Whole-brain imaging reaches new heights (and lengths)

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Whole-brain imaging reaches new heights (and lengths) are large samples of brain tissue.

Researchers at the Allen Institute for Brain Science recently used fluorescence microscopy to produce the first brain-wide projectome for the mouse brain (Oh et al., 2014). This involved using automated vibratomes and two-photon microscopes to slice and image brains at intervals of 0.1 mm (Ragan et al., 2012). However, the use of such a large interval meant that it was not possible to track individual neurons (Figure 1b).

Now, in eLife, Jayaram Chandrashekar of the Janelia Research Campus and colleagues – including Michael Economo and Nathan Clack as joint first authors – report that they have used fluorescence microscopy to visualize whole neurons in a mouse brain (Economo et al., 2016). To make this breakthrough Economo et al. combined a technique called tissue clearing with automated tissue sectioning and imaging to obtain a three-dimensional image of the entire brain (Figure 1c). Tissue clearing is a sample preparation strategy that renders a biological tissue optically clear by removing lipids and/or
introducing a medium that has the same refractive index as the cells. Economo et al. tested a number of emerging tissue clearing techniques – such as CUBIC (Susaki et al., 2015), CLARITY (Chung et al., 2013) and iDISCO (Renier et al., 2014) – but none of them were compatible with tissue sectioning, so they developed a partial tissue clearing protocol that allowed fluorescence from up to 0.25 mm below the surface of the tissue to be detected.

Brains were imaged for about 10 days with a custom-built high-speed two-photon microscope, generating 10 TB of data. To track the projections from individual neurons over long distances (and through large numbers of other neurons), Economo et al. used a technique called sparse labeling; this involved injecting a low dose of adenovirus into the brain so that only 10–50 neurons were labeled. The projections from these neurons could then be mapped throughout the brain by recording fluorescence from the adenovirus (to which fluorescent labels had been attached). Manual reconstructions revealed that just five neurons innervated some 28 different regions of the brain and covered distances over 300 mm.

The combination of tissue clearing and serial-sectioning has provided the first ever tracking of individual neurons in the whole brain using optical microscopy. However, this achievement comes with some problems that are familiar when we try to balance speed and high resolution. Continuous whole-brain imaging enables a 10-fold increase in imaging resolution, but takes 10-times longer than the serial imaging studies with intervals of 0.1 mm performed at the Allen Institute. This limits the experimental throughput, the statistical power of observations, and potential applications. And since Economo et al. were only able to image a sparse distribution of fluorescent neurons, producing a whole-brain projectome at single-cell resolution is still out of reach at this point.

Future studies will need to build on this progress made by Economo et al., and may require the development of new technologies that do...
not require sparse labeling in order to accurately and simultaneously reconstruct many neurons within a single brain. Nevertheless, by bringing neuroscientists closer to the possibility of creating full-resolution projectome maps of the brain, this work represents an important milestone in our understanding of the brain.

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References


