COMPUTATIONAL NEUROSCIENCE: A BRIEF OVERVIEW

Ali A. Minai

Department of Electrical and Computer Engineering, University of Cincinnati, Cincinnati, Ohio, USA.

Correspondence to: Dr. Ali A. Minai, Associate Professor of Electrical and Computer Engineering, University of Cincinnati, Cincinnati, OH 45221-0030, USA. Tel. +01-513-556-4783. Email: Ali.Minai@uc.edu

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ABSTRACT

Computational and mathematical modeling is an increasingly useful approach for investigating the functionality of the nervous system. Though such modeling has been used for decades, recent advances in computational power and numerical techniques have greatly expanded its scope, with a corresponding increase in research activity. This paper presents a brief - and necessarily incomplete - review of methods and applications in computational neuroscience.

Computational neuroscience refers to the use of mathematical and computational models in the study of neural systems. It is part of the larger - increasingly active - discipline of computational biology, which applies computational modeling to all aspects of biological organisms. Quantitative modeling has been a key component of research in neuroscience for many decades. Indeed, one of the most celebrated achievements in the field - the Hodgkin-Huxley model for the generation of action potentials[1] - was a triumph of the quantitative approach. Also, much of what is understood about the functionality of the visual, auditory and olfactory systems, as well as the neural basis of learning and memory, has been informed by mathematical and computational modeling. Nevertheless, it is fair to say that, until recently, computational modeling represented only a small part of the total research effort in neuroscience, which has traditionally been dominated by experimental studies. This has begun to change for several reasons which are discussed in the next section. The recent move towards computational modeling has opened up new directions of research, and allowed investigation of issues beyond those that are accessible to direct experimental study. More importantly, it has brought new ideas from fields such as statistical physics, information theory, nonlinear systems theory and engineering into neuroscience, providing a richer conceptual framework for answering the most difficult fundamental questions in the field. This overview discusses the motivation for the use of computational modeling in neuroscience, briefly describes some of the approaches, and looks at a few areas where these approaches have been fruitful. Several excellent texts providing details of methods and applications in computational neuroscience are now available.[2,3,4,5,6,7,8,9,10,11]

MOTIVATION

The primary motivation for using computational modeling is, of course, to understand the behavior of the system under study using mathematical analysis and computer simulation. This is certainly the case in neuroscience. However, the application of computational modeling to living systems - and especially to the nervous system - is significant because, unlike many physical systems where such modeling is used (e.g., planetary systems, fluid flows, mechanical devices, structures, etc.), biological systems can be seen explicitly as processors of information. Thus, computational models in these systems are not just tools for calculation or prediction, but often elucidate essential functionality. In the case of neuroscience, this can be seen in terms of two related roles served by computational modeling. These are: 1) Determining what the various parts of the nervous system do; and 2) Determining how they do it. Each of these is discussed next.

OBTAINING A FUNCTIONAL DESCRIPTION OF THE NERVOUS SYSTEM

Experimental studies of the nervous system at all levels - sub-cellular, cellular and systemic - are critical for understanding the anatomical structures and physiological processes of the system, but these observations must then be organized into a coherent model of system functionality. This is only possible if the appropriate conceptual elements for such a functional description are available. Psychologists and neurologists have traditionally used performance (or its deficits) as the basis for assigning functionality to components of the nervous system, which has produced useful qualitative and phenomenological models. These are often sufficient for clinical purposes, but

provide only limited understanding of the system per se. An alternative (or complementary) approach is provided by viewing the nervous system as acquiring, transforming, storing and using information to control an extremely complex system - the body - embedded in a complex dynamic environment. In this view, the functionality of the system emerges from lower level phenomena such as membrane potential dynamics, dendritic current flows, channel kinetics, synaptic plasticity, etc., much as the functionality of a computer emerges from the currents and voltages in its components. As with the computer, the emergent functionality of the nervous system depends on the underlying phenomena but cannot be described entirely in their terms. To truly understand this functionality, it is necessary to relate the concrete phenomena measured by experiments to the abstractions of information processing - and ultimately to the phenomena of cognition and behavior. Computational modeling does this by providing a well-developed formalism relating signals and information. Through such modeling, mathematical and computational can be applied directly to the nervous system, leading to a coherent quantitative and testable functional description of the brain rather than a qualitative model or a compendium of observations.

