Commentary

# The Mind of a Mouse

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Large scientific projects in genomics and astronomy are influential not because they answer any single question but because they enable investigation of continuously arising new questions from the same data-rich sources. Advances in automated mapping of the brain's synaptic connections (connectomics) suggest that the complicated circuits underlying brain function are ripe for analysis. We discuss benefits of mapping a mouse brain at the level of synapses.
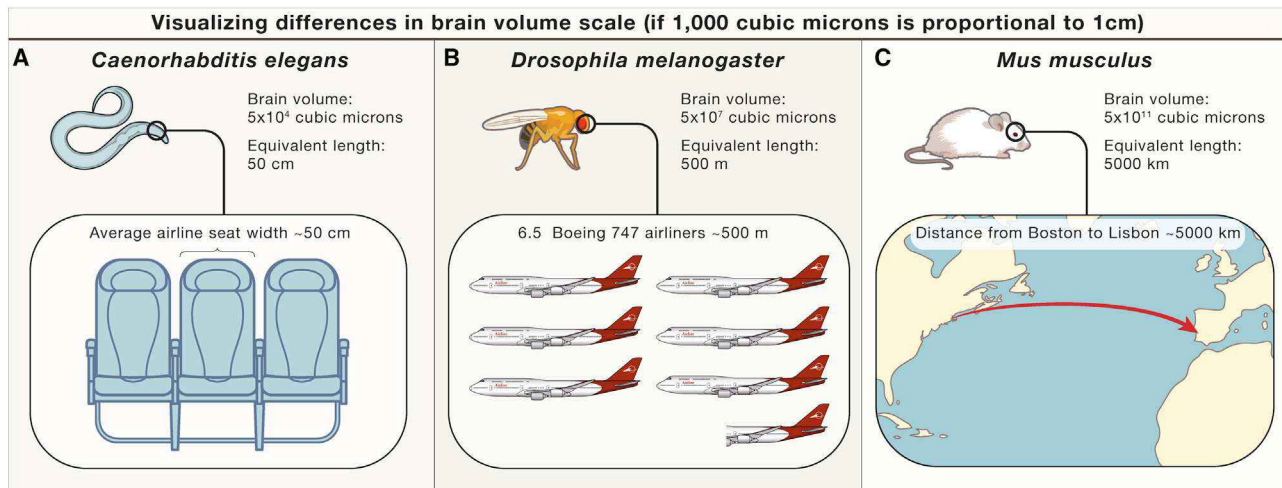
In April 2019, the great molecular biologist Sydney Brenner died at the age of 92. Among his many accomplishments was a radical experiment: might it be possible to obtain the complete wiring diagram of an animal's nervous system by serially sectioning it into many exceedingly thin slices, imaging each of these sections at high resolution with an electron microscope (EM), and painstakingly tracing each neuron's branches and synaptic connections with other neurons? This audacious idea became reality in 1986 when Brenner, John White, and several other extraordinary scientists produced a 340 page magnum opus, "The Structure of the Nervous System of the Nematode *Caenorhabditis elegans*" (with the running head "The Mind of a Worm") for the *Philosophical Transactions of the Royal Society* (White et al., 1986). Brenner was interested in the relation between genes and behavior and wondered if behavioral mutants of this small worm might be explained by alterations in the structure of its nervous system. Such a strategy might be used to harvest principles of neural organization that underlie behavior.

This work was ahead of its time. Computers, although tried, were not of much use: digital image processing was inadequate to the task, and as a consequence, everything was done by manual effort. Nonetheless, the result was a great accomplishment. One testament to its value is that this paper has been cited thousands of

**Figure 1. Scaling Connectomic Reconstruction from a Worm to a Mouse: A 10-Million-Fold Increase in Brain Volume**
Each 1,000 cubic microns of brain volume is schematically represented by a 1cm linear distance.

times, and in almost every year since its publication 33 years ago, the number of citations has increased. In addition to "The Mind of a Worm," Brenner's legacy has been the birth of the connectomics discipline, in which researchers in systems neuroscience, applied physics, and computer science have begun to collaborate on more automated and computer-assisted approaches to untangle ever-larger nervous systems. Efforts to reconstruct complete wiring diagrams of invertebrates and non-mammalian vertebrate nervous systems are now underway (Hildebrand et al., 2017; Eichler et al., 2017; Zheng et al., 2018; Scheffer et al., 2020).

