

# Synaptic Interactions

Alain Destexhe, Zachary F. Mainen, and Terrence J. Sejnowski

## Introduction

Modeling synaptic interactions in network models poses a particular challenge. Not only should such models capture the important physiological properties of synaptic interactions, but they must do so in a computationally efficient manner in order to facilitate simulations of large networks. This article reviews several types of models that address these goals.

Synaptic currents are mediated by ion channels activated by neurotransmitter released from presynaptic terminals. Kinetic models are expressive enough to describe the behavior of ion channels underlying synaptic currents. Although full representation of the molecular details of the synapse generally requires highly complex kinetic models, we focus here on simpler kinetic models that are more computationally efficient. We show that these models can capture the time course and dynamics of several types of synaptic responses, allowing them to be useful tools for modeling synaptic interactions in large networks.

## Models of Synaptic Currents

For neural models that do not include action potentials, synaptic currents are typically modeled as a direct function of the 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. Another possibility is to interpret 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).

A different approach is needed to model synaptic interactions between spiking neurons. It is usually assumed that a presynaptic spike triggers a conductance waveform postsynaptically. A popular model of postsynaptic conductance increase is the alpha function introduced by Rall (1967):

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

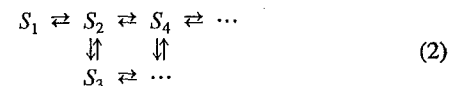
where  $r(t)$  resembles the time course of experimentally recorded postsynaptic potentials (PSPs) with a time constant  $\tau_1$ . The alpha function and its double-exponential generalization can be used to approximate most synaptic currents with a small number of parameters that require, implemented properly, low computation and memory requirements (Srinivasan and Chiel, 1993). The disadvantages of the alpha function, or related approaches, include the lack of direct biophysical interpretation and the absence of a natural method for handling successive temporally overlapping postsynaptic currents (PSCs) from a train of presynaptic impulses.

A natural 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 Hille, 2001). Kinetic models can 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 (Destexhe, Mainen, and Sejnowski, 1994). In the next section, we show how to model various types of ion channels with the kinetic formalism.

## 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 rapidly and stochastically (reviewed in Sakmann and Neher, 1995). It has furthermore been shown that the behavior of single ion channels is well-described by *Markov models*, in which stochastic transitions between states occur 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 analogue of Markov models posits the existence of a group of conformational states  $S_1 \dots S_n$  linked by a set of transitions



Define  $s_i$  as the fraction of channels in state  $S_i$  and  $r_{ij}$  as the rate constant of the transition



which obeys the kinetic equation

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

The wide range of interesting behavior exhibited by channels arises from the dependence of certain transitions on factors extrinsic to the channel, such as 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.

For 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

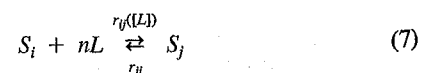


The functional form of the voltage-dependence can be obtained from single-channel recordings (see Sakmann and Neher, 1995). The kinetics-based description of the voltage-dependence of channels is quite general. In particular, the well-known model of Hodgkin and Huxley (1952) for the fast sodium channel and the delayed-rectifier potassium channel can be written in the form of a Markov model that is equivalent to the original Hodgkin-Huxley equations.

For ligand-gated ion channels, the transition between two states  $S_i$  and  $S_j$  can depend on the binding of  $n$  molecules of a ligand  $L$ :



which can be rewritten as

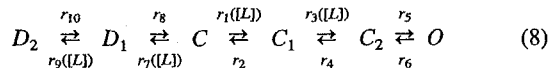


where  $[L]$  is the concentration of ligand and  $r_{ij}([L]) = r_{ij}[L]^n$ . In this model, there is a simple functional dependence of the rate constants on ligand concentration. For some receptor types, rate constants may also depend on the voltage.

Ligand-gating is typified by *ionotropic synaptic receptors*, which are ion channels that are directly gated by neurotransmitter molecules. By contrast, *metabotropic synaptic receptors* do not have an ion channel and neurotransmitter binding to the receptor induces the formation of an intracellular messenger (calcium or G proteins, for example) that controls the gating of an ion channel independent of the receptor. These two types of synaptic receptors will be considered in the next two sections.

