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An Efficient Method for Computing Synaptic Conductances Based on a Kinetic Model of Receptor Binding

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Synaptic events are often formalized in neural models as stereotyped, time-varying conductance waveforms. The most commonly used of such waveforms is the α-function (Rall 1967):

$$g_{\mathrm{syn}}(t) = \frac{(t - t_0)}{\tau} \exp\left[-\frac{(t-t_0)}{\tau}\right], \qquad t \geq t_0 \tag{1}$$

where g_{syn} is the synaptic conductance and t_0 is the time of transmitter release. This function peaks at a value of $1/e$ at $t = t_0 + \tau$, and decays exponentially with a time constant of τ. When multiple events occur in succession at a single synapse, the total conductance at any time is a sum of such waveforms calculated over the individual event times.

There are several drawbacks to this method. First, the relationship to actual synaptic conductances is based only on an approximate correspondence of the time-course of the waveform to physiological recordings of the postsynaptic response, rather than plausible biophysical mechanisms. Second, summation of multiple waveforms can be cumbersome, since each event time must be stored in a queue for the duration of the waveform and necessitates calculation of an additional exponential during this period (but see Srinivasan and Chiel 1993). Third, there is no natural provision for saturation of the conductance.

An alternative to the use of stereotyped waveforms is to compute synaptic conductances directly using a kinetic model (Perkel *et al.* 1981). This approach allows a more realistic biophysical representation and is consistent with the formalism used to describe the conductances of other ion channels. However, solution of the associated differential equations generally requires computationally expensive numerical integration.

In this paper we show that reasonable biophysical assumptions about synaptic transmission allow the equations for a simple kinetic synapse model to be solved analytically. This yields a mechanism that preserves the advantages of kinetic models while being as fast to compute as a single α-function. Moreover, this mechanism accounts implicitly for sat-

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uration and summation of multiple synaptic events, obviating the need for event queuing.

Following the arrival of an action potential at the presynaptic terminal, neurotransmitter molecules, T, are released into the synaptic cleft. These molecules are taken to bind to postsynaptic receptors according to the following first-order kinetic scheme:

$$R + T \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} TR^* \tag{2}$$

where R and TR^* are, respectively, the unbound and the bound form of the postsynaptic receptor, α and β are the forward and backward rate constants for transmitter binding. Letting r represent the fraction of bound receptors, these kinetics are described by the equation

$$\frac{dr}{dt} = \alpha\ [T]\ (1 - r) - \beta\ r \tag{3}$$

where $[T]$ is the concentration of transmitter.

There is evidence from both the neuromuscular junction (Anderson and Stevens 1973) and excitatory central synapses (Colquhoun *et al.* 1992) that the concentration of transmitter in the cleft rises and falls very rapidly. If it is assumed that $[T]$ occurs as a pulse, then it is straightforward to solve equation 3 exactly, leading to the following expressions:

1. During a pulse ($t_0 < t < t_1$), $[T] = T_{\max}$ and r is given by

$$r(t - t_0) = r_\infty + [r(t_0) - r_\infty]\ \exp[-(t - t_0)/\tau_r] \tag{4}$$

where

$$r_\infty = \frac{\alpha\ T_{\max}}{\alpha\ T_{\max} + \beta}$$

and

$$\tau_r = \frac{1}{\alpha\ T_{\max} + \beta}$$

2. After a pulse ($t > t_1$), $[T] = 0$, and r is given by

$$r(t - t_1) = r(t_1)\ \exp[-\beta\ (t - t_1)] \tag{5}$$

If the binding of transmitter to a postsynaptic receptor directly gates the opening of an associated ion channel, then the total conductance through all channels of the synapse is r multiplied by the maximal conductance of the synapse, $\bar{g}_{syn}$. Response saturation occurs naturally as r

approaches 1 (all channels reach the open state). The synaptic current, I_{syn}, is given by the equation

$$I_{syn}(t) = \bar{g}_{syn} \ r(t) \ [V_{syn}(t) - E_{syn}] \tag{6}$$

where V_{syn} is the postsynaptic potential, and E_{syn} is the synaptic reversal potential.

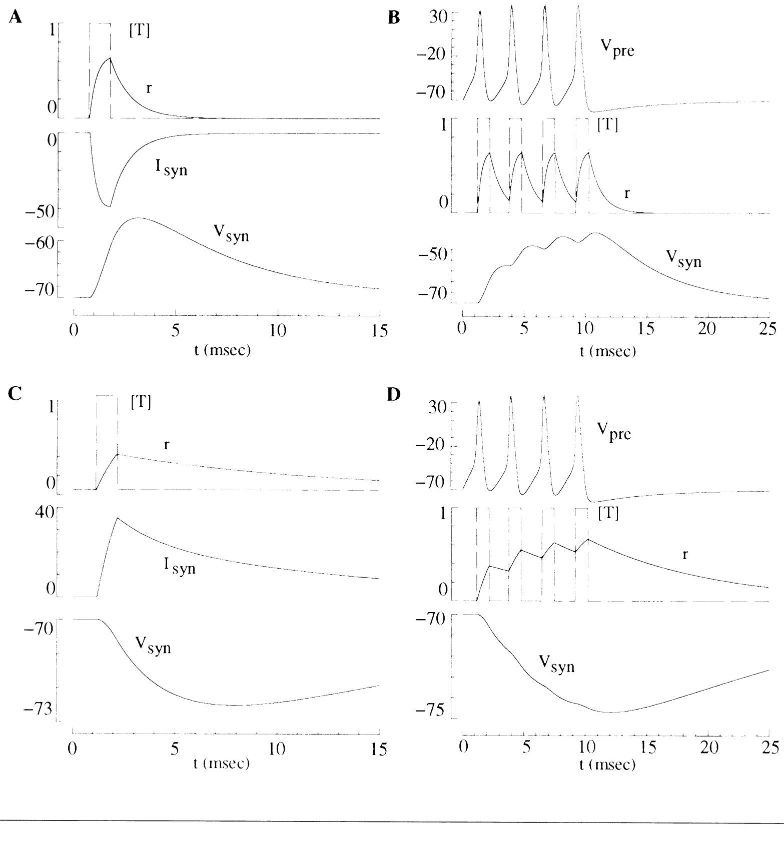
These equations provide an easily implemented method for computing synaptic currents and have storage and computation requirements that are independent of the frequency of presynaptic release events. To simulate a synaptic connection, it is necessary only to monitor the state of the presynaptic terminal and switch from equation 5 to equation 4 for a fixed time following the detection of an event. At each time step, this method requires the storage of just two state variables [either t_0 and $r(t_0)$ or t_1 and $r(t_1)$], and the calculation of a single exponential (either equation 4 or equation 5). This compares favorably to summing α-functions, which requires storage of n release times and n corresponding exponential evaluations, where n is the product of the maximum frequency of release events and the length of time for which the conductance waveform is calculated.

