Toward a Computational Microscope for Neurobiology

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Although great strides have been made in neurobiology, we do not yet understand how the symphony of communication among neurons leads to rich, competent behaviors in animals. How do local interactions among neurons coalesce into the behavioral dynamics of nervous systems, giving animals their impressive abilities to sense, learn, decide, and act in the world? Many details remain cloaked in mystery. We are excited about the promise of gaining new insights by applying computational methods, in particular machine learning and inference procedures, to generate explanatory models from data about the activities of populations of neurons.

NEW TOOLS FOR NEUROBIOLOGISTS

For most of the history of electrophysiology, neurobiologists have monitored the membrane properties of neurons of vertebrates and invertebrates by using glass micropipettes filled with a conducting solution. Mastering techniques that would impress the most expert of watchmakers, neuroscientists have fabricated glass electrodes with tips that are often less than a micron in diameter, and they have employed special machinery to punch the tips into the cell bodies of single neurons—with the hope that the neurons will function as they normally do within larger assemblies. Such an approach has provided data about the membrane voltages and action potentials of a single cell or just a handful of cells.

However, the relationship between neurobiologists and data about nervous systems is changing. New recording machinery is making data available on the activity of large populations of neurons. Such data makes computational procedures increasingly critical as experimental tools for unlocking new understanding about the connections, architecture, and overall machinery of nervous systems.

New opportunities for experimentation and modeling on a wider scale have become available with the advent of fast optical imaging methods. With this approach, dyes and photomultipliers are used to track calcium levels and membrane potentials of neurons, with high spatial and temporal resolution. These high-fidelity optical recordings allow neurobiologists to examine the simultaneous activity of populations of tens to thousands of neurons. In a relatively short time, data available about the activity of neurons has grown from a trickle of information gleaned via sampling of small numbers of neurons to large-scale observations of neuronal activity.

Spatiotemporal datasets on the behaviors of populations of neurons pose tantalizing inferential challenges and opportunities. The next wave of insights about the neurophysiological basis for cognition will likely come via the application of new kinds of computational lenses that direct an information-theoretic "optics" onto streams of spatiotemporal population data.

We foresee that neurobiologists studying populations of neurons will one day rely on tools that serve as *computational microscopes*—systems that harness machine learning, reasoning, and visualization to help neuroscientists formulate and test hypotheses from data. Inferences derived from the spatiotemporal data streaming from a preparation might even be overlaid on top of traditional optical views during experiments, augmenting those views with annotations that can help with the direction of the investigation.

Intensive computational analyses will serve as the basis for modeling and visualization of the intrinsically high-dimensional population data, where multiple neuronal units interact and contribute to the activity of other neurons and assemblies, and where interactions are potentially context sensitive—circuits and flows might exist dynamically, transiently, and even simultaneously on the same neuronal substrate.

COMPUTATION AND COMPLEXITY

We see numerous opportunities ahead for harnessing fast-paced computations to assist neurobiologists with the science of making inferences from neuron population data. Statistical analyses have already been harnessed in studies of populations of neurons. For example, statistical methods have been used to identify and characterize neuronal activity as trajectories in large dynamical state spaces [1]. We are excited about employing richer machine learning and reasoning to induce explanatory models from case libraries of neuron population data. Computational procedures for induction can assist scientists with teasing insights from raw data on neuronal activity by searching over large sets of alternatives and weighing the plausibility of different explanatory models. The computational methods can be tasked with working at multiple levels of detail, extending upward from circuit-centric exploration of local connectivity and functionality of neurons to potentially valuable higher-level abstractions of neuronal populations—abstractions that may provide us with simplifying representations of the workings of nervous systems.

Beyond generating explanations from observations, inferential models can be harnessed to compute the *expected value of information,* helping neuroscientists to identify the best next test to perform or information to gather, in light of current goals and uncertainties. Computing the value of information can help to direct interventional studies, such as guidance on stimulating specific units, clamping the voltage of particular cells, or performing selective modification of cellular activity via agonist and antagonist pharmacological agents.

We believe that there is promise in both automated and interactive systems, including systems that are used in real-time settings as bench tools. Computational tools might one day even provide real-time guidance for probes and interventions via visualizations and recommendations that are dynamically generated during imaging studies.

Moving beyond the study of specific animal systems, computational tools for analyzing neuron population data will likely be valuable in studies of the construction of nervous systems during embryogenesis, as well as in comparing nervous systems of different species of animals. Such studies can reveal the changes in circuitry and function during development and via the pressures of evolutionary adaptation.

