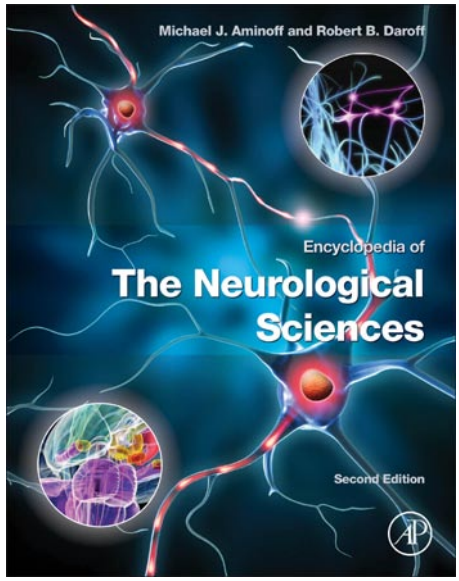

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Computational Neuroscience

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Computational neuroscience uses computer models and mathematical insight to bridge the gaps between the objects of neuroscience study, from the level of chemical concentrations, up through neurons and networks, to the level of behavior and cognition. At these highest levels of study, the goal is to bridge intellectual domains into areas traditionally handled phenomenologically by psychology and even philosophy. Bridging levels provides understanding of electrical activity in terms of underlying chemical processes. A further aim is to understand thought, memory, and learning in terms of coordinated electrical signaling.

Computational neuroscience is a tool to be used alongside the traditional techniques utilized in neuroanatomy and neurophysiology. The necessity of such an approach has become increasingly clear over the past decade with the explosion of information at multiple levels of the nervous system expressed in the various '-omes': genome, proteome, interactome, electrome, etc. There is particular interest in better understanding signaling, both within the cell and between cells. The latter is studied in the context of connectomes (connection diagrams), both at the microscopic level of small pieces of tissue and at the macroscopic level of projections between areas of the brain. At all levels, enormous amounts of data are being gathered that must be stored by computer, data-mined, and eventually understood via computer modeling. Saying this, the author does not in any way discount the importance of the researcher as an agent of discovery but rather notes that the computer has become an indispensible tool in these multiple roles.

Though the computer is a necessary tool, ultimate answers to questions about neural coding, and about mind and behavior, may well be expressible in more traditional forms: as theorems, sets of equations, pictorial depictions, or verbal descriptions. In fact, although the '-omes' continue to push us toward greater complexity of computer simulations, there is a corresponding and simultaneous effort to reduce this complexity by identifying simplifying concepts and extracting encapsulating equations that provide a compact expression for complex underlying phenomena.

Computers and computer engineering have made a significant contribution to our understanding of neuroscience through the development of methods for quantifying previously qualitative notions of memory and communication. However, it must be emphasized that the design and functioning of a digital computer is very different from the design and functioning of the brain. The old description of the computer as an 'electronic brain' is misleading and should be retired. Much of the quest of computational neuroscience is to discover how it is that the brain does things that computers cannot do. Even where computer programs have been developed to replicate human activities, for example, playing chess or understanding speech, these are accomplished through a brute force approach that necessarily loses the flexibility of brain function.

It is generally agreed that the brain's business is information. Information content can be inferred or predicted at many levels of investigation, from ion concentrations up to differential cortical perfusion patterns. We have a variety of information-theoretic tools for assessing the information content of signals. However, information remains a slippery notion because the information content of a signal depends not only on the signal itself but also on the preexisting knowledge of a particular receiver, or on the set of similar signals that receiver has access to. One person's information is another person's nonsense. This conundrum is related to one of the many great unanswered questions about the brain: Which of the signals being measured are part of signaling and which are simply background noises?

The brain is a complex system with many individual components, neurons, and synapses, acting in concert. As a complex system, the brain is said to show emergent properties, properties that cannot be explained by considering the individual properties of the underlying units. The classic example comes from thermodynamics, where large-scale properties emerge from Newtonian approximations of the behavior of individual particles. In neural systems, emergent properties are seen in distributed representations and parallel distributed processing. Information is parceled out among many units. The individual unit does not carry individually interpretable information or an individually interpretable processing task. The role of the unit is useful and meaningful only in the context of the ensemble of units as a whole.

