Voltage- and Space-Clamp Errors Associated With the Measurement of Electrotonically Remote Synaptic Events

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SUMMARY AND CONCLUSIONS

1. The voltage- and space-clamp errors associated with the use of a somatic electrode to measure current from dendritic synapses are evaluated using both equivalent-cylinder and morphologically realistic models of neuronal dendritic trees.

2. As a first step toward understanding the properties of synaptic current distortion under voltage-clamp conditions, the attenuation of step and sinusoidal voltage changes are evaluated in equivalent cylinder models. Demonstration of the frequency-dependent attenuation of voltage in the cable is then used as a framework for understanding the distortion of synaptic currents generated at sites remote from the somatic recording electrode and measured in the voltage-clamp recording configuration.

3. Increases in specific membrane resistivity (Rm) are shown to reduce steady-state voltage attenuation, while producing only minimal reduction in attenuation of transient voltage changes. Experimental manipulations that increase Rm therefore improve the accuracy of estimates of reversal potential for electrotonically remote synapses, but do not significantly reduce the attenuation of peak current. In addition, increases in Rm have the effect of slowing the kinetics of poorly clamped synaptic currents.

4. The effects of the magnitude of the synaptic conductance and its kinetics on the measured synaptic currents are also examined and discussed. The error in estimating parameters from measured synaptic currents is greatest for synapses with fast kinetics and large conductances.

5. A morphologically realistic model of a CA3 pyramidal neuron is used to demonstrate the generality of the conclusions derived from equivalent cylinder models. The realistic model is also used to fit synaptic currents generated by stimulation of mossy fiber (MF) and commissural/associational (C/A) inputs to CA3 neurons and to estimate the amount of distortion of these measured currents.

6. Anatomic data from the CA3 pyramidal neuron model are used to construct a simplified two-cylinder CA3 model. This model is used to estimate the electrotonic distances of MF synapses (which are located proximal to the soma) and perforant path (PP) synapses (which are located at the distal ends of the apical dendrites) and the distortion of synaptic current parameters measured for these synapses.

7. Results from the equivalent-cylinder models, the morphological CA3 model, and the simplified CA3 model all indicate that the amount of distortion of synaptic currents increases steeply as a function of distance from the soma. MF synapses close to the soma are likely to be subject only to small space-clamp errors, whereas MF synapses farther from the soma are likely to be substantially attenuated. Synaptic currents from more remote synapses such as C/A and PP inputs are shown to be enormously attenuated.

8. In conclusion, we show that despite experimental manipulations to eliminate somatic leak conductances and increase Rm, synaptic currents generated in neuronal dendrites and measured at the soma can still be significantly attenuated and distorted. Estimates of synaptic conductances and kinetics from voltage-clamp measurements made at the soma should therefore be paired with estimates of the errors associated with these measurements. Such estimates will require a knowledge of the location and kinetics for the synapse under study as well as the electrotonic structure of the postsynaptic neuron. The unclamped nature of remote synaptic events also raises the possibility that voltage-gated channels in dendrites may be activated by synaptic inputs, even under voltage-clamp conditions.

INTRODUCTION

The dendrites of central neurons can receive thousands of synaptic inputs producing postsynaptic potentials that are attenuated as they propagate within the dendritic tree. Cable properties are therefore of central importance to our understanding of the integrative function of neurons. Furthermore, consideration of the cable properties of neurons is an essential step in the interpretation of experiments performed to investigate synaptic conducances in neurons with complex dendritic structures. The problems associated with voltage clamping remote synaptic conducances have been widely acknowledged in the literature and extensive efforts have been made to quantitatively assess the cable properties of neurons and the resulting difficulties inherent in the interpretation of data obtained with electrodes placed at the soma (Carnevale and Johnston 1982; Clements and Redman 1989; Durand 1984; Iansek and Redman 1973a; Johnston and Brown 1983; Kawato 1984; Poznanski 1987a,b; Rall and Segev 1985).

With the recent application of patch-clamp techniques to neurons in brain slice preparations (Blount et al. 1989; Edwards et al. 1989), it is now possible to reevaluate the cable properties of neurons under conditions of a dramatically reduced somatic leak conducance. We have combined patch-clamp estimates of the passive membrane properties of hippocampal neurons (S pruston and Johnston 1992) and published anatomic data (Blackstad 1956; Blackstad et al. 1970; Hjorth-Simonsen 1973; Johnston and Brown 1983) to construct models with which the attenuation of potential in a dendritic tree is estimated for voltage changes of various frequencies. We also estimate errors associated with imperfect space-clamp and discuss the differences expected between recordings made with conventional microelectrodes and patch-clamp electrodes. Finally, we assess the errors associated with estimating reversal potential, 10-90% rise time, half-decay time, and synaptic
conductance for remote synaptic inputs to hippocampal neurons. We find that, in spite of the elimination of the somatic leak conductance and the resulting increase in input resistance \(R_n\) and specific membrane resistivity \(R_m\) when using patch-clamp recording and intracellular channel blockers, space-clamp errors are substantial, even for synapses located relatively close to the soma.

**METHODS**

*Equivalent cylinder model*

Variations of the model shown schematically in Fig. 1A were used for all equivalent cylinder simulations. The model does not represent a specific type of neuron, but rather demonstrates the general features of voltage and current attenuation in dendritic cables. Using patch-clamp recordings of central neurons, we determined that 50,000 \(\Omega cm^2\) was a reasonable estimate of \(R_m\) (see Spruston and Johnston 1992). A specific intracellular resistivity \(R_i\) of 200 \(\Omega cm\) was chosen. A specific membrane capacitance \(C_m\) of 1.0 \(\mu F/cm^2\) was assumed. With these parameters, a cable with radius \(a\) 0.8 \(\mu m\) and a length \(L\) 1,000 \(\mu m\) was used to model a collapsed dendritic tree having a DC electrotonic length \(L\) of 1.0. The electrotonic length of the cylinder is defined by the equation

\[
L = l/\lambda
\]

where \(\lambda\) is the space constant of the cable given by

\[
\lambda = \sqrt{\frac{aR_m}{2R_i}}
\]

A sphere with a radius \(r\) of 5 \(\mu m\) was added to one end of the model to simulate the soma. A resting potential of −70 mV was used for all simulations.

*Morphological model of the CA3 pyramidal neuron*

The geometry used in the morphological model was obtained from a camera lucida drawing of a Golgi-stained guinea pig hippocampal CA3 pyramidal neuron, provided by Russel Fricke (Fig. 9A). The neuron was divided into cylindrical compartments, each modeling a section of dendrite between two branch points. Some compartments were further subdivided to facilitate the division of the dendrites into proximal, medial, and distal sections. There were a total of 149 compartments (Fig. 9B), with a mean compartmental length of 53 ± 44 \(\mu m\) (mean ± SD; range: 1–197 \(\mu m\)). An \(R_m\) value of 100,000 \(\Omega cm^2\) and an \(R_i\) value of 205 \(\Omega cm\) were used because these provided good fits of mossy fiber (MF) and off-center associative (CA) excitatory postsynaptic conductance (EPSC) kinetics recorded from rat CA3 neurons using the single-electrode voltage clamp with conventional microelectrodes (see RESULTS for more details). With these \(R_m\) and \(R_i\) values, the mean electrotonic length of the individual compartments was 0.05 ± 0.04 (mean ± SD; range: 0.0001–0.12). The camera lucida drawing did not contain sufficient detail to include spines in the model, but the effects of spines are considered in the simplified two-cable model described below.

*Simplified two-cable CA3 model*

Simplified best-case and worst-case models of a CA3 neuron were also constructed to estimate a range of possible scenarios for attenuation of measured synaptic current. Both models consisted of a pyramidal soma (identical to that shown in Fig. 9B) and two separate equivalent cylinders to represent the basal and apical dendritic trees.

The parameters used in the two models are shown in Table 1. The best case (min. attenuation) was modeled with low \(R_i\), high \(R_m\), and low \(C_m\) \((R_i = 70 \Omega cm, R_m = 200,000 \Omega cm^2, C_m = 0.7 \mu F/cm^2)\). The low \(R_i\) value was taken from estimates in cortical pyramidal neurons (Barrett and Crill 1974a). The high \(R_m\) was chosen to reflect the use of channel blockers and the low \(C_m\) is a lower-limit estimate based on modeling of physiological transients with morphologically realistic compartmental models (Major 1992). The worst case (max. attenuation) was modeled with high \(R_i\), low \(R_m\), and high \(C_m\) \((R_i = 300 \Omega cm, R_m = 33,000 \Omega cm^2, C_m = 2.0 \mu F/cm^2)\). Because the morphological model did not include spine data, \(R_m\) was halved and \(C_m\) doubled (with respect to physiological values; Spruston and Johnston 1992), to account for the increased surface area of spines.

The electrotonic length of the apical and basal dendritic trees was estimated for the best and worst cases using the parameters described above and calculating the mean electrotonic length along each branching dendritic path from the soma to the tips of the apical and basal dendrites for the model shown in Fig. 9. Using this approach, a lower limit of \(L = 0.12 ± 0.01\) (mean ± SD; \(n = 7\)) was arrived at for the apical dendritic cable, and \(L = 0.06 ± 0.02\) (mean ± SD for 7 representative branches) for the basal cable. The upper limits calculated were \(L = 0.62 ± 0.12\) for the apical cable and \(L = 0.30 ± 0.09\) for the basal cable.

