Neurons and Neural Networks: Computational Models

Horacio G. Rotstein
Farzan Nadim
New Jersey Institute of Technology, USA

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Abstract

Neural networks produce electrical activity that is generated by the biophysical properties of the constituent neurons and synapses and is affected by several factors including neuromodulators and the network topology. Individual neurons produce electrical signals through processes that are highly nonlinear and communicate these signals to one another through synaptic interactions, resulting in emergent network outputs. The output of neural networks underlies behaviors in all higher animals. 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 analyzed using mathematical techniques or numerically simulated with computers. In this article, we briefly review the current mathematical and computational techniques involved in modeling neurons and neural networks.

Key Concepts

- An *action potential* is a brief nonlinear rise and fall of the membrane voltage of a cell and is the primary signal used for neural communication.
- *Excitability* is the ability of neurons and other cell types to produce action potentials when the trans-membrane voltage crosses a threshold.
- *The Hodgkin-Huxley model* is a mathematical description of how action potentials are generated in neurons and propagate along their axons.
- *The integrate-and-fire neuron* is a simplified mathematical model of excitability in neurons, useful for the ability to do mathematical analysis and used primarily in network models.
- *Bifurcation* is a mathematical term for a change in the qualitative structure of a dynamical system when a parameter value is changed.
- *Neural oscillations* are repetitive or rhythmic changes in the voltage activity of a neuron or a network of neurons. Neural oscillations may arise in individual neurons or through network synchrony.
- *Bursting* is the ability of some neurons and networks to produce periodic spiking activity followed by an interval of no activity.
- A *half-center oscillator* is a network of two neurons that produce bursting activity out of phase with one another and are a key sub-network of central pattern generators.

Introduction

The electrical activity of neural networks underlies behaviors 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 less than one, to a few, milliseconds (Hodgkin and Huxley, 1952). Action potentials are typically generated at the initial segment of the neuron's axon (known as the axon hillock) 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 (or postsynaptic) currents. These signals can facilitate (excite) or impede (inhibit) production of action potentials in the postsynaptic neuron. In the latter case, action potentials can be either delayed or suppressed. In addition to such chemically-mediated synaptic transmission, neurons can also communicate via direct electrical pathways known as gap junctions. Thus, signaling via action potentials, synapses and gap junctions results in the production of complex functional networks from otherwise disjoined neuronal activity. See also Action Potentials: Generation and Propagation, Neural Networks and Behaviour, and Synapses

Neurons produce action potentials, or fire, when integrated inputs to the neuron reach a voltage 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 far from understanding exactly how a variety of behaviors emerges from the operations of neuronal networks within the nervous system and through interactions with the body as a whole. One major obstacle towards a detailed understanding is that behaviors often emerge from the interaction of thousands or more neurons, each with complex and detailed anatomical, biophysical and biochemical structure. Individual parameters such as single ion 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, and 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 the 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 sub-cellular, cellular and network levels. Here we review the important approaches in neural modeling at various levels of organization (Koch, 2004; Izhikevich, 2007; Ermentrout and Terman, 2010a; Ermentrout and Terman, 2010b; Gabbiani and Cox, 2017; Miller, 2018; Borgers, 2017).

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" and their extensions (e.g., Runge-Kutta methods). Such algorithms can be implemented in

many standard programming languages like Fortran or C as well as higher-level languages such as Python or MATLAB. Alternatively, a variety of software packages are available that can be used to numerically solve systems of differential equations in general, such as XPPAUT www.math.pitt.edu/~bard/xpp/xpp.html (Ermentrout, 2002), or are specialized for solving neuronal models, such as GENESIS genesis-sim.org (Bower and Beeman, 1998), NEURON www.neuron.yale.edu/neuron/ (Carnevale and Hines, 2006) or BRIAN briansimulator.org (Goodman and Brette, 2008).

