2. Coding depends on numerous variables (e.g., synaptic type, discharges involved). Discharge variabilities have simplifying influences.
3. In addition to discharge assimilation to point processes, formal issues with physiological implications include, the neuron's analyzer role, the definition of coding, and probabilistic and informational aspects.

Linking this article to brain theory are questions regarding generalizations to other discharges and synapses, long-term changes (neuromodulation, plasticity), participating membrane and molecular mechanisms, and the roles of deterministic issues and noise. Coding fidelity is useful biologically in some sensory or motor situations (although not always); its compensation poses an interesting problem.

Behaviors are reproduced satisfactorily by models, mainly formal and incorporating variables recognized in living preparations that refer to presynaptic spikes, thresholds, currents, conductances, and so forth. Models ignore issues such as the neuron's regional inhomogeneity and the individual synapse's complexity.

Circuit-oriented concepts are indispensable for understanding nervous systems. Synapses are operational units therein, but claiming their hegemony is similar to claiming that the atom holds the key that unravels the universe. However, the relative significance of the whole should not be exaggerated. Synaptic coding and neuronal entrainments, although not sufficient, are indispensable for comprehending neural networks and the nervous systems that they are intended to mimic. Networks with simple units reveal surprisingly complex behaviors; those with more realistic units show great promise and will add important dimensions to the body of knowledge (Aihara, Takabe, and Toyoda, 1993).

tion of Locomotor Patterns

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Synaptic Currents, Neuromodulation, and Kinetic Models

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Introduction

Synaptic interactions are essential to neural network models of all levels of complexity. Synaptic interactions in "realistic" network models pose a particular challenge, since the aim is not only to capture the essence of synaptic mechanisms, but also to do so in a computationally efficient manner to facilitate simulations of large networks. In this article, we review several types of models which address these goals.

Synaptic currents are mediated by ion channels activated by neurotransmitter released from presynaptic terminals. *Kinetic models* are a powerful formalism for the description of channel behavior, and are therefore well suited to the description of synaptic interactions, both traditional and neuromodulatory. Although full representation of the molecular details of the synapse generally requires highly complex kinetic models, we focus on simpler kinetic models which are very efficient to compute. We show how these models capture the time courses of several types of synaptic responses as well as the important phenomena of summation, saturation, and desensitization.

Models of Synaptic Currents

For neural models that do not include action potentials, synaptic currents are typically modeled as a direct function of some presynaptic activity measure. In the simplest case, synaptic interactions are described by a sigmoid function, and presynaptic activity is interpreted as the average firing rate of the afferent neuron. Alternatively, the postsynaptic currents can be described by a first-order differential equation in which one term depends on the presynaptic membrane potential through a sigmoid function (Wang and Rinzel, 1992). Another possibility is to intepret the activity level as the fraction of neurons active per unit of time, thus representing the interaction between neural populations rather than single neurons (Wilson and Cowan, 1973).

For spiking neurons, a popular model of postsynaptic currents (PSCs) is the alpha function

$$r(t - t_0) = \frac{(t - t_0)}{\tau_1} \exp[-(t - t_0)/\tau_1] \qquad (1)$$

(Rall, 1967), where $r(t)$ resembles the time course of experimentally recorded postsynaptic potentials (PSPs) with a time constant τ_1. The alpha function and its double-exponential generalization can be used to approximate most synaptic currents with a small number of parameters and, if implemented properly, at low computation and storage requirements (Srinivasan and Chiel, 1993). Other types of template functions were also proposed for spiking neurons (Tsodyks, Mitkov, and Sompo-

linsky, 1990; Traub and Miles, 1991). The disadvantages of the alpha-function, or related approaches, include the lack of correspondence to a plausible biophysical mechanism and the absence of a natural method for handling the summation of successive PSCs from a train of presynaptic impulses.