The length and radius of the two cables were calculated to conserve the surface area \(S\) of the apical and basal dendritic trees of the neuron shown in Fig. 9A. The appropriate cable radius was calculated from the equation

\[
a = \sqrt[3]{\frac{S^3 R_m}{2\pi L}}
\]

which was derived from the expression for the surface area of the cable.

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<th>Table 1. Parameters used in constructing maximum and minimum attenuation cases for a 2-cable CA3 equivalent-cylinder model</th>
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<tr>
<td>Min. Attenuation</td>
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<td>(C_m), (\mu F/cm^2)</td>
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<td>Apical cable (S), (\mu m^2)</td>
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<td>MF (x), (\mu m)</td>
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1 Although values of 50–70 \(\Omega cm\) have commonly been used for \(R_i\), recent modeling studies (Jonas et al. 1993; Major 1993; Shelton 1985; Spruston and Johnston 1992; Stratford et al. 1989) suggest that high values of \(R_i\) are likely to be more appropriate for central neurons.
AFTER calculating the appropriate $a$, $l$ was calculated from Eqs. 2 and 1 and rounded to the nearest 10 μm. As expected from Eq. 4, the lengths and radii of the apical and basal cables were different, but independent of $R_m$, $C_m$, and $R_t$. The model parameters are summarized in Table 1.

We preferred the method of halving $R_m$ and doubling $C_m$ described above over doubling the surface area to account for spines because the electrotonic lengths of each dendritic path are affected by spines in a way that is best approximated by lowering $R_m$. Calculating the $L$ values along each path using the higher $R_m$ value and later doubling $S$ would lead to an underestimate of the effective $L$ with spines.

**Numerical models**

All numerical solutions for both equivalent cylinder models and the CA3 morphological model were computed using a version of CABLE (Hines 1989) modified to include synaptic conductance simulation. CABLE simulations were performed on a Solbourne Series 300 computer (SUN-4 compatible SPARC station; Sun OS/SMP 4.0) and a Sun SPARC station 2 (Solaris 1.0).

Synaptic conductance changes ($Δg$) in both equivalent cylinder models and the morphological CA3 model were modeled using an alpha function of the form

$$Δg = g_{syn}αtα^1−αt$$

where $t$ is time in seconds, $α$ is a constant determining the speed of the conductance change (and having the units s$^{−1}$), and $g_{syn}$ is the maximum synaptic conductance.

Synaptic current ($ΔI$) is therefore given by the equation

$$ΔI = Δg(V_m - E_{syn})$$

where $V_m$ is the membrane potential at the site of the synapse and $E_{syn}$ is the synaptic reversal potential.

MF synapses (Fig. 10) were simulated on compartments within 100 μm of the soma. C/A synapses were simulated on compartments 250–350 μm from the soma, which is approximately halfway to the end of the apical dendritic tree. These synaptic locations were chosen on the basis of published anatomic distances of MF and C/A synapses from the soma (Blackstad 1956; Blackstad et al. 1971; Blackstad and Rjaerheim 1961; Hjorth-Simonsen 1973; Johnston and Brown 1983).

**Analytical solutions**

When analytical solutions for the simulations exist, these are plotted as solid lines for comparison with the numeric solutions plotted as individual points (as noted in the figure legends). All analytical solutions were computed using Mathematica (Wolfram Research) running on a Macintosh IIci computer (Mac-OS, 68030 microprocessor with 68882 math coprocessor). Analytic solutions could not be calculated for simulations involving synaptic conductance changes (but can be if simple current injection is modeled; see Rall 1964), so points corresponding to the numeric computations are simply connected by solid lines.

Analytical solutions for the attenuation of steady-state voltage changes were computed from the following equation (Rall 1977)

$$V_X\ =\ \cosh (L - X)\ \cosh (L)\ \cosh (L)\ \cosh (L)\ \cosh (L)$$

where $V_0$ is the amplitude of a steady-state voltage change at the soma and $V_X$ is the attenuated amplitude of the voltage change at a given electrotonic distance ($X = α/λ$, where $α$ is the physical distance from the end of the cable and $λ$ is the space constant of the cable).

Equation 7 holds only for the steady state, however, and a different equation must be used to calculate the attenuation of the amplitude of a sine wave of frequency $ω = 2πf$ (where $f$ is in kHz). The analytical solutions for the attenuation of sine-wave voltage changes in finite scaled-cylinder equivalent cylinder models were therefore computed using the equation (Eq. 14 of Rall and Segev 1985)

$$\frac{V_X}{V_0} = \left[ \frac{\cosh (2aL) + \cos (2bL)}{\cosh (2aL) + \cos (2bL)} \right]^{1/2}$$

where $V_0$ is the amplitude of a sine-wave voltage change at the soma and $V_X$ is the attenuated amplitude of the voltage change at $X = L - X$, and $a$ and $b$ are the real and imaginary parts of $\sqrt{1 + jωr_m}$ (where $j$ is $\sqrt{-1}$ and $r_m$ is the membrane time constant). The solution to Eq. 8 can be computed using the following equations (from the Appendix of Rall and Segev 1985)

$$r = \sqrt{1 + ω^2r_m^2}$$

$$θ = \arctan (ωr_m)$$

$$a = \sqrt{r} \cos (θ/2)$$

$$b = \sqrt{r} \sin (θ/2)$$

**RESULTS**

**Voltage attenuation in equivalent cylinder models**

The effects of increases in $R_m$ on voltage attenuation in equivalent cylinder models are shown in Fig. 1 both for the steady state and for sine waves of various frequencies. Figure 1A shows a schematic of the model (with electronic length, $L_e = 1.0$) with step and 50-Hz sine wave voltage responses evoked at the soma and measured both at the soma (- - -) and the end of the cable (---). Both the DC and the AC potential changes were simulated with a perfect voltage clamp at the soma, but attenuate along the cable in a frequency-dependent manner, with higher-frequency voltage changes being attenuated to a greater extent than lower-frequency or steady-state changes. This is shown further in Fig. 1B, which plots the attenuation of potential from the soma to the end of the cable and vice versa. While the frequency dependence of voltage attenuation in cables is well known (see, for example, Johnston and Brown 1983; Rall and Segev 1985), we investigate here the effects of increases in $R_m$ on this attenuation.

The effect of increasing $R_m$ from 50,000 to 500,000 Ωcm$^2$ (such as might be achieved by filling neurons with Cs$^+$ or other channel blocking agents) is shown in Fig. 1C. The higher $R_m$ substantially decreases the attenuation of a DC voltage change, but only slightly decreases the attenuation of 10- and 100-Hz voltage changes.

Figure 1B also demonstrates the effect of a somatic leak (to mimic impalement of the soma with a microelectrode) on these "voltage attenuation profiles." In the left column, the voltage change is imposed at the soma ($x/l = 0$) and the effect of a somatic leak is simply to change the amount of current required to clamp the soma; the voltage decay toward the end of the cable is the same as when there is no leak. In the right column, deviation of the open symbols from the theoretical curves is a consequence of the soma at the end of the cable, which acts like a leak even in the case of uniform $R_m$. Further increasing this leak by lowering the effective $R_m$ at the soma to 200 Ωcm$^2$ results in more deviation of the voltage attenuation from the analytic curves (shown only for the DC case; Fig. 1B). At higher frequencies, the attenuation by the cable itself dominates and the additional attenuation due to a somatic leak becomes
EFFECTS OF SYNAPSE DISTANCE AND $R_m$

Figure 3A shows synaptic currents measured with a voltage clamp at the soma and a leak on the soma for $R_m = 500,000 \, \Omega \text{cm}^2$. The current required to clamp the membrane potential at the soma is therefore smaller than the actual current at the synapse by an amount related to the synapse-to-soma voltage attenuation properties. Further error arises from the fact that the current injected at the soma attenuates as it propagates passively back to the synapse because of the soma-to-synapse attenuation properties. Both of these factors result in inadequate voltage control at the synapse, which results in "synaptic voltage escape" (see Fig. 3B). In addition, this synaptic voltage escape causes the synaptic driving potential ($V_{\text{syn}} - E_{\text{rev}}$, where $V_{\text{syn}}$ is the membrane potential at the synapse) to be reduced and consequently, the actual charge entry at the synapse is less than what it would be under ideal space-clamp conditions.

Rall and Segev (1985) have previously shown that the attenuation of synaptic current measured at the soma (modeled by $\alpha$-function current injection at different distances on an equivalent cylinder) is severe, even for synapses located quite close to the soma. Here we extend this analysis by modeling synaptic input as an $\alpha$-function conductance change on the cable and examining the effects of changes in various parameters of both the synaptic conductance change and the equivalent cylinder model.

