NEUROSCIENCE

Zooming into the larval zebrafish brain

A serial-section electron microscopy data set of larval zebrafish brain—imaged at several scales—provides a resource for structure–function analyses of the animals' neural circuitry.

While access to the high-resolution connectome has proven invaluable for studying the relationship between neural circuits and their function in invertebrate model organisms, generating such a resource for the larger brains of vertebrates is still a major endeavor, despite advances in data acquisition, analysis and storage. Even though zebrafish larvae have comparatively small brains in relation to other vertebrates, the animals display a complex repertoire of behaviors, and they are a popular model for systems neurobiology studies; hence, a closer view of their brains could inform and complement such studies. Jeff Lichtman and Florian Engert from Harvard University teamed up with several collaborators to reconstruct the brain of larval zebrafish at nanoscale resolution.

Along the way, the researchers had to overcome several obstacles. As intact fish larvae could not be sufficiently fixed, the researchers had to dissect the larvae, removing skin and membranes in order to improve fixation of the brain. Furthermore, sectioning proved difficult, and problems typically occurred at the interphase between the tissue and the resin. The researchers solved this issue by embedding the zebrafish larvae within tissue from mouse cortex, which served to physically support the larval tissue. They then acquired close to 18,000 serial sections of about 60-nm thickness, using a modified automated tape-collecting ultramicrotome. They imaged all or a subset of the sections at various resolutions to obtain an overview of the specimen or to zoom into regions of interest. The resulting data sets are up to 5 TB in size.

Engert, Lichtman and their colleagues analyzed the data set by tracing myelinated projection neurons, thereby generating a 'projectome' of the zebrafish brain. The longest neuron they traced was an amazing 1.2-mm long. Furthermore, the researchers assessed the degree of mirror symmetry in the zebrafish projectome. They found little evidence for asymmetry, which is in contrast to instances of asymmetry observed for mammalian motor nerves.

These analyses only scratch the surface of what is possible now that this resource is generated. The data set is available as an open-access resource, inviting further exploration by the zebrafish research community.

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RESEARCH PAPERS

Hildebrand, D.G.C. *et al.* Whole-brain serial-section electron microscopy in larval zebrafish. *Nature* **545**, 345–349 (2017).