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## Synaptic Currents, Neuromodulation and Kinetic Models

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Kinetic Models of Synaptic Currents

# 1 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 paper, 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.

# 2 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 (Wang and Rinzal, 1992). 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).

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

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

(Rall, 1967), where  $r(t)$  resembles the time course of experimentally-recorded postsynaptic potentials (PSP’s) 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 and, if implemented properly, at low computation and stor-

age requirements (Srinivasan and Chiel, 1993). Other types of template function were also proposed for spiking neurons (Tsodyks et al., 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 PSC's from a train of presynaptic impulses.

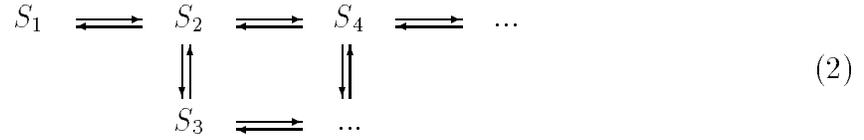
The most fundamental way to model synaptic currents is based on the kinetic properties of the underlying synaptic ion channels. The kinetic approach is closely related to the well-known model of Hodgkin and Huxley (1952) for voltage-dependent ion channels (reviewed in Armstrong, 1992). Kinetic models 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.

### **3**    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 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

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

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



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  $L$ :



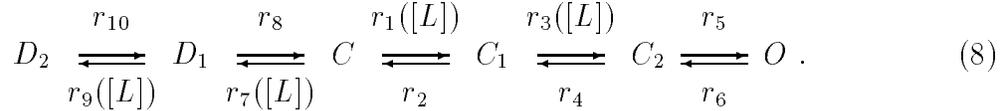
which can be rewritten as



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, may also depend on the voltage.

## 4 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

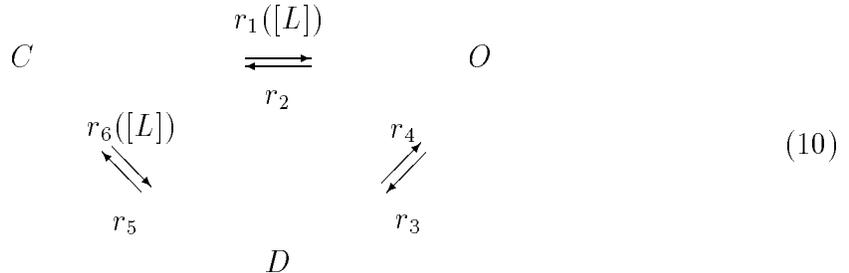


(Standley et al., 1993) where  $C$  is the unbound closed state,  $C_1$  and  $C_2$  are respectively the singly- and doubly-bound closed states,  $O$  is the open state, and  $D_1$  and  $D_2$  are respectively the desensitized singly- and doubly-bound states.  $r_1$  through  $r_{10}$  are the associated 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 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 (Destexhe et al., 1994c). 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 (Destexhe et al., 1994b; 1994c).

Another useful mean to simplify the model is suggested by experiments using artificial application of neurotransmitter, where it has been that synaptic currents with a time course very similar to intact synapses can be produced using very brief pulses of agonist (Colquhoun et al., 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 ( $\approx 1$  msec) 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 (Fig. 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. Fig. 1A-C shows the AMPA response resulting from a high-frequency train of presynaptic spikes. The amplitude of successive PSC's decreased progressively due to 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 (shown in Fig. 2A) and to the response desensitization that occurs during multiple successive events (Fig. 1D). Alpha functions, in contrast, did not match the summation behavior of the synaptic current (Fig. 1E).

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 PSC's (Fig. 2B-C; see Destexhe et al., 1994c for more details).

## 5 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 than ligand-gated channels 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,  $G_\alpha$  (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 (Fig. 3) was compared to 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 captured 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 Eqs 9 and 10. These elementary schemes provide excellent fits to whole-cell recordings of GABA-B PSC's (Fig 2D), and are also fast to compute.