FIG. 1. Increases in membrane resistivity ($R_m$) reduce attenuation of steady-state and low-frequency voltage changes much more than higher-frequency voltage changes. A: schematic diagram of equivalent cylinder model used. Parameters used in model were $R_m = 50,000 \, \Omega \text{cm}^2$, specific membrane capacitance ($C_m$) = 1 $\mu\text{F/cm}^2$, $R_i = 200 \, \Omega$, cable radius ($a$) = 0.8 $\mu\text{m}$, cable length ($l$) = 1,000 $\mu\text{m}$, soma radius ($r$) = 5 $\mu\text{m}$. Soma and cable radii are drawn to scale, but length of cable is 10 times shorter on this scale. Also shown are voltage responses at soma (---) and end of cable (----) for both step (left) and 50-Hz sine wave (right). Voltage changes produced by voltage clamp at the soma from resting potential of -70 mV. B: voltage changes ($\bullet$, steady state; $\Delta$, 10-Hz sine wave; $\triangle$, 100-Hz sine wave) plotted as ratio of voltage amplitude at a given electrotonic length ($x$) on cable to amplitude at origin of voltage change ($V_x/V_0$ or $V_x/V_L$) as a function of position on cable ($x/l$). These "attenuation profiles" are plotted for voltage changes generated at soma (left, arrow on x/l axis indicates origin of voltage change) and at end of the cable (right) for $R_m$ values of 50,000 $\Omega \text{cm}^2$. Effects of a somatic leak (somatic $R_m$ reduced to 200 $\Omega \text{cm}^2$) on steady-state voltage attenuation from the end to the soma are also shown (---). Analytical solutions calculated from Eqs. 7 and 8 are plotted as solid lines. These equations do not apply for the case of decay from the end of cable to the soma when a leak is placed at soma, so points are simply connected in this case. Deviation in analytical and numerical solutions for voltages generated at end of the cable is due to effects of soma, which are not taken into account by Eqs. 7 and 8. C: same plots as B for $R_m = 500,000 \, \Omega \text{cm}^2$. Effects of a somatic leak not shown.

Attenuation of synaptic currents in equivalent cylinder models

One of the most practical reasons for assessing the degree of voltage attenuation from the soma-to-end and end-to-soma of a cable is to determine the errors associated with the measurement of remote conductances by the use of voltage-clamp methods. Voltage attenuation errors affect the measurement of current generated by synaptic inputs that are remote from the voltage-clamp electrode in the following way: synaptic current produces a change in voltage at the synapse that is attenuated as it propagates passively to the soma. The current required to clamp this change in potential at the soma is therefore smaller than the actual current at the synapse by an amount related to the synapse-to-soma voltage attenuation properties. Further error arises from the fact that the current injected at the soma attenuates as it propagates passively back to the synapse because of the soma-to-synapse attenuation properties. Both of these factors result in inadequate voltage control at the synapse, which results in "synaptic voltage escape" (see Fig. 3B). In addition, this synaptic voltage escape causes the synaptic driving potential ($V_{\text{syn}} - E_{\text{rev}}$, where $V_{\text{syn}}$ is the membrane potential at the synapse) to be reduced and consequently, the actual charge entry at the synapse is less than what it would be under ideal space-clamp conditions.

Rall and Segev (1985) have previously shown that the attenuation of synaptic current measured at the soma (modeled by $\alpha$-function current injection at different distances on an equivalent cylinder) is severe, even for synapses located quite close to the soma. Here we extend this analysis by modeling synaptic input as an $\alpha$-function conductance change on the cable and examining the effects of changes in various parameters of both the synaptic conductance change and the equivalent cylinder model.

Effects of Synapse Distance and $R_m$

Figure 3A shows synaptic currents measured with a voltage clamp at the
Soma for synapses located at 0, 100, 500, and 1,000 μm from the soma of the equivalent cylinder model shown in Fig. 1A. The peak amplitudes of the somatic clamp current at 70 mV (I_{syn})^2 and the peak synaptic escape voltage are plotted as a function of synapse position in Fig. 3, C and D, respectively. All synaptic currents were generated using identical α-function conductance changes (α = 2,850 s⁻¹) that simulated currents with a 10–90% rise time of 0.2 ms, a half-decay time of 0.39 ms, and a peak conductance (g_{syn}) of 1.0 nS under perfect voltage-clamp conditions. Note that because perfect somatic voltage-clamp conditions were simulated, the voltage at the soma is always a flat line (not shown), regardless of synapse position. The clamp at remote synapses, however, is far from perfect, as can be seen by the synaptic escape voltages (Fig. 3B, — —). At synaptic locations away from the soma, the escape voltage approaches the unclamped synaptic potential (Fig. 3B, — —). At locations relatively close to the soma, the somatic voltage clamp does little more than speed up the decay of the synaptic voltage, without significantly affecting the peak synaptic voltage. Simulation results using R_m values of 50,000 and 500,000 Ωcm² demonstrate that the attenuation of synaptic current at sites remote from the soma is severe, and that there is very little difference between the synaptic currents measured, with R_m values differing by a factor of 10.

Because fast synaptic currents can have frequency components well in excess of 100 Hz (Johnston and Brown 1983), the severe attenuation of synaptic currents located distant from the synapse is consistent with the steep attenuation of high-frequency voltage changes as a function of distance (both from the soma to the synapse and vice versa) shown in Fig. 1. The lack of improvement of the voltage clamp by a large increase in R_m is readily explained by the fact that fast synaptic currents are attenuated primarily by the membrane capacitance and internal resistance.

Figure 4 shows current-voltage plots obtained at the soma for synapses located at x/l = 0 and x/l = 1.0 (Fig. 4, A and B, respectively; note the small scale of the current axis in Fig. 4B compared with Fig. 4A). As expected for conditions of perfect voltage clamp, the correct synaptic conductance (g_{syn}) of 1.0 nS is measured from the slope of the current-voltage plot for synapses located at the soma (x/l = 0), independent of the R_m value used. For the same synapse located at the end of the cable (x/l = 1.0), however, the measured synaptic conductance (g_{syn}) is much lower and the measured reversal potential (E_{rev}) is more positive at the low R_m value (50,000 Ωcm²) than at the high R_m value (500,000 Ωcm²). Although g_{syn} for the synapse at the end of the cable is slightly larger for the higher R_m value (note the different slopes in Fig. 4B), this increase is negligible relative to the total amount of attenuation of the synaptic current (again, note the smaller scale of the abscissa in Fig. 4B). The lack of improvement in measured synaptic conductance by increases in R_m is illustrated in Fig. 4C, which shows the decrease in g_{syn} (measured from the slope of the current-voltage plot) as a function of distance of the synapse from the soma for the two R_m values. These plots are similar to the plots of peak current shown in Fig. 3C, except that there is one additional source of error. Because g_{syn} is estimated from the slope of the current-voltage curve, any error in E_{rev} will cause an error in g_{syn}. For distal synapses E_{rev} appears more positive than is actually the case, leading to an underestimate of g_{syn}. Because the measurement of E_{rev} strongly depends on R_m (Fig. 4D), this effect is only seen for the low R_m value.

When the synapse is clamped to E_{rev}, no synaptic current flows, and accordingly the only error incurred is related to the electrotonic distance of the synapse (X). This was first shown by Calvin (1969) for the case of excitatory postsynaptic potentials (EPSPs) clamped to the reversal potential with a current clamp at the soma. Because the X for a given synaptic location is smaller for higher R_m values, increasing R_m has the effect of dramatically improving the accuracy of measured values of E_{rev} (see Fig. 4D). This result suggests that increasing the value of R_m through the use of channel blockers (such as Cs⁺) in patch-clamp electrodes may result in accurate estimates of E_{rev}, even for synapses located distant from the soma, whose currents measured at the soma will have significantly attenuated amplitudes and distorted kinetic properties.

The kinetics of synaptic currents originating distant from the soma are actually slowed at higher R_m values (Fig. 4, E and F). Synapses located farther from the soma have increasingly long rise times and half-decay times. The plots

---

2 For convenience, the actual values of the synaptic parameters (i.e., under perfect clamp conditions: peak synaptic current, I_{syn}; synaptic conductance, g_{syn}; synaptic reversal potential, E_{rev}; synaptic charge, q_{syn}; 10–90% rise time, t_{rise}; and half-decay time, t_{decay}) are distinguished here from the measured values by the use of the prime symbol (i.e., under imperfect clamp conditions: I'_{syn}, g'_{syn}, E'_{rev}, q'_{syn}, t'_{rise}, t'_{decay}).

3 Synapse position is designated on the abscissa by the unitless ratio x/l rather than the physical distance (x) or the electrotonic distance (X) because the length of the equivalent cylinder was chosen arbitrarily and therefore has no particular significance. This convention was also preferred over the use of electrotonic distance to denote synapse position because it allows differences in results from simulations using two different R_m values to be plotted and compared on the same abscissa.

4 Half-decay time was chosen over decay time constant as a measure of synaptic decay because, as shown previously (Johnston and Brown 1983), we found that the decay of current from synapses located distant from the soma was not well fit by single or multiple exponential functions.
A Somatic Currents

○ $R_m = 50,000 \Omega \text{cm}^2$

Δ $R_m = 500,000 \Omega \text{cm}^2$

\[ x/l = 1.0 \]

\[ 0.5 \]

\[ 0.1 \]

\[ 0 \]

15 pA

5 ms

B Synaptic Escape Voltage

○ $R_m = 50,000 \Omega \text{cm}^2$

Δ $R_m = 500,000 \Omega \text{cm}^2$

\[ x/l = 0 \]

\[ 0.1 \]

\[ 0.5 \]

\[ 1.0 \]

10 mV

10 ms

C

D

FIG. 3. Increasing $R_m$ from 50,000 to 500,000 $\Omega \text{cm}^2$ has almost no effect on attenuation of peak current measured at soma for synapses located at different distances from the soma [synaptic conductance ($g_{syn}$) = 1.0 nS, $a = 2,850$s$^{-1}$]. All simulations used equivalent-cylinder model shown schematically in Fig. 1A. A: Superimposed synaptic currents measured with a voltage clamp at soma (clamp potential is $-70$ mV) for synapses located at $x/l = 0, 0.1, 0.5,$ and $1.0$. Simulations with $R_m$ values of 50,000 and 500,000 $\Omega \text{cm}^2$ are plotted on left and right, respectively. B: Synaptic escape voltage during somatic voltage clamp (—) and unclamped synaptic voltage (---) for synapses at same 4 positions as in A. Simulations with $R_m$ values of 50,000 (top) and 500,000 $\Omega \text{cm}^2$ (bottom) are shown. C: Peak current measured at soma as a function of synapse position for both low (○) and high (△) $R_m$ values. D: Peak synaptic escape voltage as a function of synapse position for low (○) and high (△) $R_m$ values.

