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Hydra: Imaging Nerve Nets in Action

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Mapping whole-brain activity during behavior represents one of the biggest and most exciting challenges of systems neuroscience. New research has taken advantage of the unique biology of an ancient organism to bring us a step closer to that goal.

With rapid advances in imaging technology, neuroscientists are ever more eager to observe the activity of the entire brain, or a large part of it, in a freely behaving animal. This ambition is starting to be realized in a number of model systems [1–5]. At the present time, however, a few technical trade-offs limit us from peeking into the mind of any animal at will [2]. One of these trade-offs lies between the structural complexity of the brain and the fraction of it that can be imaged simultaneously at high resolution. Factors such as sheer size, tissue opacity, and cell density make it nontrivial to image large areas of the brain and deep brain structures [6]. Another important limitation lies at the balance between the behavioral freedom of the animal and the extent to which we can observe its brain activity. High quality imaging often depends critically on the stability of the recording device; meanwhile, natural behavior is often compromised by mechanically constraining the animal. These tradeoffs continue to challenge most existing model organisms, from the nematode *Caenorhabditis elegans* to zebrafish to primates. In a fresh attempt to alleviate these constraints, a new study by Dupre and Yuste [7] reported in this issue of *Current Biology* introduces Hydra as a new model for imaging the activity of an entire nervous system.

Hydra is a small, freshwater animal of the phylum Cnidaria [8]. Its small size and regenerative nature has made it a popular guest in biology labs since the time of Antonie van Leeuwenhoek [9]. A less celebrated aspect of Hydra biology is that it is one of the earliest animals to have evolved a *bona fide* nervous system (Figure 1). Its nervous system consists primarily of two functional hierarchies: sensory cells that detect environmental or internal cues; and a group of interconnected ganglion cells that synapse onto epithelial or muscle-like cells across the body. The topological simplicity of the Hydra neural network holds promise to reveal neuronal computation at its most primitive yet most fundamental form. In addition, the unique anatomy of Hydra is particularly well suited for *in vivo* functional imaging. The body of the animal is fully transparent. The nervous system, commonly referred to as the nerve net, consists of just two sheets of neurons whose soma are well-separated from one another. Lastly, the entire animal (500 μm to 1.5 cm in length) can fit under the field of view of a standard dissection microscope, making it possible to simultaneously image the entire nervous system.

To unearth the potential of Hydra as a model for functional imaging, Dupre and Yuste [7] implemented a series of technical innovations. First, they leveraged recently developed transgenic technology to express a bright calcium sensor, GCaMP6s [10], in all neurons of the Hydra nerve net. To image the entire nervous system in a behaving Hydra, the authors next designed an imaging chamber sufficiently shallow to bring all neurons into focus, while allowing animal motion in two dimensions. Under this preparation, the animals exhibited several modes of behavior reminiscent of its natural behavioral repertoire. To faithfully extract the activity of individual neurons, the authors then carefully tracked the movement of every neuron across the lengths of the recordings. These meticulous endeavors resulted in a high-dimensional dataset consisting of simultaneously-recorded activity from hundreds of neurons along with the behavioral history.

Mining this rich dataset, Dupre and Yuste [7] identified several interesting patterns in the circuit-level neuronal activity. First, they found that the dynamics of the Hydra nervous system is effectively low-dimensional. In particular, they observed large groups of neurons whose activity is strongly coupled in time. The authors distinguished these coactive groups by the functional events that coincided with the activation of each neuronal population. For example, the CB group displayed activity when the animal underwent a sudden longitudinal contraction. The RP1 and RP2 groups exhibited rhythmic activity that occurred during longitudinal elongations and radial contractions, respectively. A fourth group (STN), concentrated under the tentacles of the animal, became active during tentacle motion. Interestingly, the authors found these coactive groups to consist of non-overlapping populations of neurons. This observation suggests the existence of functionally segregated sub-circuits within the nerve net of Hydra. Furthermore, the authors observed that neural activity could propagate bi-directionally and at different speeds. These findings support previous observations that certain Hydra neurons possess bidirectional chemical synapses [11] and communicate through a mixture of electrical and chemical synapses.

Three hundred years after the first report of Hydra by Antonie van Leeuwenhoek [9], the study by Dupre and Yuste [7] marks the debut of this ancient species as an exciting new model for systems neuroscience. The initial observations made in this study spark a number of exciting questions: First, what is the functional importance of the large, coactive neuronal groups? Do coactive

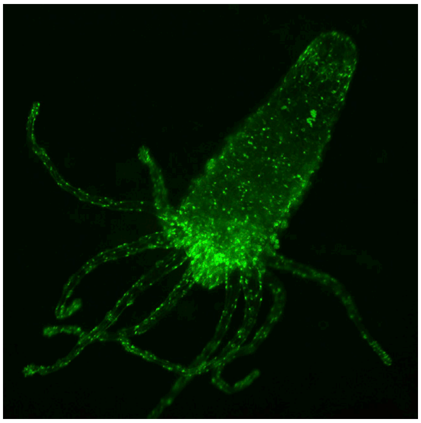

Figure 1. The nervous system of Hydra.
Neurons throughout the Hydra nervous system, visualized by labeling with GFP. (Image courtesy of Christophe Dupre.)

neurons share common targets, or release complementary transmitters that coordinate movement patterns? Second, what are the modes of neural transmission that enable the strong coupling of neural activity? Are coactive neurons part of a large gap junction network, or do they communicate through strong chemical synapses? To what extent are these circuits flexible, perhaps changing in different contexts?

Solving these open questions will require further advances in technology. Better microscopes and better sensors will allow for better spatial and temporal resolution imaging. Molecular tools, building off of the recently sequenced Hydra genome [12], might help access different neuronal cell types. Genetic and optogenetic tools will enable circuit perturbations that could establish causality between neural activity and behavior. A full understanding of circuit function will also require a more complete study of ethologically relevant behaviors [13]: feeding, phototaxis, and even somersaulting. Finally, powerful machine vision and data analysis tools [14,15] have the potential to fast-track biological discoveries.

As a new model for systems neuroscience, the tiny Hydra holds great potential to reveal fundamental mechanisms by which a whole nervous system coordinates neural activity to drive behavior. Neuroscientists have yet to declare victory in understanding any single nervous system — will this finally become possible in the small and ancient nervous system of Hydra?

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Evolution: Fangtastic Venoms Underpin Parasitic Mimicry

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Venomous teeth are rare in fishes, which typically utilise spines for defence. A new study reveals the evolutionary origins of fangs and venom in the Nemophini blennies and shows that, in contrast to snakes and lizards, the fangs pre-date the venom.

Venom has evolved multiple times across the tree of life [1] as a response to two evolutionary pressures — facilitating prey capture and as a defence against potential predators. Snakes, spiders, scorpions, Cnidarians (jellyfish and anemones), molluscs and centipedes have all independently evolved venoms that incapacitate prey [1,2]. Some groups such as the snakes and the spiders have evolved oral delivery systems (fangs), whereas others have evolved stingers