
(a) When blue light hits the neuron, the opsins open.	(b) When the opsins open, they change the voltage of the neuron, activating the neuron. Image courtesy of Ed Boyden, MIT

When, for example, one type of neuron is made light sensitive by encoding only that type of neuron to produce the opsin, then you can activate a specific neural network. This is what was done in the case of the left-turning mouse.[1]

When blue light hits a neural network in which one kind of neuron is light sensitive, only that kind of neuron is activated. Neurons can also be made to turn off when yellow light shines on them. In the image above basket neurons are shown. These neurons inhibit or quiet down neighboring neurons.
Image courtesy of Ed Boyden, MIT

Current Research

Researchers are currently looking into ways to refine these neural switches and to create more switches. They are looking for different types of molecules to act as light sensitive switches so that they can utilize different frequencies of light to activate or inhibit a neuron from firing. They have already found molecules from fungi. Inhibiting the neuron from firing with yellow light uses a molecule from an organism (archaea) that lives in the salt mines in Egypt. Researchers are also creating special fiberoptic waveguides as probes to introduce different frequencies of light to different locations within a brain.[2]

It has been shown that mice can be “rewired” after psychological stress and nerve damage. For example, mice with certain types of blindness can have information sent through their optical nerve to utilize visual stimulation.6 The fact that currently neurons can be turned on and off using blue and yellow light means that brain activity can be encoded as a series of ones and zeros – think future upload and download of brain activity! Investigations are being done on recording brain activity and driving the brain with it.[6]

To Learn more see Ed Boyden's TED talk about the field of optogenetics: www.ted.com/talks/ed_boyden.html,[6] the Stanford University YouTube video called: Cracking the Neural Code,[7] Karl Deisseroth and Mark Schnitzer, and the Stanford University You Tube video entitled *Controlling the Brain with Light*, Karl Deisseroth.[8] More in depth information can be found in the *Neuron Primer*[9], and *A History of optogenetics: the development of tools for controlling brain circuits with light*.[10]

References and Links

1. YouTube video of left turning mouse: Karl Deisseroth - Thy-1::ChR2-EYFP Mouse

2. Cole Johnson, Sally, *Optogenetics: An Illuminating Journey Into the Brain*, Optics and Photonics News, Optical Society of America, July/August 2011.

3. Neuroscience For Kids

4. Lemon Battery

5. Nobel Prize. Org, *Nerve Signaling*

6. TED talk, Ed Boyden.

7. YouTube video: Karl Deisseroth and Mark Schnitzer, Stanford University: *Cracking the Neural Code*.

8. YouTube video: Karl Deisseroth , Stanford University: *Controlling the Brain with Light*.

9. Yizhar, O., Fenno, L. E., Davidson, T. J., Mogri, M., & Deisseroth, K., *Optogenetics in Neural Sytems*, Neuron Primer, Cell Press Neuron 71, July 14, 2011 a2011 Elsevier Inc.

10. Boyden, E, *A history of optogenetics: the development of tools for controlling brain circuits with light*, Faculty of 1000, Post-Publication Peer Review, Reports, May 2011.

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