The decay of the escape voltage is strongly influenced by the membrane time constant $\tau_m = R_mC_m$; increases in $R_m$ increase $\tau_m$, thereby prolonging the decay of the voltage escape. The rising phase is more sensitive to axial resistance and membrane capacitance, so the slowing
FIG. 4. Increasing $R_m$ from 50,000 to 500,000 $\Omega$cm$^2$ causes a shift in reversal potential of synaptic current-voltage plot with only a nominal change in measured slope conductance (simulated synaptic conductance, $g_{syn} = 1.0$ nS, $\alpha = 2,850$ s$^{-1}$).

A: current-voltage relations for synaptic currents generated at soma ($x = 0$ $\mu$m) for both low (○) and high (△) $R_m$ values. Because somatic synapse is perfectly clamped, there is no difference in 2 current-voltage relations. B: current-voltage relations for synaptic currents generated at end of cable ($x = 1,000$ $\mu$m) for both low (○) and high (△) $R_m$ values. Note that current axis is on a scale 20 times smaller than that for somatic synapse plotted in A. Current-voltage plot for high $R_m$ value yields a reversal potential much closer to real value of 0 mV than does low $R_m$ value, but because of the small scale of current axis, the difference in synaptic conductance measured from slope of plot with these 2 $R_m$ values is nominal relative to real synaptic conductance of 1.0 nS. C: measured synaptic slope conductance as a function of synapse position for models having low (○) and high (△) $R_m$ values. D: measured synaptic reversal potential as a function of synapse position for models having low (○) and high (△) $R_m$ values. Solid lines are analytical solutions for $E_{rev}$ calculated from Eq. 7. E: 10–90% rise time measured at soma as a function of synapse position for both low (○) and high (△) $R_m$ values. F: similar plots of half-decay time measured at soma as a function of synapse position.
of synaptic kinetics produced by increases in $R_m$ is more pronounced for half-decay time than for 10–90% rise time. The sigmoidal shapes of the plots in Fig. 4, $F$ and $F_1$, are caused by increases in the amount of distortion at locations close to the end of the cable (compared with those of infinite cables). The effects of $R_m$ and sealed ends on EPSC kinetics are therefore very similar to the effects on EPSPs (see Figs. 7.19 and 7.20 of Jack et al. 1983).

Another consequence of higher $R_m$ values is that the amount of charge measured at the soma from distal synapses is increased. The transfer of charge from the synapse to the soma is determined by the DC electrotonic distance of the synapse (Barrett and Crill 1974b; Carnevale and Johnston 1982; Janse and Redman 1973b; Rinzel and Rall 1974), which is decreased by increases in $R_m$. In contrast, the total charge entry at the synapse is affected by the AC soma-to-synapse attenuation properties, which are relatively insensitive to changes in $R_m$. For a given $g_{syn}$, a synapse located farther from the soma produces slightly less charge entry because of the decrease in synaptic driving force caused by voltage escape. The effects of $R_m$ on charge transfer to the soma have been described previously by Barrett and Crill (see Fig. 6 of Barrett and Crill 1974b).

**EFFECTS OF SYNAPTIC KINETICS.** Figure 5 compares the distortion of measured synaptic current for synapses having rise times of 0.2 or 2.0 ms. Each plot shows the synaptic parameters measured at the soma as a function of the synapse position. All values plotted (except $V_{ms}$) are normalized to the value measured when the synapse is placed at the soma and perfectly voltage clamped. The results show that, as predicted from the frequency dependence of voltage and current attenuation in the cable, faster synaptic conductance changes result in greater distortion of the measured synaptic parameters. Note, however, that the measured synaptic reversal potential, which is affected only by the DC attenuation properties of the cable, is not affected by the kinetics of the synapse (Fig. 5C). Also, the amount of charge measured at the soma for remote synapses (relative to the charge entry for a perfectly clamped somatic synapse) is actually greater for faster synaptic conductances. This reflects the fact that less reduction in charge entry because of voltage escape at the synapse occurs during faster synaptic conductance changes.

**EFFECTS OF SYNAPTIC CONDUCTANCE.** The peak conductance at the synapse can also affect the amount of current distortion measured at the soma, as shown in Fig. 6. The plots are arranged identically to Fig. 5, except that two synapses differing only in the peak conductance (1.0 and 10 nS) are compared. Relatively slow synaptic conductance changes were simulated ($t_{rise} = 2.0$ ms, $t_{decay} = 5.9$ ms) because differences in measured synaptic parameters resulting from different peak conductance are smaller for faster events, particularly at distances farther from the soma. The results show that the peak current (and conductance) measured at the soma is attenuated more for the larger synaptic conductance. The predominant effect of increasing the peak synaptic conductance is to increase the amount of voltage escape at the synapse. This reduces the peak current and total amount of charge that enters at the synapse, thus accounting for the increase in decay of measured peak current and the relatively large increase in the reduction of measured charge produced by increasing the peak conductance. It is important to point out, however, that this behavior will be seen only if the increased conductance is localized; such results would not necessarily be expected in a branching neuron if the increase in synaptic conductance was distributed across the dendritic tree.

Another interesting effect of increasing the synaptic conductance is to shorten the 10–90% rise time while lengthening the half-decay time (compare Fig. 6, $E$ and $F$). This occurs because the voltage escape at the synapse is larger and has a faster rising phase during a larger synaptic conductance. The time course of this rising phase influences the rise time of the current measured at the soma, and therefore $t_{rise}$ is faster during larger conductance changes than during smaller ones. Because of the slower time course of the decay phase of the poorly clamped potential, however, the ability of the somatic electrode to control the voltage during the decay phase of the synaptic voltage escape is influenced to a lesser extent by the magnitude of the conductance change than it is during the rising phase. The half-decay time during a smaller conductance change is therefore decreased by virtue of the fact that the peak amplitude of the voltage escape occurs at a later time compared with a larger conductance change.

**EFFECTS OF CABLE LENGTH.** In addition to being affected by the electrotonic distance of the synapse from the soma, the distortion of measured synaptic currents is also affected by the overall electrotonic structure of the dendritic tree. In finite equivalent-cylinder models, a synaptic current originating at any given distance from the soma will attenuate to a greater extent for cables having longer electrotonic lengths. This result is a simple consequence of Eqs. 7 and 8 (see METHODS), which predict that the voltage measured at any given distance along the cable will be smaller for cables having longer $L$ values.

The consequence of longer cables on the distortion of synaptic current measured at the soma is illustrated in Fig. 7. The synaptic parameters measured at the soma for synapses located at $X = 0.1$ and $X = 0.5$ are plotted as a function of $L$ for cables having $L$ values of 0.1–2.0 and 0.5–2.0, respectively. All values plotted are normalized to the value measured for the same synapse placed at the soma. The plots of current and conductance attenuation as a function of $L$ (Fig. 7, $A$ and $B$) demonstrate that attenuation is increased only by increasing the total length of the cable when the original cable has a length close to that of the distance of the synapse from the soma. In other words, the attenuation of measured current and conductance for a synapse at a given distance from the soma depends on whether or not the synapse is located close to the end of the cable; when it is not located close to the end of the cable, the total length of the cable does not have a dramatic effect.