The advent of large-scale connectomics data in *Drosophila* (Zheng et al., 2018), including a complete reconstruction of over 25,000 neurons in the central brain of the adult (Scheffer et al., 2020), has been transformative. Roughly half of all reconstructed cells in Scheffer et al. (2020) were previously unknown, despite a substantial amount of prior work characterizing *Drosophila* cell types using molecular genetics, light microscopy, and other sparse neuroanatomical labeling techniques. The advantage of the volumetric EM reconstruction approach is that it provides an unbiased rendering of every cellular and subcellular structure in the nervous system. In the fly, more than 40 papers have presented novel findings based on connectomics. Each work is a detailed analysis with new discoveries, and, in toto, they contain the most detailed atlas

of a nervous system ever assembled. These data are generating many hypotheses that are already being put to the test with new experiments. In areas of the fly brain that have seen particularly intense connectomic study, such as the mushroom body, central complex, and visual system, it is increasingly difficult to envision studies that ignore the insights generated by studying their connectomes.

This recent progress raises the question of what the payoff would be to scale up whole-brain connectomics substantially to tackle nervous systems closer to our own. This question arises at a propitious moment. The advisory committee to the NIH Director for the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) 2.0 Initiative has released an assessment of the progress in the BRAIN Initiative. In it, the advisory committee (which includes authors C.D., A.L.F., J.H.R.M., B.R.R., and D.T.) identifies mapping a whole mouse brain connectome as a transformative project "to apply new and emerging tools to revolutionize our understanding of brain circuits." This project would be orders of magnitude larger than any previous connectome project (see Figure 1) and probably would be the largest project (if measured by data size) ever attempted in biology. Roughly 1 million terabytes of data will need to be acquired and analyzed to provide a complete mouse brain connectome that includes all inter-areal projections and all synaptic connec-

tions. Importantly, this project will require a consortium of academic, philanthropic, and corporate partners working in close cooperation.

To be sure, this project will be an immense challenge. Many technical hurdles will need to be overcome such as uniform osmium staining of nearly a cubic centimeter of brain tissue, lossless sectioning and imaging of that volume at nanometer resolution, sufficient speed via parallelization to complete the map in years as opposed to decades, and scaling up the many essential computational methods that will need to be deployed. This effort will have a high price tag, likely to be hundreds of millions of dollars; although, once the infrastructure is in place, subsequent connectomes would be vastly less expensive. Perhaps the greatest, and most interesting, challenges will manifest only after the connectome is completed. For example, any mouse connectome will inevitably be unique; even isogenic worms have substantial inter-animal variations in their connectomes (Hall and Russell, 1991; Witvliet et al., 2020). Understanding statistical regularities and learning which variations are stochastic and which are secondary to an animal's life history will help define the substrate upon which individuality rests and require comparisons between circuit maps within and between animals. Indeed, making sense of something as complex as the mammalian brain will be a supreme challenge and will

require the development of novel theoretical and analytical approaches.

There are many reasons that mapping the mouse connectome is both timely and important, some of which are described below.

### An Unbiased Catalog of Cells and Their Synaptic Connections

A nanometer-resolution image database and reconstructed connectome of a mouse brain will at a minimum provide (1) a complete census of anatomical cell types in the mouse brain, including their detailed morphology and some aspects of subcellular composition, (2) upstream and downstream synaptic partners for all neurons, including the precise long range targets of each axon, and (3) structural parameters of each synapse, such as bouton size and vesicle counts, that have been found to correlate with physiological parameters (Holler-Rickauer et al., 2019). These data will lay the foundation of all future studies of circuit-scale rodent neurobiology and enrich their conclusions.