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 modeled as a "single compartment" or a "point neuron." An isopotential neuron can be electrically represented by an equivalent circuit of parallel branches connecting the inside (IN) and outside (OUT) of the cytoplasmic membrane (Fig. 1A). The OUT node is often assumed to be at zero potential (grounded). In such a circuit, one branch includes the membrane capacitor and the others, each, represent a different ionic current as a resistor –representing the conductance of the ion channels, in series with a battery –representing by the Nernst equilibrium potential as an electromotive force. The electromotive forces capture the metabolic processes that provide the necessary energy to maintain the neuron's resting potential. Additional parallel branches may be included to represent ion transporters such as the sodium-potassium exchange pump. Mathematically, these models involve a system of coupled nonlinear ordinary differential equations (ODEs).

If isopotentiality cannot be assumed, then the neuron's spatial distribution must be taken into account, resulting in multi-compartmental models describe by higher-dimensional systems of ODEs. In such models, the soma, dendrites and axon are spatially separated into multiple isopotential compartments that are electrically connected. In this case too, an equivalent circuit can be used to represent a multi-compartment model. Such an equivalent circuit is represented by a series of single-compartment circuits as described above (Fig. 1B), connected in a chain by a set of resistors (conductors) connecting the IN nodes (representing the intracellular conductance) and another chain connecting the OUT nodes (representing the extracellular conductance). As with single-compartment models, the extracellular conductance, however, is often assumed to be infinite and the OUT nodes are all grounded.

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, and Oscillatory Neural Networks

Conductance-based neuron models

The currently-accepted view of how neurons produce action potentials was described in terms of ionic mechanisms by Hodgkin and Huxley in the 1950's (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 unknown at that time, 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 (Catterall et al., 2012). See also Action Potential: Ionic Mechanisms, Axons, Hodgkin, Alan Lloyd, Huxley, Andrew Fielding , Sodium Channels, and Voltage-gated Potassium Channels

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) constant (DC) current (*I*) (Izhikevich, 2006; Ermentrout and Terman, 2010a). 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 non-zero value as the applied current is increased. In contrast, some neural models describe the behavior of *Type I* neurons, where *f* is a continuous function of *I* and therefore the firing frequency can be arbitrarily small. See also Repetitive Action Potential Firing

This classification of neural excitability reflects differences in the underlying dynamic mechanisms that govern the transition from rest to persistent spiking that can be described in terms of bifurcation phenomena. A bifurcation is a structural transition of a dynamical system from one qualitative state to another, for example from quiescent to oscillatory or from monostable to bistble, by changing a parameter of the system. A set of mathematical tools known as bifurcation theory allows one to characterize analytically the behavior of a system in the vicinity bifurcation points. Bifurcation theory is a powerful tool to gain insight into the dynamics of low-dimensional neuronal systems. For Type II neurons excitability occurs primarily through an *Andronov-Hopf bifurcation*, while the *saddle-node in an invariant circle (SNIC) bifurcation* underlies excitability for 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 behavior of the biological neuron.

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 a variety of other ion channel currents which are not present in the squid giant axon but are commonly found in other neuron types. These ionic currents include currents that are activated in subthreshold voltage ranges close to the resting potential (the membrane voltage in the absence of any input) and contribute to the generation of small-amplitude membrane potential (sub-threshold) oscillations and to resonance properties (maximum impedance and zero-phase response at a preferred frequency of input current). Other types of ionic current 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 producing various characteristic inter-spike time intervals or bursting activity (aggregated action potential firing separated by intervals of quiescence.)

There has been a concerted effort over the years to identify and characterize the properties of bursting neurons in various systems. In parallel, there is a large literature documenting various models that exhibit bursting. One interest in the community of modelers is to classify neurons based on the type of dynamics they exhibit as a result of intrinsic properties or in response to external current injection. The most complete classification of bursting is due to Izhikevich who proposed over 100 different types of bursting in an individual cell and related different characteristics of individual bursters to the different types of bifurcations that gave rise to oscillations (Izhikevich, 2000). This work built on the earlier work of others including Rinzel (Rinzel, 1987)who first classified square, elliptic and parabolic bursters.

Spatial structure of neurons

All neurons have complex anatomical structures that include elongated axons and ramified dendritic trees. The assumption of isopotentiality of neurons greatly simplifies the construction and analysis of models and, for some modeling 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 19th 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. It assumes isopotentiality in the radial, but not in the axial direction. 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.