In contrast to the effect of cable length on current and conductance attenuation, the measured reversal potential for a synapse at a given distance from the soma continues to deviate from its real value as the cable is lengthened (see Fig. 7C). This increase in error in $E_{rev}$ by increasing the length of the cable is larger for synapses located farther from the soma. Similarly, the attenuation of measured synaptic charge for a synapse at a given distance from the soma is greater for longer total cable lengths, and this effect is partic-
FIG. 5. Faster synaptic kinetics result in greater error in all measured synaptic parameters except reversal potential and charge transfer. All plots show measured synaptic parameters normalized to value at soma (except reversal potential) as a function of synapse position ($x/l$) for conductance changes modeled by relatively fast ($\alpha = 2,850$ s$^{-1}$, $t_{\text{rise}} = 0.2$ ms, $t_{\text{decay}} = 0.59$ ms) and slow ($\alpha = 285$ s$^{-1}$, $t_{\text{rise}} = 2.0$ ms, $t_{\text{decay}} = 5.9$ ms) synaptic conductance changes ($g_{\text{syn}} = 1.0$ nS). A: decay of peak synaptic current (measured at $-70$ mV) as a function of distance from soma is greater for faster synaptic conductances. B: measured synaptic conductance also decreases more as a function of distance from the soma for faster synaptic conductances. C: measured reversal potential is unaffected by synaptic kinetics at all synapse positions. D: plot of charge measured at soma (relative to amount of charge entering at a perfectly clamped somatic synapse) as a function of distance from soma shows that $t_{\text{rise}}$ is much larger at a given distance for faster synaptic currents than for slower events. This reflects decreased amount of charge entering at synapse because of more prolonged voltage escape during slower conductance change. E: plot of increase in measured 10–90% rise time as a function of synapse position from soma shows that $t_{\text{rise}}$ is much larger at a given distance for faster synaptic currents than for slower events. F: plot of increase in measured half-decay shows that this kinetic measure is also greater for faster synaptic events at any given distance from soma.
FIG. 6. Larger synaptic conductances result in greater error in all measured synaptic parameters except for reversal potential and rise time. All plots show measured synaptic parameters normalized to value at soma (except reversal potential) as a function of synapse position for synaptic conductances of 1.0 (△) and 10 nS (○). Relatively slow synaptic currents (τ = 285 s⁻¹) were simulated to enhance effects of changes in conductance, which are smaller for faster conductance changes. A: peak synaptic current (measured at −70 mV) decays more as a function of distance from the soma for larger conductance than for smaller event. B: decay of measured conductance with distance of synapse from soma is also greater for larger absolute synaptic conductances. C: measured synaptic reversal potential, however, is unaffected by absolute conductance under perfect somatic voltage-clamp conditions. D: synaptic charge measured at soma (relative to amount of charge entering at a perfectly clamped somatic synapse) is also smaller for larger synaptic conductance changes at any given distance from the soma. This reflects the decreased charge entry caused by increased voltage escape with a larger synaptic conductance. E: measured 10–90% rise time is actually shorter (for a synapse at any given distance from soma) for larger synaptic conductances than for smaller conductances, F: in contrast to rise time, half-decay time for a given remote synapse is longer for larger synaptic conductances than for smaller conductances.
FIG. 7. Effects of increasing cable length on attenuation of measured synaptic parameters. All plots show measured synaptic parameters for synapses at $X = 0.1$ (○) and $X = 0.5$ (△) normalized (except reversal potential) to value measured for same conductance change ($g_{syn} = 1.0$ nS, $a = 2.850$ s$^{-1}$) placed at soma. Fixed synapse positions (○ $X = 0.1$, △ $X = 0.5$) and variable cable length are shown schematically in insets of A (not to scale). A: increasing cable length has a significant effect on peak synaptic current (measured at -70 mV) only for lengths slightly longer than the electrotonic distance of the synapse. B: a similar result is observed for plot of measured synaptic conductance as a function of cable length. C: measured synaptic reversal potential increases steadily as total length of cable is increased; effect is more dramatic for synapses located farther from soma. D: proportion of perfectly clamped synaptic charge that is measured at soma for imperfectly clamped remote synapses decreases as length of cable is increased; effect is more dramatic for synapses located farther from the soma. E: 10–90% rise time measured at soma increases only transiently for cables of increasing length but is relatively independent of total cable length for cables much longer than location of synapse. F: half-decay time measured at soma also shows a transient increase for cables slightly longer than the distance of the synapse from the soma, but is relatively independent of cable length for substantially longer cables.
ularly pronounced for synapses located farther from the soma (see Fig. 7D).

The effect of increasing cable length on the kinetics of the measured synaptic current are nominal (see Fig. 7, E and F). A slight increase in both 10–90% rise time and half-decay time is observed, however, for cables only slightly longer than the electrotonic distance of the synapse. The reason for this effect is related to the edge effect, shown in Fig. 4, E and F, where synapses at locations close to the end of a finite cable are kinetically more distorted than synapses located at the same distance on much longer cables.

**Effects of series resistance**

The previous sections have discussed the effects of space-clamp errors under conditions in which there is a perfect clamp at the soma. Under real experimental conditions, however, a perfect clamp at the soma is not normally achieved and additional errors arise because of imperfect voltage clamp. These additional errors exist because of the finite current passing capabilities of the electrode and amplifier. During whole-cell patch-clamp recordings, the ability to pass current is limited by the series resistance from the electrode to the cell ($R_e$) and the capacitance of the electrode-neuron combination. In simple isopotential cells, the settling of the clamp has a time constant given by $RC$, where $C_N$ is the total capacitance of the neuron (Marty and Neher 1983). In nonisopotential neurons, there is not one but many time constants determining the settling of the clamp; these depend in a complex way on the electrotonic structure of the neuron (Major 1993; Major et al. 1993a). Nevertheless, the overall effect of series resistance is the same; larger series resistances or larger neurons will limit the rate of charging of the membrane capacitance, thus resulting in worse somatic voltage clamp. This increases the error in the measurement of synaptic currents, even for synapses that are located very close to the soma. This effect is of course well known and has been noted by many investigators (Jonas et al. 1993; Llano et al. 1991; Marty and Neher 1983; Silver et al. 1992).

The effects of series resistance on the measured parameters of synaptic currents are shown in Fig. 8. It is clear from this figure that further error is introduced into all measured parameters by increasing $R_s$ from 0 to 100 MΩ. Although 100 MΩ is a high $R_s$ value for patch-clamp recordings, the effective cell capacitance coupled to the electrode is also rather low in this model, and therefore comparable errors could be observed in larger cells even with much lower $R_s$ values.

**Anatomically reconstructed CA3 pyramidal neuron model**

The results presented in the previous section demonstrate the general features of voltage attenuation and distortion of synaptic current measurements in equivalent-cylinder models. These simple models are useful in many ways, but fail to preserve the complex branching structure of dendritic trees, even in neurons whose structure fulfills the requirements for simplification to an equivalent-cylinder model (Rall 1977). One drawback of using equivalent-cylinder models is that voltage attenuation and synaptic current distortion along individual dendritic branches cannot be assessed. Furthermore, dendritic trees not having the requisite geometry to be reduced to an equivalent cylinder cannot be analyzed properly with this method.

To assess the voltage-attenuation properties and distortion of measured synaptic currents in a neuron with complex dendritic branching, we used a compartmental model reconstructed from a Golgi-stained CA3 pyramidal neuron of the hippocampus (see Fig. 9A). This model (shown schematically in Fig. 9B) allowed for both the evaluation of voltage attenuation properties and synaptic current distortion in a non-equivalent-cylinder model and for the comparison of simulated data to physiological data available for voltage-clamped MF to CA3 and recurrent C/A to CA3 synaptic currents.

**Passive membrane properties of the model.** The parameters used in the model consisted of a high $R_m$ value of 100,000 Ω cm$^{-2}$ (to reflect filling of the neuron with Cs$^+$) and a relatively high $R_i$ value of 205 Ω cm. The resting potential was set to -70 mV and $C_m$ was assumed to be 1.0 μF cm$^{-2}$. These parameters were chosen to provide good fits of both the measured synaptic currents and reversal potentials for MF and C/A synaptic inputs (see Fig. 10). In some simulations a somatic conductance was included to model the leak introduced by microelectrode penetration. A leak of 11.2 nS produced $R_L$ and $\tau_L$ values similar to those obtained in a CA3 neuron from which both MF and C/A synaptic currents were obtained using a conventional microelectrode recording (without leak: $R_L$ = 342 Ω cm, $\tau_L$ = 100 ms; with leak: $R_L$ = 78 Ω cm, $\tau_L$ = 25 ms).

The higher $R_N$ at the soma in the absence of a leak conductance results in larger and slower voltage responses to current steps at the soma than in the presence of a leak conductance. The voltage response obtained in the presence of a leak is misleading if the $\tau_L$ value obtained from the charging of the voltage response is used to calculate $R_m$. In fact, because of the leak conductance at the soma, $R_m$ is highly nonuniform, with a high value in the dendrites and a lower value in the soma; $\tau_L$ falls somewhere between $\tau_L$ for the dendrites and $\tau_m$ for the soma (Iansek and Redman 1973a; Kawato 1984; Poznanski 1987a;Spruston and Johnston 1992). As shown previously, however, the current attenuation under voltage clamp is determined by $R_m$ of the dendrites and is not affected by the somatic leak conductance.

**Voltage attenuation as a function of distance from the soma.** The attenuation of potential from the soma to dendrites is much smaller for steady-state (DC) voltage changes. Of note is the fact that the attenuation increases with distance from the soma and is much greater for high-frequency voltage changes than for steady-state (1kHz) voltage changes. Of note is the fact that attenuation from the soma to dendrites is much smaller for the basal dendritic tree than for the apical dendritic tree.