**Kinetic Models of Ionotropic Receptors: AMPA, NMDA, and GABA<sub>A</sub>**

The most common types of ligand-gated synaptic channels are the excitatory AMPA and NMDA types of glutamate receptor and the inhibitory GABA<sub>A</sub> receptor. Many kinetic models have been proposed for these receptors (reviewed in Sakmann and Neher, 1995; Destexhe, Mainen, and Sejnowski, 1998). For example, a multistate Markov scheme for AMPA-Kainate receptors (Standley, Ramsey, and Usherwood, 1993) is:

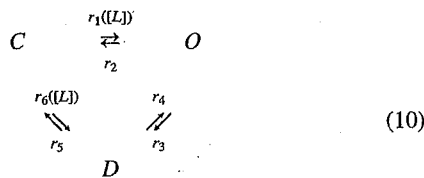


where  $C$  is the unbound closed state,  $C_1$  and  $C_2$  are respectively the singly and doubly bound closed states,  $O$  is the open state, and  $D_1$  and  $D_2$  are respectively the desensitized singly and doubly bound states.  $r_1$  through  $r_{10}$  are the associated rate constants and  $[L]$  is the concentration of neurotransmitter in the synaptic cleft.

The six states of this AMPA model are required to account for the electrophysiological properties of these receptors as determined by single-channel recordings (Standley et al., 1993). However, simplified kinetic schemes with fewer states and transitions can constitute fairly good approximations for the time courses and the dynamic behavior of synaptic currents (Destexhe et al., 1994, 1998). In particular, consider the simplest kinetic schemes involving two states



or three states

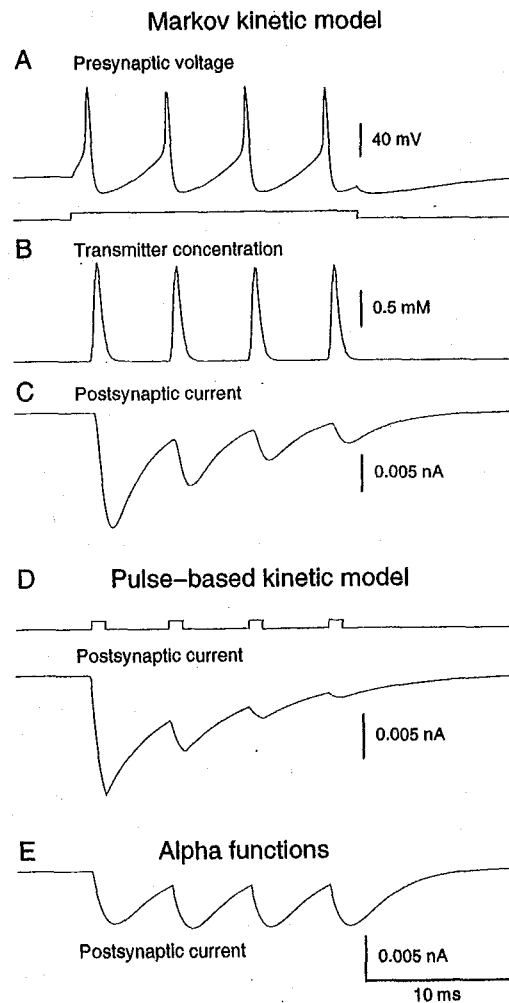


In these two schemes,  $C$  and  $O$  represent the closed and open states of the channel,  $D$  represents the desensitized state, and  $r_1 \dots r_6$  are the associated rate constants. Not only are these simple schemes easier to compute than more complex schemes, but the time course of the current can be obtained analytically under some approximations (Destexhe et al., 1994).

