Neurons and Neural Networks: Computational Models

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Based in part on the previous version of this Encyclopedia of Life Sciences (ELS) article, Neurons and Neural Networks: Computational Models by Farzan Nadim and Yair Manor.

Advanced article

Article Contents

doi: 10.1002/9780470015902.a0000089.pub2

Neural networks produce electrical activity that is generated by the biophysical properties of the constituent neurons and synapses. Mathematical equations can be used to describe the electrical activity of neurons and neural networks and the underlying biophysical properties. These equations give rise to computational models of neurons and networks that can be analysed using mathematical techniques or numerically simulated with computers.

Introduction

The electrical activity of neural networks is believed to underlie behaviours ranging from sensory processing and motor activity to cognitive processes in humans and other animals. These neuronal networks arise as the result of complex electrical and chemical interactions among the participating neurons (Johnston and Wu, 1995). The nonlinear biophysical properties of neuronal membranes result in large voltage excursions (action potentials or spikes) that occur in a few milliseconds (Hodgkin and Huxley, 1952). Action potentials are typically generated at the initial segment of the neuron's axon and travel, with little or no attenuation, along the axon to synaptic contact points where the voltage signal results in release of chemicals known as neurotransmitters. The neurotransmitter diffuses and binds to receptors on the postsynaptic neuron(s), resulting in synaptic currents. These signals can facilitate (excite) or impede (inhibit) production of action potentials in the postsynaptic neuron. In addition to such chemically mediated synaptic transmission, neurons can also communicate via direct electrical pathways known as gap junctions. Thus, signalling via action potentials, synapses and gap junctions results in the production of complex networks from otherwise disjoined neurons. **See also**: Action Potentials: Generation and Propagation; Neural Networks and Behaviour; Synapses

Neurons produce action potentials, or fire, when integrated inputs to the neuron reach a threshold value. In general, increased levels of input above this threshold cause an increase in the action potential (firing) frequency. However, most neurons produce complex patterns of firing depending both on the synaptic inputs they receive and their own intrinsic biophysical properties. Despite numerous experimental studies, we are still far from understanding exactly how behaviour emerges from the operations of neuronal networks within the nervous system and their interactions with the body as a whole. One major obstacle toward a detailed understanding is that behaviour emerges from the interaction of thousands or more neurons, each with complex and detailed anatomical, biophysical and biochemical structure. Individual parameters such as single ionic channel properties can be experimentally isolated, but the integrative functions that arise from the interplay of many variables are much harder to decipher. **See also**: Coordination and Integration in Vertebrates: Overview; Neural Information Processing; Synaptic Integration

Because of the complexity of the nervous system, computational and mathematical models have been used since the early years of neuroscience to facilitate our understanding of neural functions and the biophysical mechanisms that underlie them. Among the important aspects of these biophysical mechanisms are the connectivity patterns of the underlying neural network circuitry, the interactions among the intrinsic and synaptic participating currents and the effects of endogenous and exogenous modulatory mechanisms that operate at the subcellular, cellular and network levels. In this article we review the important approaches in neural modelling at various levels of organization.

Computational models of neurons and networks are often solved numerically to find appropriate solutions that mimic experimental results. Such simulations involve numerical approximations to systems of differential equations using one or more existing numerical algorithms, such as 'Euler's Method'. Such algorithms can be implemented in many standard programming languages like Fortran or C. Alternatively, a variety of software packages are available that can be used to numerically solve systems of differential equations in general (such as XPPAUT (Ermentrout, 2002)) or are specialized for solving neuronal models (such as GENESIS (Bower and Beeman, 1998) or NEURON (Carnevale and Hines, 2006)).

Single Neuron Models

Mathematical models of single neurons have been constructed at various levels of description. Conductance-based models take into account the biophysical properties of the neuronal membrane to describe the generation and evolution of electrical activity as a result of the interaction between the membrane voltage and other dynamic variables. In some models neurons are considered to be approximately isopotential; consequently, their spatial structure can be neglected and the neuron is modelled as a single compartment or a 'point neuron'. If isopotentiality cannot be assumed, then the neuron's spatial distribution has to be taken into account resulting in multicompartmental models. In such models, the soma, dendrites and axon are spatially separated into multiple isopotential compartments that are electrically connected. In addition to these biophysically realistic models, several simplified mathematical models have been used that account for some biophysical or dynamic properties while neglecting others. **See also**: Cellular Neuromodulation; Membrane Potential; Neuronal Firing Pattern Modulation; Oscillatory Neural Networks