**Comparison of MF and C/A synaptic current distortion.** The distortions of MF and C/A synaptic currents were compared in the model by assuming a location consistent with anatomic studies (Blackstad 1956; Blackstad et al. 1970; Blackstad and Kjaerheim 1961; Hjorth-Simonsen 1973; Johnston and Brown 1983) and by fitting MF and C/A currents measured with a single-electrode voltage clamp by iteratively adjusting the synaptic kinetics and pas-
Fig. 8. Series resistance results in greater error in all measured synaptic parameters for synapses at all locations. Synaptic parameters measured at soma are plotted as a function of synapse position (synaptic conductance, $g_{\text{syn}} = 1.0 \text{nS}$, $a = 2.850 \text{s}^{-1}$) for case of perfect somatic voltage clamp ($R_s = 0$) and for $R_s = 100 \text{M}\Omega$ ($\triangle$). A: peak synaptic current (measured at $-70 \text{mV}$) is attenuated by increases in $R_s$ for all synapse locations. Effect of $R_s$ is most dramatic for synapses located near the soma, where effect is larger relative to filtering caused by cable. B: effects of $R_s$ on measured synaptic conductance are same as for peak current. C: measured synaptic reversal potential increases with increases in $R_s$ for synapses at all distances from the soma. D: synaptic charge measured at the soma is reduced by increases in $R_s$ for synapses at all locations. E: 10–90% rise time measured at the soma increases with increases in $R_s$ for all synaptic locations. F: half-decay time measured at the soma is also longer with larger $R_s$ for all synaptic locations.
FIG. 9. Morphology and voltage attenuation profiles for CA3 neuron used to construct a detailed anatomic model of a neuron with complex branching dendritic trees. A: camera lucida drawing of a Golgi-stained CA3 pyramidal neuron. Scale bar, 100 μm. B: schematic drawing of model constructed from neuron shown in A. Each of the 149 compartments is numbered. C: voltage amplitudes normalized to amplitude at the soma ($V_x/V_{soma}$) and plotted as a function of distance from the soma (origin of voltage change) for steady-state (○), 10-Hz (△), and 100-Hz (●) responses. Positive numbers on distance axis represent distance along branched apical dendritic path (from the soma to compartment 75) and negative numbers represent distance along basal dendritic path (from the soma to compartment 106).
sive membrane properties of the model. An $\alpha$-function conductance change with an $\alpha$ value of 300 s$^{-1}$ was chosen because it has kinetic properties ($t_{\text{rise}} = 1.3$ ms, $t_{\text{decay}} = 5.6$ ms) reasonably close to the experimentally measured MF synaptic currents (see Fig. 10). The MF synapse was simulated on the primary proximal dendrite at a distance of 100 $\mu$m from the soma. The fast synaptic conductance kinetics were assumed to be the same at the C/A synapse as at the MF synapse, so the same $\alpha$ value was used to model the C/A synaptic currents. The total C/A conductance change was distributed over 10 compartments 250–350 $\mu$m from the soma.

The $R_m$ and $R_i$ values used in the model were arrived at by adjustment to yield fits of both the kinetics and reversal potential of the measured MF ($t_{\text{rise}} = 1.3$ ms, $t_{\text{decay}} = 6.1$ ms, $E'_{\text{rev}} = -3$ mV) and C/A ($t_{\text{rise}} = 3.3$ ms, $t_{\text{decay}} = 7.3$ ms, $E'_{\text{rev}} = -4.5$ mV) synaptic currents. The synaptic reversal potentials were sensitive to both $R_m$ and $R_i$, particularly for the more distal C/A input), whereas the kinetics of both synapses were relatively insensitive to changes in $R_m$. First $R_i$ was adjusted to obtain fits of the kinetics of both synapses. $R_m$ was subsequently increased (with corresponding small adjustments of $R_i$) from the mean value for CA3 neurons of 66,000 $\Omega$cm$^2$ (see Spruston and Johnston 1992) to the higher value of 100,000 $\Omega$cm$^2$ to obtain fits of the measured synaptic reversal potentials (and to reflect filling of the cell with Cs$^+$. Figure 10, A and C, demonstrates that with these parameters, reasonably good fits of both MF and C/A synaptic currents were obtained. In addition, Fig. 10, A and C, shows that elimination of the somatic leak in the model does not affect the synaptic currents measured with a voltage clamp at the soma.

The synaptic current-voltage relations shown in Fig. 10, B and D, demonstrate the relative attenuation of synaptic conductance for the modeled MF and C/A synapses. For the MF synapse, a total conductance of 11 nS had to be modeled to match the measured conductance of 10 nS. This small amount of attenuation is in sharp contrast to that of the C/A synapse, where a total conductance of 60 nS had to be modeled to match the value of 12 nS measured at the soma. It should be emphasized, however, that the parameters used here do not necessarily constitute a unique means of fitting the measured synaptic currents, but rather provide a consistent model that incorporates physiologically realistic values. The model is particularly sensitive to the combination of the synaptic kinetics and location; with slight changes in the passive membrane properties of the model, it is possible to use faster synaptic conductances and greater electrotonic distances to model any measured synaptic current. The salient point, however, is that for any given combination of parameters, the attenuation of the C/A synaptic current is much more severe than that of the MF current, simply because of the greater electrotonic distance of the C/A synapse from the soma.

**SYNAPTIC CURRENT ATTENUATION AS A FUNCTION OF DISTANCE FROM THE SOMA.** Figure 11 shows the effect of distance of the synapse from the soma on synaptic parameters measured with a voltage clamp at the soma. These plots display shapes similar to those obtained with the use of equivalent-cylinder models (compare with Fig. 5) and demonstrate that errors in the measured peak current and kinetics of distal synaptic currents can be substantial, even when reversal potential measurements yield values close to the expected value of 0 mV. Note that the $E'_{\text{rev}}$ for a synapse located at the end of the apical dendritic branch can be in error by $<10$ mV, in spite of 86% attenuation of $I_{\text{syn}}$ and $g'_{\text{syn}}$. 88% attenuation of $q'_{\text{syn}}$, a 310% increase in $t_{\text{rise}}$, and a 262% increase in $t_{\text{decay}}$.

**Estimates of synaptic current attenuation with a simplified two-cylinder cable model of a CA3 pyramidal neuron.**

Estimates of the absolute amount of attenuation of synaptic currents are hindered by the difficulty in knowing the absolute synaptic location and kinetics with certainty. We have therefore used another approach to estimating the amount of attenuation for two classes of synapses on CA3 neurons: the MF and perforant path (PP) synapses. These two synapses are of particular interest because they provide examples of the extreme range of possible attenuation for synapses located on central neurons; MF synapses occur exclusively in a relatively narrow band on the proximal dendrite quite close to the soma (Johnston and Brown 1983) and PP synapses occur in a narrow band at the extreme distal end of the apical dendritic tree (Steward 1976).

The approach we have used to estimate the space-clamp errors associated with these two synapses is to construct a best-case model and a worst-case model using a simplified two-cylinder and soma representation of the CA3 neuron shown in Fig. 9A. The model was constructed in a manner similar to that described by others (Major et al. 1993b; Stratford et al. 1989). Details of the model are given in the METHODS and in Table 1. It should be noted that this simplified model is in no way intended to provide a representation of all aspects of current and voltage attenuation in CA3 pyramidal neurons (see, for example, Brown et al. 1992), but rather to provide a simplified representation that can be used to estimate a range of possible electrotonic lengths, electrotonic distances, and attenuation of synaptic parameters for comparison to previously published data (Brown et al. 1981; Johnston 1981; Johnston and Brown 1983).

The range of reasonable electrotonic distances for MF synapses is given in Table 1. These values were calculated using the previously published distances of proximal and distal MF synapses from the soma (Johnston and Brown 1983). The short electrotonic distances of MFs calculated here are consistent with the results from previous studies (Johnston and Brown 1983). PP synapses were positioned at the end of the apical cable.

The effects of the calculated range of electrotonic distances of measurement of parameters for a 1.0-nS synaptic conductance change at MF and PP synapses are given in Table 2. Results of simulations using two different conductance changes are also shown: a slow conductance change ($\alpha = 285$ s$^{-1}$, $t_{\text{rise}} = 2.0$ ms, $t_{\text{decay}} = 5.9$ ms) and a faster synaptic conductance change ($\alpha = 2,850$ s$^{-1}$, $t_{\text{rise}} = 0.20$ ms, $t_{\text{decay}} = 0.59$ ms). These values were chosen to represent a range of reasonable kinetic parameters (see discussion); the faster $\alpha$-function is likely to be a reasonable estimate of the kinetics of small, unitary EPSCs, whereas the slower kinetics were simulated because larger, compound EPSCs may be slowed due to asynchronous release of neurotransmitter (Silver et al. 1992; Stuart and Redman 1990). To
FIG. 10. Modeling of mossy fiber (MF) and commissural/associational (C/A) synaptic currents using model shown in Fig. 9 B. A: MF synaptic currents measured at -80 mV with a single electrode voltage clamp (trace with noise; \( t_{\text{rise}} = 1.3 \) ms; \( t_{\text{decay}} = 6.1 \) ms) were fit by simulating a synaptic conductance change (smooth trace; \( \alpha = 300 \) s\(^{-1}\)) at a distance of 100 \( \mu \)m from the soma (passive parameters: \( R_m = 100,000 \) \( \Omega \)cm\(^2\), \( R_i = 205 \) \( \Omega \)cm). Simulated trace at left was modeled with a leak to reproduce conditions of experiment. Trace at right was simulated without a leak and demonstrates that a somatic leak has no effect on measured synaptic current under voltage-clamp conditions. B: current-voltage plots of real (●) and simulated (—) MF currents. Total synaptic conductance change of 11 nS had to be simulated at synapse to match 10-nS conductance measured at soma. C: C/A synaptic currents measured from same cell (also at -80 mV; trace with noise; \( t_{\text{rise}} = 3.3 \) ms; \( t_{\text{decay}} = 7.3 \) ms) were fit by simulating a synaptic conductance change (smooth trace; \( \alpha = 300 \) s\(^{-1}\)) distributed over 10 compartments at distances of 250–350 \( \mu \)m from soma in same model as in A. Smooth traces at left and right were simulated with and without a somatic leak, respectively. D: current-voltage plots of real (●) and simulated (—) C/A currents. Because attenuation of C/A synaptic currents is much greater than that of MF currents, a total synaptic conductance change of 60 nS (—–) had to be simulated at synapse to fit 12-nS conductance measured at soma.

make the simulations as realistic as possible, series resistances of 2 and 10 \( \Omega \) were included in the best-case and worst-case simulations, respectively. The results of these simulations demonstrate that a wide range of attenuations are possible, even for synapses occurring relatively close to the soma. Close MF synapses may be reasonably well clamped under some conditions, but the error associated with the measurement of very fast synaptic currents is significant even in the best case. MF synapses located farther from the soma are likely to be substantially distorted by space-clamp errors. Similar parameters listed in Table 2 for PP synapses demonstrate that these synapses undergo severe attenuation regardless of the parameters used in the model.

