Biophysical Mosaic of the Neuron

Lyle J. Graham and Raymond T. Kado

Introduction

In this article we broadly review the biophysical mechanisms of neurons that are likely to be relevant to computational function (Table 1). These mechanisms operate within the complex three-dimensional anatomy of the single neuron and are manifested by electrical and chemical interactions between ions on either side of the cell membrane and the diverse proteins and other molecules embedded in the membrane and within the cytoplasm (Figure 1). The signals mediating these interactions may be defined by the voltage across the cell membrane or by concentrations of specific molecules in specific conformational or metabolic states. The first case relies on the voltage sensitivity of various membrane proteins; the second relies on a vast multitude of receptor proteins that link the functional state of neuronal proteins with the external or internal concentrations of ions and molecules.

It may be noted that none of these cellular mechanisms is unique to neurons. For example, essentially all the mechanisms discussed in this article may be relevant when considering a possible computational role of the neuroglia network (Laming et al., 2000). By the same token, neurons (and glial cells) include the essential mosaic of biochemical systems found in all cells required for metabolism, reproduction, growth, and repair. The complexity is daunting. Here we focus on the better-known elements most clearly linked to the reception, processing, and transmission of neuronally represented information. It may seem that there are so many such elements, and an even larger number of unknown relationships, that it would not be possible for a model to take all of the actual dynamic behaviors into consideration. Nevertheless, it also seems likely that an oversimplification of these interactions—for example, in the extreme case by describing single neuron function as an abstracted trigger device—may put fundamental limits to the explanatory and predictive power of any neural model. The challenge remains, then, to develop a description of single neuron function that can serve as the foundation for a practical yet sufficient neural theory.

We start with a metaphor, the mosaic neuron. A *mosaic* is a collection of discrete parts, each with unique properties, fitted together in such a way that an image emerges from the whole in a nonobvious way. Similarly, the neuronal membrane is packed with a diversity of receptors and ion channels and other proteins with a recognizable distribution. In addition, the cytoplasm is not just water with ions, but a mosaic of interacting molecular systems that can directly affect the functional properties of membrane proteins. Whether for the developing or for the mature neuron, this mosaic is not stationary. To begin with, neuronal proteins are constantly recycled, as is the case for all cells. Furthermore, on both long and short time scales, most mechanistic theories for learning and memory implicate physical changes in various cellular constituents. On time scales of seconds or less, different signaling systems impinging on the neuron from the network or present in the cytoplasm can modify the properties of the mosaic elements, and in some cases their distribution within the cell (see ACTIVITY-DEPENDENT REGULATION OF NEURONAL CONDUCTANCES). Thus, just as a mosaic painting provokes perception of a complete image out of a maze of individually diversified tiles, current thinking holds that a given neuron performs a well-defined computational role that depends not only on the network of cells in which it is embedded but also to a large extent on the dynamic distribution of macromolecules throughout the cell.

The Minimal Essential Model and the Biophysical Mosaic

It remains an open question as to what constitutes a minimal neuron

model for reproducing functional neuronal computation (Meunier and Segev, 2000; see also CANONICAL NEURAL MODELS). This is in part because to date, only a handful of neuron circuit models come close to predicting known experimental data in any nontrivial way. The question of finding a minimal model is hardly an academic one, as can be appreciated by reviewing the dimensionality of the mosaic neuron (Table 2).

Whatever the minimal essential model turns out to be, a detailed knowledge of neuronal biophysics is most likely necessary for understanding the system behavior (even if this understanding is not sufficient). The clearest evidence for this point of view comes from psychopharmacology: although we lack a clear understanding of the mechanisms, we know that adding certain chemicals to the brain parenchyma can qualitatively alter cognitive behavior. We know that the direct action of psychotropic drugs is probably to change one or more biophysical properties at the microscopic cellular level, such as blocking an ion channel, altering the binding kinetics of a receptor, modulating a biochemical pathway, and so on, rather than acting at a more macroscropic systems level, such as cleanly disconnecting a circumscribed subcircuit from the entire network. We know that physical access to the brain is necessary for this action (preventing a drug from crossing the blood-brain barrier eliminates its effect), and we also know, in many cases, that some neurons have highly specific membrane receptors for a given psychotropic molecule that are often localized in very restricted areas at the level of brain substructures and even at the single-cell level. Often there is direct evidence of a drug's effect in electrophysiological measurements of single cells, when a change in intrinsic response properties or synaptic dynamics is seen after a given chemical is added to the fluid bathing the nervous tissue.

