SUB-MILLISECOND COINCIDENCE DETECTION IN ACTIVE DENDRITIC TREES

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Abstract—Simulations of a morphologically reconstructed cortical pyramidal cell suggest that the long, thin, distal dendrites of such a cell may be ideally suited for nonlinear coincidence-detection at timescales much faster than the membrane time-constant. In the presence of dendritic sodium spiking conductances, such hypothetical computations might occur by two distinct mechanisms. In one mechanism, fast excitatory synaptic currents inside a thin dendrite create strong local depolarizations, whose repolarization—resulting from charge equalization—can be 100-fold faster than the membrane time-constant; two such potentials in exact coincidence might initiate a dendritic spike. In the alternate mechanism, dendritic sodium spikes which do not fire the soma nonetheless create somatic voltage pulses of millisecond width and a few millivolts amplitude. The soma may fire upon the exact coincidence of several of these dendritic spikes, while their strong delayed-rectifier currents prevent the soma from temporally summing them. The average firing rate of a compartmental simulation of this reconstructed cell can be highly sensitive to the precise (submillisecond) arrangement of its inputs; in one simulation, a subtle reorganization of the temporal and spatial distribution of synaptic events can determine whether the cell fires continuously at 200 Hz or not at all.

The two cellular properties postulated to create this behavior—fast, strong synaptic currents and spiking conductances in the distal dendrites—are at least consistent with physiological recordings of somatic potentials from single and coincident synaptic events; further measurements are proposed. The amplitudes and decays of these simulated fast EPSPs and dendritic spikes can be quantitatively predicted by approximations based on dendritic properties, intracellular resistance, and membrane transconductance, without invoking any free parameters. These expressions both illustrate the dominant biophysical mechanisms of these very transient events and also allow extrapolation of the simulation results to nearby parameter ranges without requiring further simulation. The possibility that cortical cells perform temporally precise computations on single spikes touches many issues in cortical processing: computational speed, spiking variability, population coding, pairwise cell correlations, multiplexed information transmission, and the functional role of the dendritic tree.

1. INTRODUCTION

The fundamental output of a cortical neuron is a single action potential lasting about 1 ms, which can in many cases cause an equally brief excitatory synaptic current. Can a single neuron use that temporal precision in its computation? Decides of electrophysiology have produced no reliable evidence that information is carried by precise spike-times in most cortical areas. Only temporal averages over much longer timescales correlate with stimuli (at least 20 ms). Furthermore, it is generally believed that cortical cells are fundamentally incapable of using such millisecond-resolution information, due to their relatively longer membrane time-constants (10–30 ms) and to dendritic attenuation of high-frequency signals.

However, there are sparse but persistent claims that some computation may occur at the time-scale of individual spikes: the "reverberation" of Hebb, precise interspike-interval patterns, and the paradoxically high spiking variability at high firing rates.

In search of a possible cellular basis for millisecond-scale computations, this paper tests the upper limit of computational bandwidth in individual cortical pyramidal cells by postulating one situation—the presence of active spiking conductances in distal dendrites—in which such a cell might preferentially respond to synchronized excitatory postsynaptic potentials (EPSPs). Rough analytic predictions and detailed simulations of a reconstructed pyramidal cell together suggest that such a cell could, in principle, perform submillisecond coincidence detection. Previous related work by others has included numerical simulations which explored the computational properties of active dendritic trees (without emphasizing fast timescales, and analytical work which yielded far more sophisticated expressions for electrical activity in dendrites than the simplified expressions used here.

This paper has two sets of goals: (1) To explore the requirements for high-frequency coincidence discrimination; to present "proof-of-concept" simulations showing that postulated membrane properties

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxalone-propionic acid; CCH, cross-correlation histogram; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; HH, Hodgkin-Huxley; LGN, lateral geniculate nucleus; NMDA, N-methyl-D-aspartate.
might perform such computations in a realistic cell morphology; to show that such fast computations are consistent with some published intracellular recordings; and to spur debate on whether such fast computations actually occur. (2) To describe the amplitude and time-course of fast intracellular potentials by simple analytical expressions accurate at the 70–80% level, which are based only on physical principles and constants, and which use no free fitting parameters. These approximations should demonstrate that the effects are mostly understood, and in addition should provide simple scaling expressions which can extrapolate results from the few simulated parameter regimes into unsimulated territory. If successful, these approximations and scaling formulæ will be a useful back-of-the-envelope adjunct to brute-force simulations, and may provide a conceptual link between the fundamental cable equations and numerical simulation of them.

This analysis invokes two unorthodox assumptions: that thin, distal dendrites contain strong and fast Hodgkin–Huxley (HH)-like conductances (e.g. sodium spiking conductances), and that synaptic conductances (excitatory postsynaptic currents, EPSCs) in those dendrites may have local depolarizations of tens of millivolts and durations well less than a millisecond. These assumptions are defended in the Discussion, where some experimental correlates for them are proposed.

2. SIMULATED PYRAMIDAL CELL

The best possible understanding of dendritic spiking comes from numerical simulation of a realistic cell model. The morphology used here was a physiologically characterized layer 5 pyramidal cell from cat striate cortex, which was filled with horseradish peroxidase and reconstructed with confocal microscopy in the lab of R. Douglas and K. Martin at Oxford. Simulations of this cell model without active dendrites have previously been successfully compared to the original cell’s behavior at rest and under d.c. current clamp: an outline and caricature of the cell are shown in Fig. 1A, B. In this section we describe the

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Fig. 1. (A) A layer V pyramidal cell, as recorded, reconstructed, and simulated from cat striate cortex. (B) A caricature of the compartmental model of that cell, as modelled and used here. All passive-membrane areas in the simulation of dendritic spiking are shown in gray; HH-like active membrane conductances were placed only on the 44 thin basal terminal branches (black). The thicker, shorter regions between the soma and the black terminal branches are parent dendritic "trunks." (C) An action potential in a single terminal branch (thin curve) will create a brief, small depolarization at the soma (thick curve).
various simulations in as brief a form as possible; in Section 3 we will explain and quantify the dominant effects using expressions from linear cable theory.