DISCUSSION

The results presented here have important implications for the interpretation of experiments involving the measurement of synaptic current with a voltage clamp at the soma of neurons with dendritic processes; namely, synapses located even in proximal regions of the dendritic tree are likely to undergo significant electrotonic filtering between the site of the synapse and the electrode at the soma. Although similar findings have been reported earlier (Johnston and Brown 1983; Rall and Segev 1985), we have extended the analysis to quantitatively assess the effects of various parameters in the model on voltage- and space-clamp errors. Such analyses are particularly warranted by the recent availability of new estimates of passive membrane properties and synaptic kinetics obtained using patch-clamp recordings.

Using neuronal models to estimate voltage- and space-clamp errors

The errors associated with measuring synaptic currents can be reduced by taking care to optimize the recording conditions (for example, by reducing series resistance and electrode capacitance as much as possible) and by studying
FIG. 11. Errors in synaptic parameters measured at soma ($R_s = 10 \, M\Omega$) for synapses ($g_{syn} = 10 \, nS$, $\alpha = 300$ and $1,000 \, s^{-1}$) simulated at various distances from soma along apical dendritic branch (from the soma to compartment 105) have same general features as for equivalent-cylinder models. A: peak synaptic current (measured at $-70 \, mV$) decays dramatically as a function of distance of synapse from the soma. B: measured synaptic conductance also decays dramatically as a function of distance of synapse from the soma. C: measured synaptic reversal potential increases as a function of distance from the soma, but error is small because of relatively short DC electrotonic length of apical dendritic tree with passive parameters used in this model. D: synaptic charge measured at the soma also decreases dramatically as a function of distance of synapse from the soma. E: $10$–$90\%$ rise time increases as a function of distance of synapse from the soma. F: half-decay time also increases (even more steeply than rise time) as a function of distance of synapse from the soma.
In experiments designed to accurately estimate parameters such as $R$, the uncertainties associated with conventional microelectrode penetration will become narrower. This underscores the importance of measuring currents. When all of the relevant data are available, it is important to consider a reasonable range of actual values.

Increasing $R$, such as can be achieved by blocking $K^+$ channels with intracellular dialysis of Cs+ or other channel blockers, is limited to steady-state and very low-frequency voltage changes, whereas higher-frequency voltage changes may result in activation of such channels, thus altering the magnitude and time-course of the current measured at the soma.

In general, estimating the errors associated with current measurements requires both a knowledge of the electrotonic structure of the postsynaptic neuron and estimates of the kinetics and location of the channels carrying the tonic structure of the postsynaptic neuron and estimates of synaptic kinetics (see Fig. 4). In fact, increases in $R$, suggested by recent studies (Jonas et al. 1993; Major 1992; Shelton 1985; Spruston and Johnston 1992, Stratford et al. 1989) result in longer electrotonic lengths and greater distortion of synaptic currents for any given model than the lower values estimated from earlier data (Barrett and Crill 1974a).

Another factor that may influence the error in measurement of current from remote synapses is the existence of voltage-gated ion channels in the dendrites (Jaffe et al. 1992; Llinas 1988; Miyakawa et al. 1992; Usowicz et al. 1992; Westenbroek et al. 1992). These channels may have an important role in amplifying synaptic signals that would otherwise be severely attenuated if they were to propagate passively toward the soma. Even under voltage-clamp conditions, voltage escape at poorly space-clamped synapses may result in activation of such channels, thus altering the magnitude and time-course of the current measured at the soma.

Because of inadequate morphological data, we were unable to simulate dendritic spines. All simulations were therefore performed using synapses directly on dendrites instead of on spines. The major difference in using spine synapses would be to increase further the voltage escape at the subsynaptic membrane (spine head) during a voltage clamp at the soma. This would lead to larger errors in estimating synaptic conductance and a greater likelihood of activating any voltage-gated channels that are present on the spine. It is unlikely, however, that there is further filtering of the synaptic waveform between the spine head and the dendritic shaft (see Brown, Chang, Ganong, Keenan, and Kelso 1988; Koch and Zador, 1993).

### Table 2: Estimates of minimum and maximum attenuation of voltage clamp parameters for fast and slow mossy fiber and perforant path to CA3 synapses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fast MF</th>
<th>Fast PP</th>
<th>Slow MF</th>
<th>Slow PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{syn}/I_{syn}$</td>
<td>0.81</td>
<td>0.41</td>
<td>0.98</td>
<td>0.94</td>
</tr>
<tr>
<td>$g_{syn}/g_{syn}$</td>
<td>1.00</td>
<td>0.98</td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>$E_{syn}$, mV</td>
<td>7.0</td>
<td>19.3</td>
<td>7.0</td>
<td>19.3</td>
</tr>
<tr>
<td>$\tau_{rise}/\tau_{rise}$</td>
<td>1.3</td>
<td>3.35</td>
<td>1.03</td>
<td>1.39</td>
</tr>
<tr>
<td>$\tau_{decay}/\tau_{rise}$</td>
<td>3.05</td>
<td>14.6</td>
<td>1.42</td>
<td>2.29</td>
</tr>
</tbody>
</table>

Minimum and maximum attenuation values are, respectively, the top and bottom numbers of each pair. Fast, $\alpha = 2.850 \times 10^{-3}$ s$^{-1}$; slow, $\alpha = 285$ s$^{-1}$. MF, mossy fiber; PP, perforant path; $I_{syn}$, somatic clamp current; $g_{syn}$, synaptic conductance; $E_{syn}$, reversal potential; $\tau_{syn}$, synaptic charge; $\tau_{rise}$ and $\tau_{decay}$, rise and decay times; prime indicates measured as opposed to actual values.

### Neuronal geometry and membrane properties

The relatively small effect of increases in $R_m$ on the attenuation of synaptic currents occurs because the attenuation of AC signals is affected much more by the membrane capacitance and axial resistance between the synapse and the recording site than by the membrane resistance between these two points. In equivalent-cylinder models, the resistance between the synapse and the soma is determined by the actual distance between these two points, the diameter of the cable, and $R$. In branching models of the dendritic tree, this resistance depends in a more complex way on the geometry of the dendritic tree, the distance of the synapse from the soma, and $R$.

In fact, $R$ is one of the most critical parameters affecting the electrotonic structure of neuronal models. The high values of $R$, suggested by recent studies (Jonas et al. 1993; Major 1992; Shelton 1985; Spruston and Johnston 1992, Stratford et al. 1989) result in longer electrotonic lengths and greater distortion of synaptic currents for any given model than the lower values estimated from earlier data (Barrett and Crill 1974a).

### Simulating microelectrode and patch-clamp recordings

A further consideration in assessing experimental estimates of synaptic currents is the type of recording used. The primary difference between microelectrode and patch-clamp recordings is the presence of an impalement-induced somatic leak in the microelectrode recordings. The major effects of this somatic leak are to decrease $R_m$ and $\tau_m$ measured at the soma and reduce the size and speed up the decay of postsynaptic potentials. Attenuation of potential from the soma to the dendrites, however, is unaffected by a somatic leak. Patch-clamp electrodes therefore do not reduce space-clamp errors by eliminating the somatic leak associated with conventional microelectrode penetration. The current required to clamp a synaptic response is not affected by the microelectrode leak (see Fig. 10). Previous
estimates of synaptic conductance and kinetics therefore need not necessarily be considered in error because micro-electrodes were used.

**Effect of synaptic distance from the soma on space-clamp errors**

The results presented here demonstrate that the synaptic currents measured at the soma for synapses located in neuronal dendrites are substantially distorted with respect to the amplitude and time course of ideally voltage- and space-clamped synapses. Various measured parameters of synaptic currents, however, are affected in different ways by the electrotonic structure of the postsynaptic neuron. Both the peak current and the slope conductance decrease dramatically as a modeled synapse is moved very small distances away from the soma, whereas further increases in distance have only smaller effects on these parameters (Figs. 3 and 4). In contrast, the 10–90% rise time and half-decay time show relatively gradual increases for synapses close to the soma and more dramatic increases at greater distances (see Fig. 4, E and F), suggesting that slow measured synaptic kinetics may be indicative of substantial distortion of synaptic current. The measured synaptic reversal potential increases almost linearly along the length of the cable, except near the end, where it begins to level off (Fig. 4D). The measured reversal potential is much less affected than the peak current, especially when $R_{ex}$ is high. It cannot therefore be assumed that measurements of $E_{rev}$ close to the expected value imply that electrotonic filtering is nominal.