The Mosaic's Tiles

We will now review the major proteins that compose the neuron mosaic and discuss some basic implications of their diversity and complexity. These macromolecules include ion channels, receptors (described along with the molecules that activate them), enzymes, gap junctions, pumps, exchangers, and transporters. Note that these classifications can sometimes overlap. For example, an ionotopic receptor is a protein multimer that includes both a receptor part and a channel part.

Several texts may be consulted for more detail on these mechanisms (Johnston and Wu, 1995; Weiss, 1996; Koch and Segev, 1998; Fain, 1999; Hille, 2002). In particular, the textbook by Koch (1999) provides an explicit foundation for the computation/algorithm/implementation trinity that is fundamental for understanding brain function.

Ion Channels

Ion channels are membrane-spanning proteins that, owing to their conformational states, which allow the passage of ionic current, are the primary basis for the dynamical electrical behavior of neurons (see ION CHANNELS: KEYS TO NEURONAL SPECIALIZATION). The permeability of the conducting states and the kinetics governing state transitions (generally referred to as channel gating) can be affected by a variety of factors, principally the membrane voltage and the intra- and extracellular concentrations of the permeable ions and other specific molecules. Sensitivity to extracellular molecules is generally mediated by either direct action on the channel or various receptor proteins (e.g., in response to neurotransmitters), as discussed below. Molecules that affect channel gating from the inside include second messengers. The kinetic relationship between membrane voltage, the concentration of neurotransmitters, second messengers, and a channel's conductance state can be quite complex, a point we return to later.

Since channels are the most direct mechanism determining the basic firing properties of the cell (e.g., regular adapting, bursting, fast spiking), and since channels are subject to functional modulation on a variety of time scales, it is not surprising that a given neuron can exhibit more than one "stereotypical" firing behavior, depending on the conditions (see NEOCORTEX: BASIC NEURON TYPES).

Receptors and Their Agonists and Antagonists: Neurotransmitters, Neuromodulators, Neurohormones, and Second Messengers

Receptors are membrane proteins whose functional action is triggered by the reversible binding of specific molecules called ligands (Cooper, Bloom, and Roth, 1996; see NMDA RECEPTORS: SYNAPTIC, CELLULAR, AND NETWORK MODELS). A given molecule may be a ligand for more than one kind of receptor, with very different or even opposite functional effects; likewise, a given receptor may be able to be activated by more than one endogenous (or artificial, that is, experimental or pharmaceutical) ligand. A ligand that tends to upregulate the functional activity of a receptor protein is called an agonist for that receptor. Conversely, antagonists are molecules that inhibit the activity of a receptor.

There are two basic types of receptors, ionotropic and metabotropic. Ionotropic receptors are directly associated with an ion channel whose gating is controlled by the presence of the receptor agonist. The action of metabotropic receptors is more complex: upon binding to an agonist, these receptors activate a G protein (so named because their action involves the conversion between guanosine diphosphate and guanosine triphosphate), which may directly control channel gating or may initiate a biochemical cascade mediated by second messengers. The end point of this "chain reaction" can be, for example, the opening of a channel, or the phosphorylation of a receptor by the activation of a kinase.

Agonists are properly called neurotransmitters when released by the presynaptic terminal of an axon (or possibly a dendrite) arising from another neuron (see NEOCORTEX: CHEMICAL AND ELECTRICAL SYNAPSES). Extracellular agonists also include neuromodulators and neurohormones, with the latter distributed through the vasculature as well as the perineuronal space (see NEUROMODULATION IN MAMMALIAN NERVOUS SYSTEMS and NEUROMODULATION IN INVERTEBRATE NERVOUS SYSTEMS). From a functional viewpoint, the main difference between these agonists and neurotransmitters is that neurotransmitters generally mediate synaptic communication between two specific pre- and postsynaptic cells, whereas the release of a neuromodulator or neurohormone into the extracellular space mediates *pancrinic* transmission, affecting a local region of tissue rather than a single postsynaptic site. Another, somewhat arbitrary, difference is that neuromodulators and neurohormones tend not to overtly excite or inhibit their targets, but rather shape the response of a neuron to classical synaptic transmitters in various and subtle ways (Kaczmarek and Levitan, 1987). Note that a given molecule can be assigned more than one of these roles (e.g., neurotransmitter versus neuromodulator), depending on the cell type or region in the nervous system.