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 modeling. In a compartmental model, the model cell is broken down into short isopotential segments, or compartments, that are electrically connected to their neighboring segments with simple voltage conductors. As mentioned above, this structure can be represented by an equivalent electrical circuit in which the inter-segmental conductors account for the intracellular conductivity of the neuron. The compartmentalization of the neuron thus produces a finite number of coupled sets of ODEs (one set per compartment) 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. The spatial resolution used in compartmental modeling (i.e., the number of compartments in the model) must be determined by the modeling 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 modeling 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 two or a handful of compartments without loss of its essential behaviors. The two compartments are often 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. Mathematically, multicompartment models can be seen as a discretization of the more realistic models using partial differential equations, where the partition of the spatial variable is not necessarily very small as required for an accurate discretization. See also Dendrites and Dendritic Spines

In addition to the role of the detailed neuronal structures in the passive spread of electrical signals, such structures are often involved actively in propagating signals across long distances. The most important instance of active signal propagation is the propagation of action potentials along axons. The original set of papers by Hodgkin and Huxley provided a mathematical description of action potential propagation in the squid giant axon, based on a nonlinear version of the cable equation. This model, in its general form, remains the accepted description of action potential propagation in unmyelinated axons. A number of mathematical techniques have been used to analyze action potential propagation in unmyelinated axons, including methods that describe the propagation of the wave front by reducing conductance-based partial differential equations to ordinary differential equations to analyze propagation using dynamical systems tools. Conductance based models have also been developed to examine the so-called saltatory conduction along myelinated axons. Detailed descriptions of action potential propagation, however, are usually done through compartmental modeling. In some cases, an explicit model of an axon is not necessary and the main contribution of an axon is considered to be to produce a delay between the generation of an action potential and the time at which synaptic communication occurs. In this case, a simplifying assumption is made to represent the axon as a simple delay line.

Low-dimensional biophysical models

Biophysical neural models are described as a group of coupled nonlinear differential equations. With advances in the geometrical analysis of differential equations, a multitude of geometrical tools is available for analyzing the behavior of these models. In particular, solution trajectories of the model neuron can be visualized in the phase space diagrams. The dimensionality of the phase space is equal to the number of state variables 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 1960's two mathematicians, Fitzhugh and Nagumo, independently produced a qualitative reduction of the original Hodgkin and Huxley neuron (a four-variable model) to two dimensions (i.e., two variables) (Fitzhugh, 1961; Nagumo and Yoshizawa, 1962). The Fitzhugh-Nagumo model is not a formal reduction of the Hodgkin-Huxley model but was developed, based on the principles of electrical oscillators, in order to describe the phenomenon of excitability in the larger model. Such simplified models are often referred to as reduced or caricature models. More systematic reductions of the Hodgkin-Huxley model to two-dimensional models that have the same type of behavior were later produced by other authors (Rinzel, 1985).

In a two-dimensional model of spiking activity, 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 describing the autocatalytic process that gives rise to the action potential and the slower negative feedback effect terminating it. The latter is typically the potassium inactivation gating variable. The geometrical representation of the neuronal model is useful for analyzing the behavior of the model neuron in various parameter regimes and in response to various stimuli (Rinzel and Ermentrout, 1998; Izhikevich, 2006). 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.

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 (fast) activation of sodium channels as compared to the (slow) activation of potassium channels or inactivation of sodium channels in the Hodgkin-Huxley model. Higher dimensional systems are not necessarily reducible to just two equations. Simple examples are single cell models involving ionic currents other than the standard fast sodium and delayed-rectifier potassium current of the Hodgkin-Huxley model, 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 might still be possible to reduce the dimensionality of the models without changing their qualitative output. In the former case, the neuron’s inter-spike interval can be divided into subintervals, or regimes, inside which lower dimensional models can be derived for the appropriate voltage ranges. 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 (e.g., the spiking voltage regime where only two ionic currents, transient sodium and delayed-rectifier potassium, are

active) . 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 sub-systems can be analyzed separately. The solutions of the sub-systems are then pieced together using the methods of singular perturbation theory to build solutions to the full system.