Models of the Single Neuron

Neurons have great anatomical and physiological complexity. It remains an open question as to how much of this complexity is used for information processing by the cell and how much is simply a consequence of having to support its life processes. One hypothesis is that the complexity of the individual neuron makes it an information processing device made up of multiple units. In this view, dendritic subregions encompassing groups of synapses would serve as processing units. With these processing units being so heavily interdependent and dynamically linked, it might be impossible to separate the units conceptually or informatically. The alternative hypothesis states that the single neuron is simple computationally, a single processing unit. In this view, the single neuron is a point neuron that can be described by a single state, such as voltage or firing rate. These two hypotheses can coexist: neurons differ vastly across different brain areas and across types within an area.

The two basic techniques for modeling the single neuron are Hodgkin–Huxley ion channel modeling and dendritic compartment modeling. Some 60 years ago Hodgkin and Huxley demonstrated that the squid axon action potential could be explained by voltage-sensitive elements. They hypothesized that

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these elements would be specific ion channels. This hypothesis turned out to be correct, a major success in the use of modeling to connect levels. They developed a set of linked differential equations that accurately modeled the action potential or spike. Since then many more voltage- and ligand-sensitive ion channels have been described. Although more sophisticated channel modeling techniques have been developed, variations on the Hodgkin–Huxley formulation are still typically used.

Compartment modeling captures the electrodynamics of complex dendritic trees. Anatomists trace out dendritic trees under the microscope and save information on topology, lengths, and diameters. These coordinates are then translated into computer code for neuron models. In these models, small segments of dendrites are defined to be electrically homogeneous compartments that are connected to each other by resistors that represent the cytoplasmic resistance to current flowing down the membrane. Each individual compartment is a variation on the Hodgkin–Huxley parallel conductance model, with a leak resistor, capacitor, and one or more active conductances connecting the cytoplasm to extracellular space (Figure 1). Synapses are similarly handled as additional conductances in the parallel conductance model. These single-neuron models can be enormous, with hundreds of compartments each modeled with 10 or more differential equations.

Compartment models are used for looking at various input–output functions for the neuron. How does a distal excitatory input differ from a proximal input in producing neuron spiking? What is the time-course and effect of spikes back-propagating from the soma up the dendrite? How do different forms of inhibition affect signal propagation in the dendrite? Many of these questions have been answered for particular neuron types in particular brain structures, but the big functional question remains elusive: How do the complexities of neuron structure contribute to information processing?

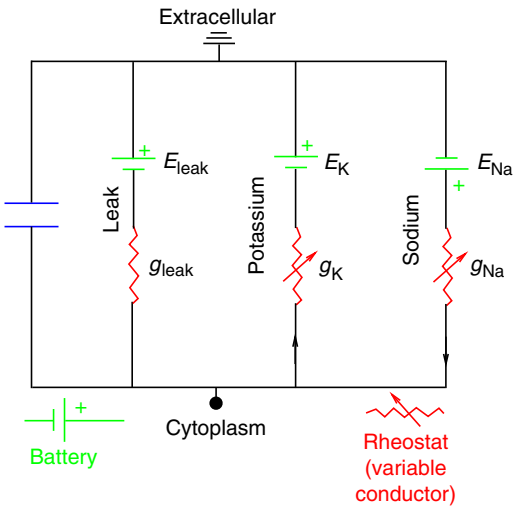

Figure 1 The Hodgkin–Huxley parallel conductance model is extended to produce compartments that include a variety of synaptic and intrinsic channels. Synapses and active channels can be handled similarly, with the rheostats controlled by ligands and voltage, respectively. The flanking cytoplasmic resistors below connect this compartment with neighboring compartments.