The compartmental model contained 1890 compartments (Fig. 1). The soma and basal dendrites (where active conductances were modelled) were simulated as connected cylinders no longer than 10 µm, using the NEURON program.20 Because fast transient events in the distal apical dendrites had a negligible effect on the soma, and would consume large amounts of computation time, the apical dendrites were kept passive and had longer compartments (up to 200 µm). These simulations concentrated on electrical events inside the cell’s 44 most distal basal terminal branches, which were very long (typically 200 µm) and thin (<1.0 µm).

2.1. Passive model properties

The passive time-constant was τ = 30 ms, resulting from a membrane resistance of 30 kΩ cm² (this membrane resistance can be interpreted in terms of background synaptic activity). This time-constant was chosen to lie near the upper end of observed membrane time-constants,22 over an order of magnitude slower than the transient events modelled here. The membrane capacitance was 1 µF cm². Dendritic aspect ratios were slightly enlarged from their reconstructed measurements (by less than 10%) to account for the additional capacitance of spines on the dendrites. However, because some researchers believe spines contribute a much larger capacitance than this, an additional correction for them was simulated below, and its magnitude is explained in Section 3.6.

Integrating time-steps were 50 µs, and individual compartments were equal to or less than 20 µm long (resulting in about 2000 compartments total in a typical simulation). While these values might be considered sufficiently fine when compared with the membrane time-constant and electrotonic length, they were actually too coarse to give precise results at the fast temporal and tight spatial scales of interest. However, we should not regard this as a significant problem for two reasons. Firstly, these simulations were only intended to give approximate results and general trends, not precise values. Secondly and more importantly, the experimental uncertainties in the simulation parameters far outweighed possible computational errors. For example, the value used for intracellular resistivity, Rᵢ = 200 Ω cm, is midway between published values which span a factor of five in magnitude, ranging from 378 Ω cm31 down to 70 Ω cm.24 As a final check on integration coarseness, a representative simulation from each set was tested to verify that improving the spatial and temporal integration scale by a factor of two would not change the result by more than 5%.

The first simulations were of EPSCs and EPSPs, resulting from fast synaptic conductances like those mediated by receptors for α-amino-3-hydroxy-5-
methyl-4-isoxalone-propionic acid (AMPA). All synaptic conductances were modelled as alpha-functions (Eqn 19), in accordance with common practice20 and in the absence of better knowledge of their properties.

The first simulations were of single synaptic events on the middle of a passive single basal terminal branch 226 µm long and 1.05 µm wide; they were fast (0.05 < t_peak < 0.4 ms) and strong (E_syn = 0 mV, g_peak = 6 nS). This simulation, shown in Fig. 2, determined that such fast dendritic EPSPs can have locally high amplitude (∆V_peak ≈ 20 mV) and fast decay (<1 ms), while still producing somatic EPSPs with amplitudes (∼200 µV), rise-times (∼1 ms), and decay times (<30 ms) in the physiological range.23,20,26

The amplitudes and spatial spread of these dendritic EPSPs depended on local membrane properties (e.g. diameter, Rᵢ, and Cᵢ, as explained in Section 3.2).

However, a surprising result is that the effective duration of these fast EPSPs did not depend in any significant way on dendritic properties, but only on the duration of the synaptic current. In particular, the time for such an EPSP to decay from its peak voltage to half that value (a time we call τ₁/₂) was about six times the value of t_peak, and was thus up to 100-fold shorter than the passive membrane time-constant (e.g. for t_peak = 0.05 ms, 6τ_peak = 0.3 ms = t_peak/100). This result suggests that the temporal precision with which synaptic events can be locally distinguished inside a long, thin dendrite is limited solely by the duration of the synaptic currents, rather than by any other membrane properties.

It can be seen in Fig. 2 that the reduction of τ_peak by a factor of two only reduces the local peak amplitude by about a third. This is consistent with a model (Section 3.2) in which the local peak amplitude scales roughly as √t_peak (rather than linearly as the total charge does), so that faster events can have a substantially greater peak depolarization, relative to the charge they deposit.

Such fast EPSPs, which result from capacitive charge-equalization inside the dendritic membrane rather than resistive decay through it, allow in principle submillisecond discrimination among individual EPSPs. If the dendritic shaft contained strong spiking conductances, then two simultaneous, co-localized synaptic events could drive the local membrane above threshold (e.g. ∆V_peak ≈ 2 × 20 mV for t_peak = 0.1 ms), but those same two events would not initiate a dendritic spike if separated by only a millisecond. In contrast, the EPSP at the soma would decay at least 10-fold more slowly, so the soma could not effectively discriminate among precisely timed synaptic events.

2.2. Single dendritic spikes

These submillisecond effects—determined entirely by the diffusion or equalization of synaptic charge within a passive membrane—give a motivation for studying the behavior of hypothetical active dendritic currents, in particular dendritic sodium spikes. The
only active properties investigated were those of the HH-like equations\textsuperscript{2} [the equations only differed from the original HH equations in containing a term $m^2$ in the sodium conductance, and in using fixed, voltage-independent time-constants $\tau(I) = 0.5$ ms, $\tau(m) = 0.05$ ms, and $\tau(K) = 2.0$ ms]. The peak conductances $G_{Na}$ and $G_{K}$ were adjustable as parameters. The reversal potentials of those conductances were $E_{Na} = 50$ mV and $E_{K} = -95$ mV; the threshold potential about which each conductance opened was $V_{th} = -40$ mV. All simulations used strong $G_{K} = 2G_{Na}$ (unless otherwise noted), as justified in Section 2.3.

The first set of dendritic-spike simulations explored the situation in which active currents were limited to the interior of a single terminal basal dendrite (such terminal branches were typically about 1.0 $\mu$m or less in diameter and over 150 $\mu$m long; there were 44 of them on this reconstructed cell, as caricatured in Fig. 1). To understand the behavior of dendritic spikes in isolation, active conductances were simulated on one terminal branch at a time, while the soma and other dendrites were left passive (interactions among multiple active branches and the soma are simulated in Sections 2.2.3 and 2.8).

Dendritic spikes were triggered in the center of terminal branches by conductance alpha-functions with peak time 0.1 ms and peak conductance 12 nS (these very strong synapses were intended only as triggers, not as realistic representations of synaptic input). In this case a single EPSP would always trigger a dendritic spike from $E_{syn} = -65$ or
- 75 mV. The dendritic and somatic voltages of such a dendritic spike are shown in Fig. 1C. The charge passed by the synaptic conductance was negligible relative to the charge passed by the open sodium channels.