Conductance-based neuron models

The ability of neurons to produce action potentials was first described in terms of ionic mechanisms by Hodgkin and Huxley in the 1950s (Hodgkin and Huxley, 1952). Based on their studies of transmembrane currents in the squid giant axon, Hodgkin and Huxley proposed a mathematical model of the action potential. In this model, the action potential generation is based on the flow of sodium and potassium ions through voltage-gated channels that gate (open and close) in a time- and voltage-dependent manner. The rates of the channel gating variables are described in terms of kinetics equations with voltage-dependent parameters. These gating variables, in turn, determine the rate of change of the membrane potential. While the biological correlates of the gating variables were at the time unknown, the Hodgkin–Huxley model reproduced most biophysical properties of neurons such as action potential generation and propagation, absolute and relative refractory periods and anode-break response. Decades later, empirical observations have provided ample experimental support for the basic mechanisms suggested by Hodgkin and Huxley. The Hodgkin–Huxley model has gained considerable popularity in the neuroscience community because of its conceptual and experimental tractability, and its biophysical accuracy. **See also**: Action Potential: Ionic Mechanisms; Axons; Hodgkin, Alan Lloyd; Huxley, Andrew Fielding

The Hodgkin–Huxley formalism constitutes the prototype for most biophysical models in studying single-neuron dynamics. However, it should be noted that biophysical models of neurons may vary considerably in their basic properties. One set of differences relates to the relationship between action potential frequency (f) versus injected (or applied) DC constant current (I) (Izhikevich, 2006). The original Hodgkin–Huxley model describes a 'Type II neuron', where f is a discontinuous function of I, jumping from zero (silent cell) to a nonzero value as the applied current is increased. **See also**: Repetitive Action Potential Firing

In contrast, some neural models describe the behaviour of 'Type I neurons', where f is a continuous function of I and therefore the firing frequency can be arbitrarily small.

The original Hodgkin–Huxley model included two voltage-dependent ionic currents, the transient sodium and delayed-rectifier potassium, which are sufficient for production of action potentials. Hodgkin–Huxley type models have since been extended to include 'nonstandard' intrinsic currents. Such nonstandard currents include those that are activated in voltage ranges close to the resting potential (the membrane voltage in the absence of any input) and contribute to the generation of small-amplitude (subthreshold) oscillations and to resonance properties (maximum impedance at a preferred frequency of input current). Other types of nonstandard currents may be activated with a slow rate or by hyperpolarization of membrane voltage or by changes in intracellular concentrations of ions such as calcium and sodium. Such currents could be involved in the creation of various characteristic interspike time intervals or bursting activity (aggregated action potential firing separated by intervals of quiescence.)

Spatial structure of neurons

All neurons have complex anatomical structures that include elongated axons and ramified dendritic trees. In many computational models, the spatial complexity of neurons is ignored, and neurons are assumed to be isopotential, point processes. This assumption greatly simplifies the construction and analysis of the model and, for some modelling questions, provides a reasonable approximation. It is now widely recognized that the reduction of neurons to point processes may not always produce a faithful representation of the neuronal electrical activity and may even introduce serious errors. In addition, in some cases it has been demonstrated that interplay between the electrical activity and the spatial structures of neurons is physiologically and functionally important for network output. For example, the spatial structure of individual neurons is involved in sound localization, directional selectivity and coincidence detection. **See also**: Neurons

The basis of mathematical analysis on passive spread of membrane potential along elongated structures is the cable equation developed by Lord Kelvin in the nineteenth century for describing signal propagation in the transatlantic telegraph cable. The cable equation is a partial differential equation that describes the relationship between the temporal and spatial rates of change of voltage in a one-dimensional conductive medium. An important basic parameter of the cable equation is the space constant. This parameter indicates the extent of spatial attenuation of voltage along the cable. Wilfrid Rall compiled a set of mathematical laws that extended cable theory to complex

structures such as dendritic trees of neurons (Rall *et al*., 1995). Rall demonstrated that in idealized cases, such as a passive dendritic tree in which all branches are symmetrical, cable theory can be used to analytically compute the spatial spread of voltage. **See also**: Dendrites

In realistic neurons, however, the analytical approach is much less feasible and it is possible only after simplifying assumptions are made. The more common computational approach for studying the spatial complexity of neurons is compartmental modelling. In a compartmental model, the model cell is broken down into short isopotential segments, or compartments, that are connected to their neighbouring segments with simple voltage conductors. The intersegmental voltage conductors account for the intracellular conductivity of the neuron. The compartmentalization of the neuron thus produces a finite number of coupled ordinary differential equations that can be numerically integrated. It is generally accepted that compartments shorter than a tenth of a space constant can be treated as isopotential. This assumption simplifies the level of detail used in compartmental models. Of course, compartmental resolution must be determined by the modelling question. If one wishes to model short structures, such as terminal branches or dendritic spines, very small compartments may be necessary. However, compartmental models can also be constructed in less detail. For example, in some models the contribution of dendritic spines is included as an increase in the dendritic membrane area, rather than by explicitly modelling the spines as additional compartments. As another example, in several instances theoretical studies have shown that a model with a large number of compartments can be reduced to a two-compartment model without loss of its essential behaviours. The two compartments are necessary to allow for the physical separation of distinct biophysical properties of the neuron, most notably the somatic compartment where action potentials are generated and the dendritic compartment where synaptic inputs are integrated. **See also**: Dendritic Spines