Artificial Neural Networks

Artificial neural networks are used for explorations of informational network behavior in the abstract, without the details of neurons or of biological neural connectivity. Although the large simplifications used in the design of these networks make them difficult to utilize directly as models of the brain, these models can provide a valuable proving ground for investigation of distributed representations and parallel distributed processing. Additionally, artificial neural networks are widely used in a number of real-world applications that involve pattern identification. These networks show several features that accord with brain function. For example, artificial neural networks show graceful degradation with damage. A digital computer will cease to function if a single transistor is pulled out. Artificial neural networks carry on despite the removal of units. In addition, these networks deal well with the noisy or incomplete information typical of real-world problems. They also provide content-addressable memory – a memory that can be retrieved based on a partial, incomplete, or even incorrect (noisy) memory fragment. By contrast, digital computer memory is based on pointers. One must know the address of a memory in order to recover it. In this, computer memory is more similar to that of a file cabinet: a location must be identified before information can be accessed.

The basic processing unit of artificial neural networks is the sigmoid sum-and-squash unit. Each unit receives and sums the synaptically weighted outputs from presynaptic neurons (Figure 2). Depending on the network, these outputs may be either binary or analog (continuous). The values are always kept within a certain range, usually -1 to 1 or 0–1. The squashing or sigmoid function serves to project, or squash, the broad domain of summed inputs into the restricted range of outputs.

This simple neuron model is loosely based on the concept of rate coding. The input/output relation of the squashing function is meant to approximately correspond to the current–frequency (I–f) curve of a neuron, which gives the increase in firing frequency with increasing current injection or synaptic activation. The idea of rate coding comes from our understanding of muscle activation: the peripheral coding of motor information. At the neuromuscular junction, increased neural firing rate increases acetylcholine release, which in turn increases calcium entry to the muscle, which augments muscle contraction. It has been suggested that rate coding is present centrally as well. For example, cortical sensory cells can be driven to high frequency by specific stimuli. One set of studies showed that stimulation of large populations of sensory cells by continuous current can alter perception. Other studies suggest that such augmentation is nonspecific and that patterned input is more effective in producing specific sensory illusions. In any case, rate coding is used implicitly or explicitly in many network models.

Because the neurons are so simple, the power of artificial neural networks lies in the organization of the network. A network's organization, or architecture, is described as being either feedforward or recurrent. Biological networks are never strictly feedforward (signals going in one direction only), but here again we have a simplification that is useful for

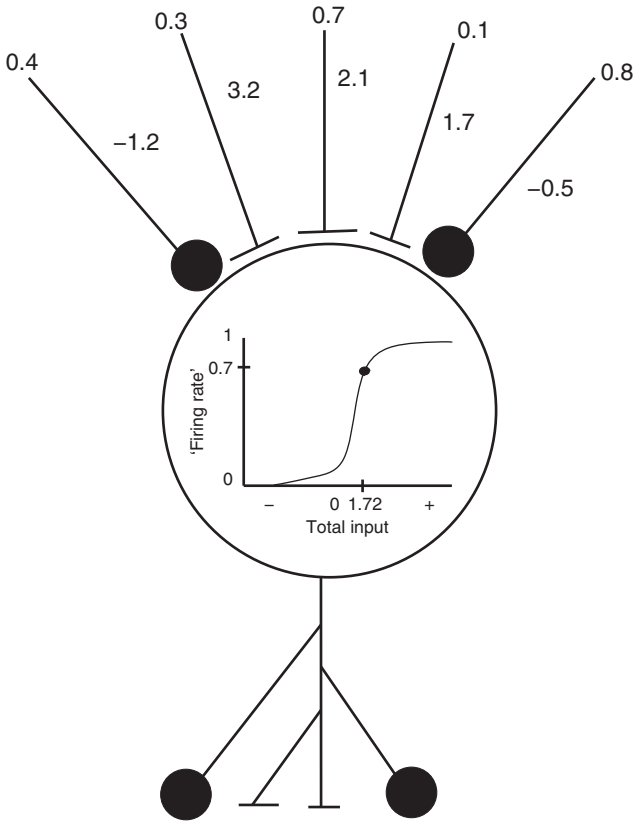

Figure 2 The simplified neural model used in artificial neural network modeling. Multiply each presynaptic state by the corresponding weight and add up the numbers to get total input. Use the squashing (sigmoid) function to determine an output. This will be the state that will then be multiplied by follower synaptic weights. Another simplification allows the neuron to have both excitatory (line segments) and inhibitory (filled circles) outputs.