Intracellular second messengers are called such because their concentration is often subsequent to the message delivered by neurotransmitters (e.g., after activation of a metabotopic receptor). Second messengers may have direct actions or, as mentioned, may participate in more complicated reaction schemes. Depending on the complexity of the reaction, the functional action of second messengers can be quite delayed and last for minutes if not longer. In addition, the more complicated the biochemical cascade, the more opportunities there are for interactions with modulatory pathways.

The most well-known second messenger is the Ca^{2+} ion, which modulates various membrane channels and biochemical cascades, including many neurotransmitter release systems, and whose intracellular concentration is mediated by a variety of Ca^{2+}-permeable channels, pumps, buffers, and intracellular stores (involving as well the extensive endoplasmic recticulum network, which may support regenerative intracellular Ca^{2+} waves [Berridge, 1998]).

There is a vast array of receptor types, some of which are associated with classical point-to-point synaptic transmission, others that mediate pancrinic transmission, and still others that function as links along intracellar pathways. Presynaptic membrane may also express extracellular receptors whose agonist is either the transmitter released by the same terminal (and thus implementing an immediate feedback loop) or another substance, which then may modulate the presynaptic terminal properties. A given neuron may

express many different types of receptors in response to the signaling molecules released from other cells, normally in a nonuniform distribution over its surface. In contrast, the number of neuroactive compounds that a single neuron releases itself is usually one, probably (according to current knowledge) at most two or three.

Enzymes

Among the wide variety of enzymes distributed in the neuron's cytoplasm, the most important types for signal processing include kinases and phosphatases, as well as those involved in the metabolism of signaling molecules (e.g., synthases and lipases). The kinases and phosphatases respectively phosphorylate (add a phosphate group) and dephosphorylate specific target proteins, as a result modifying the functional properties of the target. This is the most common mechanism of regulating the activity of neuronal proteins, for example, by altering the responsiveness of a receptor to an agonist, or the voltage dependency or conductance of an ion channel.

Gap Junctions

Gap junctions are membrane proteins that form a direct electrical path between two neurons, essentially as a nonlinear, nonselective ion channel (see NEOCORTEX: CHEMICAL AND ELECTRICAL SYNAPSES). Thus, on the one hand, these connections are like conventional synapses in that they mediate information flow from cell to cell, but on the other hand, they are quite unlike conventional synapses in that this flow is (more or less) reciprocal and instantaneous. As with essentially all the other neuronal elements, gap junctions can be functionally modulated, typically by Ca^{2+} or other second messengers.

Pumps, Exchangers, and Transporters

Pumps, exchangers, and transporters are membrane proteins responsible for the active maintenance of concentration gradients of different ions and molecules crucial for neural signal processing, and thus are able to modify the membrane potential, either directly or indirectly.

For example, the enzyme Na/K ATPase maintains the characteristic Na^+ and K^+ gradients across all cell membranes; related proteins include the calcium and proton pumps. The action of these pumps depends on the hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), and thus they are tightly coupled to the metabolic machinery of the neuron. Since these cations directly or indirectly contribute to the membrane potential, and since the kinetics of the pump can be modulated, a pump can set the neuron's long-term electrical behavior.

In addition to driving channel currents, the Na^+ and K^+ gradients across the cell membrane also provide the energy for exchangers and transporters. Exchanger proteins move ions such as Ca^{2+} and protons out of the neuron, against their gradients, in exchange for Na^+ moving down its gradient. The exchangers react faster than pumps and thus provide early protection against excessive accumulation of various ions. Transporter proteins move molecules such as glutamate and GABA (respectively the principal excitatory and inhibitory neurotransmitters in the central nervous system) back into the neuron (and into surrounding glia as well) after being released into the extracellular space during synaptic transmission.