ELUCIDATING THE PHYSICAL BASIS OF NERVOUS SYSTEM FUNCTIONALITY

The nervous system processes information at many scales, ranging from molecules to large networks comprising millions of neurons. For the information-based model of nervous system functionality to work, it is essential to explain how phenomena at each level arise from those at lower levels, e.g., how the recognition of objects in the visual field relates to signals generated by visual system neurons, or how the activity of individual motor neurons produces smooth limb trajectories. Unfortunately, experimental methods often do not provide the data necessary for this. In particular, the data needed to understand how networks of neurons process information collectively is very difficult to obtain. Current technology allows in vivo access to the nervous system mainly at the extremes: high resolution intracellular and extracellular data through single electrode recordings, and low resolution regional activity data through functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). Though electrode arrays[12] are now fairly widely used, they still provide extracellular access only to a few hundred neurons at best. However, most functional networks in areas such as the hippocampus and cerebellum (two of the better studied regions) comprise anywhere from a few hundred thousand to several million cells. Information processing in these networks occurs through self-organized dynamic patterns of activity spanning large parts of the system.[12,13,14,15,16,17] These emergent patterns can no more be understood by looking at the activity of individual cells (or even a few hundred cells) than the meaning of a book discerned by reading individual letters. Nor can large-scale data from fMRI studies supply the resolution necessary to see these patterns and relate them to interactions between cells. Computational modeling provides a way out of this dilemma by allowing the study of network models - as large as desired - constructed using neuron models that are themselves based on cell-level data obtained from experiments.[18,2,3,4,5,9,10] These model networks can be simulated computationally under a variety of situations to give insight into how the corresponding networks in the brain might work. Specific issues such as the effect of synaptic modification, modulation by external signals, or the significance of particular connectivity patterns, can be studied, and hypotheses that cannot be tested directly can be provisionally validated or rejected in simulation. In many cases, models are becoming an indispensable tool in the hypothesize-and-test loop of neuroscience . Computational models allow investigators to try out their "what-if" intuitions in simulation, leading to better hypotheses and better designed experiments with greater likelihood of success. Of course, the quality of the results depends on the quality of the models, but the models have become increasingly good with advances in numerical techniques, computational power and experimental methods.[5,10]

As the focus of interest in neuroscience moves from phenomena to functionality, computational modeling is also being used to address previously inaccessible problems such as the neural basis of cognition and even consciousness.[20,21,11] Issues of representation, intention and executive control are being explored at the interface of neuroscience and artificial intelligence,[22] and the understanding of the brain as an extremely sophisticated information processing system continues to advance.

METHODS

Computational neuroscience is an extensive discipline encompassing many approaches. This overview only considers two principal categories of methods that account for most of the research in the field. These are: 1) Single neuron models; and 2) Network models. Network models use the neuron models, often in their simpler forms.

Single Neuron Models

A large number of models have been proposed for modeling the behavior of single neurons, ranging from the extremely complex to the extremely simple (or simplistic). However, it is useful to identify the following broad classes:

1. Compartmental Models: This is the most detailed class of neuron models, where the cell is modeled as a set of compartments, each representing a small patch of the cell membrane assumed to be isopotential (i.e., having a uniform membrane potential).[3] Each dendritic compartment is modeled as an electrical circuit (Figure 1) with the equation:

$$C\frac{dV}{dt} = -\sum_j g_j(t)\left[E_j - V\right] + \frac{V_r - V}{R}$$

where V is the membrane potential, Vr is the resting membrane potential, R is the passive membrane resistance of the patch, C is its capacitance, Ej is the reversal potential of synapse j on the path, and gj (t) is the time-varying conductance of synapse j. The synaptic conductance undergoes a transient change following the arrival of each action potential spike at the pre-synaptic terminal, producing a post-synaptic potential (PSP) of the appropriate polarity. The term dV/dt represents the rate of change for V with respect to time.