SPECTRUM OF SOPHISTICATION

Neurobiologists study nervous systems of invertebrates and vertebrates across a spectrum of complexity. Human brains are composed of about 100 billion neurons that interact with one another via an estimated 100 trillion synapses. In contrast, the brain of the nematode, *Caenorhabditis elegans (C. elegans),* has just 302 neurons. Such invertebrate nervous systems offer us an opportunity to learn about the principles of neuronal systems, which can be generalized to more complex systems, including our own. For example, *C. elegans* has been a model system for research on the structure of neuronal circuits; great progress has been achieved in mapping the precise connections among its neurons.

Many neurobiologists choose to study simpler nervous systems even if they are motivated by questions about the neurobiological nature of human intelligence. Nervous systems are derived from a family tree of refinements and modifications, so it is likely that key aspects of neuronal information processing have been conserved across brains of a range of complexities. While new abstractions, layers, and interactions may have evolved in more complex nervous systems, brains of different complexities likely rely on a similar neuronal fabric—and there is much that we do not know about that fabric.

In work with our colleagues Ashish Kapoor, Erick Chastain, Johnson Apacible, Daniel Wagenaar, and Paxon Frady, we have been pursuing the use of machine learning, reasoning, and visualization to understand the machinery underlying decision making in *Hirudo*, the European medicinal leech. We have been applying computational analyses to make inferences from optical data about the activity of populations of neurons within the segmental ganglia of *Hirudo*. The ganglia are composed of about 400 neurons, and optical imaging reveals the activity of approximately 200 neurons at a time—all the neurons on one side of the ganglion. Several frames of the optical imaging of *Hirudo* are displayed in Figure 1. The brightness

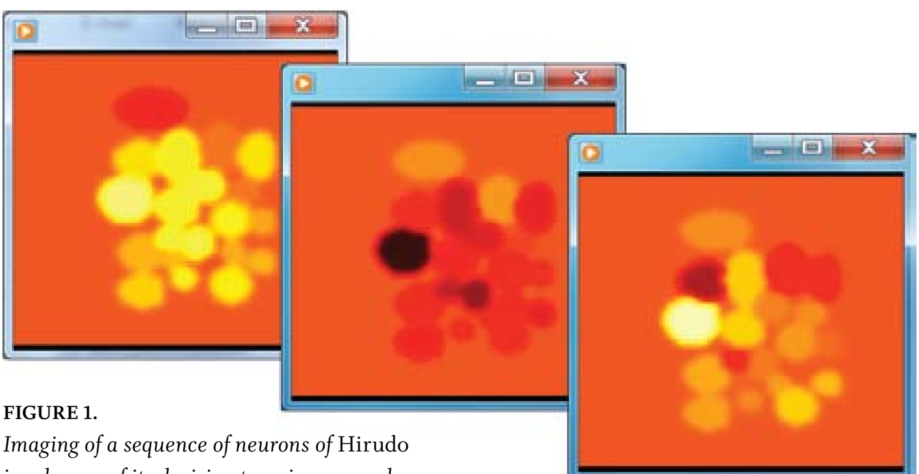

FIGURE 1.
Imaging of a sequence of neurons of Hirudo *in advance of its decision to swim or crawl.*

of each of the imaged neurons represents the level of depolarization of the cells, which underlies the production of action potentials.

We are developing analyses and assembling tools in pursuit of our vision of developing computational microscopes for understanding the activity of neuronal populations and their relationship to behavior. In one approach, we generate graphical probabilistic temporal models that can predict the forthcoming behavior of *Hirudo* from a short window of analysis of population data. The models are generated by searching over large spaces of feasible models in which neurons, and abstractions of neurons, serve as random variables and in which temporal and atemporal dependencies are inferred among the variables. The methods can reveal modules of neurons that appear to operate together and that can appear dynamically over the course of activity leading up to decisions by the animal. In complementary work, we are considering the role of neuronal states in defining trajectories through state spaces of a dynamical system.

EMERGENCE OF A COMPUTATIONAL MICROSCOPE

We have started to build interactive viewers and tools that allow scientists to manipulate inferential assumptions and parameters and to inspect implications visually. For example, sliders allow for smooth changes in thresholds for admitting connections among neurons and for probing strengths of relationships and membership in modules. We would love to see a world in which such tools are shared broadly among neuroscientists and are extended with learning, inference, and visualization components developed by the neuroscience community.