The activity of some of these proteins is electrogenic. For example, the Na/K pump cycles two K^+ ions in for three Na^+ ions out, and therefore directly generates a net outward current that can cause a hyperpolarization of many millivolts, depending on conditions. Although not always inherently electrogenic, there is an indirect link between the activity of exchangers and transporters and the membrane potential. Since they are driven by the inward movement of Na^+, an increase in exchanger or transporter activity leads to an increase in the cytoplasmic concentration of Na^+, which will then be countered by increased Na/K ATPase activity and its attendent electrogenic effect.

Implications of Neuronal Macromolecule Diversity and Complexity

Channels, receptors, pumps, enzymes, and so on are comprised of one or several individual proteins, called subunits, each of which is coded by a specific gene. For any given type of channel (etc.) there may be many variations of the complete ensemble, or *multimer*, as one subunit substitutes for another, which often imparts different peculiarities to the functional properties of the multimeric protein (binding sites, effect on kinetics, etc—in fact, the same sort of properties that may be affected by protein phosphorylation). Thus, a particular Ca^{2+} channel type, for example, may have ten or so identified variants or subtypes (with the strong likelihood that more remain to be discovered). There are as yet but few demonstrations, either by explicit functional studies or by model prediction, that these differences between subtypes are relevant for neural computation. Nevertheless, correlations are increasingly being found between particular disease states and subtle functional alterations of cellular elements, or, in the opposite sense, functional (e.g., behavioral) expressions of genetic manipulation (e.g., knockout) protocols. Thus, the reality of subtype diversity suggests an important limitation for models that employ a single stereotypical kinetic model of a given type of neural protein.

Subunit substitution in a receptor, channel, or other neural protein can, among other things, determine different endogenous modulatory agonists or antagonists. Since there are many candidates for pancrinic pathways at most neurons, this mechanism is important for understanding circuitry dynamics in the intact brain. This functional diversity also has extremely important implications for clinical pharmacology: different subunits can also impart sensitivities to different exogenous compounds, allowing the eventual possibility of targeting very specific synapses or other cellular elements with the appropriately chosen (or designed) drug.

Individual proteins are comprised of contorted chains of thousands of amino acids. This fundamental complexity allows for, in principle, several mechanisms by which a protein may be influenced by its local environment. Thus, there may be an important location dependence of the functional properties of a particular kind of protein, reflecting subtle variations in the protein's microenvironment. For the same reason, it is not surprising that the behavior of a channel, for example, may be modified by the membrane voltage or by binding with a signaling molecule. In this context, we may note that quantitative experimental measurements of a given channel or receptor type in different cell types are inevitably different, beyond what would be expected from experimental variability. Sometimes such differences are seen even between different locations of a single cell type (in particular somatic versus dendritic). Thus, there are at least two possible explanations for such differences: they may be intrinsic to the neural protein under investigation (i.e., a difference in subunit composition), or they may reflect how different local environments, specific to different cell types or location within a single cell, can influence the protein's behavior.

Neuron Models and the Biophysical Mosaic

We now return to the question of neuron models and how they might relate to cellular details. In the most general sense, a single neuron provides a dynamic mapping from a spatiotemporal pattern of pulsed inputs impinging on its dendrites and soma, into a single sequence of output spikes at the axon hillock, which may then be further altered by distinct mechanisms in the axonal tree and presynaptic boutons. Overall, the neuron models employed by theorists describe the time-varying three-dimensional biophysical mosaic underlying this complex signal processing to varying degrees (see PERSPECTIVE ON NEURON MODEL COMPLEXITY and SINGLE-CELL MODELS).

