WARNING CONCERNING COPYRIGHT RESTRICTIONS

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted materials. Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be "used for any purpose other than private study, scholarship, or research". If a user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use", that user may be liable for copyright infringement. This institution reserves the right to refuse to accept a copying order if, in its judgement, fulfillment of the order would involve violation of copyright law.
A Brief History of Time (Constants)

That the cerebral cortex processes information at prodigious speeds cannot be doubted. Yet the passive time constant, $\tau_m$ of neurons, often thought of as a measure of the neuron's "response time" to synaptic input, is relatively long. In the 1950s, $\tau_m$ was estimated to be only a few milliseconds for mammalian central neurons; with improvement in recording techniques, its estimated value grew over the years and it now stands near 20–100 msec. However, as we will argue here, the functional meaning of $\tau_m$ is ambiguous. On the basis of a newly introduced definition of local delay, we show that the time window for synaptic integration in passive dendritic trees can be much smaller than the time constant. We argue that the voltage response to very brief synaptic inputs is essentially independent of $\tau_m$. We discuss how $\tau_m$ can change dynamically with the global activity of the network, as well as the difficulties of defining a time constant in structures with voltage-dependent elements. We conclude that the classically defined $\tau_m$ only provides a very rough estimate, typically an overestimate, of the response time of neurons and that alternative measures are required to capture the dependency of the time course of the membrane potential on ligand-gated and/or voltage-dependent membrane conductances.

In the following pages, we will review what we know about time constants in neurons. Why, it can be asked, should this topic be of any great relevance to readers of Cerebral Cortex? First, and most important, time constants help us to understand the dynamics of the membrane potential $V_m(t)$ in nerve cells. Time constants should help us to answer such questions as how fast $V_m(t)$ can rise and fall in response to synaptic input or current injections, what is the time window for integration of two or more synaptic inputs, or what influence the dendritic geometry has on the dynamics of the membrane potential.

To give a concrete example (from T. Poggio, personal communication): in the dark, few cells are active in visual cortex and the membrane time constant $\tau_m$ is long, enabling the cell to integrate the input over a long time. Conversely, for bright, high-contrast visual stimuli, the overall network activity may be much higher, causing many more synaptic inputs to impinge spontaneously onto the cell, transiently increasing the local membrane conductance. As shown by Bernander et al. (1991) and Rapp et al. (1992), this additional conductance can lower the membrane time constant by an order of magnitude, reducing the integration times for these bright stimuli. This sort of adaptive gain-control strategy is somewhat akin to that used by the network of coupled rods in the retina (Detwiler et al., 1978).

We will discuss the theoretical status of various definitions of time constants and their experimentally measured values. Second, time constants should tell us something about the computational abilities of the nervous system. It is clear that how fast neurons can respond to synaptic input will significantly influence how fast the entire organism can respond to some stimulus in the world. And how do such time constants affect the ability of the organism—and of individual nerve cells—to discriminate very fine time differences? Although we will introduce the reader to these last two issues, we do not have space in these pages to fully develop the link between the dynamics of the membrane potential in neurons and overall system performance.

Classical Definition of the Passive Time Constant

How does the membrane potential across a small and isopotential patch of passive neuronal membrane evolve over time? If the membrane is characterized by a single membrane capacitance $C_m$ (in units of $\mu$F/cm$^2$) in series with a voltage-independent membrane "leak" resistance $R_m$ (in units of $\Omega$cm$^2$), Ohm's law tells us that the dynamics of the potential $V_m$ across this circuit in response to a current injection $I(t)$ changes as

$$
\tau_m \frac{dV_m(t)}{dt} = -V_m(t) + R_m I(t),
$$

with the time constant $\tau_m = R_m C_m$ and the input resistance $R_m$ given by $R_m$ times the surface area of the patch of membrane being considered. If a current step of amplitude $I_0$ is injected at time $t = 0$, the charge flows onto the capacitance and the potential rises as

$$
V_m(t) = V_m(0) e^{-t/\tau_m}.
$$

This time course is governed by exponential decay toward the steady-state $V_m = R_m I_0$, as illustrated in the lower trace of Figure 1.