Low-dimensional biophysical models

Biophysical neural models are described as a group of coupled differential equations. With advances in the geometrical analysis of differential equations, a multitude of geometrical tools is available for analysing the behaviour of these models. In particular, solution trajectories of the model neuron can be visualized in the phase space. The dimensionality of the phase space is equal to the number of differential equations used to describe the model. Hence, if the model neuron is described with only two differential equations, the geometry of the phase space (called the phase plane in two dimensions) is relatively simple and suitable for analysis. Phase plane analysis is a commonly used tool in today's computational neuroscience. In the 1960s two mathematicians, Fitzhugh (1961) and Nagumo, independently produced a formal qualitative reduction of the original Hodgkin and Huxley neuron (a four-variable model) to two dimensions (i.e. two variables). In a two-dimensional model the two variables generally represent the neuron's membrane potential and a recovery variable responsible for the refractory period; i.e. an activator and an inhibitor variable. The geometrical representation of the neuronal model is useful for analysing the behaviour of the model neuron in various parameter regimes and in response to various stimuli (Rinzel and Ermentrout, 1998). In particular, it is possible to determine under what circumstances the neuron is quiescent, continuously spiking, producing rhythmic activity, behaving as a bistable system (where quiescence and continuous spiking are two stable solutions), or transforming from one state to another. **See also**: Sodium Channels; Voltage-gated Potassium Channels

The transition of a mathematical system from one qualitative state to another, for example, from quiescent to oscillatory, is known as a bifurcation. A set of mathematical tools known as bifurcation theory allows one to characterize analytically the behaviour of a system in the vicinity of bifurcation points. Bifurcation theory can be a powerful tool to gain insight into the dynamics of low-dimensional neuronal systems. For example, in the Type II neurons mentioned earlier, periodic firing arises through a Hopf bifurcation while a saddle node bifurcation on invariant circle is involved in Type I neurons (Izhikevich, 2006). The distinct bifurcations that give rise to periodic spiking in the two model types can be calculated using linear analysis methods and help in fitting the model parameters to match the behaviour of the biological neuron.

The reduction of the four-dimensional Hodgkin–Huxley model to a lower dimensional one is based on the possibility of separating the variables according to their time scales; i.e. when some variables evolve with significantly faster kinetics than others. An example is the activation of sodium channels (fast) as compared to the activation of potassium channels or inactivation of sodium channels (slow) in the Hodgkin–Huxley model. Higher dimensional systems are not necessarily reducible to just two equations. Simple examples are single cell models with nonstandard currents, in addition to the standard spiking ones used by Hodgkin–Huxley, and two-cell models where each cell is defined with a minimum of two equations (each synaptic connection between two neurons adds a differential equation or dimension). However, in these cases it is might still be possible to reduce the dimensionality of the models without changing their qualitative output. In the former case, the neurons interspike interval can be divided into subintervals, or regimes, inside which lower dimensional models can be derived. These are constrained to be good approximations to the 'full' model in the corresponding regime. The key observation in applying this technique is that currents activate and inactivate as the neuron's voltage goes through the various voltage regimes. The abruptness of these changes is helpful in creating the various regimes where only a subset of the participating currents is active. The gating variables associated to the inactive currents are then decoupled from the reduced system, thus lowering its dimensions. Further reductions are achieved by separating

variables according to their time scales. In the latter case (two-cell model), it is often possible to separate the variables according to their time scales.

In such fast–slow systems the dynamics of the fast and the slow subsystems can be analysed separately. The solutions of the subsystems are then pieced together using the methods of singular perturbation theory to build solutions to the full system.

Simplified models of neurons

For some modelling questions one may not be interested in the spike details but in the mechanisms by which they are generated. These mechanisms typically operate in the subthreshold voltage regime (close to resting potential). In these cases one can build 'integrate-and-fire' type models by combining a biophysical description of the subthreshold dynamics with artificial spikes. Such models are effectively lower dimensional than Hodgkin–Huxley models. The classic integrate-and-fire neuronal models were first proposed by Lapicque in 1907 (Lapicque, 1907). In an integrate-and-fire neuron the membrane potential increases according to a single linear differential equation. When the membrane potential reaches a certain threshold the neuron produces a 'spike' and the membrane potential is immediately reset to a low voltage value. A 'leaky' integrate-and-fire neuron has an internal state, which is governed by a linear or 'passive' ionic conductance which determines the input resistance and the membrane time constant and dictates the time course of voltage change. Integrate-and-fire models have been generalized to describe some basic nonlinear behaviours, such as refractory periods, nonlinear f–I curves, linear and nonlinear subthreshold oscillations and resonance. These generalizations involve the addition of appropriate subthreshold currents to the leaky integrate-and-fire model.

