

Computational Neuroscience

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Abstract

The goal of computational neuroscience is to understand how brains generate behaviors using computational approaches. Computational models of the brain explore how populations of highly interconnected neurons are formed during development and how they represent, process, store, act upon, and become altered by information present in the body and the environment. Techniques from physics, computer science, and mathematics are used to simulate and analyze these computational models and provide links between the wide range of levels that brains are investigated, from molecular interactions to large-scale systems. Models are also used for interpreting experimental data and providing a conceptual framework for the dynamical properties of neural systems, which should lead to more comprehensive theories of brain function.

Many different types of physical systems can solve computational problems, including slide rules and optical analog analyzers as well as digital computers, which are analog at the level of transistors and must settle into a stable state on each clock cycle. What these have in common is an underlying correspondence between an abstract computational description of a problem, an algorithm that can solve it, and the states of the physical system that implement it. This is a broader

approach to computation than one that is based purely on symbol processing (Marr, 1982; Schwartz, 1990; Churchland and Sejnowski, 1992; Dayan and Abbott, 2001; Arbib, et al., 2002; Eliasmith and Anderson, 2003; Sterratt et al., 2011). (Figures 1 and 2).

There is an important distinction between general-purpose computers, which can be programmed to solve many different types of algorithms, and special purpose computers, which are designed to solve only a limited range of problems. Most neural systems are specialized for particular tasks, such as the retina, which is dedicated to visual transduction and image processing. As a consequence of the close coupling between structure and function, the anatomy and physiology of a brain

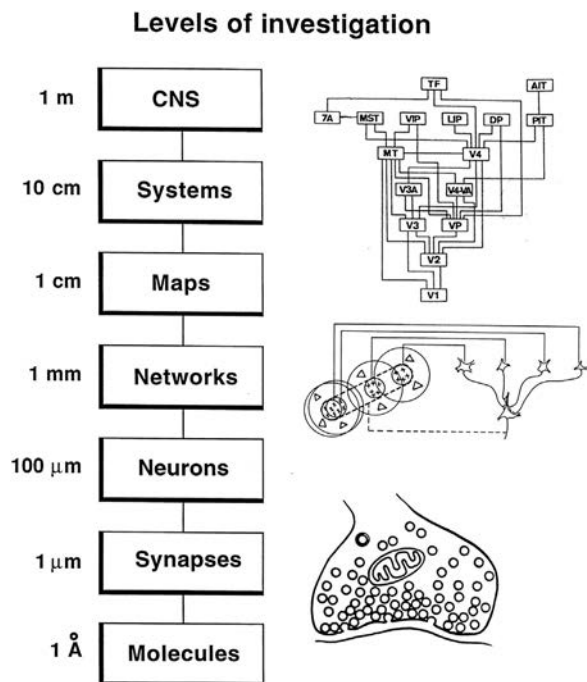


Figure 1 Multiscale levels of investigation for studying the brain. Each level requires a different type of model to explain the dynamical interactions between structures over a wide range of timescales. Integration across levels occurs by mapping the details of a lower level model into the parameters of a model at a higher level. Adapted from Churchland, P.S., Sejnowski T.J., 1992. *The Computational Brain*. MIT Press, Cambridge, MA.

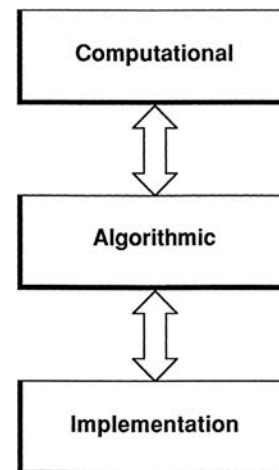


Figure 2 Levels of analysis. The computational level defines the problem to be solved; the algorithmic level provides procedures for solving the problem; the implementation level has devices that instantiate the algorithms. The two-way arrows indicate that constraints between levels can be used to gain insights in both directions. Theoretical approaches often start at the computational level and proceed downward toward the implementation level. Research in computational neuroscience often starts at the implementation level and proceeds up to the computational level. Adapted from Marr, D., 1982. *Vision*. Freeman, New York.

area can provide important clues to the algorithms that it implements and its computational function; in contrast, the hardware of a general-purpose computer may not reveal its function, which also depends on what software it is running.