What happens in the simplest spatially extended structure, an infinite cable of constant diameter $d$ and constant membrane properties? Here, the dynamics of $V_m$ is governed by the well-known linear cable equation. We refer the reader to the standard monograph by Jack et al. (1975) for the relevant equation (3.24; first solved by Hodgkin and Rushton, 1946). For a current step, the voltage response at the site of current injection (upper trace in Fig. 1) is governed by

$$
V_m(t) = V_m(0) \times \text{erf}(\sqrt{t/\tau_m}),
$$

where $V_m(t)$ is the input resistance in the infinite cable $R_m = (R_n R_s) \times (\pi d^2) / \tau_m$, $R_n$ is the specific intracellular resistivity in units of $\Omega$cm; and erf(x), the error function. The dynamics of the membrane potential in the cable is also shown in Figure 1.

To understand these curves it should be pointed out that $V_m(t)$ is plotted in normalized units (relative to its steady-state value $V_m = R_m I_0$) in both cases. Equivalently, it can be assumed that the input resistance for the membrane patch is identical to the input resistance in the infinite cable. Under these conditions, the potential in the infinite cable will reach its steady-state value faster than the potential in the patch of membrane. Indeed, in an infinite cable, $V_m$ rises to 84% of its steady-state value in one time constant compared to 63% in the isopotential case. The reason for this nonintuitive behavior is that, in a cable, some of the injected current charges up neighboring regions in addition to charging the local membrane (as in the uniform case).

A different way to understand this is by considering the
in a tree with uniform membrane properties and sealed ends (and without a shunt or a voltage clamp), the slowest time constant $\tau_m$ is always equal to the membrane time constant $\tau_m = R_mC_m$. Second, all time constants scale with the specific membrane capacitance $C_m$. Third, introducing either a shunt conductance at the soma—mimicking the effect of an intracellular electrode—or a voltage clamp changes (typically reduces) all the time constants, including $\tau_m$. In other words, under realistic experimental conditions, the slowest measured time constant represents a lower bound on the actual value of $\tau_m$. Fourth, the $\tau_s$ have a particularly pleasing and simple interpretation for a single finite passive cable with scaled-end boundary conditions that can be used to estimate the electrotonic length of the cable (dendritic tree) being recorded from (Rall, 1969).

**The Experimental Determination of $\tau_m$**

The appeal of determining more than just the first equalizing time constant $\tau_m$ lies in the fact that the $\tau_s$ provide us insight into certain aspects of the electroanatomy of the neuron. In other words, a local measurement reveals something about the global geometry. Direct measurements of $\tau_m$ in neurons depended on the development of the intracellular electrode, introduced by Graham and Gerard (1946) for muscles and first applied to central, mammalian neurons (spinal motoneurons) by Woodbury and Patton (1952) and Brock et al. (1952). As discussed above, these early studies neglected the cable properties of the dendrites and estimated $\tau_m = 2$ msec (a further source of error was very noisy film records that contaminated the “tail” where the time constant is “buried”).

A common numerical technique for extracting time constants involves the peeling of low-order exponents from a semilogarithmic plot of the voltage decay (Rall, 1969; see also Fig. 2; for a history of all of this, see the commentaries in Segev et al., 1994).

Peeling was first applied to the problem of extracting the $\tau_s$ in α motoneurons by Burke and Ten Bruggengate (1971). They estimated that $\tau_m$ ranges from 5 to 7 msec. To remove noise, they averaged 50 voltage transients, thereby obtaining a relatively smooth tail. Indeed, the smoothed transients allowed them to “peel” another time constant, the first equalizing time constant, $\tau_1$, of about 1 msec. The ratio between $\tau_m$ and $\tau_1$ was then used in a formula derived by Rall (1969) to estimate the electrotonic length ($L$, in units of $\lambda$, the space constant) of the motoneuron dendrites. After this work, peeling was applied to many vertebrate and invertebrate neurons. With the development of improved intracellular electrodes, $\tau_m$ could be better estimated and larger values were obtained (see below).