The most fundamental way to model synaptic currents is based on the kinetic properties of the underlying synaptic ion channels. The kinetic approach is closely related to the well-known model of Hodgkin and Huxley (1952) for voltage-dependent ion channels (reviewed in Armstrong, 1992; see AXONAL MODELING). Kinetic models are powerful enough to describe in great detail the properties of synaptic ion channels and can be integrated coherently with chemical kinetic models for enzymatic cascades underlying signal transduction and neuromodulation. The drawback of kinetic models is that they are often complex, with several coupled differential equations, making them too costly to be used in simulations involving large populations of neurons. We show how these limitations can be ameliorated.

The Kinetic Description

Ion channels are proteins that have distinct conformational states, some of which are *open* and conduct ionic current and some of which are *closed*, *inactivated*, or *desensitized* and do not conduct. Single-channel recording techniques have demonstrated that the transitions between conformational states occurs both rapidly and randomly or stochastically (reviewed in Sakmann and Neher, 1983). It has furthermore been shown that the behavior of single-ion channels is well described by *Markov models*, a class of stochastic model in which transitions between states occurs with a time-independent probability.

It is straightforward to move from a microscopic description of single-channel behavior to a macroscopic description of a population of similar channels. In the limit of large numbers, the stochastic behavior of individual channels can be described by a set of continuous differential equations analogous to ordinary chemical reaction kinetics. The kinetic analog of Markov models posits the existence of a group of conformational states $S_1 \ldots S_n$ linked by a set of transitions

$$S_1 \rightleftarrows S_2 \rightleftarrows S_4 \rightleftarrows \ldots$$
$$\updownarrow \qquad \updownarrow \qquad\qquad (2)$$
$$S_3 \rightleftarrows \ldots$$
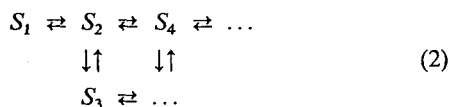
Define s_i as the fraction of channels in state S_i and r_{ij} as the rate constant of the transition

$$S_i \underset{r_{ji}}{\overset{r_{ij}}{\rightleftarrows}} S_j \qquad (3)$$

which obeys the kinetic equation

$$\frac{ds_i}{dt} = \sum_{j=1}^{n} s_j r_{ji} - \sum_{j=1}^{n} s_i r_{ij} \qquad (4)$$

The wide range of interesting behavior exhibited by channels arises from the dependence of certain transitions on factors extrinsic to the channel, primarily either the binding of another molecule to the protein or the electric field across the cell membrane. These influences are referred to as *ligand-gating* and *voltage-gating*, respectively. Ligand-gating is typified by synaptic receptors, which are ion channels that are gated by neurotransmitter molecules. Other channels are gated by molecules inside the cell, most prominently the so-called second-messengers such as calcium ions or G-proteins.

In the case of voltage-dependent ion channels, the transition between two states S_i and S_j occurs with rate constants that are dependent on voltage, such as

$$S_i \underset{r_{ji}(V)}{\overset{r_{ij}(V)}{\rightleftarrows}} S_j \qquad (5)$$

The functional form of the voltage dependence can be obtained from single-channel recordings (see Sakmann and Neher, 1983). The kinetics-based description of the voltage dependence of channels is quite general. In particular, the well-known model of Hodgkin and Huxley (1952) for the fast sodium channel and the delayed-rectifier potassium channel can be written in a kinetic form which is equivalent to the original Hodgkin-Huxley equations.

In the case of ligand-gated ion channels, the transition between two states S_i and S_j can depend on the binding of a ligand L:
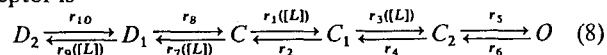
$$L + S_i \underset{r_{ji}}{\overset{r_{ij}}{\rightleftarrows}} S_j \qquad (6)$$

which can be rewritten as

$$S_i \underset{r_{ji}}{\overset{r_{ij}([L])}{\rightleftarrows}} S_j \qquad (7)$$

where $r_{ij}([L]) = [L]r_{ij}$ and $[L]$ is the concentration of ligand. The functional dependence of the rate constants is linear in the ligand concentration, and in some cases, can also depend on the voltage.

