

Computational Methods

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Introduction

Computational neuroscience uses techniques from computer science and applied mathematics to simulate and analyze computational models of neurons and neural systems at many levels of investigation. Digital computers have continued to increase in speed, making it possible to approach more complex neural systems. The number of investigators using computational tools is expanding, and a variety of new journals, summer schools, and scientific conferences that focus on computational neuroscience have proliferated (Table 1). The second edition of a comprehensive handbook on brain theory is available, and there are 33 specialized articles covering many aspects of computational neuroscience in this encyclopedia. Comprehensive introductions to the methods used to develop computational models are also available. This article provides an overview and a discussion of the major methods and techniques in computational and theoretical neuroscience.

The brain regulates behavior by gathering, storing, and accessing information. The brain solves computational problems with specialized circuits, which evolved to process information rapidly and efficiently, in contrast with digital computers, which can be programmed to solve many different types of algorithms inefficiently. For example, the retina is dedicated to visual transduction and image processing and cannot be reprogrammed to process sounds. Because of the close coupling between structure and function in a dedicated system, the anatomy and physiology of a brain region provide important clues to its function. The connectivity between neurons and their properties is shaped by the environment during development and remain plastic even in adulthood. Thus, as the brain processes information, it changes its own structure in response to the information. This plasticity is important in allowing brains to respond flexibly to a changing world through adaptation and learning.

One of the major constraints on the evolution of brains has been their high energy cost. In humans, 20% of the energy budget is consumed by the brain, which constitutes 2% of the body weight. The energy constraint has consequences for coding strategies and communications protocols.

Brain Models

Brain models used as an adjunct to experimental techniques have several advantages: (1) models provide intuition about the possible behaviors of complex, dynamical brain systems, especially when they are non-linear and have feedback loops; (2) the predictions of a model make explicit the consequences of the underlying assumptions, and comparison with experimental results can lead to new insights and discoveries; and (3) the results of difficult experiments can be simulated with a model, such as reversible lesions of selected channels or neurons, to optimize the design of the experiment for distinguishing between competing explanations.

There are three different types of brain models. The first type, called an interpretive model, is used to analyze experimental data in order to determine whether they are consistent with a particular computational assumption. For example, Apostolos Georgopoulos has used a vector-averaging technique to compute the direction of arm motion from the responses of a population of cortical neurons, and William Newsome and his colleagues have used signal detection theory to analyze the information from single cortical neurons responding to visual motion stimuli. In these examples, the computational model was used to explore the information in the data but was not meant to be a model for the actual cortical mechanisms. Nonetheless, these models were highly influential and have provided new ideas for how the cortex may represent sensory information and motor commands. These models in turn have affected experimental design, which has then led to improved models.

A second type of model, called a confirmatory model, has been used extensively to test whether a set of data can account for the phenomena being studied. In many biophysical experiments, such as the classic Hodgkin–Huxley studies of the squid action potential, sets of data are collected under a variety of conditions, and a model is later constructed to integrate the data into a unified framework. A highly realistic Monte Carlo model of synaptic transmission in the chick ciliary ganglion recently predicted that the majority of vesicles in the nerve terminal were not released at active zones, identified by presynaptic and postsynaptic specializations, but ectopically where they stimulated extrasynaptic receptors; this surprising prediction was subsequently confirmed experimentally. This type of model is most effective when most of the variables in the model have been measured experimentally and

Table 1 Resources for computational neuroscience

Summer schools and conferences
Computation and Systems Neuroscience (COSYNE) (February)
Okinawa Computational Neuroscience Summer Course (June)
Canadian Summer School in Computational Neuroscience (June)
Cold Spring Harbor Laboratories Summer Course on Computational Neuroscience: Vision (July)
Computational and Neural Systems (CNS) Conference (July)
Telluride Neuromorphic Engineering Workshop (July)
Advanced European Course in Computational Neuroscience (August)
Summer Course on Methods in Computational Neuroscience at the Marine Biological Laboratory in Woods Hole (August)
Frankfurt Institute for Advanced Studies Summer School in Theoretical Neuroscience and Complex Systems (August)
Goettingen Course on Computational Neuroscience (September)
Neural Information Processing Systems Conference and Workshop (December)
Selected journals
<i>Journal of Computational Neuroscience</i> (Springer Netherlands)
<i>Neural Computation</i> (MIT Press)
<i>Neural Networks</i> (Elsevier)
<i>Network: Computation and Neural Systems</i> (Taylor and Francis)
<i>Biological Cybernetics</i> (Springer Verlag)
Computer programs
MCell: Monte Carlo models of subcellular chemical signaling
GENESIS: realistic compartmental models of neurons and networks
NEURON: realistic compartmental models of neurons and networks
NSL: neural simulation language for large-scale models of neural systems
PDP++: parallel distributed processing models based on abstract neural networks