Experimentally, $\tau_m$ is usually determined by injecting a brief current pulse into the soma and recording the voltage response at the same point. The slope of the tail of the decaying phase of $V_{\text{mem}}$ when plotted on a semilogarithmic scale, is $-1/\tau_m$. Typically, a short hyperpolarizing current pulse is used, since long current steps tend to activate voltage-dependent components (e.g., the over- and undershoot investigated in detail by Ito and Oshima, 1965) that interfere with the measurement of the passive time constant. In a linear system, the response to a current pulse is given by the temporal derivative of the response to a step. The derivative of Equation 4 leaves an infinite number of exponential terms with the slowest term decaying as $e^{-\tau_m}$. Thus, the “peeling” method is also directly applicable with the advantage that, now, the steady-state component of the voltage disappears. Figure 2 shows an example of the voltage decay following a brief hyperpolarizing current transient plotted on a semilogarithmic scale for a cortical pyramidal cell. One can clearly observe that the voltage differences over the cell surface equals

---

**Figure 1.** The voltage dynamics in two simple model cases: the evolution of the membrane potential $V_m$ in an infinite, passive cable of constant diameter at the site of current injection (Eq. 3) and in a patch of passive membrane (Eq. 2) in response to a current step at $t = 0$. Time is expressed in units of $\tau_m$ and the membrane potential in terms of the steady-state potential, $V_s$. We here assume that the input resistance $R_m$ of the membrane patch is the same as $R_m$ for the infinite cable. In the cable, the voltage rises faster to its final value than in a patch of membrane. Indeed, in the infinite cable it reaches 84% of the maximal value at $t = \tau_m$ and only 63% of the maximum in the case of an isopotential patch of membrane (dashed line).

**V**

**t/\tau_m**

---

input resistance. While we here assumed that the steady-state input resistance $R_m$ is the same in both model systems, the effective input resistance at small times will be higher in the cable (since the current only “sees” a small part of the cable early on) than the resistance of the membrane patch, explaining why the same current causes a larger initial voltage rise in the distributed system than in the isopotential one.

The same argument holds for an electrode injecting current into the soma of a neuron with an extended dendritic tree. A significant portion of the injected current will flow onto the extensive dendritic membrane surface, and as a result the buildup (and decay) of the somatic voltage is faster compared to the isopotential patch of membrane. This effect was first recognized by Rall (1957). Coombs et al. (1955) had fitted the experimentally observed membrane transients at the motoneuron soma with a single exponential with $\tau_m = 2$ msec. Rall argued that the cable properties of the dendrites needed to be incorporated and—on the basis of Equation 3—estimated $\tau_m = 4$ msec (for a detailed exposition of this, see Segev et al., 1994).

What is the voltage response to current input in spatially complex structures? Rall (1969) showed that the voltage in an arbitrary passive cable structure (whether a single finite cylinder or a large dendritic tree) with uniform electrical parameters throughout the cable can always be expressed as an infinity sum of exponential terms:

$$V_m(x, t) = V_s(x) + B_1 e^{-t/\tau_m} + B_2 e^{-t/\tau_1} + B_3 e^{-t/\tau_2} + \ldots,$$

where the $B_i$s depend both on the initial conditions and on $x$, and $V_s$ is the steady-state component of the voltage. The $\tau_s$ can be thought of as equalizing time constants that are associated with the rapid flow of current (and reduction of voltage differences) between different regions of the cable. They are independent of the site of the current input, the site of recording, or the initial voltage distribution in the tree. In general, solving for these $\tau_s$ involves extracting the root of a recursively defined transcendental equation (for more recent work on this, see Holmes et al., 1992; Major et al., 1993).

Several important points need to be mentioned here. First,
Figure 2. Peeling the voltage transient in a neocortical pyramidal cell. The morphology of this cell, stained with Lucifer yellow, is shown in the inset. The cell is from a slice preparation of the frontal cortex of the guinea pig. A brief (0.5 msec, 2.7 nA) hyperpolarizing current pulse was injected via intracellular electrode at the soma. The decay of the voltage response, plotted on a logarithmic scale, is shown as a function of time. Due to the electrically distributed (non-isopotential) nature of the dendrites, the voltage initially decays faster than $\tau_0 = \tau_1$, and only later (i.e., toward the tail) does $V(t)$ reach the final (slowest) exponential decay, with $\tau_0 = 16$ msec. In this cell, it was also possible to "peel" the next equalizing time constant, $\tau_1 = 1.7$ msec. Experiments were conducted in normal, physiological Ringer solution. The resting potential was $-65$ mV and the temperature was 32°C. The intracellular electrode was filled with 3 m K-acetate (courtesy of Y. Gutfreund; see details in Gutfreund et al., 1995).
after about 5 msec; from this time on the voltage decays exponentially, as in the isopotential case. The slowest time constant \( \tau_\text{m} \) (\( \sim 16 \) msec) corresponds to the inverse of the slope at the tail of the voltage decay. Subtracting this component from the original voltage curve gives rise to a new transient (noisy curve at bottom) whose tail can now again be fitted with a straight line whose slope is \(-1/\tau_\text{m}\). In this case, \( \tau_\text{m} \) = 1.7 msec. If we assume that the membrane of this cell is uniform and that the intracellular electrode did not cause a significant shunt (injury), then \( \tau_\text{m} = \tau_\text{m} \). Our estimate for \( \tau_\text{m} \) is in agreement with Kim and Connors (1993), who report for the larger, layer 5 pyramidal cells in slice from somatosensory cortex \( \tau_\text{m} \) = 16 ± 5.3 msec in the soma.