At the simplest level, an extreme abstract model might be a point integrator whose output is passed through a static sigmoid transfer function, where the scalar output is analogous to the firing rate of a spiking neuron. Here the biophysical basis is essentially limited to the resistive nature of the neuron membrane and the spike thresh-

old. As a next step, the basic temporal characteristics of neuronal function may be represented by a leaky integrate-and-fire model that captures the resistive-capacitive nature of the neuron membrane and the action potential–based point process communication between neurons (see INTEGRATE-AND-FIRE NEURONS AND NETWORKS). Among other things, this scheme allows for encoding by both firing rate and higher-order statistics of spike trains, as well as a more tractable analysis of generalized stochastic mechanisms (see ADAPTIVE SPIKE CODING, RATE CODING AND SIGNAL PROCESSING, and SENSORY CODING AND INFORMATION TRANSMISSION).

A more explicit description of biophysical mechanisms might start with the characteristics of membrane channels and dendritic cables (see DENDRITIC PROCESSING). For example, a single neuron model may include transmitter-gated synaptic conductance inputs distributed on a linear (or "passive") cable tree topology, with conductance-based (i.e., voltage-dependent channels) spike generation at a central somatic node. An anatomically based dendritic cable structure provides an explicit basis for synaptic weights via different coupling impedances to the soma, as well as cable-dependent (e.g., "on-the-path") nonlinear synaptic interactions. Simple channel models can capture basic spike firing properties such as absolute and relative refractory period, adaptation, or nonzero minimum firing rates.

A model with increased biophysical realism could include voltage-dependent membrane properties distributed throughout the cell (Stuart, Spruston, and Häusser, 1999; see DENDRITIC PROCESSING). Intrinsic and synaptic mechanisms can be modeled with less or more sophisticated kinetic descriptions, either deterministic or stochastic (see TEMPORAL DYNAMICS OF BIOLOGICAL SYNAPSES, SYNAPTIC INTERACTIONS: KINETIC MODELS, and SYNAPTIC NOISE AND CHAOS IN VERTEBRATE NEURONS). Further details of functional properties may require descriptions of the microphysiology of extra- and intracellular systems, and thus explicit modeling of biochemical dynamics, including Ca^{2+} diffusion, buffering, sequestration, and release; protein conformations; and enzyme activation/inactivation. Finally, the most faithful cellular model would require a four-dimensional construct whose biophysical properties vary with both space and time, in particular depending on past activity, or "experience" (see HEBBIAN SYNAPTIC PLASTICITY).

State Variables and Functional Compartments of the Mosaic Neuron

The many cellular elements we have described suggest a similar number of variables that characterize the functional state of a neuron as a signal processing device, each of which may be thought of as representing information. The most classical variable, of course, is the membrane voltage, which defines the immediate integration of synaptic input onto the dendritic tree and soma and, eventually, the action potential output of the cell. However, it may be argued that for predicting spike output, the first derivative of the membrane voltage may be nearly as important as the actual value of the voltage, a behavior that is easily predicted by Hodgkin-Huxley-type models (see AXONAL MODELING and ION CHANNELS: KEYS TO NEURONAL SPECIALIZATION). Other variables that may be important include the concentration of ions and various neuroactive molecules (e.g., transmitters and second messengers) both inside and outside the cell, and the metabolic or conformational state of various membrane and intracellular proteins. Finally, it may be useful to consider structural or anatomical parameters of the single neuron as functional state variables, such as number and distribution of spines or postsynaptic sites.

All of these state variables are determined by complex relationships between the cellular constituents. For example, the membrane voltage at any given point in the neuron is determined by the spatial distribution of electrically conducting membrane channels and their reversal potentials, the membrane capacitance, and the electrical coupling to the rest of the cell as determined by the three-dimensional branching cable structure and cytoplasmic resistivity. In turn, the ion concentration gradients that underlie channel reversal potentials are determined by an interplay between the cur-

rents through the appropriate channels (which tend to reduce the gradients) and membrane pumps, exchangers, transporters, and intracellular buffer and sequestering systems (which in general tend to maintain the gradients). Finally, in some cases ions passing through a given membrane channel can subsequently bind with and then modulate the conduction state of either the same or possibly other types of channels. Clearly, feedback pathways are the rule rather than the exception in the mosaic's interactions (see Figure 1).