Ligand-Gated Channels: AMPA, NMDA, and GABA-A Receptors

The most common types of ligand-gated channels are the excitatory AMPA and NMDA types of glutamate receptor and the inhibitory GABA-A receptor. Many kinetic models have been constructed. For example, an accurate model of the AMPA receptor is

$$D_2 \underset{r_9([L])}{\overset{r_{10}}{\rightleftarrows}} D_1 \underset{r_7([L])}{\overset{r_8}{\rightleftarrows}} C \underset{r_2}{\overset{r_1([L])}{\rightleftarrows}} C_1 \underset{r_4}{\overset{r_3([L])}{\rightleftarrows}} C_2 \underset{r_6}{\overset{r_5}{\rightleftarrows}} O \qquad (8)$$
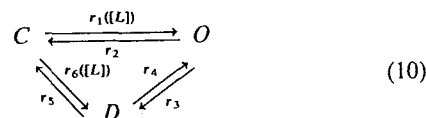
(Standley, Ramsey, and Usherwood, 1993), where C is the unbound closed state, C_1 and C_2 are, respectively, the singly and doubly bound closed states, O is the open state, and D_1 and D_2 are the desensitized singly and doubly bound states, respectively. r_1 through r_{10} are the associated rate constants, and $[L]$ is the concentration of neurotransmitter in the synaptic cleft.

The six states of this AMPA model are required to account for some of the subtle dynamical properties of these receptors, yet simplified schemes with far fewer states and transitions are often very good approximations for the time course and the dynamic behavior of most synaptic currents (see Destexhe et al., 1994c). In particular, consider the simplest kinetic schemes involving two states

$$C \underset{r_2}{\overset{r_1([L])}{\rightleftarrows}} O \qquad (9)$$

or three states

$$C \underset{r_2}{\overset{r_1([L])}{\rightleftarrows}} O$$
$$\underset{r_5}{\overset{r_6([L])}{\diagdown}} \; D \; \overset{r_4}{\underset{r_3}{\diagup}} \qquad (10)$$
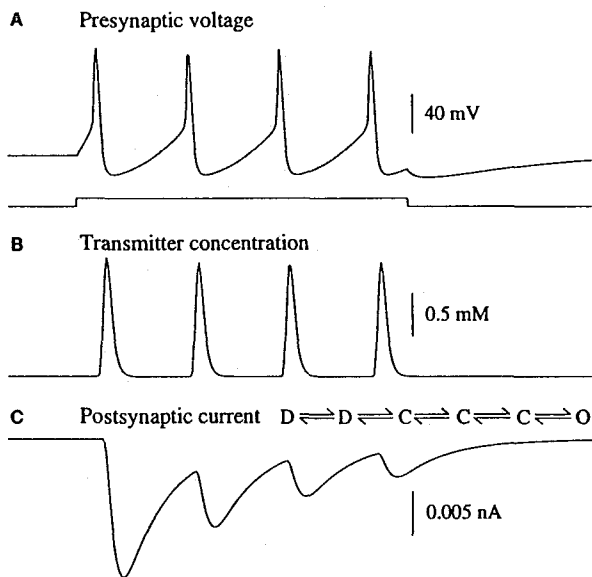
In these two schemes, C and O represent the closed and open states of the channel, D represents the desensitized state, and $r_1 \ldots r_6$ are the associated rate constants. Not only are these simple schemes easier to compute than more complex schemes, but the time course of the current can be obtained analytically (Destexhe et al., 1994b, 1994c).

Another useful means to simplify the model is suggested by experiments using artificial application of neurotransmitter, where it has been seen that synaptic currents with a time course very similar to intact synapses can be produced using very brief pulses of agonist (Colquhoun, Jonas, and Sakmann, 1992).
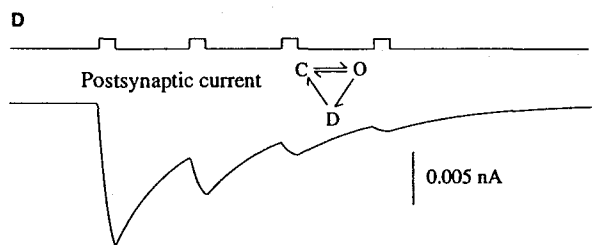
These data suggest that a model for the AMPA synapse does not require a detailed kinetic model for transmitter release, as the response time course is dominated by the postsynaptic kinetics rather than the time course of the neurotransmitter concentration. Hence, we can assume that the neurotransmitter is delivered as a brief (≈ 1 ms) pulse triggered at the time of each presynaptic spike.

