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FAST KINETIC MODELS FOR SIMULATING AMPA, NMDA, GABA$_A$ AND GABA$_B$ RECEPTORS

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Abstract

Since the introduction of the alpha function by Rall in 1967 [12], there has been significant progress in our understanding of the molecular events underlying synaptic transmission. Particular receptor types have been identified and their activation kinetics characterized. It is now possible to develop models of these receptors, using a formalism similar to that introduced by Hodgkin and Huxley [9]. In this paper, we present recently-introduced models obtained by simplifying more detailed biophysical models of postsynaptic receptors [7]. The simplified models are fully compatible with the Hodgkin-Huxley formalism, are very efficient to simulate, and account for important phenomena such as synaptic summation and desensitization. These models should be useful in large-scale network simulations.
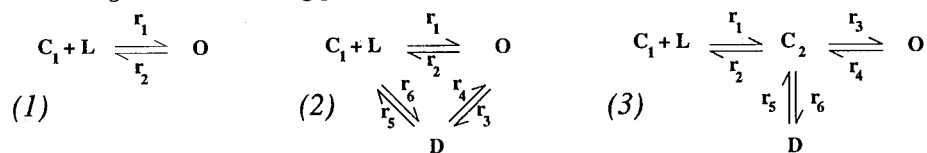
Fast kinetic models

In a previous paper [7], we developed a model of synaptic transmission that incorporated the kinetics of voltage-dependent channels, the kinetics of exocytosis of neurotransmitter in the synapse, diffusion of the neurotransmitter and binding to postsynaptic receptors, and finally the kinetics of activation of these receptors. It was shown that introducing simplifying assumptions leads to much simpler kinetic models for a variety of receptor types, including fast transmission and neuromodulation.

Synaptic receptors activate or deactivate ion channels located in the postsynaptic cell. In the case of "fast" synaptic transmission, the receptor and the channel are part of the same protein complex. In these so-called *ionotropic receptors*, the ligand is a neurotransmitter and its binding to the complex leads to the opening of the associated ionophore. Ionotropic receptors include the glutamate AMPA/kainate and NMDA types, the fast GABAergic receptors

(GABA$_A$) and nicotinic acetylcholine (ACh) receptors. However, for a variety of neurotransmitters, the channel is independent of the receptor and the gating occurs through the production of an intracellular second messenger. These so-called *metabotropic receptors* include the slow GABAergic type (GABA$_B$), muscarinic ACh receptors, noradrenergic receptors, serotonergic receptors, as well as other types.

We have considered relatively detailed kinetic schemes for both ionotropic and metabotropic types of synaptic receptors. For both types, we derived simple kinetic schemes that account for most of their properties. The simplified models assume that the time course of the ligand, L, occurs as a pulse, triggered by the presynaptic spike. The ligand then gates the opening of a ion channel, according to the following possible schemes:

$$C_1 + L \underset{r_2}{\overset{r_1}{\rightleftharpoons}} O \qquad\qquad C_1 + L \underset{r_2}{\overset{r_1}{\rightleftharpoons}} O \qquad\qquad C_1 + L \underset{r_2}{\overset{r_1}{\rightleftharpoons}} C_2 \underset{r_4}{\overset{r_3}{\rightleftharpoons}} O$$

$$\text{(1)} \qquad\qquad \text{(2)} \quad {}_{r_5}\!\!\diagdown \overset{r_6}{} \quad \overset{r_4}{}\!\!\diagup{}_{r_3} \qquad\qquad \text{(3)} \qquad r_5 \updownarrow r_6$$

$$\qquad\qquad\qquad\qquad D \qquad\qquad\qquad\qquad\qquad\qquad D$$

In these schemes, C_1 and C_2 represent the closed states of the channel, O is the open state, D represents the desensitized state and $r_1...r_6$ are the associated rate constants. The synaptic current I_{syn} is obtained from the relation:

$$I_{syn} = \bar{g}_{syn}\, m\, (V - E_{syn})$$

where $\bar{g}_{syn}$ is the maximal synaptic conductance, m is the fraction of channels in open state, V is the postsynaptic membrane potential and E_{syn} is the reversal potential.

The time course of the ligand L and the kinetic constants distinguish ionotropic from metabotropic receptors. In the former, L represents the neurotransmitter and occurs as a pulse of 1 mM amplitude and 1 ms duration, as estimated from patch-clamp recordings [4]. In the latter, L is a second messenger and occurs as a pulse of 1 μM amplitude and 50-100 ms duration. These values were estimated from kinetic data of second-messenger transduction.