It is important to emphasize that the quality of the electrical recording depends to a large extent on the tightness of the resistive seal around the electrode. During the impalement of the neuronal membrane, the intracellular electrode can rip a large hole in the membrane, allowing ions to flow through, thereby seriously compromising the quality of the recording. The introduction of whole-cell recordings of *in vitro* cells and the perforated patch clamp technique (Edwards et al., 1989; Spruston and Johnston, 1992) has dramatically improved the situation, with an effective electrode shunt on the order of 0.1 nS. Indeed, over the last four decades the estimate for \( \tau_\text{m} \) in central neurons has grown significantly. As discussed above, in the 1950s it was assumed to be only a few milliseconds. With improved averaging and recording techniques, the recent estimates of \( \tau_\text{m} \) from intracellular sharp-electrode recordings range from 20 to 50 msec for the major types of central neurons (see, e.g., for motoneurons: Fleshman et al. 1988; Clements and Redman, 1989; for three types of hippocampal neurons: Brown et al., 1981; for vagal motoneurons: Nitzan et al., 1990; for cerebellar Purkinje cells: Rapp et al., 1994). With tight-seal whole-cell recordings, the estimates have grown even further and are approaching 100 msec in slice preparations (e.g., Andersen et al., 1990), found time constants ranging from 50 to 140 msec in the hippocampus; Major et al., 1994, report an average value of 93 msec in CA3 pyramidal cells; see also Spruston et al., 1994). A notable exception to such high values is the 2 msec time constant in slices in the avian cochlear nucleus using whole-cell recording with tight seal (Reyes et al., 1994). We conclude this section by noting that \( \tau_\text{m} \) estimates depend heavily on the composition of the physiological solution during the experiment. Adding specific blockers to the solution as is frequently done, such as cesium ions to block K-dependent rectification or aminophosphonovorone (APV) to block NMDA-dependent channels, directly affects estimates of \( \tau_\text{m} \) (usually increasing the estimates).

**A New Functional Definition for \( \tau \)—The Local Delay**

One problem with the standard definition of \( \tau_\text{m} \) (and the associated equalizing time constants \( \tau_\text{m} \)) is that they assume the convenient fiction of a steady-state input. Thus, they only tell us how slowly the membrane can respond. However, synaptic input can be much faster than \( \tau_\text{m} \), and we need a measure that tells us how rapidly the membrane can respond to such physiological input. Furthermore, it is unclear how the local geometry, that is, whether the current injection occurs at a soma or in a distal dendrite or spine, affects the dynamic of voltage. These problems were addressed and solved (for passive membranes) by Agmon-Snir and Segev (1993; see also Zador et al., 1995).

Agmon-Snir and Segev (1993) introduced a simple yet powerful method to calculate delays associated with arbitrary current and voltage signals in passive cable structures. They base their method on the use of moments to characterize the properties of the signal. In particular, the centroid, or “center of mass,” of the signal \( f(x,t) \) at location \( x \) is defined as the ratio of the first to the zero-th moment of a transient signal, \( f(x,t) \):

\[
\int_{-\infty}^{\infty} \frac{f(x,t) \, dt}{\int_{-\infty}^{\infty} f(x,t) \, dt} \quad (5)
\]

where \( f \) can be either a current or a voltage of (practically) any shape. The input or local delay, \( D_{\text{loc}} \), is defined as the difference between the centroid of the input current and the centroid of the voltage response at the same location:

\[
D_{\text{loc}} = \bar{x} - \bar{v} \quad (6)
\]

The same approach can be used to define the *transfer delay* as the difference between the centroid of the induced voltage change at location \( y \) and the centroid of the current injected at location \( x \). However, we will not pursue this topic here.