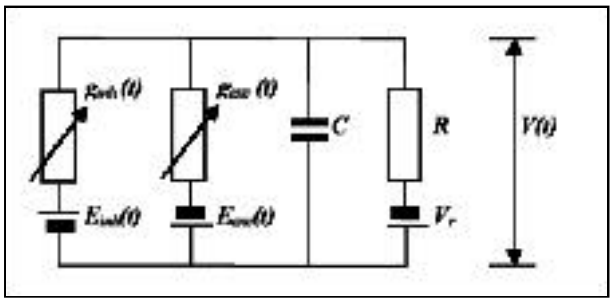

Figure 1: Equivalent circuit model of a dendritic compartment. Excitatory and inhibitory conductances are shown separately with reversal potentials of opposite polarity.

Inhibitory and excitatory synapses are handled naturally in this method by having opposite polarities of reversal potential. Dendritic trees with branching topologies are represented by individual compartments connected together by conductances. The theory of conduction in electrical cables provides a remarkably accurate model of dendritic conduction.[23,24] The soma and the axon are also modeled using compartments, but each compartment corresponds to a Hodgkin-Huxley (H-H) model circuit[1] with synaptic conductances replaced by active conductances corresponding to the various ion channels. Sometimes, simpler oscillator models of action potential generation, such as the Fitzhugh-Nagumo or the Morris-Lecar model, are used.[3]

Compartmental models have been developed to include such details as dendritic delays, nonlinear synaptic interactions, receptor properties (e.g., NMDA vs. AMPA), spine geometries, neurotransmitter release dynamics, etc.[3,4,5,10] Typically, simulations with compartmental models focus on single cells, or a small number of cells, though large-scale models are becoming more common. An early example of successful compartmental models at the network level was the work of Traub and Miles on the hippocampus.[19]

2. Integrate-and-Fire Models: These models are derived from the compartmental models by making three crucial simplifications: 1) The entire neuron is modeled by a single compartment, thus ignoring the cell's geometry (and most other complexities); 2) Synapses are not modeled using ion channels (and their reversal potentials) but as nominal parameters; and 3) The generation of the action potential is modeled phenomenologically rather than by a H-H or oscillator model. A typical integrate-and-fire model for the membrane potential of a neuron i would be:

$$C\frac{dV_i}{dt} = -\frac{V_i}{R} + \sum_j w_{ij} \sum_k \delta(t - t_{jk})$$

where wij is the weight (efficacy) of the jth synapse, tjk is the time at which the kth spike arrives at synapse j, and ¥(t) is the Dirac delta function representing the spike. Each time the membrane potential reaches a threshold Vth, neuron i fires a spike of its own. Integrate-and-fire models have been used most widely in network-level modeling of the nervous system.[2,3,4,7,8,9,25] More complex versions where the neuron is represented by a full Hodgkin-Huxley type model instead of Eq. (2) are also used because they allow explicit study of specific ionic currents and their effects on cell behavior.[3,9,26]

3. Rate Models: These models are a simplification of the integrate-and-fire models, where the spike train represented by ¥(t-tjk) is replaced by a continuous variable, fj(t), representing the spiking rate - or firing rate - of the pre-synaptic cell, j, at time t. Typically, the firing rate is a sigmoidal function of the cell's membrane potential, for example:

$$f_j(t) = \left[1 + \exp(-\lambda V_j)\right]^{-1}$$

where ª is a parameter controlling the nonlinearity of the dependence. Rate models are much easier to simulate and analyze than integrate-and-fire models, and are widely used in neural network models.[27,28,25]

4. Threshold Models: Finally, the simplest class of neuron models simply views neurons as all-or-none devices,[29,30] essentially replacing the sigmoid function of Eq. (3) above with a binary threshold. A cell that is sufficiently excited thus has a nominal firing rate of 1 (active), while an insufficiently excited cell has a rate of 0