Simplified models of neurons

One common modeling simplification in the analysis of spiking activity is done by ignoring the biophysical details of action potentials and instead focusing on (simplified) mechanisms through which the spikes are generated. These mechanisms typically operate in the subthreshold voltage regime (close to the resting membrane potential). To do such analyses, 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 and, in some cases, can be derived from them as described above. 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 (usually linear) differential equation. When the membrane potential reaches a certain threshold, the neuron is considered to produce 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 the subthreshold voltage change. Integrate-and-fire models have been generalized to describe some basic nonlinear behaviors, such as refractory periods, nonlinear *f-I* curves, linear and nonlinear subthreshold oscillations, and resonance. These generalizations involve *ad hoc* nonlinearities in the subthreshold dynamics, such as in the so-called quadratic and exponential integrate-and-fire models, or the addition of appropriate subthreshold currents to the leaky integrate-and-fire model. Depending on the type of nonlinearity, the onset of a spike can be described by the subthreshold component of the model and the voltage threshold simply indicates the occurrence of a spike, as opposed to be the mechanisms of spike generation as in the classic leaky integrate-and-fire models.

For some questions related to the oscillatory behavior 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 and the transient dynamics. 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 dynamics in the subthreshold voltage regime.

"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 fundamental property 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 modeling and analyzing large-scale networks (see below). However, in general modelers who 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, post-inhibitory 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. Classical couplings include chemical synapses that can be either spike-mediated or graded. Coupling between neurons can also be mediated through direct connections via gap-junctions; this type of connection is usually referred to as electrical coupling (Fig. 2). 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 modeled 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 modeled using kinetic equations similar to these used for voltage-gated ion channels. Chemical synapses can be excitatory or inhibitory depending on whether the synaptic current facilitates or impedes the production of postsynaptic action potentials. Inhibitory synapses delay or suppress the occurrence of 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 modeling 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) which 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. Synaptic facilitation can be modeled in an analogous way. See also Synaptic Plasticity: Short Term

One simple network that has been comprehensively analyzed using computational and mathematical tools is the network of two cells that are reciprocally connected by inhibitory synapses (Fig. 2A). When the two cells in this reciprocally inhibitory network are active (e.g., oscillating or spiking) in alternation, the circuit is referred to as a half-center oscillator (Brown, 1914). A general classical framework to study half-center 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. 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 non-standard currents. Neurons need not be sustained oscillators in order for the network to generate anti-phase or in-phase oscillations. In fact, inhibitory networks of damped oscillators or non-oscillatory resonators can produce half-center oscillations. Similarly, excitatory networks of non-oscillatory resonators can produce in-phase oscillations. Resonators have the property of exhibiting a peak in their amplitude voltage response to oscillatory input currents at a characteristic frequency and need not be damped oscillators. See also Central Pattern Generators, and Oscillatory Neural Networks

A number of modeling studies have examined networks of neurons connected with mutually excitatory synapses (Fig. 2B). Mutual excitation of active neurons leads to destabilization. Modeling work has 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, modeling studies have demonstrated that mutual excitation may lead to more complex network behavior. 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 behavior. Electrical coupling between two neurons act to equalize their membrane potentials (Fig. 2C). Thus, intuitively, electrical coupling is a way to synchronize the activity of the two cells. Modeling 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 behavior of the two-cell network can be completely different from that of either neuron. An example would be coupling two quiescent neurons 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 those in the buccal ganglion in Aplysia or the stomatogastric ganglion in crustaceans, often have a small number of neurons that range from several to tens of cells and, therefore, the properties and connectivity in these networks is often readily described. Although these invertebrate networks can produce a rich repertoire of activities, the network function is generally well-defined and in most cases can be directly related to behavior (Marder, 2002). The close association with behavior provides small networks with an immense advantage over very large cortical networks that are often only loosely correlated with behavior. These advantages in a small neuronal network enable the construction of a realistic synaptic connectivity (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 modeled with conventional numerical integration techniques. Because small networks have the advantage that the neural circuitry can be identified both anatomically and physiologically, computation models that describe neuromodulatory effects on small neuronal networks have provided 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 above, 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, and 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 (synchrony), 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, and Neural Activity and the Development of Brain Circuits

One approach to study large neural networks is to reduce the network size. 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 behaviors 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 modeling in which network models are designed using a "bottom-up" scheme. In realistic large-network models single neurons belonging to the same type are modeled 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. Modelers 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. See also Biological Computation

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 synchrony 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, on the other hand, the

average number of synaptic neurons is independent of network size and therefore the synaptic strengths are not scaled down.