Agmon-Snir and Segev (1993) prove that the local delay is always positive and independent of the shape of the transient input current; in other words, \( D_{\text{loc}} \) is a property of the passive structure and not of the input and provides a measure for the time window for synaptic integration. It is straightforward to show that for an isopotential neuron, \( D_{\text{loc}} = \tau_\text{m} \); the centroid of an EPSP (or an IPSP) occurs exactly one time constant later than the centroid for the current underlying this potential. In this case, synaptic input arriving with temporal dispersion smaller than \( \tau_\text{m} \) will affect each other (integrate); for larger temporal dispersion the inputs do not interact. In an infinite (or semi-infinite) cylinder, a portion of the injected charge flows along the cable, and therefore the potential at the input site rises and decays faster, as we saw already in Figure 1. Indeed, for an infinite cylinder, the input delay between any current input and the corresponding local potential is only half a time constant, namely, \( D_{\text{loc}} = \tau_\text{m}/2 \). In this case, the effective time window for synaptic interaction is smaller than \( \tau_\text{m} \).

The method of moments can be applied to calculate analytically the local delay at any point in an arbitrary dendritic tree. Figure 3 shows the local delays computed for a detailed compartmental model of a layer 5 pyramidal cell reconstructed during *in vitro* experiments in the primary visual cortex of an adult cat (Douglas et al., 1991). Each of the four panels shows the depolarizing current input waveform (lower trace) and the resultant local EPSP (upper trace). Since the dendritic tree, and in particular, the basal dendrites making up a very large part of the cell, is very compact from the point of view of the soma, \( D_{\text{loc}} = 17.7 \) msec at the soma (lower left panel in Fig. 3), not very far from the \( D_{\text{loc}} = \tau_\text{m} \) relationship expected of an isopotential membrane patch. For distal, dendritic locations, additional current sinks provided by the rest of the dendritic tree reduce \( D_{\text{loc}} \). The local delay is very small for distal basal sites in layer 5 (lower right panel in Fig. 3), since the current can “escape” very quickly because of the proximity to the large current sink at the soma. This effect is less pronounced in the distal apical tree (upper right panel in Fig. 3), since the conductance load imposed by the apical tree and the distant soma is relatively less significant. Indeed, \( D_{\text{loc}} \) (here 5.5 msec) is closer to what is expected at the sealed end of an semi-infinite cable (\( \tau_\text{m}/2 \); Agmon-Snir and Segev, 1993) As is visualized in this figure, small values of \( D_{\text{loc}} \) imply that the associated EPSPs decay very rapidly (see also Rinzel and Rall, 1974). Thus, local synaptic inputs have to be very well synchronized to interact. Moving synaptic input from a dendrite onto a spine reduces \( D_{\text{loc}} \) by an amount depending on the exact electroanatomy (H. Agmon-Snir, personal communication).
A major drawback of using the local delay is that in the presence of voltage-dependent components, $D_{\text{loc}}$ can rapidly become zero or even negative (even for very small inputs). This results from the activation of potassium-dependent conductances that cause the EPSP to undershoot. Although this hyperpolarization may never be very deep, it can be quite prolonged, rendering the definition of the voltage centroid less useful. In this case, one should only consider the positive phase of the EPSP for computing $D_{\text{loc}}$.

**Fast, Local EPSPs Are Independent of $\tau_m$**

It is important to understand what aspects of the voltage dynamics are, and what aspects are not, constrained by the membrane time constant.

Given the very fast rise times of synaptic currents at voltage-independent AMPA receptors (Hestrin et al., 1990; Hestrin, 1992; Jonas et al., 1993; Trussell et al., 1993), synchronized synaptic input can easily deliver a large and powerful current within a narrow time window to the postsynaptic membrane (Sofiky, 1994). Depending on the location of the synapse, this inward current can rapidly depolarize the local membrane. It can be shown that for fast inputs the rise time of the EPSP is independent of $R_m$ but does depend on $C_m$ and $R_e$. At first glance this appears counterintuitive, since $\tau_m = R_e C_m$ should govern the dynamics of the voltage. However, early on, the injected current primarily charges up the membrane capacitance, both at the site of current injection and at neighboring locations (via the axial resistance $R_e$). The larger $R_e$ or the smaller $C_m$, the faster the voltage will change. This is illustrated in a dramatic fashion in Figure 4, where the EPSP due to a fast, excitatory synaptic input in the dendritic tree is plotted for $R_m = 100,000 \ \Omega \ \text{cm}^2$ and for an $R_m$ value 10 times lower. Although the time constant changes also by a factor of 10, the rise time and peak amplitude of the local EPSP are barely affected. Because of the distributed capacitance between the site of the input in the distal dendritic tree and the soma, the signal becomes slower while the EPSP propagates toward the soma. For EPSPs with slow time course, more current flows across the membrane, and $R_m$ becomes more relevant. For a larger $R_m$ value, less current leaks out through the membrane and the somatic EPSP is larger and slower.