Another major difference between brains and general-purpose digital computers is that computers are hardwired, but the connectivity between neurons and their properties are 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 that is being processed. Adaptation and learning are important mechanisms that allow brains to respond flexibly as the world changes on a wide range of timescales, from milliseconds to years. The flexibility of the brain has survival advantage when the environment is nonstationary and the evolution of some cognitive skills may deeply depend on genetic processes that have extended the timescales for brain plasticity.

Brains are complex, nonlinear dynamical systems with feedback loops, and brain models provide intuition about the possible behaviors of such systems. 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. Emergent properties of neural systems, such as oscillatory behaviors, depend on both the intrinsic properties of the neurons and the pattern of connectivity between them. For example, the large-scale coherent brain rhythms that accompany different states of alertness and sleep arise from intrinsic properties of thalamic and cortical neurons that are reciprocally connected (Destexhe and Sejnowski, 2001).

Models at Different Levels of Detail

Realistic Models

Perhaps the most successful model at the level of the neuron has been the classic Hodgkin–Huxley model of the action potential in the giant axon of the squid (Koch, 1999; Koch and Segev, 2003). Data were first collected under a variety of conditions, and a model was later constructed to integrate the data into a unified framework. This type of model requires that most of the parameters in the model have been measured experimentally and only a few unknown parameters need to be fit to the data. Detailed models can be used to distinguish between different explanations of the data. Realistic models of thousands of interacting neurons can be explored with computer simulations.

In realistic models of neuron, synaptic signals are integrated on dendrites, leading to action potentials that are initiated near the soma and carried to other neurons through long axons. In compartmental models of neurons, dendrites and axons are modeled as cables with voltage-dependent ion channels, ligand-gate receptors, and ion transporters (Stuart et al., 1999; De Schutter, 2009). The great diversity of ion channels found in different combinations in different types of neurons gives rise to a wide range of properties. More than one set of parameters can reproduce a particular set of electrical recordings, which emphasizes the need for additional constraints on realistic models (Prinz et al., 2004). Active currents allow nonlinear

integration to take place in dendritic branches and can support backpropagating action potentials that carry information in a retrograde direction from the cell body back to the distal synapses tree and influence synaptic plasticity through mechanisms that discussed below in the Section [Learning and Memory](#).

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. Although there is strong experimental evidence for this model, local cortical circuits have been shown to be important in amplifying weak signals and suppressing noise as well as performing gain control through inhibitory feedback to normalize responses and extend the dynamic range. Models of competition between neurons in cortical circuits can explain many properties of single cortical neurons in awake, behaving monkeys during attention tasks (Reynolds and Heeger, 2009). These cortical models are governed by the type of attractor dynamics that was analyzed by John Hopfield (1982), who provided a conceptual framework for the dynamics of feedback networks.

Although the spike trains of cortical neurons are highly irregular, and are typically treated statistically, information may be contained in the timing of the spikes in addition to the average firing rate. This is well established for a variety of sensory systems in invertebrates and peripheral sensory systems in mammals (Rieke et al., 1996), but whether spike timing carries information in cortical neurons is an open research issue. In addition to representing information, spike timing could also be used to control synaptic plasticity through Hebbian mechanisms for synaptic plasticity, as discussed below in the Section [Learning and Memory](#).

Small neural systems have been analyzed with dynamical systems theory (Izhikevich, 2006; Gerhard et al., 2013). This approach is feasible when the numbers of parameters and variables are small. Most models of neural systems 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, rate constants, and ionic conductances. In the limit that the number of neurons and parameters is very large, techniques from statistical physics become applicable in predicting the average behavior of large systems (van Vreeswijk and Sompolinsky, 1998). There is a midrange of system sizes where neither type of limiting analysis is possible, but where simulations can be performed (Bower and Beeman, 2007). One danger of relying solely on computer simulations is that they may be as complex and difficult to interpret as the biological system itself.

Signal Processing Models

Other types of models have been used to analyze experimental data in order to determine whether they are consistent with a particular computational assumption. For example, a 'vector averaging' technique has been used to compute the direction of arm motion from the responses of cortical neurons (Georgopoulos et al., 1986) and signal detection theory was used to analyze the information from cortical neurons responding to visual motion stimuli (Movshon and Newsome,

1996). The spatial tuning curves for neurons in the motor cortex could also be used to solve the equations of motion for multijoint arm movements (Tanaka and Sejnowski, 2013). Bayesian methods can effectively decode the position of a rat in a maze from place cell recorded in the hippocampus (Zhang et al., 1998). 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 have been highly influential and have provided new ideas for how populations of neurons may represent sensory information and motor commands.