Because we expected our dendritic currents to be capable of helping trigger spikes in an active soma, we measured their somatic depolarization. \( \Delta V_{\text{soma}} \) represented the peak increase in voltage above the initial "resting" value \( E_{\text{rest}} = -75 \text{ mV or } -65 \text{ mV} \),

\[
\Delta V_{\text{soma}} = \max [V_{\text{soma}} - E_{\text{rest}}]. \tag{Eqn 1}
\]

As can be seen from the trace in Fig. 1C, the peak spiking voltage inside a dendrite was near the sodium potential (50 mV), representing an amplitude change from rest to peak of \( \Delta V = 120 \text{ mV} \); but the peak somatic voltage was 15-fold smaller (\( \Delta V_{\text{soma}} = 10 \text{ mV} \)), because the thin dendrite's intracellular resistance prevented it from charging up the large capacitance of the soma and other dendrites.

2.2.1. Peak dendritic voltages. As shown in Fig. 3A, the peak voltage inside the dendrite decreased toward its proximal end, as the lower impedance of the soma began to dominate. (Note that this figure shows the peak voltage values, which occurred at slightly different times, rather than a particular "snapshot" at any one time.) One of the two dendritic spikes shown was in a single thin branch connected directly to the soma (with no widenings or other branchings); its proximal end thus had a peak voltage at the somatic peak voltage of about -65 mV. The other dendrite was a very distal branch, whose proximal end (where it joins its thicker parent dendrite) had a peak voltage almost 40 mV higher, due to a current-induced voltage drop along the parent dendrite.

For both dendrites simulated, the peak voltage was nearly constant (near \( E_{\text{rest}} \)) for most of the length of the dendrite (note that only 80 \( \mu \text{m} \) of the more than 200 \( \mu \text{m} \) of each dendrite are shown). This constant peak voltage suggests that there was no net voltage difference along that section, and hence no net flow of charge there. However, if the majority of the dendrite's length contributes no net charge toward the soma, then the peak somatic voltage ought not to depend on the existence of that section of dendrite. This is in fact the case. A truncated dendrite only 30 \( \mu \text{m} \) long generated a \( \Delta V_{\text{soma}} \) only 10\% less than that generated by an otherwise identical dendrite of length 274 \( \mu \text{m} \).

2.2.2. Peak current and somatic voltage. The approximate peak current delivered to the soma by a spiking dendrite can be calculated from the same graph. For the more proximal of the two dendrites shown, the peak slope \( dV/dx \) (measured at the dendrite's most proximal end) can be multiplied by the known intracellular axial resistance to infer a peak current of 3.0 nA (a value which corresponds to the prediction made later, in Section 3.3).

But clearly the current from the dendrite into the soma—and hence the peak somatic voltage—will depend on the strength of the sodium conductances inside the dendrite. Spikes in the same two dendrites were simulated at values of \( G_{\text{Na}} \) spanning almost two orders of magnitude, from 0.01–0.4 S/cm². The peak somatic depolarization (Fig. 3B) scaled roughly as \( \sqrt{G_{\text{Na}}} \) (as explained in Section 3.3), not linearly in \( G_{\text{Na}} \) as one might naively expect.

The peak somatic voltage \( \Delta V_{\text{soma}} \) was measured in this manner for each of the 44 terminal basal branches separately. With active conductances on only one branch at a time, one could ensure that only a single dendrite was spiking. Simulations were done at \( E_{\text{rest}} = -75 \text{ mV} \), for both high and low peak sodium conductances ("strong HH": \( G_{\text{Na}} = 0.2 \text{ S/cm}^2 \); "weak HH": 0.033 S/cm²). The simulated somatic depolarizations are shown on the vertical axis of Fig. 4 (plotted against the values predicted from Section 3.3, Eqn 44, so that a good match lies on the line with unit slope). Histograms of

![Image](Image)
Fig. 4. Spikes in individual terminal branches produce somatic depolarizations consistent with predictions. Each of the 44 terminal branches was separately given active HH-like kinetics and triggered to spike, while its 43 neighbors and the remaining cell contained only passive membrane properties. Plots of $\Delta V_{soma}$ (resulting from those dendritic spikes) against the values predicted by Eqns 44 lie near the diagonal line of unit slope, which represents a perfect prediction (A, $G_{Na} = 0.033 S/cm^2$; B, $G_{Na} = 0.2 S/cm^2$). Histograms show that $\Delta V_{soma}$ clusters around 3 mV (C, $G_{Na} = 0.033 S/cm^2$) or 6 mV (D, $G_{Na} = 0.2 S/cm^2$). In both A and B, filled points represent predictions by the current-source model (Eqns 33 and 39), while open points were predicted by the resistive model (Eqns 38 and 39).

2.2.3. Multiple dendritic spikes. The preceding simulation—in which only a single branch at a time contained active conductances—was biologically implausible. A more realistic simulation would let all dendrites have the same conductances.

For such simulations, each of the 44 terminal branches was triggered separately, and peak $\Delta V_{soma}$ plotted as above (this was identical to the simulation above, except that now all terminal basal branches contained HH-like conductances, and $E_{rest} = -65$ mV was higher, encouraging neighboring branches to fire). The results (Fig. 5) show that most somatic depolarizations were above the values obtained for isolated dendrites. For the “weak HH” case ($G_{Na} = 0.033 S/cm^2$), the mean depolarization was shifted from 2.7 to 3.5 mV, and for the “strong HH” case ($G_{Na} = 0.2 S/cm^2$) from 6 mV to about 13 mV. The “strong” case had four dendrites whose individual firings were capable of triggering all the basal dendrites to fire, and about one-sixth of the 44 dendrites in this case delivered $\Delta V_{soma} \geq 15$ mV, which would be sufficient to bring the soma to firing threshold.

These substantially larger depolarizations occurred because a spike in one dendrite might trigger or “recruit” neighboring dendrites to fire spikes. This effect is similar to the “chain reaction” observed among simulated active dendritic spines, and depends strongly on the local dendritic geometry: a neighboring dendrite is somewhat more likely to be recruited if it is electronically close to the initially firing branch, and much more likely to fire if the two branches share a long, highly resistive section of parent dendritic trunk between them and the soma.

As the recruited branches fire, they increase the voltage drop still further, and recruit even more branches. The magnitude of this effect can roughly be predicted from expressions shown elsewhere.