exploration and understanding of phenomenology. In addition to these structural features, artificial neural networks typically also utilize some sort of learning rule that changes the weights connecting the units. These learning rules are usually variations on Hebbian learning, whereby synaptic strength increases with simultaneous pre- and postsynaptic activity. A popular learning rule, which has been identified biologically, is spike timing-dependent plasticity (STDP). STDP increases the strength of a connection from cell A to cell B if cell A spikes before cell B, and decreases the strength if cell A spikes after cell B. Conceptually, this serves to reinforce connections that may have or be associated with a causal influence.

Oscillations

There has long been debate as to whether oscillations in the brain are evidence of noise or reflect a vital component of signaling or information processing. There is growing evidence that the latter may be the case, with particular frequency bands and interband relations serving different coordinating roles. In this view, the firing of neurons at a particular phase of a cycle would serve to associate the activity of that neuron with others on the same phase. This then would define a neural ensemble through which a set of cells could form a distributed representation or perform distributed processing.

Computational investigations of oscillations have largely focused on the alpha (8–12 Hz) and low gamma (30–60 Hz) bands. It is hypothesized that the alpha oscillation may represent a sensory sampling rate that does not coincidentally coordinate closely with the motoric frequency of the mu oscillation and of physiological tremor. Note that this view of alpha appears to contradict the traditional view of scalp alpha as a resting state oscillation demonstrated at the occiput in the eyes-closed condition. However, investigation of cortical alpha at various sites through magnetoencephalography and intracranial electrodes suggests that these two viewpoints can be reconciled.

In this context, the primary clinical disorders that have been investigated are epilepsy, Parkinson's disease, and schizophrenia. The former two diseases have obvious pathological oscillations: high-amplitude coordinated neural activity in epilepsy and the prominent tremor of Parkinson's disease. In the case of schizophrenia, there is growing evidence to suggest a failure of gamma/alpha coordination that may produce dissociation between percepts or concepts, producing a thought disorder.

Seizures may be regarded as an emergent property of a network where the underlying physiological oscillatory coordination has given way to excessive coordination. In this context, it may be significant that the medial temporal cortex, an area where high-amplitude oscillation appears to play a role in episodic memory, is particularly susceptible to seizure. By contrast with this physiological exaggeration, the emergence of a dominant pathological oscillation as tremor in Parkinson's disease may replace the physiological oscillation and thus lead to loss of normal motor oscillatory pacing, producing the symptoms of postural instability and bradykinesia. In schizophrenia, there is growing agreement that the core dysfunction may be a failure of cognition, manifested by difficulties in properly putting together myriad perceptions into coherent concepts or scenes. This core dysfunction would then underlie the more obvious, long recognized, positive and negative symptoms. Abnormalities in cognitive coordination would in turn be manifestations of abnormalities in neural coordination associated with either excessive or inadequate involvement of neural subsets in oscillation-defined ensembles.

Conclusions

In the long run, computational neuroscience holds promise for the emerging area of rational pharmacotherapeutics. Currently, the traditional trial-and-error approach to new drug development is giving way to rational design at the molecular level. In the brain, the interaction of ligand and receptor is only the first step in a complex series of feedback loops that progressively involve synaptic, dendritic, cellular, and network interactions leading to disease manifestations in the behavioral or cognitive realm. Therefore, rational pharmacological approaches to brain disease will come out of

understanding of emergent properties at these various levels, and understanding will emerge only through study of complex explicit simulations.

See also: Action Potential, Generation of. Brain Anatomy. Central Nervous System, Overview. Neurons, Overview. Sensory System; Overview

Further Reading

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Relevant Website

http://senselab.med.yale.edu/ModelDB
Yale University: ModelDB.