The interaction between excitatory and inhibitory synaptic activity plays an important role in neuronal network computations. Of particular interest are the so-called *E-I balanced networks* where the ratio between the strength of excitation and inhibition is constant over certain amount of time and across a range of experimental conditions both *in vitro* and *in vivo*. These include network responses to external stimuli and spontaneous, intrinsically generated network activity as in cortical up states. Because there are typically more excitatory than inhibitory neurons and the time courses of synaptic excitation and inhibition have different time scales, balanced network activity is expected to be maintained by different mechanisms in different brain areas or experimental conditions. Different types of computational models have been used to understand the properties of balanced networks (Vogels et al., 2005). Early work was carried out using firing rate network models where the sum of the input currents (external and synaptic) are translated into firing rates, which evolve with time according to a first order kinetic equation with a characteristic time constant. These models account for the interaction between excitation and inhibition, but do not take into account the time dependence of these currents or the effects of the intrinsic currents of the participating neurons. The latter has been achieved using conductance-based network models.
In the study of neural oscillators with any type of synaptic or electrical coupling, a general mathematical formalism has been developed to examine the activity phase of the neurons or sub-networks. This formalism, known as the theory of weakly-coupled oscillators, is based on the assumption that the interactions among neurons or sub-networks is weak and makes use of the Averaging Theorem for time-periodic differential equations, which states that when the interactions between coupled oscillators is weak, this interaction can be described by its mean value, averaged over a cycle period (Kopell and Ermentrout, 2002). The theory of weakly coupled oscillators has provided insight into network synchrony and phase locking underlying the oscillatory activities in the brain and the spinal cord .

Problems in Neural Modeling

In the past decades 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 modeling need to be overcome. Below, we summarize a few such issues that modelers 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 sub-processes 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 modeling.

Biological systems show stability and homeostasis: the behavior 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 behavior 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 neural or hormonal 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-term 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 modeling studies that examine the consequences of such plasticity for network output. 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 modeling 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. See also Long-term Depression and Depotentiation, and Long-term Potentiation

A major problem faced by modelers 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 modelers 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 behavior. 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 skepticism by experimental neuroscientists. Indeed, one set of parameter values, as successful as it may be in reproducing the biological behavior, may not be a unique solution and hence may have little relation to the biological system. Recent modeling 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 multi-stability or weak-attractor solutions (Ermentrout, 2002).

Fitting models to experimental data requires developing efficient parameter estimations tools. Different methods exist for fitting model equations to data (e.g., genetic algorithms, maximum likelihood estimation). One major problem that arises, independently of the technique used, is that of unidentifiability or degeneracy: multiple sets of model parameter values that produce the same observable output, therefore making the inverse problem of finding parameters from data ill-posed. This is not a problem associated with scarcity of data, uncertainty, or the noise present in data, but a structural problem of mathematical models. Therefore, tools need to be developed to overcome these difficulties. These tools are likely to involve combined experimental and computational approaches that also account for responses to perturbations.

Summary

Computational modeling is an effective tool for quantifying biological hypotheses and provides a rigorous mathematical means to examine biological intuitions. Often, computational modeling is the most efficient means for simplifying complex systems. More importantly, a well-designed model can provide experimentally-testable results and the combination of modeling and experiments provide a powerful tool for understanding biological systems. Neuronal modeling 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.