only a few unknown parameters need to be fit to the experimental data. One danger with this approach is that even if the model fits the data, the resulting model may not be unique. However, automated techniques have been developed for systematically exploring large parameter spaces to determine all combinations of parameters that fit the data. As the number of experiments increases, the number of possible solutions that fit all the data should converge to a unique set.

Finally, a third type of model starts with a general principle and produces an abstract model that implements the principle within known biological constraints. These models can be quite fruitful in helping to motivate experiments that might not have been otherwise undertaken. An example of this approach is the model of coupled nonlinear oscillators analyzed by Nancy Kopell, Bard Ermentrout, and others, which has led to new experiments on fictive swimming in the lamprey spinal cord. One of the strengths of this type

of model is that it can be used to identify the critical variables that determine the qualitative behavior of a system. One corresponding weakness is that because much of the fine detail is often absent, it may not be possible to make detailed comparisons with data.

Dynamical systems theory provides a global analysis of neural systems, but is mainly applicable when the numbers of parameters and variables are small. Most models of neural networks involve a large number of variables, such as membrane potentials, firing rates, and concentrations of ions, with an even greater number of unknown parameters such as synaptic strengths, time constants, and conductances. In the limit that the number of neurons and parameters is very large, techniques from condensed matter physics become applicable in predicting the average behavior of large networks. There is a midrange of systems where neither type of limiting analysis is possible, but where simulations can be performed. One danger of relying solely on computer simulations is that they may be as complex and difficult to interpret as the biological system itself.

Compartmental Models

At the cellular and molecular levels, significant advances have taken place in modeling specific neurons and synapses based on biophysical measurements of ionic mechanisms. Markov models that are used to model ionic channels can be applied to every aspect of synaptic signaling, including transmitter release and the intracellular second messenger systems that modulate synaptic transmission. The original Hodgkin–Huxley models for the fast sodium and delayed rectifier potassium channels are special cases of a Markov model, as are the detailed biophysical models of receptor kinetics.

The pioneering work of Wilfrid Rall on the electrical properties of dendrites was based on the analysis of simplified dendritic geometries. It is now possible to simulate multicompartment models of dendrites from the geometries of reconstructed neurons. Voltage-dependent sodium and calcium channels have been observed in the dendrites of cortical neurons, which greatly increases the complexity of synaptic integration. The experimental confirmation first predicted by compartmental models that active currents can carry information in a retrograde direction from the cell body up to the distal synapses also has theoretical significance for Hebbian forms of synaptic plasticity. Another intriguing observation made with modeling techniques is that the wide variety of spiking patterns in cortical neurons can be reproduced from the same distribution of ionic channels by varying only the geometry of the dendritic tree.

Network Models

Realistic models with several thousand cortical neurons can be explored on the current generation of workstation, which allows the dynamics of cortical columns to be explored in detail. The first model for the orientation specificity of neurons in the visual cortex was the feedforward model proposed by Hubel and Wiesel, which assumed that the orientation preference of cortical cells was determined primarily by converging inputs from thalamic relay neurons. Experimental evidence now favors this model over other models in which the orientation specificity was determined by local cortical circuits. Simulations of orientation columns have shown that the intrinsic circuits in the cortex could be used to increase feature selectivity, amplify weak signals, and suppress noise as well as to perform gain control to extend its dynamic range. This is an important step forward in understanding the function of visual cortex.

A good example of an abstract model that provided a conceptual framework for understanding experimental results is the strongly nonlinear Hopfield network, which exhibits attractor dynamics. This model can be analyzed and convergence proven from any initial state to one of several possible attractor states. Realistic network models of spiking neurons with similar self-sustaining dynamics are now used to study delay-period activity in prefrontal cortical areas and head direction cells in the hippocampus.