There is a qualitative difference between the “strong HH” and “weak HH” simulations: strong active dendritic conductances tended to make neighboring branches more likely to fire together, and weak conductances made them more likely to fire independently. In all cases, some branches were much more influential than others, and it was often (counterintuitively) the more distal branches which had the largest somatic influence, because the greater voltage drop across their shared parent trunk could recruit many neighbors to fire.
2.3. Somatic repolarization by dendritic $I_{\text{inh}}$

There are two important ways a dendritic spike can influence the soma—it can depolarize the soma, and its delayed-rectifier ($I_{\text{inh}}$) currents can repolarize the soma after the voltage peak has occurred. Because such repolarization can severely limit the temporal summation of sequential spikes, it is worth understanding.

A very brief somatic depolarization will decay a bit even without $I_{\text{DR}}$, as the somatic charge equilibrates into the proximal dendrites and subsequently decays with the membrane time-constant. What determines the additional role of $I_{\text{inh}}$ in repolarizing the soma?

We triggered spikes in a typical basal terminal branch (as above, Section 2.2.3), and recorded the somatic voltage traces, using values of 0.2 and 0.02 S/cm² for peak sodium conductance, and various values for the peak potassium conductance. Single spikes could be elicited with ratios of peak potassium to peak sodium conductance from as low as 0.05 up beyond 4.0, a factor of nearly 100, at two different reversal potentials. (Some sample curves from such simulations are shown in Fig. 6). There are several noteworthy points. The first is that the peak somatic voltage following the dendritic spike was very insensitive to the strength of potassium conductances: at both reversal potentials and values of peak sodium conductance, an increase of nearly 100 in peak potassium conductance elicited a decrease in $\Delta V_{\text{soma}}$ of only about 30% (Fig. 6). This happened because the peak somatic voltage occurred before the longer-lasting potassium currents had a chance to repolarize it. (In fact, a successful analysis of this mechanism can idealize the sodium and potassium currents as completely non-overlapping in time, as in Fig. 14; see also Section 3.3.).
The most important effect of dendritic $I_{on}$ currents is their ability to "suck out" depolarization from the soma. As Fig. 6 shows, the weakest potassium conductances left the soma with substantial depolarization persisting after the dendritic spike. However, stronger values of $G_K$ could not only remove the dendritic spike's charge from the soma, but could even leave the soma at a lower potential than before the dendritic spike (Fig. 6B). (The intracellular dendritic resistance caused this hyperpolarizing effect to saturate, so that even stronger potassium conductances could not create correspondingly larger currents or hyperpolarizations.)

The strength of this effect also depended strongly on the difference between the resting and potassium reversal potentials. At lower values of $E_{rest}$ (closer to $E_K$), the driving voltage across the potassium channels was smaller and the $I_{on}$ had less ability to repolarize the soma. As a benchmark estimate of the repolarization at $E_{rest} = -65$ mV, a peak potassium conductance double the peak sodium conductance could leave the soma at almost exactly the same potential as before the dendritic spike. This two-to-one ratio was used for all the simulations of dendritic spikes (unless explicitly listed otherwise).

With these strong repolarizing conductances, a spike's somatic voltage pulse was exceedingly brief (Fig. 6). From the simulation of Section 2.2.3, a histogram of the pulses' full-width-at-half-max durations $t_{1/2}$ for all 44 terminal branches is shown in Fig. 7. The "weak HH" spiking conductances created somatic voltage transients about 1.1-1.2 ms wide, comparable to a single pulse from Fig. 6. The "strong HH" conductances gave similarly narrow pulses

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**Fig. 6.** The amount of somatic depolarization (due to a dendritic spike) which persists afterwards depends on the strength of the spike's delayed-rectifier current $I_{on}$. The time-course of somatic depolarization (simulated using strong active dendritic conductances $G_{Na} = 0.2$ S/cm$^2$) is plotted for various ratios $G_K/G_{Na}$

(A, $E_{rest} = -75$ mV; B, $E_{rest} = -65$ mV). The strongest repolarizing currents can create very brief somatic voltage pulses, which leave the soma at a lower potential than before the dendritic spike.

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**Fig. 7.** Somatic depolarizations from dendritic spikes with strong $G_K$ have very brief durations. Histograms show somatic pulse-width $t_{1/2}$ (full-width at half-max) for $\Delta V_{soma}$ (in response to separately triggered synapses at each of the 44 terminal branches, with active conductances in all branches, $E_{rest} = -65$ mV, and $G_K = 2G_{Na}$, as above in Fig. 5). With weak sodium conductance (A, $G_{Na} = 0.033$ S/cm$^2$), depolarizations were smaller and fewer neighboring dendrites were recruited to fire, so that pulse-widths clustered near the value 1.2 ms predicted in Section 3.4. For larger sodium conductances (B, $G_{Na} = 0.2$ S/cm$^2$), larger depolarizations sometimes recruited several branches to fire sequentially, broadening the somatic pulse to values near 1.5 ms (the few cases in which all dendrites fired are not shown here). With depolarizations of such short duration, the soma might only fire in response to sub-millisecond coincidences among dendritic spikes.
when only single dendrites fired, but in a few cases created pulses almost twice as long, when many branches were recruited into firing sequentially (corresponding to very large somatic depolarizations, such as $dV_{soma} > 60$ mV in Fig. 5D).

The key features of these very brief voltage transients are that they typically had amplitudes below somatic firing threshold, they had very short duration, and they were quickly and completely repolarized, so that temporal summation of them was impossible. A soma subject to a barrage of such dendritic spikes could only fire an action potential upon the millisecond-level coincidence of several such dendritic spikes, allowing a degree of nonlinearity and temporal precision not usually thought to exist in cortical cells.

2.4. Spines’ capacitance

There are claims that the additional area of spines on the dendrites of spiny neurons (such as the pyramidal cell simulated here) might increase the effective dendritic area (and hence the values of passive membrane conductance and capacitance) by factors of up to two or three.24

As a test of the simulations’ sensitivity to a change in membrane capacitance, the membrane capacitance for the entire simulated cell was thus doubled. This extra capacitance is equivalent to placing spines over the entire cell, including the soma; the simulation program could not assign separate $C_m$ for dendrites and soma. The isolated 19-mV EPSP simulated earlier inside a dendrite (Section 2.1 and Fig. 2, $t_{rise} = 0.1$ ms) now peaked instead at 14.4 mV, a reduction of about 25%. (Expressions quantitatively accounting for these changes are given in Section 3.6.)