The state variables of a neuron can be associated with a variety of functional compartments, with spatial scales that range from less than a micron to the entire cell. These compartments may correspond to the spatial gradients of voltage (e.g., as determined by dendritic cable properties) or second messenger concentration (e.g., determined by diffusion constant and geometry of the intracellular space), or to the localization of a given biochemical pathway, or to an explicit subcellular structure (e.g., a dendritic spine, an organelle, the cell nucleus). In summary, for most state variables the neuron is far from a classical "well-mixed" system. Rather, an extreme internal heterogeneity is usually the case: a single cell thus becomes a cell of cells.

Emergent State Properties of Intracellular Chemical Systems

Recent work has demonstrated the possibility of various stable arrangements between the concentrations of certain intracellular molecules or the metabolic states of certain proteins, all of which in turn can participate in various biochemical pathways, including those regulating membrane properties and plasticity (Weng, Bhalla, and Iyengar, 1999). From an information processing viewpoint, these combinations can be thought of as essentially distinct states that partially define the functional input/output properties of the neuron. It has also been proposed that changes in cellular properties on even longer time scales may be due to self-stabilizing conformational states of proteins such as CAM kinase II or others. Of course, any mechanism underlying a long-lasting modification of the neuronal transfer function is a candidate for the molecular basis of memory (see INVERTEBRATE MODELS OF LEARNING: *APLYSIA* AND *HERMISSENDA*).

Discussion: How Much Biophysics Needs to Be Known for a Compelling Brain Theory?

Where does the complexity of the mosaic neuron leave us in terms of formulating a theory for the brain? In particular, how detailed does a model of the neuron have to be, and how does the power of current methods compare with the computational complexity inherent at various levels of biophysical description? These open questions have a very practical importance, since there are few opportunities for formal analyses of these nonlinear dynamical systems. Furthermore, the increasing experimental knowledge of neuronal cellular mechanisms is daunting. The details seem to have an almost fractal quality; no matter what level is being examined, underneath any given mechanism there is another Pandora's box of parameters waiting to be described. Today, so many biophysical properties are known to be present in the neuron membrane that the biggest risk is to choose to include only those that will give the model the properties desired. This leads to a model that is unlikely to fail, and therefore unlikely to teach us anything that we did not know before.

The brute force strategy is to construct a bottom-up, biophysically detailed cell model in order to cover as much as possible the high-order interactions between various mechanisms. Once the map has been laid out, sufficiently rich deterministic or stochastic kinetic equations for the membrane elements and intracellular dynamics may then be assigned. Such maps can be evaluated, at least in principle, since all known biophysical mechanisms can be described by nonlinear partial differential equations, and thus are amenable to standard numerical integration techniques.

However, it may appear that at some point there will be too many equations with too many free parameters for practical evaluation

or, more important, for true *understanding*. (On the other hand, the rapid evolution of computing power suggests that the threshold for "impractical" is hard to define.) An optimistic view is that once a sufficiently elaborate biophysical cellular model is constructed, its behavior may be well enough understood so that a more abstract model that captures the functional essentials with considerably less computational expense may be derived. But until there are some formal criteria for establishing what exactly "essential" means, this process will inevitably be an iterative one, moving back and forth between an analysis of detailed cell models in isolation and in nontrivial networks (limited most probably by the available tools) and an analysis of more abstract neural networks. The fundamental challenge to theorists, then, is to go beyond this sort of "reverse engineering" approach and develop a method that is at once commensurate with the complexity of the brain, yet can produce a bona fide theory whose detail avoids that of the actual biological reality.

Roadmap: Biological Neurons and Synapses
Related Reading: Activity-Dependent Regulation of Neuronal Conductances; Adaptive Spike Coding; Axonal Modeling; Dendritic Processing; Hebbian Synaptic Plasticity; Ion Channels: Keys to Neuronal Specialization; Neocortex: Chemical and Electrical Synapses; NMDA Receptors: Synaptic, Cellular, and Network Models; Rate Coding and Signal Processing; Synaptic Interactions: Kinetic Models; Synaptic Noise and Chaos in Vertebrate Neurons; Temporal Dynamics of Biological Synapses

References

Berridge, M. J., 1998, Neuronal calcium signaling, *Neuron*, 21:13–26.

