**Optical control of brain circuits.**

(1) Optogenetic dissection of a behavioural module in the vertebrate spinal cord
Authors: Wyart C., Del Bene F., Warp E., Scott E.K., Trauner D., Baier H. and Isacoff E.Y
Nature 461, doi:10.1038/nature08323. arXiv:0910.2683

(2) Parvalbumin neurons and gamma rhythms enhance cortical circuit performance
Authors: Sohal V.S., Zhang F., Yizhar O. and Deisseroth K.
Nature 459: 698, doi:10.1038/nature07991.

**Recommended with a Commentary by Elisha Moses,
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Understanding the brain is so complex and ramified a problem that Neurobiology has naturally split into numerous sub-fields that are far apart and often do not interact. The most obviously distant are the molecular and the behavioral levels, but in recent work the gap between the two has been significantly bridged. This is brought about by a number of genetic tools, in which ion channels and pumps that are activated by light are inserted into the membrane of a neuron that normally uses channels that are activated by voltage changes. This enables the excitation and inhibition of neuronal activity by light in the neurons of living animals, with the hope of eventual application also in humans.

Up to now, the best known optogenetic tool is a molecular marker, the green fluorescent protein, or GFP. Organisms are tricked into producing this protein along with a regular protein targeted in their genome, so that GFP serves as a marker for the production and location of the tagged protein. Surprisingly, in the majority of cases the mobility and functionality of the targeted protein is not affected. Unfortunately for neuroscientists, GFP does not respond to the changes in the electric potential of the cell that characterize the spiking electrical activity of neurons. A number of recently developed markers for neuroscience have been developed in the past years with suggestive names such as cameleon and mermaid.

What has recently been having a profound effect on neuroscience is the introduction of light activated ion channels and pumps [1,2]. Channels con-

trol the transfer of ions across the membrane, enabling not only the action potential characteristic of neurons, but also the detection of a multitude of external signals such as spicy food, pressure or temperature changes. Ion pumps maintain the ion gradient across the cell membrane, which eventually enables the creation of action potentials. The dominant and most popular pair of optogenetic tools, developed by Karl Deisseroths group at Stanford [2], is taken from algae and microbes - these are the channelrhodopsin ChR2, which allows sodium ions to cross the membrane and increase the potential, and hallorhodopsin NpHR, which pumps chloride to reverse the potential. A large number of new and similar tools are currently being developed (see [Meissen]).

A flurry of papers and activity surrounds these new tools, and the papers selected here stand out because they shed light also on behavior in the animal. The work by the Isacoff group, (1) above, implanted a light sensitive channel into several distinct groups of neurons of the zebrafish. Although the molecule they use needs a co-factor that is externally supplied, this is easily achieved in a thin transparent animal like the zebrafish. They then identified one specific group of neurons that, when stimulated, created swimming patterns in the developing fish larvae. They were able to identify this group of neurons as forming a central pattern generator that is usually associated with automated motor responses.

For physicists, the recent work described in (2) above is especially interesting, since it involves the control of a particular frequency in brain oscillation - the gamma band, with activity in the range of 30-80 Hz. Synchronization of brain activity at this frequency between different parts of the brain is known to occur when these separate areas all respond to the same stimuli, creating a unified representation (binding) of an external input. For example, locusts recognize a particular odor because a specific subgroup of receptors in the olfactory area to begin oscillating in phase in response to its presentation [3].

The Deisseroth group, (2) above, identified a fast-spiking subgroup of inhibitory neurons (the parvalbumin interneurons) whose activation brought on gamma frequency activity, while their inhibition decreased it. Analysis of the mutual information between incoming spike trains and activity of the neurons showed that the external activation of neurons at gamma band frequency increased the mutual information in both gamma and lower frequency ranges. Inhibitory neurons create potential changes in the membrane that counter the excitatory effect of regular neurons, and can therefore serve as regulatory parts of the neuronal network. Malfunction of this particular

group has been implicated in the disease of schizophrenia.

Currently the emphasis is on enhancing the control on these channels, using mutations that rely on the known structure and activity of the protein bacteriorhodopsin, a well-characterized relative of channelrhodopsin. For example, by having the channel transfer a smaller current for a controllable time span  gating both the opening and closing of the channel, with different light wavelengths. This will allow not only the creation of spikes, as the situation is now, but also the controlled elevation of membrane potential, causing an increased sensitivity to intrinsic signals. As for the introduction into humans for curing diseases like schizophrenia  this awaits further developments, since a viral infection process, which is not used on humans, currently does the delivery.

**References.**

[1] Miesenbock G. (2009), The optogenetic catechism, Science 326:395 doi: 10.1126/science.1174520.

[2] Zhang F., Aravanis A.M., Adamantidis A., de Lecea L. and Deisseroth K. (2007), Circuit-breakers: optical technologies for probing neural signals and systems Nat. Rev. Neurosci. 8 : 577, doi:10.1038/nrn2192.

[3] Laurent, G. and Davidowitz, H. (1994), Encoding of olfactory information with oscillating neural assemblies Science 265: 1872-5.