Cognitive Models

It is becoming possible to begin simulating cognitive functions such as perceiving, attending, deciding, and moving as computing continues to expand (van Hemmen and Sejnowski, 2006; Eliasmith et al., 2012). Neural network models that simplify the intrinsic properties of neurons can be helpful in understanding the computational consequences of information contained in large populations of neurons. An example of this approach is model of parietal cortex based on the response properties of cortical neurons (Pouget and Sejnowski, 2001). The parietal cortex is involved in representing spatial location of objects in the environment and computing transformations from sensory to motor coordinates. The model examined the issue of which reference frames are used in the cortex for performing these transformations. The model predicted the outcomes of experiments performed on patients with spatial neglect following lesions of the parietal cortex.

The oculomotor system has had a long tradition of using control theory models to guide experimental studies. Large-scale models of vertebrate brains are also becoming possible, especially in highly organized structures such as the retina, cerebellum, and cerebral cortex. However, despite the relatively stereotyped anatomical structure of the cerebellum, we still do not understand its computational functions. Early theories of the cerebellum as a motor controller have to be modified based on functional imaging studies that suggest that the cerebellum is also involved in higher cognitive functions. Modeling studies may help in exploring competing hypotheses.

Learning and Memory

One of the goals of computational neuroscience is to understand how long-term memories are formed through experience and learning. The strengths of interactions between neurons can be altered by activity. For example, high-frequency trains of stimuli at synapses in the hippocampus induce a form of long-term potentiation (LTP) that can last for days (Cooke and Bliss, 2006). Moreover, these synapses require simultaneous presynaptic activity and postsynaptic depolarization, as suggested by Hebb (1949). Hebbian synaptic plasticity can also be used to form maps and has been used to model the early development of the projection from the thalamus to the visual cortex (Toyoizumi and Miller, 2009). In particular, these models can explain why inputs from the right and left eyes form alternating stripes in primary visual cortex of cats and monkeys called ocular dominance columns. Specific mappings

arise in the cortex because temporal contiguity in axonal firing is translated into spatial contiguity of synaptic contacts.

The change in the strength of synapses in the hippocampus and neocortex depends on the relative timing of spikes in the presynaptic neuron and the postsynaptic neuron. Reliable LTP occurs when the presynaptic stimulus precedes the postsynaptic spike, but there is long-term depression (LTD) when the presynaptic stimulus immediately follows the postsynaptic spike (Feldman, 2012). This temporally asymmetry in synaptic plasticity solves the problem of balancing LTD and LTP since chance coincidences should occur about equally with positive and negative relative time delays. When sequences of inputs are repeated in a network of neurons with recurrent excitatory connections, temporally asymmetric synaptic plasticity will learn the sequence and the pattern of activity in the network will tend to predict future inputs. There is evidence for this in the hippocampus where place cells representing nearby locations in a maze may be linked together (Blum and Abbott, 1996) and in visual cortex where simulations of cortical neurons can become directionally selective when exposed to moving visual stimuli (Shon et al., 2004).

The temporally asymmetric Hebbian learning rule can be used to implement the temporal difference learning algorithm in reinforcement learning and classical conditioning (Montague and Sejnowski, 1994; Sutton and Barto, 1998; Rao and Sejnowski, 2001). The unconditioned stimulus in a classical conditioning experiment must occur before the reward for the stimulus–reward association to occur. This is reflected in the temporal difference learning algorithm by a postsynaptic term that depends on the time derivative of the postsynaptic activity level. The goal is for the synaptic input to predict future reward: if the reward is greater than predicted the postsynaptic neuron is depolarized and the synapse strengthens, but if the reward is less than predicted, the postsynaptic neuron is hyperpolarized and the synapse decreases in strength. There is evidence in primates that the transient output from dopamine neurons in the ventral tegmental area carry information about the reward predicted from a sensory stimulus (Schultz et al., 1997).