For some questions related to the oscillatory behaviour of neurons, one may not be interested in the description of the neuron internal states, but in the spiking dynamics. 'Phase models' are used for describing the oscillatory state of neurons while ignoring the mechanisms underlying the oscillations. In these models a phase variable characterizes the relative phase of the oscillatory dynamics along the limit cycle. A single differential equation is typically used to describe the evolution of this phase variable with time, and thus there is no description of the subthreshold voltage regime dynamics.

'Formal neurons' are the simplest models of neuronal elements. In this formalism the neuron is viewed as a binary element (silent or spiking) operating in a discrete time scale. The formal neuron is a node, to which inhibitory and excitatory synaptic inputs are connected. When excitation exceeds inhibition by a threshold, the neuron produces an action potential; otherwise it is silent.

By setting the threshold value and the individual synaptic weights, the model neuron computes basic logical operations. McCulloch and Pitts demonstrated that any formal computation can be performed with a network of interconnected binary neurons (McCulloch and Pitts, 1943). This, however, does not explain how the nervous system actually performs computations. Indeed, formal neurons lack one of the fundamental properties of biological neurons, namely that neuronal output is determined not only by the nature and strength of its inputs, but also by its intrinsic properties.

In some cases, simplified models such as formal, integrate-and-fire or phase models are advantageous for modelling and analysing large-scale networks (see later). However, in general modellers that use these simplified models are restricted by the type of questions that can be asked (Dayan and Abbott, 2001). Indeed, realistic neurons are typically endowed with a multitude of active nonlinear ionic conductances that are dependent on time, membrane potential and intrinsic concentrations of calcium or other agents. Hence the internal state of a biological neuron can be much more complex than that captured by even the most sophisticated of integrate-and-fire models. Indeed, nonlinear conductances are essential in determining the electrical activity of individual neurons and thus the output of individual neurons or small networks of neurons. Even in the case of large-scale networks, simplified models are often not satisfactory because the dynamics of the network may depend on complex properties of neurons, such as spike rate adaptation, postinhibitory rebound or subthreshold activity. In these cases, simplified models are too simple and other models, which explicitly include nonlinear properties, must be used.

Neuronal Networks Models

Small networks

Small neuronal networks are circuits consisting of a few connected neurons. Typical couplings include spike-mediated synapses, graded synapses and electrical or gap-junctional coupling (**Figure 1**). In general, the coupling represents some kind of input–output relationship between two connected neurons. A synaptic input from a presynaptic neuron to a postsynaptic neuron is typically modelled as a current that affects the postsynaptic membrane potential. The strength of the synaptic current, however, is dependent on the presynaptic membrane potential through a synaptic transfer function. If this transfer function only depends on the occurrence of a presynaptic action potential, the synapse is known as spike-mediated. In this case, the postsynaptic current typically rises rapidly to a peak and then decays with a characteristic time constant. Alternatively, the strength of the synaptic current may increase as a smooth function of the presynaptic membrane potential, in which case the synapse is called graded. Transfer functions are typically modelled using kinetic equations similar to these used for voltage-gated ion channels. Synapses can be excitatory or inhibitory depending on whether the synaptic current facilitates or impedes