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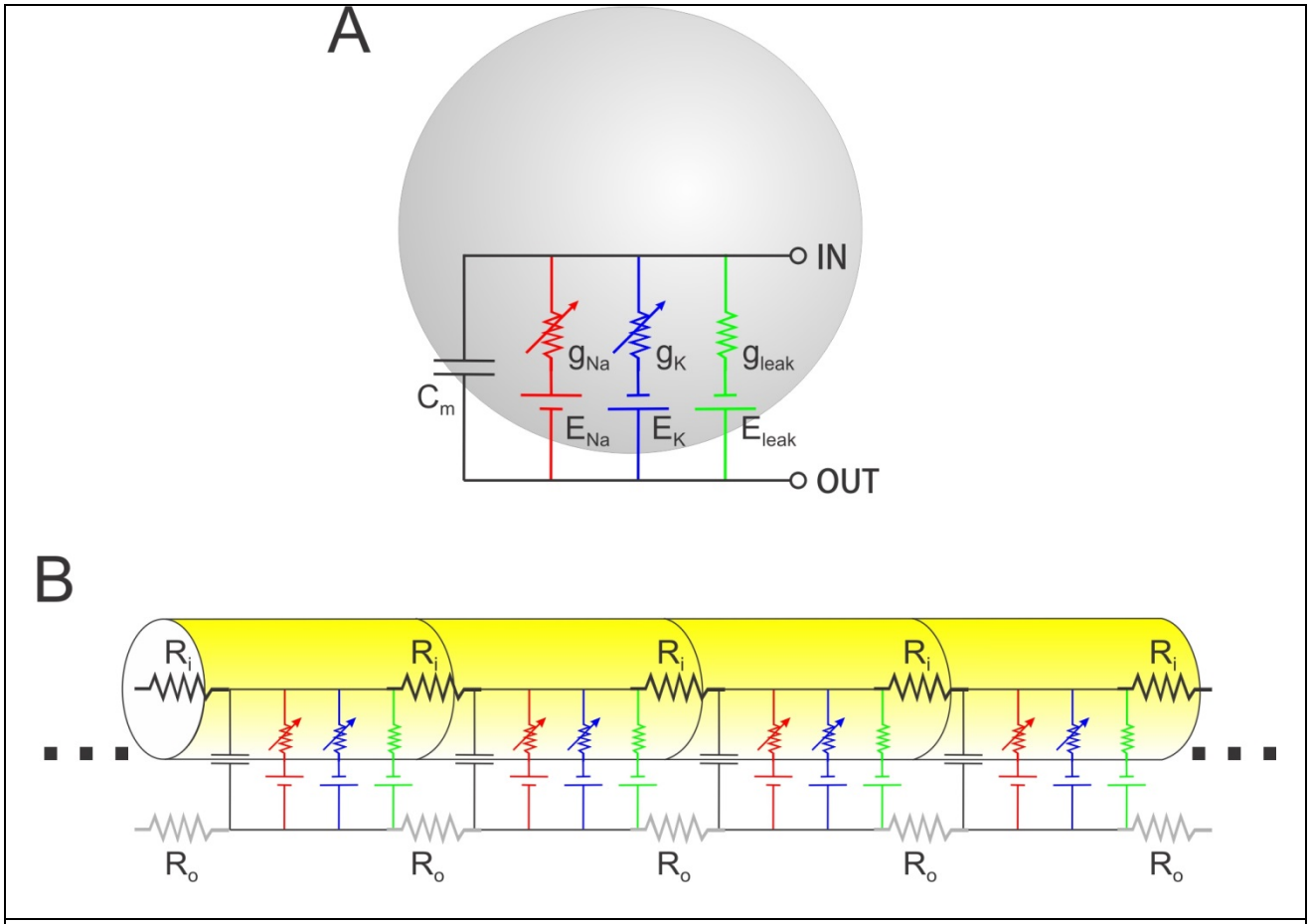

Figure 1. Equivalent circuits of neural models. (A) Circuit diagram for a single-compartment neuron representing ionic currents of the Hodgkin-Huxley model. C_m is the membrane capacitance, Resistor symbols indicate ionic conductance (with arrows show varying conductances). Batteries represent the Nernst equilibrium potential for sodium (Na) and potassium (K) and the reversal potential of the passive leak current. (B) The equivalent circuit for a compartmental model, representing a uniform cable such as an axon. Each compartment is represented with the equivalent circuit as in panel A. The circuits representing each compartment are coupled through resistors representing the intracellular resistance (R_i) and the extracellular resistance (R_o). Ellipses indicate that the cable continues in both directions.