The neuromodulators listed above 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).

## 6 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).

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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 summed alpha functions. Modified from Destexhe et al. (1994c).

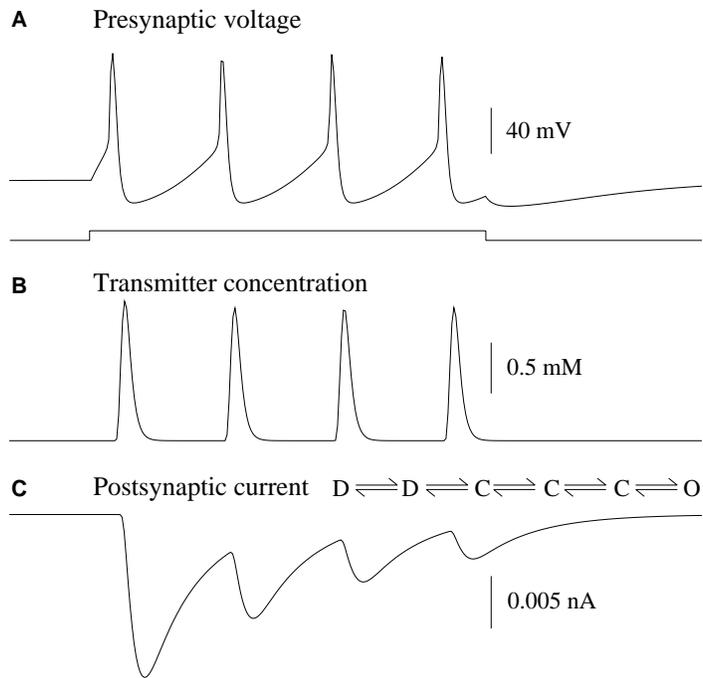
Figure 2:

Elementary kinetic schemes provide good models of postsynaptic currents. A. AMPA-mediated currents (obtained from Z. Xiang, A.C. Greenwood and T. Brown). B. NMDA-mediated currents (obtained from N.A. Hessler and R. Malinow). C. GABA-A-mediated currents (obtained from T.S. Otis and I. Mody). D. GABA-B-mediated currents (obtained by 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 and 85 *ms* for D). A and D modified from Destexhe et al. (1994c), B unpublished, C modified from Destexhe et al. (1994a). Values of rate constants and other parameters are found in Destexhe et al. (1994c).

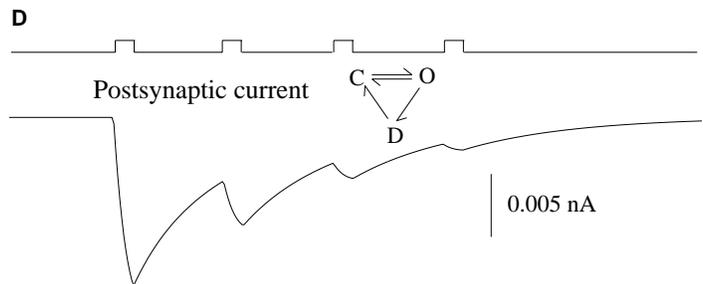
Figure 3:

Kinetic model of synaptic currents acting via 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).