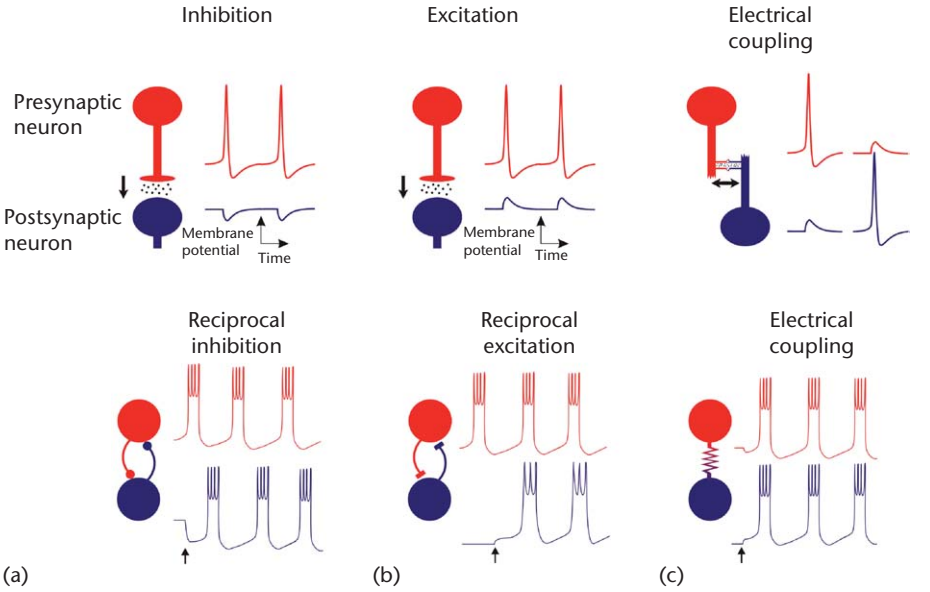

Figure 1 Some common models of two-cell networks. (a) Synaptic inhibition is due to the release of a neurotransmitter that typically causes a negative change in the postsynaptic membrane potential. Two cells that are reciprocally coupled by synaptic inhibition can produce out-of-phase oscillatory activity (half-centre oscillation). (b) Synaptic excitation is caused by a neurotransmitter that typically produces a positive change in the postsynaptic potential. Two cells coupled with reciprocal excitation can oscillate in phase but the action potentials are not necessarily time-locked. (c) Electrical coupling is due to ion channels (gap-junctions) that span the membranes of two cells and allow free flow of ions between the two. Electrically coupled cells typically demonstrate synchronous activity, which may be oscillatory even if the two cells are not rhythmically active in isolation.

the production of postsynaptic action potentials. **See also**: Chemical Synapses

In biological synapses, the strength of the synaptic connection between two neurons is most often not fixed but a dynamic variable. In the short time range (seconds to minutes), the synaptic strength may increase or decrease with repetitive utilization of the synapse. In the former case the synapse is called facilitating, while in the latter case it is called depressing. Recent models have examined the effects of short-term synaptic dynamics in models of neural networks. One way of modelling synaptic depression, for example, is to define a finite pool of synaptic resources (the number of vesicles, the number of postsynaptic receptors, the calcium conductance at the presynaptic terminal, etc.) that undergoes depletion or inactivation following each action potential. Between action potentials, the resources are automatically replenished or restored with a typical time constant, which determines the recovery process. **See also**: Long-term Depression and Depotentiation; Long-term Potentiation; Synaptic Plasticity: Short Term

The network most comprehensively analysed using computational and mathematical tools is the network of two cells that are reciprocally connected by inhibitory synapses (**Figure 1a**). When the two cells in this reciprocally inhibitory network are active (spiking) in alternation, the circuit is referred to as a half-centre oscillator (Brown, 1914). A general framework to study half-centre oscillators categorized two such modes of oscillations. In the escape mode, the transition from the inactive to the active state is controlled by the properties of the inactive neuron, whereas in the release mode the transition is controlled by the active neuron. More recent models have shown that reciprocal inhibition can lead to synchronous oscillations, provided that the rise times of the synapses are slow compared to the duration of the action potential. These synchronization properties, however, may change if the participating neurons have nonstandard currents. **See also**: Central Pattern Generators; Oscillatory Neural Networks

A number of modelling studies have examined networks of neurons connected with mutually excitatory synapses (**Figure 1b**). Mutual excitation in its purest form leads to destabilization. Modelling works have shown that synaptic depression may contribute to stabilize such circuits, acting as a gain-control mechanism. In general, mutual excitation also tends to synchronize oscillations. However, modelling studies have demonstrated that mutual excitation may lead to more complex network behaviour. For example, coupling two bursting neurons may lead to synchronized bursts although the spikes within the burst may drift out of phase.

Electrical (gap-junctional) coupling is a physical connection between two neurons that allows direct transfer of ions. Experimental study of electrical coupling has been limited by the ability to manipulate the gap junctions without affecting other network components. For this reason, computational models have been crucial in understanding the role of electrical coupling in shaping network behaviour. Electrical coupling between two neurons acts to equalize their membrane potentials (**Figure 1c**). Hence, intuitively, electrical coupling is a way to synchronize the activity of the two cells. Modelling studies have shown, however, that under some conditions this intuition is wrong. For example, several mathematical models

demonstrate that weak electrical coupling between two neurons leads to stable out-of-phase oscillations. Another lesson learned from models of electrical coupling is that when the coupled neurons are different in their intrinsic properties, the behaviour of the two-cell network can be completely different from that of either neuron. An example would be coupling two quiescent neurons that may result in oscillations, which can vary in frequency and amplitude as function of the coupling strength. Moreover, variation in coupling strength may destroy oscillations, create oscillations or produce different oscillatory patterns.