Simplified kinetic schemes for the AMPA response can be compared with detailed kinetic models to judge the quality of the approximation (Figure 1A–D). Both simple and detailed synaptic 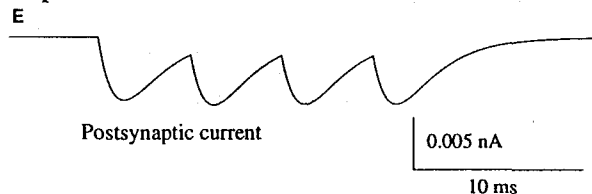responses first require a trigger event, corresponding to the release of neurotransmitter in the synaptic cleft. In simulations of the detailed kinetics, the time course of neurotransmitter was derived using a model which included presynaptic action potentials, calcium-dependent fusion of presynaptic vesicles, and clearance of neurotransmitter. Figure 1A–C shows the AMPA response resulting from a high-frequency train of presynaptic spikes. The amplitude of successive PSCs decreased progressively because of an increasing fraction of receptors in desensitized states. One of the simplified schemes gave a good fit both to the time course of the AMPA current and to the response desensitization that occurs during multiple successive events (Figure 1D). Alpha functions, in contrast, did not match the summation behavior of the synaptic current (Figure 1E).
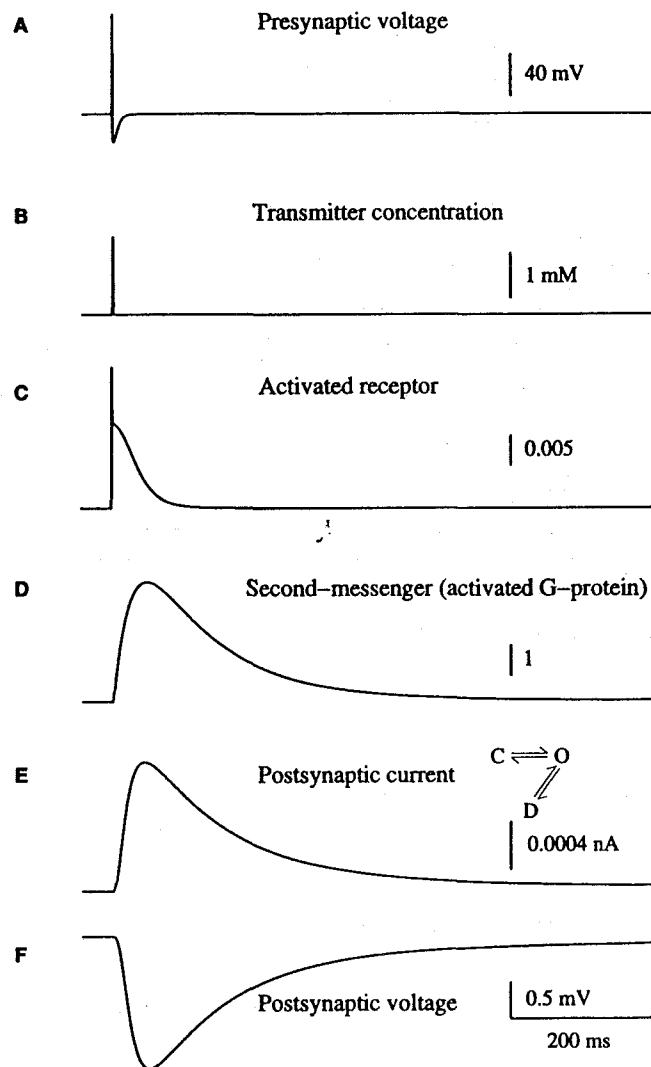
Figure 1. Comparison of three models for AMPA receptors. A, Presynaptic train of action potentials elicited by current injection. B, Corresponding glutamate release in the synaptic cleft obtained using a kinetic model for transmitter release. C, Postsynaptic current from AMPA receptors modeled by a six-state Markov model (Standley et al., 1993). D, Same simulation with AMPA receptors modeled by a simpler three-state kinetic scheme and transmitter time course approximated by spike-triggered pulse (above current trace). E, Postsynaptic current modeled by summated alpha functions. (Modified from Destexhe et al., 1994c.)