The temporal window for classical conditioning is several seconds, much longer than the window for LTP/LTD observed at cortical and hippocampal synapses. A circuit of neurons in the basal ganglia and frontal cortex may be needed to extend the computation of temporal differences to these long time intervals (Sejnowski et al., 2014). It is surprising to find the same learning algorithm in different types of learning systems in different parts of the brain. This suggests that the temporal order of input stimuli is a useful source of information about causal dependence in many different learning contexts and over a range of time scales.

Future Directions

Molecular/Synaptic

Almost all of the proteins that make up synapses are now known and they sequencing of the human genome will make it possible to complete that list within the next 5 years. Coupled with high-voltage electron microscopy and methods for labeling these proteins it should be possible to develop a reasonably complete model for the neuromuscular junction and central synapses

within the next decade. This will allow us to understand the synapses as a molecular machine and to understand the mechanisms that are involved in synaptic plasticity (O'Donnell and Sejnowski, 2014). It is highly likely that advances in modeling and computational theory at this level will have direct impact on the pharmaceutical industry through the design of new drugs and new approaches to mental disorders.

Neuron/Network

Progress in this area has been slower because experimental technique for recording from many neurons simultaneously still lags behind. However, the advent of large electrode arrays and optical recording and stimulation techniques (Fenno et al., 2011) and reconstruction methods for circuits from electron microscope images (Denk et al., 2012) have made possible rapid progress. Computer models are being used to understand how the intrinsic properties of neurons and the synapses that join them produce complex spatiotemporal patterns of activity and how these networks are used to encode, store, and retrieve information in large neural systems.

Map/System

Functional magnetic resonance imaging has made it possible to localize activity within the human brain. New approaches, such as diffusion tensor imaging of long-range fiber tracts and magnetic resonance spectroscopy, should make it possible to extend current techniques to explore other structural and functions aspects of the brain (Smith et al., 2013). However, until the time resolution of these new techniques is improved, or they can be integrated with other techniques such as electroencephalography and magnetoencephalography, it will not be possible to uncover the mechanisms that underlie the activity that is observed with functional imaging. Understanding of brains at this integrated level will provide the ultimate insights into major philosophical questions about consciousness and autonomy (Koch, 2004).

Technology for Brain Modeling

Do new properties emerge as the number of neurons in a neural system becomes large? This question can be explored with large simulations of millions of neurons. Parallel computers have become available that permit massively parallel simulations, but the difficulty of programming these computers has limited their usefulness. An approach to massively parallel models introduced by Carver Mead is based on subthreshold CMOS VLSI (complementary metal-oxide-semiconductor very large-scale Integrated) circuits with components that mimic the analog computational operations in neurons. Several large silicon chips have been built that mimic the visual processing found in retinas. Analog VLSI cochleas have also been built that can analyze sound in real time. Analog VLSI chips have been built that mimic the detailed biophysical properties of neurons, including dendritic processing and synaptic conductances. 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 (Liu et al., 2015).

Conclusions

Although brain models are now routinely used as tools for interpreting data and generating hypotheses, we are still a long way from having explanatory theories of brain function. Digital computers have been increasing in computing power and data storage exponentially since 1950 and have transformed how experiments are performed, data are analyzed and the development of brain models and theories. Advance in brain imaging techniques, which has made it possible to study human brain activity noninvasively, would not have been feasible without fast digital computers. Similarly, improvements in optical imaging have been made by counting photons and computationally reconstructing subcellular structure with unprecedented resolution. The increasing power of computers is transforming our ability to analyze complex neural systems at many levels of investigation and will have far-reaching consequences.

At this stage in our understanding of the brain, a model should only be considered a provisional framework for organizing thinking and designing new experiments. Many partial models need to be explored at many different levels of investigation (Figure 1), each model focusing on a different scientific question. As computers become faster, and as software tools become more flexible, computational models will become increasingly important for guiding research. Close collaborations between modelers and experimentalists, facilitated by the Internet, should lead to an increasingly better understanding of the brain as a computational system.

See also: Cognitive Neuroscience; Eye Movement, Control of; Oculomotor Control; Information Processing Architectures: Fundamental Issues; Learning and Memory, Neural Basis of; Long-Term Potentiation and Long-Term Depression; Neural Synchrony as a Binding Mechanism; Neurons and Dendrites, Integration of Information in.

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