Invertebrate networks such as the buccal ganglion in Aplysia or the stomatogastric ganglion in crustaceans are small. The number of neurons range from several to tens of cells and the coupling relationships can be readily described. Although the activity of these invertebrate networks is quite rich, the network function is generally well-defined and in many cases can be related to behaviour (Marder, 2002). The close association with behaviour provides small networks with an immense advantage over very large cortical networks that are often only loosely correlated with behaviour. These advantages in a small neuronal network enable the construction of a realistic wiring diagram, where each model neuron or synapse corresponds to its biological equivalent. Such a wiring diagram is transformed to a set of differential equations that can be modelled with conventional numerical integration techniques. Because small networks have the advantage that the neural circuitry can be identified both anatomically and physiologically, recent computation models that describe neuromodulatory effects on small neuronal networks have provided great insight into the actions of neuromodulation (Nadim *et al*., 1998).

Small network models have been used as reduced models to investigate various dynamic phenomena occurring in biologically larger networks. Examples include the study of the synchronization properties in excitatory and inhibitory networks referred to earlier, and the mechanism of generation of rhythmic activity in various areas of the hippocampal formation. These small networks typically consist of one or two neurons representative of each neuronal type that has been anatomically identified and known to play a role in the dynamic process. These reduced models capture the relevant qualitative aspects of the network output that cannot be captured by a network consisting of fewer neurons or neuronal types. **See also**: Cellular Neuromodulation; Coordination, Integration and Behaviour in Invertebrates; Heterosynaptic Modulation of Synaptic Efficacy

Large networks

A central question in neuroscience is the code used by nervous systems to represent information about the internal state of the animal and the inputs it receives from the environment. Most recent studies of large neuronal networks focus on how correlated firing activity (synchronicity), which is believed to be involved in the neural code, is produced or destroyed in cortical circuits. Thus, it is of crucial importance to understand the rules that govern the dynamics of large neuronal networks. Large networks, such as the hippocampus or the piriform cortex, comprise hundreds of thousands to millions of neurons, and billions of synapses. It is therefore not practical to model these structures by construction of complete wiring diagrams, such as done for small neuronal networks, and a different approach must be taken. **See also**: Hippocampus; Neural Activity and the Development of Brain Circuits

One approach to study large neural networks is to reduce the network to as described earlier. This can be done by grouping together neurons of a given type into a few representative neurons or building blocks. The full circuitry is condensed into a cartoon circuit, which is much smaller but can still capture some essential behaviours of the large network. This approach has allowed for the analysis of some population dynamics properties in the neocortex and the hippocampal region CA1, but it is not adequate in cases where the network output emerges from interactions between neurons of the same type, for instance, in the hippocampal CA3. In addition, in many cases, the reduction of large networks into representative building blocks may be counterproductive because the phenomenon under study is apparent only when large numbers of cells and synapses are involved. Such is the case in the clustering phenomenon and formation of cell assemblies, where neurons within a large-scale network spontaneously segregate themselves into several synchronous clusters within which firing activity is correlated (Harris *et al*., 2003).

An alternative approach is realistic modelling in which network models are designed using a 'bottom-up' scheme. In realistic large-network models, single neurons belonging to the same type are modelled according to known biological data and used as generic templates to construct networks consisting of thousands of neurons where the pattern of connectivity is described according to general statistical rules. For example, in many brain regions experimental data indicate that the probability of synaptic connectivity between neurons decreases with distance. Modellers of large networks often use this observation to define a simplified 'footprint' synaptic connectivity rule in the network. It is important to realize that, in general, the connectivity in the large-network model is not faithful to the precise connectivity within the biological network, which is shaped by complex developmental rules. Hence, such large network models typically address questions that are independent of the particular network connectivity but depend on general large-scale rules. A problem in realistic large network models is that the model complexity is often comparable to the complexity of the biological system. Nevertheless, realistic large-network models are valuable for two reasons. First, a successful model can demonstrate that a set of synaptic and cellular properties can be sufficient to explain experimental observations. Second, experiments that are difficult to perform in the biological system can be easily performed numerically to provide additional insight.

Theoretical physicists attack the problem of large neuronal networks with yet another tool. Imported from the

field of statistical physics, the notion of the infinite-size network is extremely useful to understand neuronal dynamics because such constructs are amenable to analytical treatment. Indeed, one of the important parameters of neuronal networks is the size or number of elements. Because numerical simulations of networks are limited to thousands of neurons (a fraction of the actual size of biological networks), it is important to understand the size-dependence of the network and how finite-sized networks relate to their thermodynamic limit, as the number of neurons approaches infinity. For example, because of finite-size effects, a measure of synchronicity may show partial synchrony even in a totally asynchronous network. To discuss the size dependence of a network, it is important to specify how network parameters vary as the network size is increased. In the case of homogenous (all-to-all) coupling, the average number of synaptic inputs is proportional to the size of the network. Hence, to keep the size of synaptic input fixed and independent of network size, a common technique is to scale the synaptic strength of individual connections in inverse proportion with the network size. In sparse networks, however, the average number of synaptic neurons is independent of network size and therefore the synaptic strengths are not scaled down.