Although thalamic neurons that project to the cortex are called relay cells, they almost surely have additional functions since the visual cortex makes massive feedback projections back to them. As an example of a speculative model that has led to a new computational hypothesis for the thalamus, Crick has proposed that the relay cells in the thalamus may be involved in visual attention, and has provided an explanation for how this could be accomplished based on the anatomy of the thalamus. This searchlight model of attention and other hypotheses for the function of the thalamus are being explored with computational models, and new experimental techniques are being used to test these models. Detailed models of thalamic networks can reproduce the low-frequency oscillations observed during sleep states, when feedback connections to the thalamus affect the spatial organization of the rhythms.

Learning Models

The precise timing of single spikes carries information about the locations of objects for echolocating bats and electric fish and for visual motion in invertebrates. Pyramidal neurons are capable of initiating spikes with high precision, and spike-timing-dependent synaptic

plasticity (STDP) has been found in the hippocampus and cerebral cortex to be sensitive to timing difference between pre- and postsynaptic events in the millisecond range. Although spike timing has also been suggested as an information code for the cerebral cortex, experimental evidence instead points toward a role for temporal patterns of spikes in regulating the flow and storage of information in the cortex, such as top-down control of attention and expectation.

Classical conditioning occurs on a timescale of seconds, and recent recordings from dopamine neurons in the ventral tegmental area of monkeys has confirmed the predictions of temporal difference (TD) reinforcement learning, which hypothesizes that the dopamine neurons signal the prediction of future reward. The dopamine neurons project diffusely throughout the cortical mantle and the basal ganglia, where they influence actions and regulate synaptic plasticity. TD learning takes advantage of temporal order to encode causal relationships. It has also been used to model honeybee foraging and is consistent with STDP, which suggests that it may be a general computational principle in nature.

Technology for Brain Modeling

Simulations of large-scale neural systems currently are performed on fast workstations and multiprocessor supercomputers. Computer programs for performing these simulations are freely available (Table 1). New technology, however, is needed to scale up simulations from thousands to millions of neurons. A new approach to massively parallel models has been introduced by Carver Mead, who uses subthreshold complementary metal-oxide semiconductor (cMOS) very large-scale integrated (VLSI) circuits with components that mimic the analog computational operations performed by the brain. For example, silicon chips that model the visual processing found in retinas have been built. Analog VLSI cochleas have also been built that can analyze sound in real time. These chips use analog voltages and currents to represent the signals and are extremely efficient in their use of power compared to digital VLSI chips. A new branch of engineering called neuromorphic engineering has arisen to exploit this technology.

Protocols have been designed for long-distance communication between analog VLSI chips that use the equivalent of all-or-none spikes in the same way that long-distance communication between neurons is accomplished. Many of the design issues that govern the evolution of biological systems also arise in these neuromorphic systems, such as the trade-off in cost between short-range connections and expensive long-range communication. Computational models

that quantify this trade-off and apply a minimization procedure can predict the overall organization of topographical maps and columnar organization of the cortex.

The increase in computer memory capacity and advances in machine learning algorithms have greatly increased our ability to automatically segment serial thin sections from electron microscopy and to reconstruct neural circuits. The goal of connectomics is to produce complete connectivity diagrams. Although connectivity cannot give a complete picture including the temporal dynamics of neural circuits, there are many questions that can be answered, such as whether the neurons in the brain are organized to minimize wire length.

Concluding Remarks

Although brain models are becoming increasingly accepted into neuroscience as tools for interpreting data and generating hypotheses, we are still a long way from having explanatory theories of brain function. For example, despite the relatively stereotyped anatomical structure of the cerebellum, we still do not understand its computational functions. Although the cerebellum is thought to be involved in motor coordination, functional imaging suggests that the cerebellum is also involved in higher cognitive functions such as attention and language. Modeling studies may help in exploring competing hypotheses and suggesting a new type of explanation, such as a common computational operation used in motor coordination, attention, and language. This has already occurred in the oculomotor system, which has a long tradition of using control theory models to guide experimental studies.

At this stage in our understanding of the brain, a model should be considered only a provisional framework for organizing thinking. Many partial models need to be explored at many different levels of investigation, each model focusing on a different scientific question. As computers become faster, and as software tools become more flexible, computational models should become increasingly important in analyzing and interpreting experimental data as well as helping to design critical experiments to test alternative hypotheses.

See also: Axonal Pathfinding; Consciousness: Theoretical and Computational Neuroscience; Executive Function and Higher-Order Cognition: Computational Models; Hippocampus: Computational Models; Hodgkin–Huxley Models; Memory: Computational Models; Spike-Timing-Dependent Plasticity Models.

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