Borg-Graham, L., 1999, Interpretations of data and mechanisms for hippocampal pyramidal cell models, *Cereb. Cortex*, 13:19–138. ◆

Cooper, J. R., Bloom, F. E., and Roth, R. H., 1996, *The Biochemical Basis of Neuropharmacology*, 7th ed., Oxford, Engl.: Oxford University Press. ◆

Fain, G. L., 1999, *Molecular and Cellular Physiology of Neurons*, Cambridge, MA: Harvard University Press. ◆

Hille, B., 2002, *Ionic Channels of Excitable Membranes*, 3rd ed., Sunderland, MA: Sinauer. ◆

Johnston, D., and Wu, S. M.-S., 1995, *Foundations of Cellular Neurophysiology*, Cambridge, MA: MIT Press. ◆

Kaczmarek, L. K., and Levitan, I. B., Eds., 1987, *Neuromodulation: The Biochemical Control of Neuronal Excitability*, Oxford, Engl.: Oxford University Press.

Koch, C., 1999, *The Biophysics of Computation: Information Processing in Single Neurons*, Oxford, Engl.: Oxford University Press. ◆

Koch, C., and Segev, I., Ed., 1998, *Methods in Neuronal Modeling*, 2nd ed., Cambridge, MA: MIT Press. ◆

Laming, P. R., Kimelberg, H., Robinson, S., Salm, A., Hawrylak, N., Müller, C., Roots, B., and Ng, K., 2000, Neuronal-glial interactions and behaviour, *Neurosci. Biobehav. Rev.*, 24:295–340.

Meunier, C., and Segev, I., 2000, Neurons as physical objects: Structure, dynamics and function, in *Handbook of Biological Physics* (F. Moss and Gielen S., Eds.), New York: Elsevier.

Stuart, G., Spruston, N., and Häusser, M., Eds., 1999, *Dendrites*, Oxford, Engl.: Oxford University Press. ◆

Weiss, T. F., 1996, *Cellular Biophysics* (2 vol.), Cambridge, MA: MIT Press. ◆

Weng, G., Bhalla, U. S., and Iyengar, R., 1999, Complexity in biological signaling systems, *Science*, 284:92–96.

