

Bidirectional optical control of neurons, neural circuits and behaviour in *Caenorhabditis elegans* (and in the nervous system of the mouse)

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Multimodal fast optical interrogation of neural circuitry

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Understanding the function of neural circuits and the contribution of individual neurons to circuit output is still a major challenge in the neurosciences. Together with our colleagues at the Max-Planck-Institute of Biophysics, Frankfurt (E. Bamberg, G. Nagel & colleagues), and at Stanford University, USA (K. Deisseroth & colleagues), we were able to establish microbial type rhodopsins for fast and reversible, **light-mediated** activation or inhibition of neurons in living *Caenorhabditis elegans* nematodes. The Stanford team did analogous work in the mouse nervous system.

These rhodopsins are Channelrhodopsin-2, a blue-light activated cation channel that photo-depolarizes (and thus activates) cells in which it is heterologously expressed, and Halorhodopsin, a yellow-light activated chloride-pump, that photo-hyperpolarizes cell analogously. In distinct neurons of the nematode, e.g. excitatory motor neurons, both proteins could be simultaneously activated by blue or yellow illumination. This mediated bidirectional control over cell activity which, importantly, became apparent at the behavioural level as contractions and relaxations of the muscles innervated by those neurons. Moreover, photocurrents in transgenic muscles could be directly measured by electrophysiology. The Stanford team could demonstrate reliable photo-activation and -inhibition of neurons in the brains of transfected mice, and this activity could further be followed by optical methods, enabling a complete, all-optical system for analysis of neural circuitry in live brain tissue (and, potentially, animals).

This new methodology may well change the ways in which general nervous system function, and the function of neural circuits, is studied to date, because it allows for exogenous control over neural activity in an essentially non-invasive fashion, with unprecedented temporal and spatial accuracy and efficiency. Since the *C. elegans* nervous system consists of just 302 neurons, whose physical connectivity is exactly known, we envision a complete functional mapping, providing information about the role of each of these neurons in effecting behaviours and other neural circuit outputs. In a broader picture, similar approaches will be taken to understand the functional interplay of neurons and brain systems in the mammalian brain, and may even provide a novel treatment for silencing aberrant “hyper”activity of neurons in pathologies like epilepsy and Parkinson’s.

Our paper was accompanied by a News & Views article and a scientific commentary in the same issue of Nature, and became 3rd place in Nature’s top 10 downloaded articles of April 2007