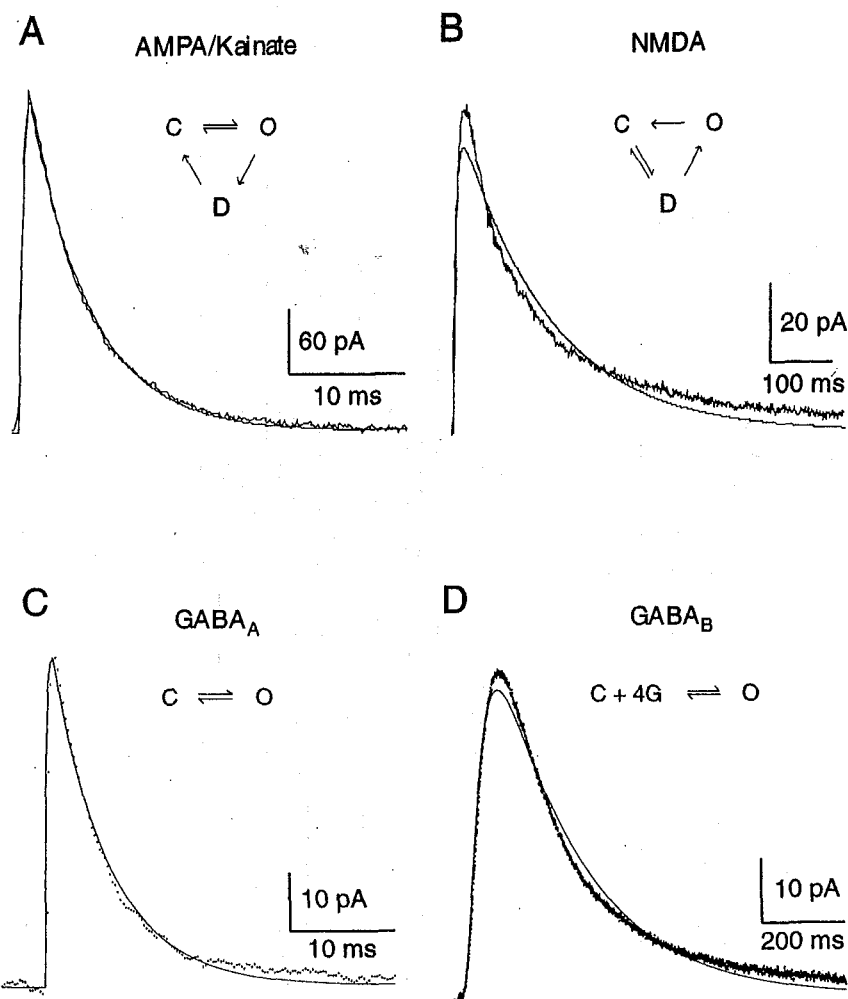
Another way to simplify the model is suggested by experiments using artificial application of neurotransmitter, where it has been shown that synaptic currents with a time course very similar to that of intact synapses can be produced using very brief pulses of agonist (reviewed in Sakmann and Neher, 1995). These data suggest that the response time course is dominated by the postsynaptic kinetics rather than the time course of the neurotransmitter concentration. Hence, one can assume that the neurotransmitter is de-

livered as a brief ( $\approx 1$  ms) pulse triggered at the time of each presynaptic spike.

Simplified kinetic schemes for the AMPA response can be compared to 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 Markov kinetic model, the time course of neurotransmitter was derived using a model that 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 due to an increasing fraction of receptors in desensitized states. A simplified kinetic scheme using transmitter pulses gave a good fit, both to the time course of the AMPA current (shown in Figure 2A) and to the response desensitization that occurs during multiple successive events (Figure



**Figure 1.** Comparison of three models for AMPA receptors. A–C, Markov model of 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. D, Same simulation with AMPA receptors modeled by a simpler three-state kinetic scheme and transmitter time course approximated by spike-triggered pulses (trace above). E, Postsynaptic current modeled by summed alpha functions. (Modified from Destexhe et al., 1994.)



**Figure 2.** Elementary kinetic schemes provide good models of postsynaptic currents. *A*, AMPA-mediated currents (courtesy of Z. Xiang, A. C. Greenwood, and T. Brown). *B*, NMDA-mediated currents (courtesy of N. A. Hessler and R. Malinow). *C*, GABA<sub>A</sub>-mediated currents (courtesy of T. S. Otis and I. Mody). *D*, GABA<sub>B</sub>-mediated currents (courtesy of T. S. Otis, Y. Dekoninck, and I. Mody). The averaged recording of the synaptic current (negative currents upwards for *A* and *B*) is shown with the best fit obtained using simple kinetics (continuous trace—1 ms pulse of agonist for *A*, *B*, *C*). (*A* modified from Destexhe et al., 1994, *B–D*, modified from Destexhe et al., 1998. Values of rate constants and other parameters can be found in Destexhe et al., 1998.)