It should be noted here that over the last several years, experimental estimates of the intracellular resistivity have increased several-fold over the widely adopted value of $R_e = 70 \ \Omega \ \text{cm}$ and now stand around 150-300 $\Omega \ \text{cm}$ (Stratford et al., 1989; Major et al., 1994; Rapp et al., 1994). A major reason for this trend may lie in the observation that a significant fraction of the cross-sectional area of dendrites is occluded by cytoskeletal and cellular organelles, increasing the value of $R_e$ compared to that obtained in aqueous solution. In contrast, estimates of the membrane capacitance $C_m$ have slowly crept downward from the early estimate of 1 $\mu F/cm^2$ to 0.7–0.8 $\mu F/cm^2$ (most likely caused by an underestimate of the membrane area; Benz et al., 1975; Major et al., 1994).

We conclude that at distal dendritic sites and for brief synaptic inputs, the time course of locally evoked synaptic potentials, as well as the temporal window within which they can interact, is not constrained by $R_m$, but rather by the geometry of the tree and by $C_m$ and $R_e$. On the other hand, the dynamics of synaptic evoked potentials that propagate from one site to another, such as toward the soma, are inexorably shaped by $\tau_m$ (Fig. 4).

**The Effect of the Synaptic Background Activity on $\tau_m$**

Neurons do not exist in isolation but are embedded within a tightly interwoven network of nerve cells. A typical neocortical pyramidal cell is the recipient of between 5,000 and 20,000 synapses (Larkman, 1991; Anderson et al., 1994). In lightly anesthetized or in behaving animals, these cells are spontaneously active, with spike frequencies ranging from...
low values of 0.3–2.5 spikes/sec in the anesthetized cat visual cortex to 5–10 spikes/sec in various extrastriate cortical areas (Gilbert, 1977; Leventhal and Hirsch, 1978; Woody et al., 1984; Abeles, 1991). This “spontaneous” firing activity, combined with massive convergence of synaptic input onto cortical cells, implies that neurons are subject to continuous synaptic bombardment. This is in sharp contrast to the situation prevailing in in vitro slice or culture preparations used extensively for biophysical studies, where very little spike activity exists in the absence of direct stimulation. What consequences does this have for the measurement of neuronal $\tau_m$ (Abbott, 1991; Bernander et al., 1991; Amit and Tsodyks, 1992; Rapp et al., 1992)?

Because synaptic input transiently increases the membrane conductance to particular ions, physical intuition tells us that massive synaptic background activity will decrease the effective membrane resistance $R_m$. Note that this is true both for excitatory and for inhibitory synapses. While a single 0.5 nS peak conductance change for 2-5 msec will not make a large difference, the joint activity of 10,000 synapses, each independently firing several times each second, can cause large overall conductance changes. Figure 5 shows what happens in a model of a layer 5 pyramidal cell (shown in Fig. 3) as the “spontaneous” firing frequency $f_s$ is varied for 4000 excitatory and 1000 inhibitory synapses distributed throughout the cell (each firing independently). Increasing $f_s$ from 0 to 10 Hz effectively decreases the time constant measured at the cell body by a factor of 50 (from 100 to 2 msec). As $f_s$ increases, the cell becomes more and more sensitive to differences in the arrival times of synaptic input (i.e., to their temporal dispersion), with possible important functional consequences for the single-cell performance (Bernander et al., 1991; Rapp et al., 1992) as well as for the performance of the network (Abbott, 1991). Because typically $f \approx 0$ in slice or cultured cells, $\tau_m$ may be much higher in an equivalent in vitro preparation (Bindman et al., 1988).