(inactive). Obviously, this is a gross simplification, but it allows the simulation and analysis of very large-scale networks, and can provide very valuable intuitive results regarding the collective behavior of such systems.[31] The use of threshold models has also allowed the application of methods from statistical physics to analyze the dynamics of large-scale networks, which has been extremely fruitful.[32]

NETWORK MODELS

Since most meaningful information processing in the nervous system occurs at the collective level, it is the behavior of networks rather than neurons that is of primary interest in explaining functionality. Anatomy obviously varies considerably across different neural regions, but two canonical types of network architectures have been identified as being of general interest because they occur in many systems. These are:

1. Feed-Forward Networks: In this architecture, signals flow unidirectionally from one set of neurons to another without any feedback. While the presence of interneurons usually means that truly feed-forward architectures are rare in the brain, such networks often comprise the most important component of larger networks where feedback effects can be ignored or modeled separately. A well-known instance of a feed-forward network is Hubel and Wiesel's model of feature detectors in simple cells and complex cells of the primary visual cortex [33,34] (see below). The projections in feed-forward networks can be excitatory or inhibitory, and feed-forward inhibition represents an important mechanism to regulate neural activity.[17] Figure 2 shows a network with the same set of pre-synaptic cells supplying monosynaptic feed-forward excitation and disynaptic feed-forward inhibition to a population of post-synaptic cells. Varying activity levels in the pre-synaptic population produce proportionate inhibition on the post-synaptic cells, thus maintaining relatively uniform sensitivity to excitatory inputs in the latter. Feed-forward networks are often used to model directed projections from the principal neurons of one area to another (e.g., from the entorhinal cortex to the hippocampus, or from the lateral geniculate nucleus (LGN) to the visual cortex).

2. Recurrent Networks: This is the other major class of networks, where the outputs of cells in a layer feed back to the same cell population or to upstream populations. As more is learned about the anatomy of the nervous system, it is becoming increasingly clear that feedback projections play a role fully as important as the primary feed-forward connections, modulating, refining and transforming the flow of information in the forward path. The thalamocortical loop is a well-known (and widely modeled) example of a large-scale recurrent system in the brain.[35] Another prominent example occurs in region CA3 of the mammalian hippocampus, which has been proposed as a model for associative memory.[36] Indeed, the hippocampus shows several levels of recurrent connectivity, which has been used in several models of the system.[19,37,38,39,40,41,42,43] Recurrent networks have also been used to model short-term memory,[44] and theoretical results from network models have been compared with data from the cortex.[45] As with feed-forward networks, recurrent connectivity can be excitatory or inhibitory. Feedback inhibition is very important for sharpening the response of a neural population to improve discrimination in response. Figure 3 shows a network comprising two groups of excitatory neurons in a cell layer with recurrent self-excitation and recurrent mutual inhibition. When stimulated by an external input, the recurrent cross-inhibition forces the groups to compete, eventually focusing activity in one group. This is an example of a competitive "winner-take-all" (WTA) mechanism, and has been proposed in models of the prefrontal cortex [17,25,26] and the hippocampus.[41] The WTA mechanism is also crucial for the tuning of feature-detectors in the visual system.[8,16]

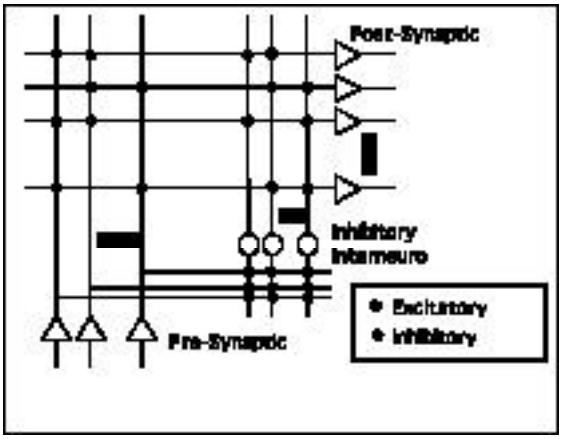

Figure 2: Feed-Forward Network

ISSUES AND APPLICATIONS

Computational models have been used to address almost every issue of interest to neuroscientists - notably for elucidating the functionality of systems such as the hippocampus, cerebellum, sensory cortices, etc. [4,7,8,9,11,13,14,15,16,19,20,21] However, it is instructive to note some very fundamental issues where computational modeling has made a crucial difference. These are presented only as a sample, and do not represent anything close to an exhaustive list.