### Connections and Projections in the Same Animal

Light microscopy has emerged as a powerful technology for whole mouse brain mapping and has been applied to reconstruct the complete axonal arbors of individual neurons (Winnubst et al., 2019). If a neuron's axon enters a target brain region, the neuron is said to "project" to that region. The target region contains numerous neuronal cell types, and any given axon may prefer to make synaptic connections onto some types while avoiding others. Electron microscopy has sufficient resolving power to reveal connection preferences: for example, whether an axon has a bias for excitatory or for inhibitory cell types, or for the nearby apical dendrites of pyramidal neurons whose cell bodies reside in different cortical layers. Such distinctions have important functional consequences. A whole mouse brain connectome will reveal not only the targets of all axonal projections but also connection preferences of axons within their targets. We envision that this nanometer-scale mapping would be preceded by millimeter-scale mapping of the same mouse brain using non-invasive modalities like functional ultrasound, magnetic resonance

imaging (MRI), functional MRI, and diffusion MRI. Comparing both non-invasive and connectomic maps of the same mouse brain would enhance our understanding of the structural underpinnings of the signals measured by current non-invasive techniques, which are widely applied to the human brain.

### A Path toward Learning the Structure of Long-Term Memory

Individual mammalian animals (including and especially humans) generate a stable behavioral repertoire that is based in part on the particular experiences they have had. Experiences are known to alter connections between nerve cells (Kessels and Malinow, 2009), and in this sense, much information is likely stored in the particularities of an individual's wiring diagram. This form of information storage is profoundly different from other types, such as hereditary information stored in DNA or digital information stored in computer memory, and much remains to be learned about it. The first complete mouse connectome will provide a baseline for comparisons; later work using the same brain mapping infrastructure will reveal aspects of neural circuits that are preserved from one animal to another, presumably based on inheritance, and importantly the ways in which connections vary between individuals, presumably based in part on different experiences. Understanding this variability likely holds a key to deciphering how experiences are stored in the brain, a profoundly interesting and important aspect of our own makeup.

### A Path toward Describing the Neuropathology of Brain Disorders

In contrast to most diseases in the rest of the body, common disorders altering brain function such as autism and schizophrenia (which affect more than 7 million Americans) are defined mainly by their behavioral symptoms and largely lack explanations based on underlying brain abnormalities. Hence treatments, such as they are, only mitigate the outward manifestations of the disorder rather than addressing underlying causes. This is an untenable situation: significant therapeutic breakthroughs are rare if the therapy is not focused on the root causes. Encouraging progress is being made in identi-

fying genetic underpinnings (Chen et al., 2015). Genes and environmental influences likely lead to neuropathologies that could be proximate causes of autism and schizophrenia (Chen et al., 2015). For most diseases, pathology (the study of diseased tissues, often with microscopy) has played a central role because it provides strong clues about proximate causes. This is immensely more challenging in the brain because normal function is based on a vast number of interconnected neuronal branches. Neurons (especially their axons) extend for long distances through a thick volume, and therefore it is impossible to see a complete neuron in a single brain section, much less an entire circuit that may be abnormal in a disease. This may help explain why many disorders of brain function show no clear-cut pathological changes. Presumably, it is not that brain disorders occur without pathology but rather that the traditional tools used in pathology are inadequate. Apprehending complete brain circuits requires the use of connectomic imaging approaches over large volumes to trace out small neuronal branches and their synapses.

Wiring disorders surely account for at least some chronic disorders of brain function. Where might we get early insights into such "connectopathies"? The mouse is an excellent animal model for studying abnormal brain connectivity because there are many mouse models of a wide range of brain disorders (Del Pino et al., 2018). The mouse has many organizational characteristics found in the human nervous system, and we believe it is technically feasible to map the complete mouse connectome (but not the complete human connectome) in the near future. The brains of all mammals contain many of the same cortical and subcortical regions, interareal projections, and connectional organization within regions. Therefore, one can learn a lot about normal human brain organization from the normal mouse brain and obtain insights into human diseases from mouse models. The first step would be to learn what the normal wiring diagram is, and that is what a mouse connectome would achieve. Importantly, once the connectomics infrastructure is set up at the scale required to map a whole mouse brain, it should be feasible to do many additional connectomes (intra-areal and whole brain)

of animal models of brain disorders, including non-human primate models such as the marmoset and macaque, which more closely resemble the human. In this way the nascent field of connectopathology, which currently focuses mainly on human neuroimaging (Rubinov and Bullmore, 2013; Van Essen and Barch, 2015), would synergize more strongly with animal models, with the hope of putting the etiologies of psychiatric and developmental brain disorders on a firmer footing.