A similar test was made for the somatic depolarization $\Delta V_{soma}$ due to a spike in that dendrite. The somatic peak simulated earlier had been $\Delta V_{soma} = 8.3$ mV, and the newly simulated peak was 5.6 mV, a reduction of 32% (which is explained in Section 3.6). We can conclude that if indeed dendritic spines add a substantial capacitance to the dendrites, this adjustment will decrease simulated depolarizations both inside the dendrites and at the soma.

The added capacitance of dendritic spines can have another effect: the broadening of an EPSP from its very fast duration inside a thin dendrite to produce a much slower rise-time as measured at the soma. This effect is important because in cortical pyramidal cells, recorded intracellular EPSPs have only been recorded at the soma, and we would like to infer their dendritic time-course from those somatic recordings. In the earlier spineless simulations, EPSPs in the center of a long, thin dendrite (such as the one with $t_{rise} = 0.1$ ms shown in Fig. 2) were moderately smoothed in transit to the soma, giving a somatic 10–90% rise-time of 0.6 ms (which is about 30% shorter than observed experimentally27,28,29). However, if spines effectively tripled the membrane capacitance to 3 pF/cm²,34 then the simulated somatic rise-time was about 1.1 ms, well in line with electrophysiological evidence. The effect of intracellular dendritic resistance and dendritic diameter on this broadening was not investigated.

2.5. Temporal summation versus coincidence-detection

A neuron’s ability to “detect” coincidences requires both that it fire in response to coincident dendritic events and also that it not fire as frequently in response to non-coincident events. So we should investigate the simulated cell’s response to a large ensemble of inputs, in order not to ignore some detail of the interactions between synaptic events. We will distinguish between two hypothetical mechanisms of coincidence-detection—among EPSPs and among dendritic spikes. Both of these mechanisms might function together in real pyramidal cells, but for this exploratory work we will simulate active and synaptic conductances which only produce one or the other of these coincidence-detection schemes.

2.5.1. Coincidence of excitatory postsynaptic potentials. One potential method of coincidence-detection allows the coincidence of two or more submillisecond EPSPs in the same dendrite to cause a dendritic spike, whose depolarization at the soma is much larger than that of the EPSPs by themselves, as described in Section 2.2. (One might crudely think of the dendritic branch as a kind of AND gate over synaptic events, with a dendritic spike as its output; see Ref. 26 for a survey of possible mutiplicative interactions in neurons, and Refs 43, 44 for a treatment of dendritic spikes as AND-gates.) The strength of a single simulated synaptic event in the center of a long terminal branch was $g_{syn} = 6$ nS ($t_{rise} = 0.1$ ms), producing a local EPSP like that in Fig. 2. A single such EPSP could not by itself reliably initiate a dendritic spike during the simulations, but two such coincident EPSPs (equivalent to a single synapse with $g_{syn} = 12$ nS) could. To evaluate this type of dendritic computation, we arranged the dendritic conductances so that almost any dendritic spike could fire the soma. This way, the soma’s output spike should only reflect the pairwise coincidence of fast EPSPs inside a single dendrite, rather than coincidences of EPSPs in different dendrites. This scheme, which we can dub “coincidence-of-EPSPs,” was created by simulating HH-like conductances over the soma and entire basal tree (not just the terminal branches). However, the sodium conductances strengths simulated earlier (Section 2.2) were too weak (and the potassium conductances too strong) for each single branch to fire the soma. So this simulation used different values—very strong $g_{Na} = 0.5$ nS/cm² and weaker $g_k = 0.25$ nS/cm² throughout the dendritic tree—to ensure that of dendritic spikes separately initiated in the 44 terminal branches, all but two (i.e. about 95%) caused the soma to fire from rest. The passive reversal potential was $E_{pass} = -65$ mV, but
passive decay was dominated by active currents whenever dendritic spikes occurred.

2.6. Coincidence of dendritic spikes

A second type of coincidence-detection could take place at the soma, rather than inside the dendrites. In this scheme (dubbed “coincidence-of-dendritic-spikes”), the fundamental input to the soma was a sodium spike from a terminal basal branch, like those simulated in Section 2.2. (For simplicity, we did not investigate here the events which caused the dendritic spike, so each dendritic spike was triggered by a single very strong EPSP of $t_{\text{peak}} = 0.1 \text{ ms}$ and $g_{\text{Na}} \text{ = 18 nS at the branch's center}}$).

Unlike the “coincidence-of-EPSPs” scheme above, this scheme required that most isolated dendritic spikes not be capable of firing the soma, because we wished the soma only to fire when several dendritic spikes were coincident. So here the simulated spiking conductances were only present on the terminal basal branches (as in Section 2.2); these dendritic spikes typically created sub-threshold somatic depolarizations, of which a few in coincidence could bring the soma to firing threshold. It was also essential to this scheme that a dendritic spike’s persistent depolarization be immediately removed by a very strong delayed-rectifier conductance ($G_k > G_{\text{Na}}$), so that the soma did not temporally integrate the dendritic spikes.

The simulation paradigm for both types of coincidence-detection relied on counting the number of somatic spikes produced in response to synaptic input (as described below); obviously, spiking conductances were thus required at the soma as well as in the dendrites. The somatic conductance strengths were $G_{\text{Na}} = 0.2 \text{ S/cm}^2$ and $G_k = 0.12 \text{ S/cm}^2$, which in the absence of active dendritic conductances provided the best match to intracellular recordings from the original reconstructed cell. The other simulation parameters were as described above (Section 2.2).

2.7. Defining coincidence-detection “effectiveness”

Here we examine the simulated neuron’s response to various idealized (but biologically implausible) forms of synaptic input (in the same spirit in which sinusoidal input has been used to characterize neurons). This approach is a reasonable way to understand the simulation’s behavior, especially in the absence of any knowledge of the fine temporal structure of synaptic input to a real cell.

The simplest way of evaluating a neuron’s “effectiveness” at coincidence-detection is by idealizing two extreme forms of pulse input: perfectly even, regular pulse trains vs pulses which are bunched optimally to fire the neuron as fast as possible. If both types of input share the same average rate, then any difference in the cell’s output firing rate will reflect only the cell’s preference for finely timed coincidences.