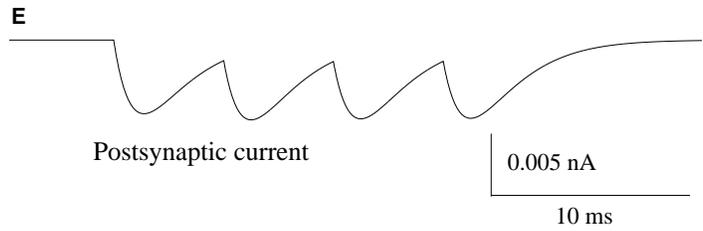
## Detailed kinetic model



## Pulse-based kinetic model



## Alpha functions



**FIG. 1**

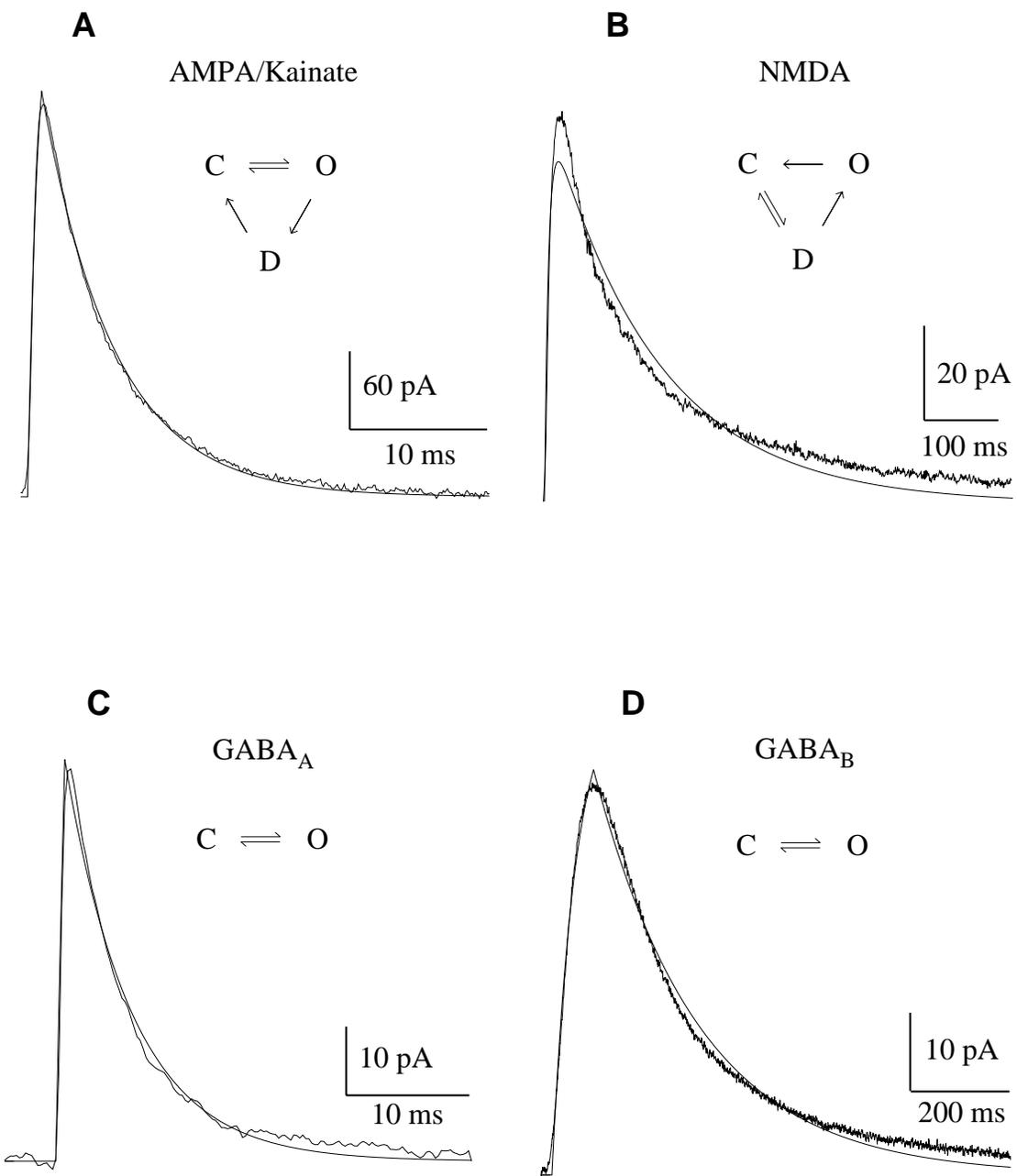
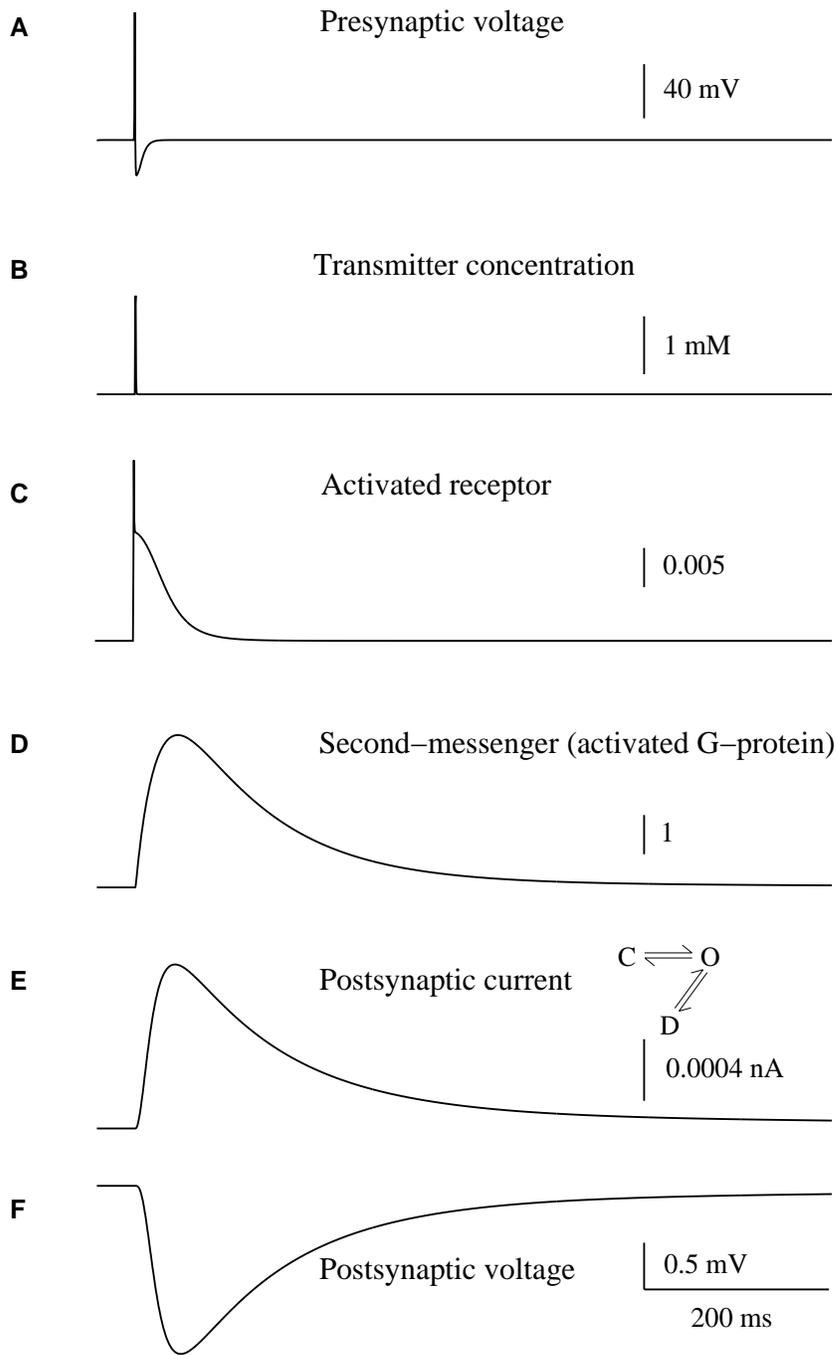


FIG. 2



**FIG. 3**