The computational advantage of simple schemes such as (1-2) is that the time course of the current can be obtained analytically [6, 7]. The analytic expressions make these models extremely powerful because they do not require differential equations to be solved numerically (see ref. [7] for more details). Another advantage is that it is easy to fit model to experimental data, as described in the next section.

Adjustment of parameters for different receptor types

AMPA/kainate glutamate receptors are among the most prominent receptors found in central synapses and mediate fast excitatory transmission. We have fit the above models to averaged AMPA/kainate-mediated postsynaptic cur-
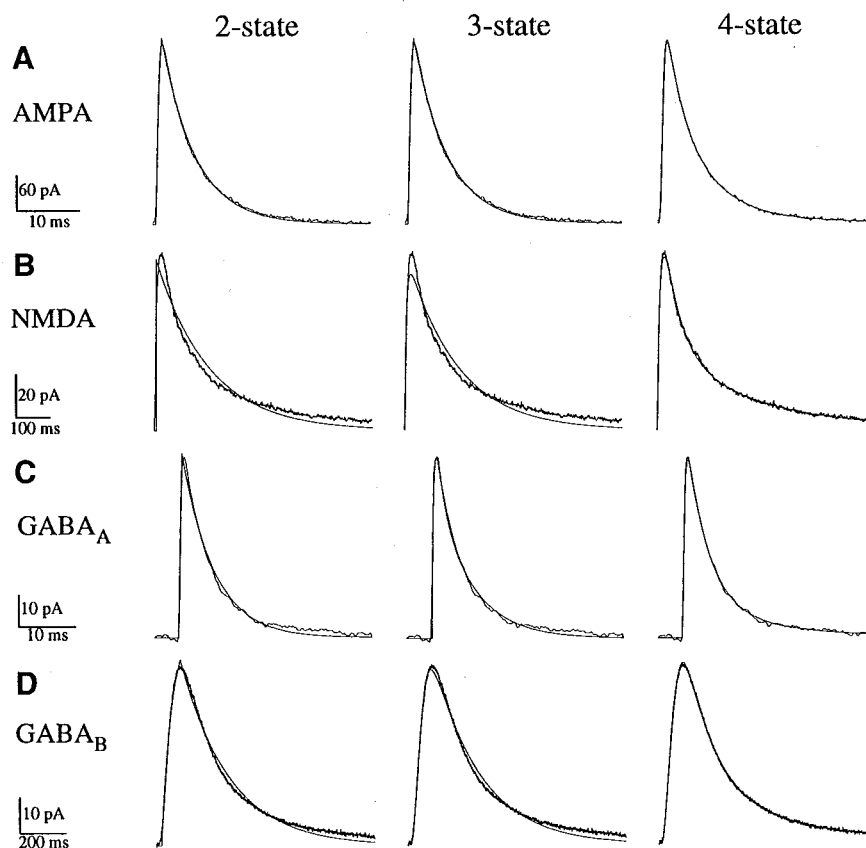
Figure 1

Fit of simple kinetic schemes to four types of synaptic currents. A. AMPA/kainate-mediated currents (obtained from Z. Xiang, A.C. Greenwood and T. Brown [14]). B. NMDA-mediated currents (obtained from N.A. Hessler and R. Malinow [8]). C. GABA$_A$-mediated currents (obtained from T.S. Otis and I. Mody [11]). D. GABA$_B$-mediated currents (obtained from T.S. Otis, Y. De Koninck and I. Mody [10]). The averaged recording of the synaptic current (noisy traces — negative currents upwards for A and B) is shown with the best fit obtained using simple kinetics with a simplex algorithm (continuous trace — parameters given in Table 1). A and D modified from [5], B unpublished, C modified from [7].

rents (PSC) from whole-cell recordings in mossy fiber synapses in hippocampal pyramidal cells [7]. For this neurotransmitter-gated channel, two-, three- or four-state kinetic schemes gave very good fits (Fig. 1A). However, only three- or four-state schemes could account for phenomena like receptor desensitization (see ref. [7]).