Consider a neuron receiving input events (either EPSPs or dendritic spikes) at fixed average frequency $f_e$. If those events are evenly spread out in time and position (arriving at regular times on alternate dendrites, with the minimum possible level of coincidences among them), then the cell’s output firing rate can be called $f_{\text{un}}$ for “frequency resulting from even pulses.” This output firing rate represents the neuron’s response to nearly “pure” temporal summation without coincidences.

However, if the input events at the same average frequency are optimally arranged—usually in exactly coincident volleys barely sufficient to fire the cell, with no events between volleys—then the cell will fire at a higher rate, $f_{\text{opt}} \geq f_e$ (for “frequency resulting from optimal pulses”); the definition that $f_{\text{opt}}$ is the highest possible output rate for a given average input rate guarantees that no more effective temporal arrangement of the same input pulses can exist. Both these arrangements of input events, the un-synchronized (“even”) and the completely synchronized (“optimal”), are highly unnatural in a biological context. We use them here only to represent the two extreme functions a cortical cell might perform: pure temporal integration and pure coincidence-detection.

The output rates $f_e$ and $f_{\text{opt}}$, which result from those inputs can be combined to produce a dimensionless number $E_e$, which represents the cell’s “effectiveness” at distinguishing between coincidence-detection and temporal integration,

$$E_e = 1 - \frac{f_e}{f_{\text{opt}}} \quad (\text{Eqn } 2)$$

$$0 \leq E_e \leq 1. \quad (\text{Eqn } 3)$$

So $E_e = 0$ represents a cell which cannot distinguish coincident from evenly timed events, and $E_e = 1$ represents a cell which fires only in response to coincident events, and cannot perform temporal integration at all.

2.8. Measuring coincidence-detection effectiveness

Defining or evaluating the coincidence-detecting effectiveness $E_e$ for a simplified “toy” model is fairly easy; examples using familiar integrate-and-fire models are given in Appendix B (Fig. 16), but finding $E_e$ for a realistic neural model is more difficult. The following sections outline pyramidal-cell simulations which estimate $E_e$ for the two types of hypothetical coincidence-detection.

2.8.1. Coincidence of excitatory postsynaptic potentials. To generate the even, regular synaptic input for the “coincidence-of-EPSPs” model, the 44 synaptic sites (one per distal basal dendrite) were fired in a particular listed order. In this case no synapse firing was immediately preceded or followed by another synapse sharing the same parent dendrite, so that sequential events were electronically “far away” from each other on the dendritic tree. Only after about five firings would another site on the same parent dendrite be fired, and only after all 43 other locations on the list had fired would the same synapse be fired again.
Because a single synaptic event ($g_{\text{syn}} = 6 \text{ nS}$) was too weak to fire a dendrite alone, the cell temporally integrated many such events until the dendritic firing threshold was reached, at which point the dendritic spike initiated a somatic spike and began the summation anew. This process looks much like a d.c. current-clamp recording (Fig. 8A). However, note that each somatic spike appears to trigger at $-70 \text{ mV}$, which occurs because each dendritic EPSP of about $20 \text{ mV}$, when superimposed on the common $-70 \text{ mV}$ potential of the soma and basal dendrites, reaches the local firing threshold of about $-50 \text{ mV}$ inside the dendrite. For every simulated input rate $f_{\text{in}}$, the output rate $f_e$ was recorded (Fig. 8A,C).

To estimate the maximum output rate $f_{\text{opt}}$ for this cell model, the same synapse order was used to generate coincident, co-localized EPSPs. This was equivalent to doubling the synaptic conductance ($g_{\text{syn}} = 12 \text{ nS}$ total) and halving the rate at which synapses fired. This pattern of input fired the cell about three times as fast as evenly spaced inputs did (i.e. $f_{\text{opt}} \approx 3 f_e$, Fig. 8B,C), because the entire cell typically fired an action potential upon each of those coincident events.

The effectiveness measure $E_c$ was calculated from these rates to be $E_c \approx 0.5-0.7$ (Fig. 8D). This does not represent “perfect” coincidence-detection, but does reflect the cell’s preference for coincident EPSPs. This preference results entirely from active dendrites and from the capacitive properties of the cell, which make dendritic EPSP’s much stronger than somatic ones.

2.8.2. Coincidence of dendritic spikes. The coincidence-of-dendritic-spikes scheme was simulated with three distinct values of active dendritic conductances. First we will describe procedures common to the three simulation paradigms, and then discuss each in detail.

The “even” synaptic input for all three coincidence-of-dendritic-spikes models was generated by synaptic events at the same 44 sites used above, and in the same order. However, here each triggering “synaptic event” had such a large local amplitude ($g_{\text{syn}} = 18 \text{ nS}$, $\Delta V \approx 50 \text{ mV}$) that it almost always triggered a dendritic spike. For each rate $f_e$ at which this regular input was supplied, the output rate $f_e$ was recorded.

However, estimating the maximum output rate $f_{\text{opt}}$ for these cell models was more difficult. For this coincident input, synaptic activity occurred in groups of $M$ synchronous EPSPs, each EPSP typically causing a spike in a different branch (depending upon refractoriness), and all $M$ dendritic spikes together typically causing a somatic spike. At the first firing time, the first $M$ sites on the list were fired simultaneously; the next time fired the next $M$ sites, and so on. Since $M$ did not divide 44 evenly, a given synapse would participate in different groups on subsequent firings; firing times were chosen so that $f_{\text{opt}}$ (in units of sites/s) equalled $f_e$, as required by their definitions (i.e. the rate of coincident events was lower than the rate of “even” stimulation by a factor of $M$).