THE NATURE OF NEURAL CODING

Perhaps the most fundamental issue for a systemic understanding of neural functionality is the nature of neural coding. If the nervous system's primary function is to process information, it is critical to understand how

information is represented and communicated. In the simplest sense, neurons encode information in an all-or-none (binary) fashion with each action potential. However, a neuron's output clearly represents a more informative signal, encoding the recent history of activity on its synapses.

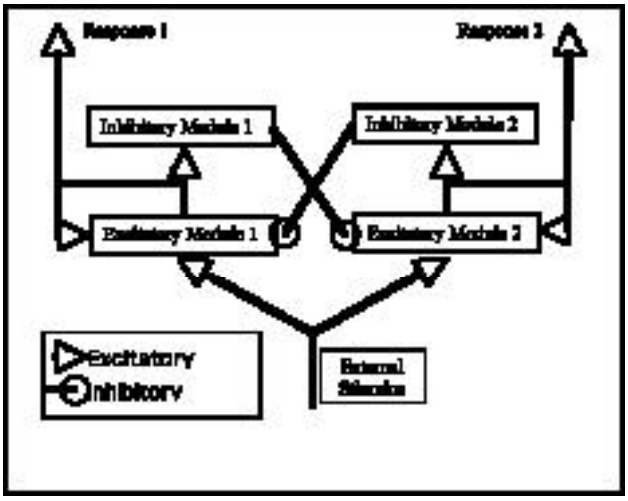

Figure 2: Recurrent Network

The debate on neural coding has focused mainly on two possibilities: 1) Rate coding, where information is represented by the average firing rate of the neuron over some suitable period, and 2) Temporal coding, where the specific timing of spikes carries information. Quantitative analysis and computational modeling have been used extensively to investigate this issue,[46,47,48,49,2] with results suggesting the both types of coding are used in the brain to carry different types of information. A related issue is whether neurons use spatial or temporal correlations between spikes to encode information. There is evidence that populations of cortical neurons use synchrony for encoding,[50,51,52] while location-coding cells of the hippocampus (place cells) use the phase of the background theta oscillation in its encoding mechanism.[53] Both these phenomena have been modeled extensively.[54,55,56,57,58,59]

THE NEURAL BASIS OF LEARNING

Another key issue that has been investigated through modeling is whether and how synaptic modification underlies learning in the nervous system. Since the discovery of long-term potentiation (LTP)[60] in synapses, it has become increasingly clear that change in synaptic efficacy based on correlation between the activities of the pre- and post-synaptic cells is a key component of learning, thus confirming a hypothesis first proposed by the psychologist Donald Hebb in 1949.[61] With the rapid growth in experimental data,[62,63,64] several computational models have been proposed for such "Hebbian" learning,[65,66,67,68,69,70,37,71,72,73,74,75,76] and it remains one of the most actively investigated issues in neuroscience.

MODELS OF MEMORY

If, as is widely held, patterns of activity across neural populations represent meaningful information (e.g., objects, concepts, identifiers, etc.), memory involves the persistence of these patterns. Most interest has focused on long-term memory, which is thought to be mediated by long-term potentiation (LTP) 6[0,62] and depression (LTD),[63] and is critically dependent on the hippocampus.[77,78] Recurrent networks in the hippocampus - especially the CA3 and CA1 regions - have been proposed as models of associative memory[36,6,37,38,40,42,59] because such networks can sustain persistent patterns of activity and recall them when cued with partial patterns.[27,31,32] Recently, researchers have also investigated short-term or working memory, which appears to involve the prefrontal cortex (PFC) and the hippocampus.[17,79] The issue of short-term memory capacity - the well-known 7±2 rule, which states that approximately seven items can be held in working memory at a time - has been studied through computational modeling.[43] It has been proposed that the PFC has a columnar structure similar to the visual cortex,[17,52] and computational models have been used to study the functionality of such systems.[80,81,82,83,84,25,45] Based on experimental data, a computational model of memory using a modular hierarchy has been proposed recently as a general framework for memory.[18,85]