Table 1

Optimal values of the rate constants obtained by fitting simple gating kinetic schemes to averaged recordings of synaptic currents for various receptors. The kinetic schemes (1-3) are as indicated in the text. The rate constants shown are from the best model of this kind that fit the experimental data using a simplex algorithm (see Fig. 1). All kinetic schemes assumed a pulse of ligand (1 mM amplitude and 1 ms duration for AMPA/kainate, NMDA and GABA$_A$; 1 μM amplitude and, from top to bottom, 84, 97 and 66 ms duration for GABA$_B$). Other receptors, such as cholinergic muscarinic ($M2$), noradrenergic ($\alpha 2$), serotonergic ($5HT - 1$), dopaminergic ($D2$), adenosinergic ($A1$) and histaminergic are likely to act through the same G-protein-based mechanisms as $GABA_B$ [2, 3] and show a similar slow time course. The units of the rate constants are as follows: $s^{-1}mM^{-1}$ for r_1 ($s^{-1}\mu M^{-1}$ in the case of GABA$_B$); s^{-1} for r_2, r_3, r_4 and r_5; s^{-1} for r_6 in scheme (3); $s^{-1}mM^{-1}$ for r_6 in scheme (2) ($s^{-1}\mu M^{-1}$ in the case of GABA$_B$).

Receptor	Scheme	r_1	r_2	r_3	r_4	r_5	r_6
AMPA/kainate	(1)	1100	190	-	-	-	-
	(2)	1000	10	180	0	0.63	0
	(3)	980	1030	1300	630	410	300
NMDA	(1)	72	6.6	-	-	-	-
	(2)	0	6.9	0	160	4.7	190
	(3)	320	29	48	28	10	11
GABA$_A$	(1)	530	180	-	-	-	-
	(2)	150	200	22	11	34	190
	(3)	1120	310	1100	1650	85	76
GABA$_B$	(1)	16	4.7	-	-	-	-
	(2)	18	4.4	1.5	1.5	0.12	0.28
	(3)	38	15	10	12	5.7	2.5

NMDA receptors are a second type of glutamate ionotropic channel which have a time course significantly slower than the AMPA/kainate type. The above models were fit to an averaged NMDA PSC obtained by whole-cell recordings in hippocampal slices [7]. The NMDA current could only be fit well by a four-state scheme, but two- and three-state schemes gave acceptable fits (Fig. 1B). Alpha functions or related double-exponential template functions gave identical results to the three-state scheme.

GABA$_A$ receptors are a primary mediator of inhibitory currents in central synapses. Kinetic models were fit to an averaged PSC obtained by whole-cell recordings from dentate granule cells [5, 7]. As in the case of fast AMPA/kainate-mediated excitatory channels, fast GABA$_A$ receptor currents were well fit by schemes involving two or more states (Fig. 1C). Note that the decay of this GABAergic current is very similar to the AMPA/kainate type. We do not expect this to be the case for all subtypes of GABA$_A$ and AMPA receptors, since the exact kinetic rates can vary among different subtypes [13].

For all the above receptors, the gating was ionotropic with a relatively fast time course. In the case of GABA (GABA$_B$), cholinergic (M2), noradrenergic (alpha2), serotonergic (5HT-1), dopaminergic (D2), as well as other receptors, a K^+ channel is gated through the action of a G-protein subunit [2, 3]. If the G-protein directly gates the K^+ channel, then a simple kinetic schemes can be derived, assuming 50-100 *ms* pulses of G-protein. This simplified model was found to be very effective in fitting averaged GABA$_B$-mediated PSC obtained by whole-cell recordings from dentate granule cells [5, 7]. As in the case of NMDA channels, the current could only be fit well with a four-state scheme, but two- and three-state schemes gave acceptable fits (Fig. 1D). Fitting is also possible using a short pulse of transmitter, but in this case the kinetics of the receptor, G-protein activation and K^+ channels must be taken into account, leading to more complex models [7].

Discussion

Although it has been possible to develop remarkably detailed models of the synapse [1], substantial simplification is necessary for large-scale network simulations involving thousands of synapses. We have described here one type of simplified model for synaptic responses, based on the kinetics of the ion channel molecules. The time course of the transmitter was assumed to be a constant pulse and the kinetics of the synaptic channel were kept as simple as possible to fit experimentally-recorded postsynaptic currents. We used a set of kinetic schemes that, although very simplified, provided good fits of postsynaptic currents.

An advantage of using kinetic models over other models, such as the alpha function, is that interactions between successive events can be easily captured [6, 7]. Another important advantage of these simplified models is that they can be computed very easily, making them good candidates for large-scale network simulations. Together with Hodgkin-Huxley-like equations for the voltage-dependent currents, the present synaptic models allow a whole network to be described by the same formalism.

Acknowledgments

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