Problems in Neural Modelling

In the past decade there has been a dramatic increase in the number of computational studies of neurons and neural networks. As the field of computational neuroscience matures, many obstacles in neural modelling need to be overcome. Later, we summarize a few such issues that modellers face today.

A significant limitation to the simulation of elaborate and detailed neural network models is computer memory and speed. There have been noteworthy approaches to resolve this limitation including algorithms developed to optimize computation speed. Examples include algorithms that calculate how to map electrical activity from complex dendritic trees to simpler structures using the rules of cable theory, or those that modify the model dynamically so as to include more or less detail as needed. A different approach is to divide the simulation to several subprocesses that can be computed in parallel, and to use multiprocessor computers. However, not every simulation can be parallelized. For example, the activity in a layer of independent units lends itself to parallelization, but this may not be the case for a different architecture such as a chain of interconnected neurons where the input to each unit depends on the output of an adjacent unit. With the technological advances in computer hardware and software, the problems of computation resources become less central in neuronal modelling. **See also**: Biological Computation

In biological systems, the behaviour is generally robust and does not change dramatically as a result of natural, biological variability or when some experimental factor such as temperature or the modulatory environment is changed. Many models, especially those that depend on a large number of variables and parameters, faithfully reproduce a given biological behaviour and yet are unrealistically sensitive to small parameter changes. One solution to this problem is to construct self-regulating models where parameter values are not static, but activity-dependent. For example, by introducing activity-dependent conductance values for the voltage-gated ionic currents networks of neurons can maintain stable activity over long periods of time despite extrinsic perturbations. In such models the maximal conductance of ionic currents are self-regulated by the neuronal activity, which is monitored, for example, by the kinetics of intracellular calcium concentration. A target of pattern of activity is defined as a set of calcium sensors differing by time scale. Any change in the neuronal activity is detected by the sensors which, in turn, adjust the maximal conductances to restore the original pattern of activity. These models are inherently robust because they automatically adjust themselves as a response to changes in activity. However, there is little direct evidence of the biological plausibility of these models.

An important and growing field of research in neuroscience is the study of mechanisms and functions of membrane and synaptic plasticity. Such studies examine the prevalent short- and long-term changes in the properties of ion channels and synaptic connections due to a variety of factors that are either built into the neuronal system or appear as a consequence of neurally or hormonaly neuromodulators. Because such plasticity changes the properties of neurons and synapses, in effect it can reconfigure the network output. Synaptic plasticity is often divided into the short- and long-term categories. Short-term synaptic plasticity refers to the use-dependent change in synaptic strength and, depending on the direction of this change, is referred to as depression or facilitation. The past decade has seen a major increase in the number of modelling studies that examine the consequences of such plasticity for network output (Markram and Tsodyks, 1996; Abbott *et al*., 1997). Much more attention has been paid though to models of long-term synaptic plasticity, referred to as long-term potentiation (LTP) and long-term depression (LTD) due to the importance of LTP and LTD in models of learning and memory. Many recent modelling studies focus on the relationship between LTP and LTD and the relative spike times in pre- and postsynaptic neurons, a phenomenon referred to as spike-timing dependent plasticity (Worgotter and Porr, 2005). Models of LTP and LTD are either empirical, ignoring the mechanisms underlying plasticity and focusing on its consequences for network output, or mechanistic, focusing on the underlying mechanisms of plasticity, especially the dependence on calcium entry and the intracellular signal transduction pathways.

A major problem faced by modellers is that often there is little or no experimental data available in order to determine the model parameters. A common solution is to use experimental data from published papers but not necessarily from

the same system. Understandably, this approach is subject to severe criticism from experimentalists. In some cases, the experimental data simply do not exist. For example, to date the exact distribution of ion channels along dendritic trees is not known, and there are few techniques for obtaining such data. In such cases modellers are forced to select parameter values in an arbitrary manner and these parameters are tuned to fit the physiological network output. This process can be extremely tedious and time consuming, especially when a large number of parameters and hence a complex set of interactions are involved. However, some techniques have been developed to automate this process. One such technique is the gradient descent method, where the gradient of a fit is computed recursively until a local minimum, or best fit, is achieved. Another method is to use an artificial neural network learning mechanism until a best match is found. A third method is the use of genetic algorithms, a method inspired by the principles of natural selection. The parameter space is viewed as a population, where each individual is assigned a fitness value according to its contribution to the desired population behaviour. Only individuals with high fitness values can reproduce, thus the population evolves and is randomly mutated from generation to generation until a best match is obtained. These methods, although quite successful as computational tools, are often met with scepticism by experimental neuroscientists. Indeed, one set of parameter values, as successful as it may be in reproducing the biological behaviour, may not be a unique solution and hence may have little relation to the biological system. Recent modelling results have involved exhaustive searches of the parameter space within a reasonable range and for a restricted set of parameters. These exhaustive searches, known as the 'brute force' method, are possible due to the increase in computing power and the innovative algorithms that automatically classify the model outcome (Prinz *et al*., 2003). Although the brute force methods provides an advantage over parameter search methods that produce local best fits, the possibility exists that this method would miss solutions of computational models in parameter domains that involve multistability or weak-attractor solutions (Ermentrout, 2002).