VISUAL INFORMATION PROCESSING

One of the earliest successful applications of computational modeling was in explaining the emergence of feature detectors in the early visual system. In their famous model, Hubel and Wiesel [33,34] showed how input from several centre-surround detectors in the lateral geniculate nucleus (LGN) could produce orientation-selective detectors in the simple cells of the visual cortex. Later work has built on these ideas to develop extremely accurate models of feature-based information extraction in the visual system.[69,86,87,88,89] Computational modeling has also been used to explain the formation of orientation and ocular dominance columns in the visual cortex,[16,90,91] and the processes of segmentation, edge-detection and object recognition.[57] The olfactory and auditory systems have also seen extensive computational modeling.

COGNITIVE CONTROL

The capacity for exerting executive control over actions is a fundamental human ability, and one that is often impaired

in diseases such as schizophrenia. It has long been known that the prefrontal cortex is involved in this function. As the functional anatomy and physiology of the PFC has become clearer,[52] it has become possible to develop computational models of cognitive control that show how the PFC can, over time, learn "rules of behavior" to modulate reflexive or stereotypical motor responses generated by the brain, [52,25,92,93] These models use recurrent networks, LTP and competitive inhibition to account for the decision processes involved in control. In addition to elucidating an essential aspect of human behavior, such models also promise better understanding of mental illness.

MODELS OF NEUROLOGICAL DISORDERS

Most serious neurological disorders are known or hypothesized to represent systemic functional disruptions, and therefore provide an ideal opportunity for useful computational modeling. By far the most widely modeled disorder is epilepsy, which is known to arise from pathological synchronized activity in the cortex or hippocampus. Several researchers have used computational models to investigate the underlying causes of this phenomenon,[94,95,96,97,98] including disinhibition, synaptic modification, entrainment and anatomical changes. Alzheimer's disease,[99,100] schizophrenia,[101,102] and other disorders have also been modeled.[103,104]

Neuroengineering: Applied Computational Neuroscience

The next frontier in the application of computational modeling in neuroscience is its use in actual devices that become part of the nervous system. As the information processing underlying cognition and sensorimotor control is understood better, deficits in these areas can be remedied by supplying the missing computation artificially. Research in this broad area has two major components. The first is brain-machine interfacting: the use of brain signals to control robotic devices such as artificial limbs [105,106] - an application of obvious utility for individuals with paralysis or amputation. An excellent review of the state-of-the art in this area is given by Lebedev and Nicolelis.[107] The other, closely related, direction is that of neuroprosthetics: devices that can be implanted in the brain to replace the function of a neural organ such as the retina or some part of the cortex or hippocampus.[108] These differ from implants such as those used to control seizures or Parkinsonism in that they actually provide the information processing function that the brain has lost. Though the field of neuroengineering (or bionics, as it is sometimes called in the popular press) is in its infancy, it is likely to provide the ultimate payoff from computational neuroscience's view of the brain as an information processing system.

CONCLUSION

As discussed above, computational modeling has been applied to many other issues and areas in neuroscience - far too numerous to even be listed in this brief review. Notable omissions include models of sensory systems, the motor system, cerebellum, hippocampus, basal ganglia, neuromodulatory mechanisms, attentional mechanisms, memory consolidation, fear conditioning, and numerous processes at the subcellular and molecular level. Several texts listed in the references below provide much more detailed information on methods and applications.[2,3,4,5,6,7,8,9,10] With two very versatile and well-documented simulation platforms - GENESIS 5 and NEURON 10 - available for modeling at all levels of detail, computational neuroscience is rapidly becoming an essential part of the larger neuroscientific enterprise.

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