1*D*). Alpha functions, in contrast, did not match the summation behavior of the synaptic current (Figure 1*E*).

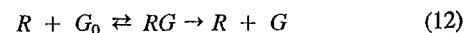
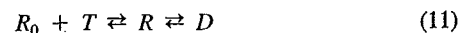
Procedures similar to those applied to the AMPA response can be used to obtain simple kinetic models for other types of ligand-gated synaptic channels, including the NMDA and GABA<sub>A</sub> receptors. Two-state and three-state models provide good fits of averaged whole-cell recordings of the corresponding PSCs (Figure 2*B–C*; for more details see Destexhe et al., 1994, 1998).

### Kinetic Models of Metabotropic Receptors: GABA<sub>B</sub> 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, called *neuromodulation*, occurs at a slower time scale than ligand-gated channels. Neuromodulators such as GABA (GABA<sub>B</sub>), acetylcholine (M2), noradrenaline (alpha-2), serotonin (5HT-1), dopamine (D2), and others gate a K<sup>+</sup> channel through the action of G-proteins (reviewed in Brown, 1990). We have developed a kinetic model of the G protein-mediated slow intracellular response mediated by GABA<sub>B</sub> receptors (Destexhe and Sejnowski, 1995) that can be applied to any of these transmitters.

Unlike GABA<sub>A</sub> receptors which respond to weak stimuli, GABA<sub>B</sub> responses require high levels of presynaptic activity

(Mody et al., 1994). This property might be due to extrasynaptic localization of GABA<sub>B</sub> receptors, but it can also be accounted solely from the kinetics of the G-protein cascade underlying GABA<sub>B</sub> responses (Destexhe and Sejnowski, 1995). The high level of activity needed to activate GABA<sub>B</sub> responses could be reproduced by the following kinetic scheme:

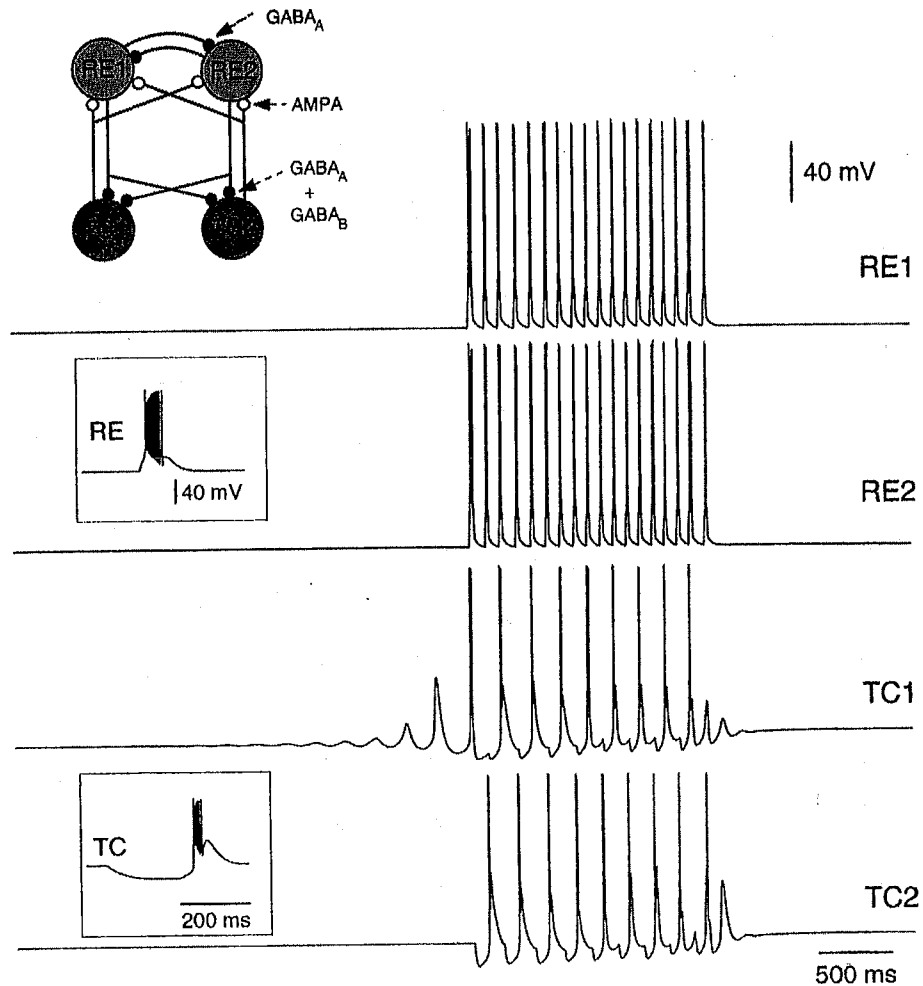


where the transmitter, *T*, binds to the receptor, *R*<sub>0</sub>, leading to its activated form, *R*, and desensitized form, *D*. The G-protein is transformed from an inactive (GDP-bound) form, *G*<sub>0</sub>, to an activated form, *G*, catalyzed by *R*. Finally, *G* binds to open the K<sup>+</sup> channel, with *n* independent binding sites. A simplified model with very similar behavior can be obtained by assuming quasi-stationarity in Equations 12 and 14, neglecting desensitization, and considering *G*<sub>0</sub> in excess, leading to:

$$\frac{dr}{dt} = K_1[T](1 - r) - K_2r \quad (15)$$

$$\frac{ds}{dt} = K_3r - K_4s \quad (16)$$

**Figure 3.** Kinetic models of synaptic currents used to simulate a small network of thalamic reticular (RE) and thalamocortical (TC) neurons. These neurons have complex intrinsic firing properties and generate bursts of action potentials following depolarization or hyperpolarization (insets). They are connected with different receptor types (scheme on top: AMPA from TC to RE, GABA<sub>A</sub> within RE and a mixture of GABA<sub>A</sub> and GABA<sub>B</sub> from RE to TC). The simulations exhibit oscillatory behavior in which the exact frequency and cellular phase relationships are dependent on intrinsic calcium- and voltage-dependent currents as well as synaptic currents. Modeling synaptic currents with the correct kinetics was needed to match experimental observations (modified from Destexhe et al., 1996; see also SLEEP OSCILLATIONS).



where  $r$  is the fraction of receptors in the activated form,  $g$  is the normalized concentration of activated G-proteins, and  $K_1 \dots K_4$  are rate constants. The fraction of K<sup>+</sup> channels in the open form is then given by:

$$[O] = \frac{s^n}{s^n + K_d} \quad (17)$$

where  $K_d$  is the dissociation constant of the binding of G on K<sup>+</sup> channels. This computationally efficient model can fit single GABA<sub>B</sub> IPSCs (Figure 2D) and account for the typical stimulus dependence of GABA<sub>B</sub> responses (Destexhe and Sejnowski, 1995; Destexhe et al., 1998). Models have shown that this property has drastic consequences for the genesis of epileptic discharges (reviewed in Destexhe and Sejnowski, 2001).

Other neuromodulators listed previously have a G protein-mediated intracellular response similar to that of GABA<sub>B</sub> receptors. Details of the rate constants obtained from fitting different kinetic schemes to GABA<sub>B</sub> PSC are given in Destexhe et al. (1998).

### Simulating Networks of Neurons

Simplified kinetic models of synaptic receptors can be used to model complex cellular interactions that depend on the kinetics of synaptic currents. For example, several types of oscillations are

generated by thalamic circuits. Thalamic neurons have complex intrinsic firing properties and can generate bursts of action potentials in rebound to inhibition due to low-threshold calcium currents (see insets in Figure 3). Thalamic neurons are also characterized by different types of synaptic receptors, such as AMPA, GABA<sub>A</sub> and GABA<sub>B</sub> (see scheme in Figure 3). Modeling this system using Hodgkin and Huxley's (1952) type of models for intrinsic currents and simple kinetics models of synaptic currents led to oscillations in the ~10 Hz frequency range (Figure 3). These simulations have been used to explore the cellular mechanisms for the different types of oscillations in these circuits (Destexhe et al., 1996), which depend on the kinetics of intrinsic and synaptic currents. For example, the ~10 Hz frequency depends on the decay of GABA<sub>A</sub>-mediated currents and the transformation of these oscillations into more synchronized ~3 Hz oscillations depends critically on the activation properties of GABA<sub>B</sub> responses (Destexhe et al., 1996).