Summary

Computational modelling is an effective tool for quantifying biological hypotheses and provides a rigorous mathematical means to examine biological intuitions. Often, computational modelling is the most efficient means for simplifying complex systems. More importantly, a well-designed model can provide experimentally testable results and the combination of modelling and experiments provide a powerful tool for understanding biological systems. Neuronal modelling can be implemented at different levels. Depending on the question at hand, the investigator must decide which details are essential, and which details can be omitted to simplify the computational model. In some cases details are crucial for understanding the dynamics of the biological system while other questions can be answered only through careful reduction of the problem. Whether dealing with detailed or reduced models, complex or simplified models, it is important to remember that computational models should be considered a tool to help unravel the complexity of neuronal systems.

Acknowledgements

Supported by NIH MH60605 (FN).

References

Abbott LF, Varela JA, Sen K and Nelson SB (1997) Synaptic depression and cortical gain control. *Science* **275**: 220–224.

Bower JM and Beeman D (1998) *The Book of GENESIS: Exploring Realistic Neural Models with the GEneral NEural SImulation System*. Cambridge, UK: Cambridge University Press.

Brown TG (1914) On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *Journal of Physiology* **48**: 18–46.

Carnevale NT and Hines ML (2006) *The NEURON Book*. Cambridge, UK: Cambridge University Press.

Dayan P and Abbott LF (2001) *Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems*. Cambridge, MA: MIT Press.

Ermentrout B (2002) *Simulating, Analyzing, and Animating dynamical systems: A guide to XPPAUT for Researchers and Students*, 1st edn. Philadelphia, PA: Society for Industrial & Applied Mathematics.

Fitzhugh R (1961) Impulses and physiological states in theoretical models of nerve membrane. *Biophysical Journal* **1**: 445–466.

Harris KD, Csicsvari J, Hirase H, Dragoi G and Buzsaki G (2003) Organization of cell assemblies in the hippocampus. *Nature* **424**: 552–556.

Hodgkin AL and Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *Journal of Physiology* **117**: 500–544.

Izhikevich E (2006) *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting*. Cambridge, MA: MIT Press.

Lapicque L (1907) Recherches quantitatives sur l'excitation electrique des nerfs traitee comme une polarization. *Journal de Physiologie et Pathologie Général* **9**: 620–635.

Marder E (2002) Non-mammalian models for studying neural development and function. *Nature* **417**: 318–321.

Markram H and Tsodyks M (1996) Redistribution of synaptic efficacy between neocortical pyramidal neurons. *Nature* **382**: 807–810.

McCulloch WS and Pitts W (1943) A logical calculus of the ideas immanent in nervous activity. *Bulletin of Mathematical Biology* **5**: 115–133.

Nadim F, Manor Y, Nusbaum MP and Marder E (1998) Frequency regulation of a slow rhythm by a fast periodic input. *Journal of Neuroscience* **18**: 5053–5067.

Prinz AA, Billimoria CP and Marder E (2003) Alternative to hand-tuning conductance-based models: construction and analysis of databases of model neurons. *Journal of Neurophysiology* **90**: 3998–4015.

Rall W, Segev I, Rinzel J and Shepherd GM (1995) *The Theoretical Foundation of Dendritic Function: selected papers of Wilfrid Rall with commentaries*. Cambridge, MA: MIT Press.

Rinzel J and Ermentrout GB (1998) Analysis of neural excitability and oscillations. In: Koch C and Segev I (eds) *Methods in Neuronal Modeling: From Ions to Networks*, pp. 251–291. Cambridge, MA: MIT Press.

Worgotter F and Porr B (2005) Temporal sequence learning, prediction, and control: a review of different models and their relation to biological mechanisms. *Neural Computation* **17**: 245–319.

Further Reading

Johnston D and Wu SM-S (1995) *Foundations of Cellular Neurophysiology*. Cambridge, MA: MIT Press.

Koch C (1999) *Biophysics of Computation*. New York: Oxford University Press.

Koch C and Segev I (eds) (1998) *Methods in Neuronal Modeling: From Ions to Networks, Second edition*. Cambridge, MA: MIT Press.

ModelDB: A Database to Support Computational Neuroscience: http://senselab.med.yale.edu/senselab/modeldb/