These results imply that $\tau_m$ should not be thought of as a fixed constant that the cell is stuck with for the rest of its life, but rather as a dynamic variable that can be rapidly modulated by the overall network activity.

$\tau_m$ in the Presence of Voltage-Dependent Conductances

In all of the above considerations we assumed that at subthreshold voltages, the dendritic membrane is essentially passive. Yet, as already discussed by Ito and Oshima (1965) for the spinal motoneuron and recently by Markram and Sakmann (1994; see also Stuart and Sakmann, 1994) for cortical pyramid cells, a perturbation as small as a few millivolts to the dendrites can lead to a nonlinear response (manifest as under- and overshoots in the voltage response). This nonlinear behavior is attributed to the activation of low-threshold, voltage-gated dendritic channels. These effects can be regarded as yet another important source for modulating the effective value of $\tau_m$.

As briefly discussed above, the presence of even relatively small amounts of potassium currents can lead to a dramatic reduction of $D_{\text{mem}}$ even causing it to be negative (due to the presence of a long-lasting hyperpolarization). Under these conditions, what operational definition for $\tau_m$ or other measures can we adopt in the presence of voltage-dependent currents? This is a difficult question that has not received suffi-
The somatic membrane potential in our compartmental model of the layer 5 pyramidal cell shown in Figure 3. Here 135 excitatory, voltage-independent, AMPA-type synaptic inputs located on layer 4 (i.e., within the first 450 μm of the apical trunk) were simultaneously activated at t = 1 msec. Each input corresponds to a brief conductance change (peaking at t = 1.5 msec with a maximal conductance change of 0.5 nS) in series with a reversal potential of 65 mV relative to the resting potential. The soma and axon hillock were endowed with Hodgkin and Huxley-like active channels (g_m = 120 mS/cm²; g_l = 36 mS/cm²; g_r = 0.3 mS/cm²). The time constants for Na and K activation were fivefold slower than in the original Hodgkin and Huxley model (for T = 20°C). Following this powerful input, the threshold for spike firing at the soma is reached after a delay of only 2.75 msec. The “resting” time constant t_r = 20 msec. For comparison, the same input was applied to a corresponding passive model where the active channels were replaced by passive channels, keeping the same time constant in both cases. The voltage response (the somatic EPSP) in this passive model is indicated by the lower curve. The threshold for spike initiation is reached in a fraction of t_r much sooner than the centroid of the underlying EPSP in the passive case (D = 17.7 msec at the soma; see the arrow at 18.7 msec).

So, What Does the Passive Neuronal Time Constant Really Mean?
As mentioned above, the problem with t_r and associated measures is not so much that they differ by a factor of 2 or 3 for cells with voltage-dependent components (i.e., for almost all neurons), but that they characterize the behavior of the cell in an operating regime of little physiological relevance. Computing t_r or Dₚₜ relies on measuring the dynamics of the membrane potential in response to a subthreshold input, such as a sub-nanomampere current injection or a single EPSP. However, when a neuron in the cortex of the cat responds to a visual input, say, a running mouse, it receives input from hundreds or more presynaptic cells and responds with a barrage of spikes. Such a cell is far removed from the subthreshold regime used to assess the response time of the membrane.

Could one argue that t_r therefore represents a lower bound on the neuronal response time? Unfortunately, even this is not true. It is straightforward to construct systems that spike with arbitrarily low frequencies. As mentioned above, a well-known example of this is the very low frequency behavior (on the order of one spike per second) seen in mollusk neurons (Connor and Stevens, 1971a,b). Here the transient potassium current, Iₖ, although endowed with time constants less or equal to 100 msec—can space successive action potentials much more widely than could be achieved with a combination of fast channels and a passive membrane (Connor, 1978). The moral here is that t_m does have its uses in characterizing the behavior of the cell under subthreshold conditions, yet it does not tell us much about the dynamics of neurons in their normal operating range.