---

**Fig. 8.** A simulated pyramidal cell can serve as a coincidence-detector when active conductances are present on its dendrites, as shown by these graphs of somatic voltage. If the entire basal tree contains strong HH-like conductances (left column; $g_{\text{syn}} = 0.5 \text{ S}/\text{cm}^2$), the cell will fire slowly in response to evenly timed EPSPs which are too small to initiate dendritic spikes (at rate $f_e$, A, C). But it will fire faster when EPSP’s at the same rate occur in coincident pairs inside the same dendrite, firing dendritic spikes which propagate to the soma (at $f_{\text{opt}}$, B, C). This preference for coincident EPSPs is quantified by values of “effectiveness” $E_c > 0$ (D, Section 2.8.1).
This method was by no means the optimal way for coincident events to fire the cell, but it was easily understood and implemented. Ideally, $M$ should just exceed the number of synchronous dendritic spikes necessary to fire the soma, in order to optimize the rate of somatic spiking for a fixed rate of coincident firing. In practice, $M$ was chosen by hand. Too small a value of $M$ often failed to trigger the soma, and a too large a value increased the time between somatic spikes (and hence reduced the output firing rate). This uncertainty (i.e., $M \pm 1$) led to a fractional uncertainty in $I_{\text{tor}}$ of 10–20%, but this uncertainty only affected the difference of $E_c$ from unity; for simulations with $E_c = 1$, this uncertainty made no difference at all.

The first of these “coincidence-of-dendritic-spikes” simulations used the “strong HHI” dendritic conductances ($G_{Na} = 0.2 \text{ S/cm}^2$, and $G_k$ twice that value) and required between $7 \leq M \leq 10$ coincident dendritic spikes to fire the soma. With these parameters the soma did not perform temporal integration of even inputs per se, since threshold dendritic spikes were quickly repolarized. However, a few branches were capable of firing the soma alone (as in Section 2.2.3), so that the soma’s spiking rate in response to evenly timed dendritic spikes was low but not always zero (Fig. 9A,C). As desired, the cell fired much more strongly in response to coincident dendritic spikes (Fig. 9B,C). As a result, this cell only performed as a perfect coincidence-detector ($E_c = 1$) at low firing rates, and dropped to $E_c \approx 0.4$ when firing above 100 Hz (Fig. 9D).

A qualitatively different response could occur if the dendritic spiking conductances were much weaker. Using the “weak HHI” parameters ($G_{Na} = 0.033 \text{ S/cm}^2$, and $G_k$ twice that value), no single dendritic spike could fire the soma, so the cell could in principle never fire in the absence of coincident dendritic spikes. This hypothesis was confirmed by the simulation of evenly timed dendritic spikes (Fig. 10A,C), whose complete repolarization prevented the cell from ever firing, even with the fastest (10,000 Hz) regular input; there was no temporal integration at all. However, if dendritic spikes were coincident (in groups of $5 \leq M \leq 40$), the cell could fire up to 200 Hz (Fig. 10B,C). This model thus acted as a perfect coincidence-detector, with $E_c = 1$ at all rates (Fig. 10D). (For comparison, Appendix B shows that a leaky integrator with $N_{\text{on}} = M = 10$ would need a very fast $\tau \approx 1 \text{ ms}$ to respond similarly, as in Eqn 62).

A third simulation demonstrated that this absence of temporal integration resulted entirely from strong dendritic $I_{\text{tor}}$ currents. When those currents were suppressed (i.e., $G_k / G_{Na} = 0.05$, with $G_{Na} = 0.033 \text{ S/cm}^2$ as above), the model fired dramatically faster in response to regular dendritic spikes (Fig. 11A). This strong temporal integration of dendritic spikes reduced $E_c$ to near zero (Fig. 11D). The difference between complete repolarization of dendritic spikes and temporal integration of them is strikingly evident in Figs 10A and 11A.

These simulations were meant to illustrate the distinctions between extremes of possible cell function, not to be realistic descriptions of actual cell.

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![Graphs](Figures/fig9.png)

Fig. 9. If the only spiking dendritic conductances in a simulated pyramidal cell exist on thin terminal branches (A, $G_{Na} = 0.2 \text{ S/cm}^2$, $G_k = 0.4 \text{ S/cm}^2$), then dendritic spikes cannot usually fire the soma when they occur at regular intervals on alternate dendrites; such a model performs very little temporal summation of dendritic spikes. Only coincident dendritic spikes ($M = 8$ at once) can fire the cell reliably (B, C) at the higher rate $I_{\text{tor}}$, so that the model’s effectiveness $E_c$ at detecting the coincidence of dendritic spikes is high (D).
behavior. As an indication of their implausibility (at least in the absence of any knowledge of actual distal dendritic conductances), both “coincidence-of-dendritic-spikes” models hyperpolarized during coincident stimulation to extremely low potentials (≈ -90 mV) as a result of strong \( I_{DR} \) currents.

**Fig. 11.** The coincidence-detection ability of Fig. 10 disappears when dendritic delayed-rectifier currents are sharply reduced (\( G_n = 0.0016 \) S/cm²). While the cell still fires well in response to coincident dendritic spikes (B), it also can perform temporal integration of them (note the ramp-like voltages in A, as contrasted with Fig. 10A). The low values of \( E_c \) (D) show that this cell cannot distinguish between coincident and evenly timed dendritic spikes.
with no counterbalancing depolarizing currents (Figs 9B, 10B). As a consequence, many more coincident events were required to fire these models from that low potential (e.g. \( M > 5 \), larger than the two or three events needed to fire from \( E_{\text{mem}} = -75 \text{ mV} \)).

In contrast, under even stimulation \( V_{\text{sen}} \) fluctuated near \(-65 \text{ mV}\), which is the potential at which each dendritic spike would be exactly repolarized for the \( K \)-conductance simulated (\( G_K / G_m = 2 \), as shown in Section 2.3 and Fig. 6). This potential served as a kind of reversal potential for the combined sodium and potassium currents which dominated the somatic voltage under regular dendritic spiking.

3. ANALYSIS OF SIMULATED PYRAMIDAL CELL

Many of the effects simulated in the previous section—strong and fast dendritic EPSPs, small and persistent somatic depolarizations, and their scaling behavior with simulation parameters—can be quantitatively explained by a few simplified mechanisms. These simplifications are in the spirit of the idealized "frictionless surface" invoked in physics textbooks, and are meant to clarify the dominant behavior rather than precisely account for all its details. While the goal will be understanding some behaviors of an active dendritic tree, these approximations will begin with passive properties.