This example shows that simplified kinetic models consisting of only a few states can capture the essential properties necessary to explain complex cellular interactions. They are useful for investigating network interactions involving multiple types of synaptic receptors. In addition, kinetic models can be used to model both synaptic currents and voltage-dependent currents, providing a single formalism to describe all currents in a neuron (Destexhe et al., 1994). This approach has been used to model different types of oscillations and pathological behavior in networks of the cerebral

cortex, the thalamus, and the thalamocortical system (Destexhe and Sejnowski, 2001).

### Summary and Conclusions

Simple and fast mechanisms are needed to model synaptic interactions in biophysically based network simulations involving thousands of synapses. A class of models based directly on the kinetics of the ion channels mediating synaptic responses can be implemented with minimal computational expense. These models capture 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 investigating the behavior of networks where neurons have complex intrinsic firing properties.

All models shown here were simulated using NEURON (Hines and Carnevale, 1997; see NEURON SIMULATION ENVIRONMENT). Computer generated movies and NEURON programs to simulate these models are available at <http://cns.iaf.cnrs-gif.fr> and <http://www.cnl.salk.edu/~alain/> or on request.

**Road Map:** Biological Neurons and Synapses

**Background:** Axonal Modeling

**Related Reading:** Biophysical Mosaic of the Neuron; Ion Channels: Keys to Neuronal Specialization; Temporal Dynamics of Biological Synapses

### References

- Brown, D. A., 1990, G-proteins and potassium currents in neurons, *Annu. Rev. Physiol.*, 52:215-242.
- Destexhe, A., Bal, T., McCormick, D. A., and Sejnowski, T. J., 1996, Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices, *J. Neurophysiol.*, 76:2049-2070.
- Destexhe, A., Mainen, Z. F., and Sejnowski, T. J., 1994, Synthesis of models for excitable membranes, synaptic transmission and neuromodulation using a common kinetic formalism, *J. Computational Neurosci.*, 1:195-230. ♦
- Destexhe, A., Mainen, Z. F., and Sejnowski, T. J., 1998, Kinetic models of synaptic transmission in *Methods in Neuronal Modeling*, 2nd ed. (C. Koch and I. Segev, Eds.), Cambridge, MA: MIT Press, pp. 1-26. ♦
- Destexhe, A., and Sejnowski, T. J., 1995, G-protein activation kinetics and spill-over of GABA may account for differences between inhibitory responses in the hippocampus and thalamus, *Proc. Natl. Acad. Sci. USA*, 92:9515-9519.
- Destexhe, A., and Sejnowski, T. J., 2001, *Thalamocortical Assemblies*, Oxford, UK: Oxford University Press.
- Hille, B., 2001, *Ionic Channels of Excitable Membranes*, 3rd ed., Sunderland, MA: Sinauer.
- Hines, M. L., and Carnevale, N. T., 1997, The NEURON simulation environment, *Neural Computation*, 9:1179-1209.
- Hodgkin, A. L., and Huxley, A. F., 1952, A quantitative description of membrane current and its application to conduction and excitation in nerve, *J. Physiol. (Lond.)*, 117:500-544.
- Mody, I., De Koninck, Y., Otis, T. S., and Soltesz, I., 1994, Bridging the cleft at GABA synapses in the brain, *Trends Neurosci.*, 17:517-525.
- Rall, W., 1967, Distinguishing theoretical synaptic potentials computed for different some-dendritic distributions of synaptic inputs, *J. Neurophysiol.*, 30:1138-1168.
- Sakmann, B., and Neher, E., Eds., 1995, *Single-Channel Recording*, 2nd ed., New York: Plenum Press.
- Srinivasan, R., and Chiel, H. J., 1993, Fast calculation of synaptic conductances, *Neural Computation*, 5:200-204.
- Standley, C., Ramsey, R. L., and Usherwood, P. N. R., 1993, Gating kinetics of the quisqualate-sensitive glutamate receptor of locust muscle studied using agonist concentration jumps and computer simulations, *Biophys. J.*, 65:1379-1386.
- Wilson, H. R., and Cowan, J. D., 1973, A mathematical theory of the functional dynamics of nervous tissue, *Kybernetik*, 13:55-80.