Even though a single neuron is unlikely to respond much faster than a few milliseconds (witness Fig. 6), it is known that animals can discriminate times that are much, much briefer. Behavioral studies show that the electric fish Eigenmannia is able to effectively discriminate temporal differences as small as 0.4 µsec (Rosen and Heiligenberg, 1985). Another instance is the barn owl, a bird of prey sensitive to differences in the arrival time of sound at its two ears of 2 µsec (corresponding to being able to localize a sound source, such as a squeaking mouse, with 1.5° precision; Konishi et al., 1985). Extracellular recordings have shown that individual cells in the inferior colliculus in the midbrain of the owl, specialized for processing interaural time differences between the two ears, have tuning curves with a half-width at half-
height of about 15 μsec (Moiseff and Konishi, 1981). The brain achieves such hyperacuity performances using a combination of neurons whose biophysical properties are optimized to respond very transiently (e.g., neurons in the avian nucleus magnocellularis have very fast time constants of 2 msec; Reyes et al., 1994), in combination with massive convergence and population coding (Konishi, 1991). Softky (1994) has shown how a few fast, excitatory synapses located at the tip of distal basal dendrites in a model pyramidal cell (recall the low value of $D_{exc} = 1$ msec in the lower right panel in Fig. 3) can perform coincidence detection with sub-milli-second resolution (see also Koch and Poggio, 1983; Segev and Rall, 1988). Thus, although the dynamics of the membrane potential in neurons might in general be limited to the milli-second range, this does not preclude individual neurons performing temporal resolution on a much finer time scale. Indeed, detecting such temporal differences is primarily limited by signal-to-noise considerations, rather than by $\tau_r$.

When thinking about the membrane time constant as co-determining the “processing speed” of neurons, it is useful to remember that in such a highly parallel architecture as the cerebral cortex, very deep (in the sense of requiring many steps) computations can be executed in a very short time. A dramatic example of this is evident in the recognition study by E. E. Cooper and I. Biederman (unpublished observations, 1994). They flashed large numbers of simple line drawings of various common objects, such as a truck, a fire hydrant, a cat, a fruit, and so on, onto a monitor at a rate between 1 and 40 images per second (this paradigm is called rapid serial visual presentation) and asked subjects to push a button if a particular image, say a lion, comes up. Most naive and untrained subjects can perform this task effortlessly at 10 Hz, that is, when on average only 100 msec is available to process each image in each part of the brain (assuming a pipelined neuronal architecture). Performance at 20 Hz is approximately 90% and does not become chance (guessing) until 40–50 Hz. Even when the task is defined by exclusion (e.g., “push the button when you see the first drawing of an object that can’t be used to as a means of transportation”) subjects can perform reasonably well at a 20 Hz presentation rate, a surprising result. A rate of 20 Hz implies 50 msec, which is only on the order of 2–10 times slower than $\tau_m$ or $D_{exc}$ or related measures. In other words, the rate of switching of the individual components (i.e., neurons) versus the execution times of the whole system is on the order of $10^4$, compared to $10^{-10}$ for a similar performance on today’s so-called “massive parallel” digital computers (if such performance can be achieved at all). This is quite a remarkable aspect of nervous systems that never ceases to amaze.

In conclusion, the rise time of local EPSPs and IPSPs is limited by the dynamics of the synaptic current (i.e., by how fast the synaptic current can be pushed through the ionic channels) and by the membrane capacitance, but not by $\tau_r$. Their decay time is relatively well characterized by the local delay $D_{syn}$, which can be small in distal structure where the current can rapidly dissipate but is on the order of $\tau_m$ at the cell body. When these postsynaptic potentials propagate to other locations (such as the cell body), $\tau_m$ does play a significant role in shaping their rise times and their long tails. Today, the passive time constant is estimated to be on the order of 20–100 msec. It has so far not been possible to introduce for neurons with voltage-dependent membranes any measure equivalent to $D_{syn}$. Such a measure is sorely needed to more fully characterize neurons in physiologically relevant situations.

Notes

We thank Öyvind Bernander and Hagai Aghnon-S narz for their detailed comments and their help in preparing the manuscript. The research reported here was funded by grants to C.K. from ONR and the NIMH Center for Neuroscience and by grants to I.S. from ONR and BSE. I.S. acknowledges the hospitality of the Mathematical Research Branch (NIDDK) at the NIH in Bethesda and C.K., the hospitality of the Santa Fe Institute in Santa Fe, New Mexico. Early versions of the manuscript were written while these two authors spent part of their summer at these institutions.

Address correspondence to Dr. Christof Koch, Computation and Neural Systems Program, Caltech, 13974, Pasadena, CA 91125.

References

- Gilbert CD (1977) Laminar differences in receptive field properties.
of cells in cat primary visual cortex. J Physiol (Lond) 268:391-421.