Figure 2 on the next page shows a screenshot of a prototype tool we call the MSR Computational Microscope, which was developed by Ashish Kapoor, Erick Chastain, and Eric Horvitz at Microsoft Research as part of a broader collaboration with William Kristan at the University of California, San Diego, and Daniel Wagenaar at California Institute of Technology. The tool allows users to visualize neuronal activity over a period of time and then explore inferences about relationships among neurons in an interactive manner. Users can select from a variety of inferential methods and specify modeling assumptions. They can also mark particular neurons and neuronal subsets as focal points of analyses. The view in Figure 2 shows an analysis of the activity of neurons in the segmental ganglia of *Hirudo*. Inferred informational relationships among cells are displayed via highlighting of neurons and through the generation of arcs among neurons. Such inferences can help to guide exploration and confirmation of physical connections among neurons.

FIGURE 2.
Possible connections and clusters inferred from population data during imaging of Hirudo.

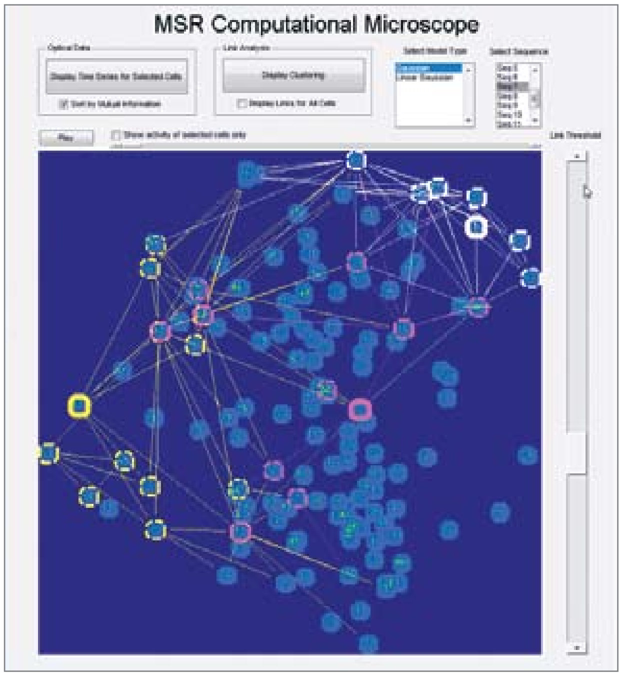

FIGURE 3.
Inferred informational relationships among neurons in a segmental ganglion of Hirudo. *Measures of similarity of the dynamics of neuronal activity over time are displayed via arcs and clusters.*

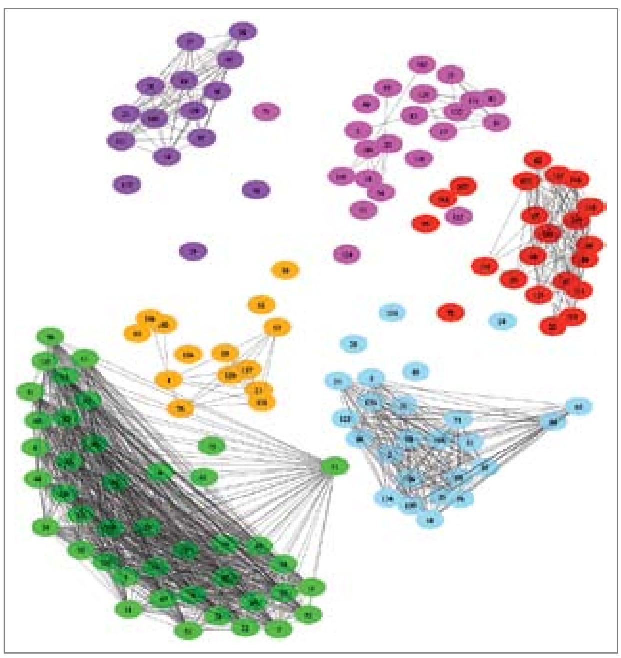

Figure 3 shows another informational analysis that spatially clusters cells that behave in a similar manner in the ganglia of *Hirudo* over a set of trials. The analysis provides an early vision of how information-theoretic analyses might one day help neurobiologists to discover and probe interactions within and between neuronal subsystems.

We are only at the start of this promising research direction, but we expect to see a blossoming of analyses, tools, and a broader sub-discipline that focuses on the neuroinformatics of populations of neurons. We believe that computational methods will lead us to effective representations and languages for understanding neuronal systems and that they will become essential tools for neurobiologists to gain insight into the myriad mysteries of sensing, learning, and decision making by nervous systems.

REFERENCES

[1] K. L. Briggman, H. D. I. Abarbanel, and W. B. Kristan, Jr., “Optical imaging of neuronal populations during decision-making,” *Science*, vol. 307, pp. 896–901, 2005, doi: 10.1126/science.110.