Because the relationship between peak current and slope conductance as a function of synaptic position are quite steep near the soma, attenuation of these parameters is likely to be severe for any synapses other than those located very close to the soma. Synapses such as the C/A synapses on CA3 neurons and the Schaffer collateral (SC) synapses on CA1 neurons are located quite far from the soma (Andersen et al. 1971; Lorente de Nó 1934), and synaptic currents measured from these synapses are therefore likely to be substantially attenuated. Even synapses such as the Mf synapses on CA3 neurons are likely to be severely attenuated unless care is taken to select for those synapses located particularly close to the soma.

**Effect of synaptic kinetics on voltage- and space-clamp errors**

Aside from the distance of the synapse from the soma, the factor affecting the attenuation of synaptic current most prominently is the time course of the underlying synaptic conductance change. Synaptic currents having faster frequency components are effectively located at longer frequency-dependent electrotonic distances and therefore are subject to more dramatic attenuation than those having slower frequency components. For example, the errors associated with measurements of fast glutamatergic synaptic currents would be much greater than the errors associated with the measurement of slow muscarinic or N-methyl-D-aspartate (NMDA)-mediated synaptic currents generated at identical electrotonic distances. The relatively fast synaptic conductance changes used in the simulations presented here were chosen because, in many published reports, recordings of synaptic currents made under good voltage- and space-clamp conditions have very fast rise and decay times (Edwards et al. 1990; Finkel and Redman 1983; Jonas et al. 1993; Livsey and Vicini 1992; Llano et al. 1991; Magleby and Stevens 1972; Nelson et al. 1986; Silver et al. 1992; Stern et al. 1992; Stuart and Redman 1990; Williams and Johnston 1991). Experiments involving fast application of glutamate to outside-out patches also suggest that synaptic currents are likely to have very rapid kinetics (Colquhoun et al. 1992; Hestrin 1992).

**Voltage-clamp errors and series resistance**

In addition to the errors caused by space-clamp problems associated with clamping remote synaptic conductances, further errors attributable to imperfect voltage clamp also affect the parameters of synaptic currents measured at the soma. In continuous voltage-clamp mode, which is normally used in the whole-cell patch-clamp recordings, these errors are caused by the limitation of the clamp rise time by the series resistance and cell capacitance (Major 1993; Major et al. 1993a; Marty and Neher 1983).

The effect of $R_s$ shown here (Fig. 8) demonstrates that series resistance can introduce substantial error into the measurement of synaptic currents when using continuous voltage clamp, especially for events located close to the soma. This result has also been demonstrated by Major (Jonas et al. 1993), who has shown that with CA3 pyramidal neurons $R_s$ values as low as 1.5 MΩ can contribute to error in the measurement of synaptic currents. Conversely, the use of smaller cells has been used to minimize (but not eliminate) the adverse effects of high $R_s$ (Silver et al. 1992).

In the discontinuous voltage-clamp mode, which is normally used with conventional micro-electrode recordings, high electrode series resistances or large electrode-cell capacitances limit the possible switching rate by increasing the time required for the voltage at the electrode to settle (Finkel and Redman 1983, 1985). Slower switching rates enhance the error in measurement of both the kinetics and amplitudes of currents measured with a somatic voltage clamp (see Finkel and Redman 1983 for discussion).

**Commonly used methods for evaluating space-clamp errors**

A few experimental methods for determining the extent of space-clamp control of synaptic inputs have been used previously. These methods warrant some discussion because they may provide misleading conclusions.

The most commonly used method for evaluating space-clamp problems is to plot the measured synaptic decay time constant ($\tau_{decay}$) as a function of the measured rise time ($\tau_{rise}$). A lack of correlation in these parameters has been used as evidence that space-clamp problems do not affect the measurement of $\tau_{decay}$. The argument is that $\tau_{rise}$ provides a measure of electrotonic location because this parameter is very sensitive to increases in electrotonic distance of the synapse (see Figs. 4 and 11). It has been inferred that if $\tau_{decay}$ is not correlated with $\tau_{rise}$, it must be measured accurately (Hestrin et al. 1990). Others have even argued that such a lack of correlation indicates that peak synaptic amplitudes are measured reliably (McBain and Dingledine 1992).

A lack of correlation in $\tau_{rise}$ and $\tau_{decay}$ can arise because of scatter of synapses over a range where $\tau_{rise}$ is affected more...
than \( t_{\text{rise}} \) — such as near the soma, where the error in \( t_{\text{rise}} \) may be much larger than the error in \( t_{\text{decay}} \). In this case, estimates of \( t_{\text{rise}} \) and \( t_{\text{decay}} \) may be reasonably accurate, whereas \( t_{\text{decay}} \) is still substantially attenuated (compare plots of \( t_{\text{rise}} \) and \( t_{\text{decay}} \) as a function of synaptic location in Figs. 3C and 4 F and Fig. 11, A and F). A lack of correlation in \( t_{\text{rise}} \) and \( t_{\text{decay}} \) can also occur near the end of the cable, where space-clamp problems are much more severe (compare plots of \( t_{\text{rise}} \) and \( t_{\text{decay}} \) as a function of synaptic location in Figs. 5, E and F). Yet another situation that could result in a lack of correlation in these two parameters would be that the currents measured all arose at the same electrotonic location but that variability in \( t_{\text{rise}} \) and \( t_{\text{decay}} \) came from sources other than scatter in electrotonic location. In this case, a lack of correlation in \( t_{\text{rise}} \) and \( t_{\text{decay}} \) would provide no information about the space-clamp error affecting the measurements. And finally, a lack of correlation between \( t_{\text{rise}} \) and \( t_{\text{decay}} \) could be due to activation of voltage-gated conductances by the voltage escape at the unclamped synapses and thus result precisely because the synapses are poorly clamped.

The above explanations could also account for the lack of correlation in \( t_{\text{decay}} \) and the time constant for NMDA switch-off (\( T_{\text{NMDA-off}} \), in response to a step from \( -40 \) to \( -80 \) mV) reported for a subset of SC to CA1 synapses (Hestrin et al. 1990). In this study, synapses with \( T_{\text{NMDA-off}} \) values in the range 2.5–7.5 ms showed no correlation with \( t_{\text{decay}} \). These values nevertheless probably reflect substantial electrotonic filtering of the true kinetics of NMDA receptor-channel current distortion for MF synapses occurring at different distances from the soma and with different kinetic properties, a second approach was used. This method involved the construction of a simple model of the CA3 neuron that represented the apical dendritic tree as one cable and the basal dendritic tree as a second cable. This approach facilitated the estimation of the DC electrotonic distances (\( X \)) for a range of MF synapses and also allowed the estimation of \( L \) for the apical dendritic tree (which in turn provides an estimate of \( X \) for PP synapses). The results of this analysis suggest that the apical dendrites are likely to have a shorter \( L \) than previously estimated (Brown et al. 1981; Johnston 1981) and that the basal dendritic tree has an even shorter \( L \). In spite of the relatively short \( L \) of the apical dendritic tree, the synaptic current measured from PP synapses occurring at the end of these dendrites is substantially attenuated. It appears likely, in contrast, that if care is taken to select for MF inputs that are closest to the soma (for example, by studying those responses with the fastest rise and decay times), it may be possible to obtain reasonably accurate estimates of synaptic conductance and kinetics. Space-clamp problems can be considerable even for these relatively close synaptic inputs, however, and estimates of the error associated with voltage-clamp recordings should routinely be provided.

Errors in measurements of synaptic currents in CA3 neurons

As an alternative to the above methods, we propose the use of neuronal models to quantitatively estimate space-clamp errors. When experimental data are not available to constrain a given parameter, a reasonable range of values should be considered. We have attempted to demonstrate this approach by the use of both morphologically realistic and simple equivalent-cylinder models to estimate the range of possible errors for measurement of current from MF, C/A, and PP synapses on hippocampal CA3 pyramidal neurons.

In the first approach, a detailed morphological model was used to provide fits of experimentally recorded MF and C/A synaptic currents. The results of this analysis demonstrated that, whereas reversal potential measurements for both synapses were very close to the expected value of 0 mV, attenuation of the MF currents was relatively small (<10% attenuation of peak current and conductance) compared with that of the C/A currents (80% attenuation of peak current and conductance). This approach has the advantage of using a morphologically realistic model and constraining the model parameters by fitting experimentally recorded synaptic currents, but suffers from the disadvantage of having to assume specific synaptic locations and kinetics.

To address the latter problems and compare the range of current distortion for MF synapses occurring at different distances from the soma and with different kinetic properties, a second approach was used. This method involved the construction of a simple model of the CA3 neuron that represented the apical dendritic tree as one cable and the basal dendritic tree as a second cable. This approach facilitated the estimation of the DC electrotonic distances (\( X \)) for a range of MF synapses and also allowed the estimation of \( L \) for the apical dendritic tree (which in turn provides an estimate of \( X \) for PP synapses). The results of this analysis suggest that the apical dendrites are likely to have a shorter \( L \) than previously estimated (Brown et al. 1981; Johnston 1981) and that the basal dendritic tree has an even shorter \( L \). In spite of the relatively short \( L \) of the apical dendritic tree, the synaptic current measured from PP synapses occurring at the end of these dendrites is substantially attenuated. It appears likely, in contrast, that if care is taken to select for MF inputs that are closest to the soma (for example, by studying those responses with the fastest rise and decay times), it may be possible to obtain reasonably accurate estimates of synaptic conductance and kinetics. Space-clamp problems can be considerable even for these relatively close synaptic inputs, however, and estimates of the error associated with voltage-clamp recordings should routinely be provided.

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