## A Path toward Designing Non-biological Thinking Systems

Seventy-five years ago, the neuroscientist and mathematician duo McCulloch and Pitts proposed that simple model neurons could be wired together in specific ways to compute interesting functions—a brain-inspired concept which underlies the artificial neural networks that dominate much of today's work in artificial intelligence (AI) (McCulloch and Pitts, 1943). Sixty years ago, Nobel prize-winning neuroscientists Hubel and Wiesel identified "simple" and "complex" cells in cat visual cortex that AI pioneers subsequently interpreted as operating as a "convolutional neural network," a visual processing architecture that has proven to be an extraordinarily successful and economically important invention in modern computing.

Neuroscience has thus *already* had a profound impact on the development of AI. But what will the mouse connectome specifically offer AI engineers and computer scientists? We describe several of the most important possibilities:

1. *A blueprint for cognitive computing systems*. AI researchers have been successful in steadily improving systems with fairly narrow competencies such as classifying images, playing board games, or transcribing speech. There has been a notable lack of success in creating computer systems that combine diverse capabilities into a generally capable intelligence that rivals the flexibility of biological intelligence. One likely reason for this is the absence of compelling principles or theories that could guide the design of such an integrative system. Studying biological intelligence offers an alternative path forward: in the mammalian brain, nature has evolved a general ar-

chitecture found in all mammals including humans that provides varying degrees of intelligence. This solution is implemented in organisms whose brains span five orders of magnitude in size, while achieving astonishing feats of multi-modal sensorimotor integration, perception, planning, reasoning, prediction, and memory. The mouse connectome will provide a comprehensive description of brain-wide synapse level communication pathways and circuit motifs that underpin the fundamental principles of biological intelligence and may guide us to the construction of integrative AI systems with comparable attributes.

2. *A blueprint for data-efficient learning.* Hallmarks of human and animal learning are profound capabilities in (1) "unsupervised learning," which enables adaptation to environmental circumstances in the absence of specific "labels" or other instructions, and (2) "few shot learning," which enables generalization from just a few examples of a stimulus or phenomenon. In contrast, today's AI systems often require millions or billions of human-labeled data points in order to perform a useful task. As mentioned earlier, the acquisition of wiring diagrams across multiple individuals will yield insights into how experiences shape neural connections. Such insights into the principles behind biological learning could lead to new algorithms for effective unsupervised and few-shot learning, complementing ongoing efforts by AI researchers.

3. *A blueprint for energy-efficient computing.* Supercomputers that today struggle to reproduce mouse-level intelligence occupy football-field sized buildings and consume megawatts of energy. Clearly, we have much to learn from biology about efficient computing. There are many differences between brains and computers including the complexity of the components, the degree of parallel processing (much greater in brains), the flow of electricity across, as well as along, fine neural branches, and the combination of chemical and electrical signaling. A mouse connectome will provide a detailed plan of how an efficient computing machine is implemented in nature and thus accelerate progress toward energy-efficient AI.

The mammalian brain is probably the most impressive intelligent system in the

natural world with our own brain being at the top of the heap. However, despite our intelligence and centuries of inquiry, we still have a paltry sense of how it works. What we do know is that the complex patterns of synaptic connectivity are almost certainly at the heart of its function. It is now time to gain access to these neural circuits and analyze them. For technical reasons, mapping a mouse brain is at present far more feasible than a human one, but even a mouse connectome will be a supreme challenge. Only a unified effort, at the frontiers of technological capability, can ultimately provide such a dataset. We have outlined several fundamental areas of science that are likely to advance from studying such data, including the description of the brain in terms of its cell types, the structural basis of memories, a better understanding of brain disease, and principles of biological intelligence. However, like genomes and large-scale cosmological surveys, which led to discoveries that were largely unexplainable in a previous era of investigation, we predict that a whole-brain mammalian connectome will generate entirely new and unanticipated questions about the nervous system and perhaps represent a turning point in the pursuit of understanding what makes us the unique animals that we are.

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