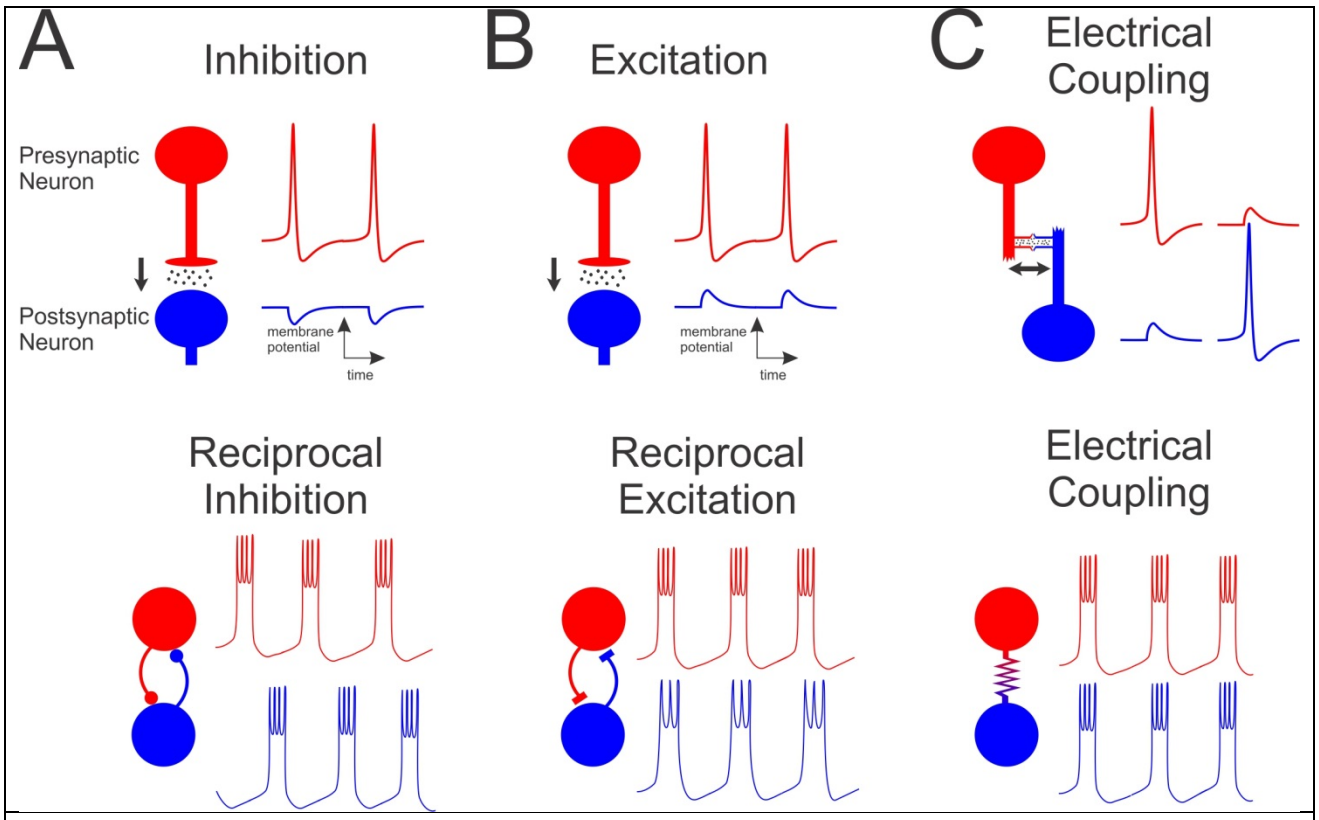

Figure 2. Some common models of two-cell networks. (A) Top: Synaptic inhibition is due to the release of a neurotransmitter that moves the postsynaptic membrane potential away from action potential threshold. Bottom: Two cells that are reciprocally coupled by synaptic inhibition can produce out-of-phase oscillatory activity (half-center oscillation). (B) Top: Synaptic excitation is caused by a neurotransmitter that moves the postsynaptic membrane potential toward action potential threshold. Bottom: Two cells coupled with reciprocal excitation can oscillate in phase but the action potentials are not necessarily time-locked. (C) Top: 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. Bottom: Electrically coupled cells typically demonstrate synchronous activity, which may be oscillatory even if the two cells are not rhythmically active in isolation.