Figure 2. Kinetic model of synaptic currents acting through second messengers. A, Presynaptic action potential elicited by current injection. B, Time course of transmitter in the synaptic cleft obtained by a kinetic model for transmitter release. C, Activated GABA-B receptors after binding with transmitter. The activated receptor catalyzes the formation of a second messenger, a G-protein subunit. D, Time course of activated G-protein. E, Postsynaptic current produced by the gating of K^+ channels by G-protein. F, Inhibitory postsynaptic potential. (Modified from Destexhe et al., 1994c.)

Procedures similar to those applied to the AMPA response can be used to obtain simple kinetic models for other types of ligand-gated synaptic channels, including the NMDA and GABA-A receptors. Two-state and three-state models provide good fits of averaged whole-cell recordings of the corresponding PSCs (see Destexhe et al., 1994c, for more details).

Second Messenger-Gated Channels: GABA-B and Neuromodulation

Some neurotransmitters do not bind directly to the ion channel but act through an intracellular second messenger, which links the activated receptor to the opening or closing of an ion channel. This type of synaptic interaction occurs at a slower time scale as ligand-gated channels and is therefore distinguished as *neuromodulation*. Examples of neuromodulators such as GABA (GABA-B), acetylcholine (M2), noradrenaline (alpha-2), serotonin (5HT-1), dopamine (D2), and others gate a K^+ channel through the direct action of a G-protein subunit, G_α (Brown, 1990; Brown and Birnbaumer, 1990). We have developed a kinetic model of the G-protein–mediated slow intracellular response (Destexhe et al., 1994c) that can be applied to any of these transmitters.

A detailed kinetic model of the GABA-B response (Figure 2) was compared with a two-state model, where it was assumed that the time course of the activated G-protein occurs as a pulse of 80–100 ms duration. As in the case of ligand-gated channels, elementary kinetic schemes capture the essential dynamics of more detailed models; the equations are the same as ligand-gated channels, but with $[L]$ representing the second messenger. The slow time course of the neuromodulators is reflected in the low values of the rate constants in Equations 9 and 10. These elementary schemes provide excellent fits to whole-cell recordings of GABA-B PSCs, and are also fast to compute.

The neuromodulators just listed share a very similar G-protein–mediated intracellular response. The basic method applied to the GABA-B response can thus be used to model these currents, with rate constants adjusted to fit the time courses reported for the particular responses. Details on the rate constants obtained from fitting different kinetic schemes to GABA-B PSC and other neuromodulators are given in Destexhe et al. (1994c).

Discussion

Although it has been possible to develop remarkably detailed models of the synapse (Bartol et al., 1991), substantial simplification is necessary for large-scale network simulations involving thousands of synapses. A variety of abstract representations of the synapse are available. We advocate a class of model based directly on kinetics of the ion channel molecules mediating synaptic responses. Simplified kinetic models can be implemented with minimal computational expense, while still capturing both the time course of individual synaptic and neuromodulatory events and also the interactions between successive events (summation, saturation, desensitization), which may be critical when neurons interact through bursts of action potentials (Destexhe et al., 1994a).

Programs that simulate the models of this article using the NEURON simulator are available by anonymous ftp to salk. edu in/pub/alain.

Road Map: Biological Neurons
Background: Ion Channels: Keys to Neuronal Specialization
Related Reading: Dynamic Clamp: Computer-Neural Hybrids; NMDA Receptors: Synaptic, Cellular, and Network Models; Oscillatory and Bursting Properties of Neurons

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