AQ 1: Author: None of the other articles have these long lists

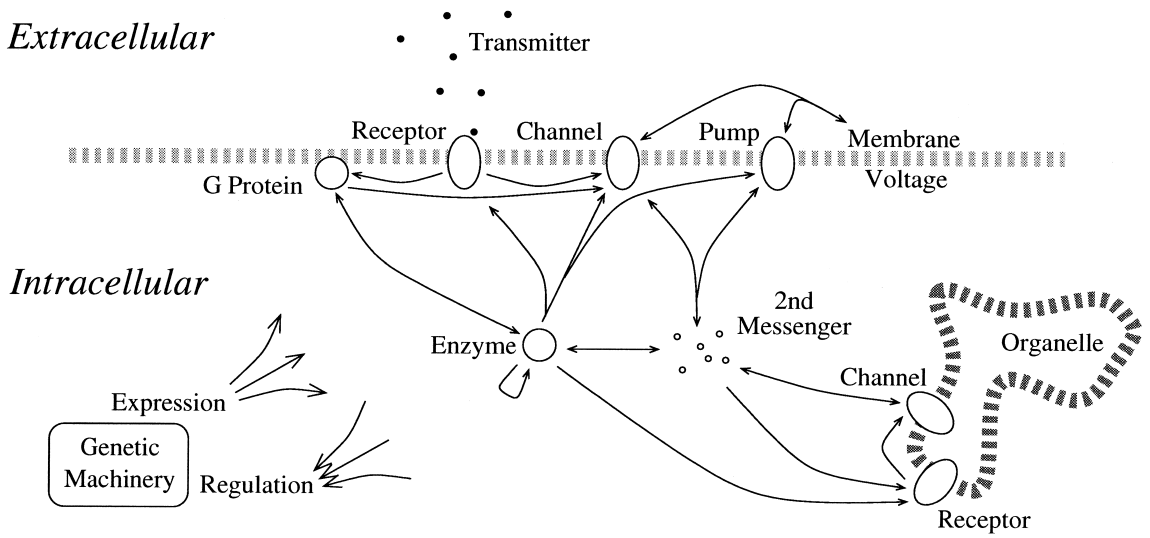

Figure 1. Sketch of the molecular circuit underlying the neuron's biophysical mosaic. This caricature outlines the many interrelated control paths among the molecular elements that determine the functional properties of the neuron. For example, activation of an ionotropic synapse starts with the binding of extracellular transmitter to the membrane receptor, which then directly turns on an associated ion channel. Alternatively, activation of a metabotropic synapse is initiated by transmitter binding to a receptor, which then activates a G protein, which turns on an enzyme, which raises the concentration of a second messenger, which, finally, activates a target ion channel. Many control pathways are immediately bidirectional: current through an ion channel changes the membrane voltage, which in turn can control the gating of that same channel. Some elements can even control themselves, for example autophosphorylating enzymes.

Table 1. Biophysical Mechanisms of Neuron's Relevant to Computational Function

Ion channels
Control by intrinsic signals (membrane voltage, intracellular molecules)
Control by extrinsic signals (extracellular molecules, e.g., released from presynaptic terminals)
Receptors
Ionotropic: Direct control of ion channels
Metabotropic: Indirect control of ion channels and other internal systems
External binding sites (synaptic and pancrinic)
Internal binding sites associated with neuronal and organelle membranes
Control of internal biochemical systems
Enzymes (kinases and phosphatases, which determine the state of most proteins; others)
Gap junctions
Pumps, transporters, exchangers (electrogenic and nonelectrogenic)
Organelles
Ca^{2+} sequestering and release (endoplasmic recticulum, mitochondria)
Protein synthesis and metabolism
Maintenance and modulation of three-dimensional structure (spines, dendritic morphology)
Transmitter sequestering and release (synaptic vesicles)
Cytoplasmic biochemical systems
Transmitter synthesis and degradation
G proteins: Initiate second messenger release after receptor activation
Second messengers: Diffusible molecules linking various stages of internal biochemical systems
Effectors: Targets of second messengers, including channels and enzymes (kinases, phosphatases)
Three-dimensional structure
Macroscopic anatomy (soma, dendritic and axonal trees)
Microscopic anatomy (spines, synaptic junctions, variations in dendritic or axonal dimensions)
"Electrotonic" anatomy (modulated by state of local membrane)
Geometrical synaptic and channel distribution
Functional synaptic localization (e.g., retinotopic, tonotropic)
Computational synaptic localization (e.g., on-the-path interactions, coincidence detection)

Table 2. Quantitative Summary of the Neuron's Biophysical Mosaic Relevant to Computational Function

Spatial scales (voltage and concentration transients): <1 to thousands of microns
Temporal scales
Kinetics of gating, binding, and diffusion: <1 ms to seconds
Gene expression: days to years?
Anatomy
Tens to hundreds of dendritic and axonal branches
Models of electrotonic structure can require thousands of compartments
Synapses and channels
Thousands of pre- and postsynaptic sites
Five major categories of charge carriers: Na^+, K^+, Ca^{2+}, Cl^-, other (e.g., "cationic," proton, etc.)
Tens of types for each category, several of which may be expressed in a single neuron
Receptors and associated agonists (neurotransmitters, second messengers, etc.)
Approximately 30 major types, several of which may be expressed in a single neuron
Possibly tens of identified subtypes for some major receptor types

A brute force map of a single neuron would be very large indeed. For example, compartmental models of the dendritic tree can require hundreds or thousands of coordinates, corresponding to spatial scales relevant for representing gradients of membrane voltage or of the concentration of intracellular molecules. A given neuron may have thousands of synaptic inputs, each associated with one of several types of receptors, and the cell membrane can include tens of types of ion channels. Furthermore, the different synaptic receptor and channel types are typically scattered inhomogeneously over the neuron. It is also important to consider the stationarity of the map. For computations over hundreds of milliseconds or less, the map may properly be thought to be static, but at longer time scales it may be necessary to consider a dynamic layout of the mosaic. For another *carte du monde* of computational cellular mechanisms and their spatial and temporal scales, see Figure 21.2 in Koch, 1999.