The parameters of the kinetic synapse model can be fit directly to physiological measurements. For instance, duration of the excitatory neurotransmitter glutamate in the synaptic cleft has been estimated to be on the order of 1 msec at concentrations in the 1 m*M* range (Clements *et al.* 1992; Colquhoun *et al.* 1992). Figure 1 shows simulated synaptic

Figure 1: *Facing page.* Postsynaptic potentials from receptor kinetics. Presynaptic voltage, V_{pre} (mV); concentration of transmitter in the synaptic cleft, $[T]$ (m*M*); fraction of open (i.e., transmitter-bound) postsynaptic receptors, r; synaptic current, I_{syn} (pA); and postsynaptic potential, V_{syn} (mV), are shown for different conditions. (A) A single transmitter pulse evokes a fast, excitatory conductance ($\alpha = 2$ msec^{-1} mM^{-1}, $\beta = 1$ msec^{-1}, $E_{syn} = 0$ mV). (B) A train of presynaptic spikes releases a series of transmitter pulses evoking excitatory synaptic conductances (parameters as in A). C and D correspond to A and B, but with parameters set for slower, inhibitory synaptic currents ($\alpha = 0.5$ msec^{-1} mM^{-1}, $\beta = 0.1$ msec^{-1}, $E_{syn} = -80$ mV). For all simulations, the synaptic current was calculated using equations 4–6, with $\bar{g}_{syn} = 1$ nS, $T_{max} = 1$ m*M*, and transmitter pulse duration $(t_1 - t_0) = 1$ msec. Membrane potentials were simulated using NEURON (Hines 1993). Presynaptic and postsynaptic compartments were described by single-compartment cylinders (10 μm diameter and 10 μm length) with passive (leak) conductance (specific membrane capacitance of 1 μF/cm^2, specific membrane resistance of 5000 Ω-cm^2, leak reversal potential of -70 mV). Presynaptic action potentials were modeled by standard Hodgkin–Huxley kinetics. A transmitter pulse was initiated when V_{pre} exceeded a threshold of 0 mV, and pulse initiation was inhibited for 1 msec following event detection.

events obtained using these values. Figure 1A and B show fast, excitatory currents resulting from a single synaptic event and a train of four events. Note that the time course of the postsynaptic potential resembles an α-function even though the underlying current does not. Figure 1C and D show the time courses of the same variables for a slower, inhibitory synapse. In this case the rates for α and β were slower, allowing a more progressive saturation of the receptors.

We have presented a method by which synaptic conductances can be computed with low computational expense using a kinetic model. The kinetic approach provides a natural means to describe the behavior of synapses in a way that handles the interaction of successive presynaptic events. Under the same assumption that transmitter concentration occurs as a pulse, more complex kinetic schemes can be treated



in a manner analogous to that described above (Destexhe *et al.* in preparation). The "kinetic synapse" can thus be generalized to give various conductance time courses with multiexponential rise and decay phases, without sacrificing the efficiency of the first-order model.

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References

Anderson, C. R., and Stevens, C. F. 1973. Voltage clamp analysis of acetylcholine-produced end-plate current fluctuations at frog neuromuscular junction. *J. Physiol. (London)* **235**, 655–691.

Clements, J. D., Lester, R. A. J., Tong, J., Jahr, C., and Westbrook, G. L. 1992. The time course of glutamate in the synaptic cleft. *Science* **258**, 1498–1501.

Colquhoun, D., Jonas, P., and Sakmann, B. 1992. Action of brief pulses of glutamate on AMPA/KAINATE receptors in patches from different neurons of rat hippocampal slices. *J. Physiol. (London)* **458**, 261–287.

Hines, M. 1993. NEURON—A program for simulation of nerve equations. In *Neural Systems: Analysis and Modeling*, F. Eeckman, ed., pp. 127–136. Kluwer Academic Publishers, Norwell, MA.

Perkel, D. H., Mulloney, B., and Budelli, R. W. 1981. Quantitative methods for predicting neuronal behavior. *Neurosci.* **6**, 823–827.

Rall, W. 1967. Distinguishing theoretical synaptic potentials computed for different somedendritic distributions of synaptic inputs. *J. Neurophysiol.* **30**, 1138–1168.

Srinivasan, R., and Chiel, H. J. 1993. Fast calculation of synaptic conductances. *Neural Comp.* **5**, 200–204.

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