3.1. A time-dependent analogue to electrotonic length

We can consider a typical terminal as a semi-infinite passive cable of fixed diameter, which contains distributed conductances and capacitances:

\[
r_s = \frac{R_s}{\pi \left( \frac{d}{2} \right)^2} \quad \text{intracellular axial resistance (} \Omega \text{/cm)}
\]

\[
g_m = \pi d C_m = \frac{1}{r_m} \quad \text{membrane conductance per fiber length (} \Omega \text{/cm}^{-1} \text{)}
\]

\[
c_m = \pi d C_m = \text{membrane capacitance per fiber length (} \text{F/cm} \text{)}
\]

\[
d = \text{branch diameter (} \text{cm} \text{)}
\]

(using the notation of Jack et al.22). In the biophysical literature, synapses and active channels are usually characterized by conductances in Siemens (S, e.g. \( g_m \)), and passive properties are usually given by resistances (\( \Omega \), e.g. \( r_m \)); but both units describe the same physical mechanisms, so we will try to use whichever units are most often cited.

For a time-independent (stationary) voltage imposed at one point on the dendrite, the distance over which that voltage decays along the dendrite is the familiar electrotonic space-constant

\[
\lambda_{\text{EC}} = \left( r_s g_m \right)^{-1/2}, \quad (\text{Eqn } 4)
\]

which limits the spatial spread of signals much as their temporal duration is limited by the membrane time-constant

\[
\tau_m = r_m c_m. \quad (\text{Eqn } 5)
\]

One emphasis of this paper is that both of these familiar scales are too large to be appropriate for typical dendritic structures. For instance, for time-dependent voltages, the presence of membrane capacitance reduces the distance over which voltages spread below the electrotonic length. So in the high-frequency regime, the capacitive (diffusive) term dominates the conductive (dissipative) leak, and the relevant length constant is given only by capacitance, intracellular resistance, and time—membrane conductance can virtually be ignored. We will investigate this regime without discussing the more difficult case of fast events with strong membrane leaks, as simulated elsewhere 24,43,44.

For this fast-transient regime we will find a time-dependent length constant \( \lambda(t) \) which will approximate the spatial scale at which voltages spread and the temporal scale at which they decay in response to a brief current pulse (such as might result from a synaptic event or a spike inside a dendrite, as sketched in Fig. 12). The key approximation here is to take the charge which actually arrives in a current pulse of non-zero duration, and approximate it by the same amount of charge arriving in an instantaneous impulse of zero duration.

In this approximation where \( r_m = \infty \), the cable equation reduces to the diffusion equation [see Ref. 22, Eqn 3.7]:

\[
\frac{\partial^2 V}{\partial x^2} = r_s c_m \frac{\partial V}{\partial t} . \quad (\text{Eqn } 6)
\]

If an instantaneous pulse containing charge \( Q \) is injected at time \( t = 0 \) at the end \( x = 0 \) of such a semi-infinite cable, then its voltage distribution will be given by the \( x > 0 \) half of a gaussian distribution which spreads out with time:

\[
V_\delta(x, t) = \frac{2Q}{\sigma c_m \sqrt{2\pi}} \exp \left[ -\frac{1}{2} \left( \frac{x}{\sigma} \right)^2 \right]. \quad (\text{Eqn } 7)
\]

where

\[
\sigma = \sqrt{\frac{2t}{r_s c_m}}. \quad (\text{Eqn } 8)
\]

We want to use this simplest possible solution as a basis for approximating a synaptic input; but real membrane currents are not infinitely brief or strong, so we must adjust this solution to include two time-scales; the duration \( t_0 \) of the current pulse (assumed to be rectangular), and the time \( t \) elapsed after the end of the current pulse. The calculation is given in Appendix A (Eqn 54) and shows that a current pulse of duration \( t_0 \) ending at \( t = 0 \) is best approximated by a single delta-function at \( t = -t_0/4 \), as
Excitatory synapse

Fig. 12. A schematic of a very brief synaptic current in a long thin dendrite (A). Such sub-millisecond currents cause a local charge distribution which equilibrates with time inside the dendrite, so that its peak voltage can decay much faster than the membrane time-constant. In fact, the decay occurs at the time-scale of the synaptic current itself (Section 2.1), and is nearly independent of dendritic properties. This situation can be approximated by the diffusion equation (B, Eqn 6), so that the amplitude and time-course of fast dendritic EPSPs can be roughly predicted (Section 3.2 and Fig. 2).

sketched in Fig. 13A,B. This gives us a new $\sigma$ to use in the expression for voltage at the synaptic site:

$$V_{syn}(x, t) = \frac{2Q}{\sigma_icm\sqrt{2\pi}} \exp\left[-\frac{1}{2}\left(\frac{x}{\sigma_i}\right)^2\right]$$

(Eqn 9)

where

$$\sigma_i = \sqrt{\frac{2(t + t_0/4)}{r_extra/cm}}$$

(Eqn 10)

for $t > 0$.

Now we can find the length-scale over which charge is distributed, by defining a length $\lambda(t)$ over which uniformly distributed charge would have the same voltage as the peak of the approximated distribution,

$$\lambda(t) = V_{avg}(0, t) \cdot \frac{Q}{\sigma_i r_extra/cm}$$

(Eqn 11)

So

$$\lambda(t) = \sqrt{\frac{\pi(t + t_0/4)}{r_extra/cm}}$$

(Eqn 12)

(this expanded form is intended to allow easy extrapolation to other parameter values by scaling each new parameter and taking its appropriate power).

This expression shows that charge is distributed up to about $\lambda(t) \approx 100 \mu$m from the synaptic site for a dendrite of diameter 1.0 $\mu$m immediately after a current pulse of duration 1.0 ms. In contrast, the standard electrophysiological length $\lambda_{EC}$ for such a fiber (with $1/G_m = 30 \text{k}\Omega \text{cm}^2$) is six-fold longer,

$$\lambda_{EC} = 610 \mu\text{m.}$$

(Eqn 15)
3.2. Fast excitatory post synaptic potentials in thin terminal branches

The basal dendritic tree of this pyramidal cell has a structure that can easily be simplified. The soma gives rise to 10 thick basal dendritic trunks or parent dendrites, each of which typically branches several times in the proximal 20–30 µm before terminating in long (> 200 µm), thin (< 1 µm) distal terminal branches (Fig. 1). When a brief synaptic conductance opens in the center of such a terminal branch, only a small region is strongly depolarized, and for a brief length of time.

The large depolarization occurs because the dendrite is thin, so that only a small, nearby capacitance can be charged by a synaptic event. The rapid repolarization occurs because the remaining portion of dendrite, the soma, and the other dendrites together have a much larger capacitance, onto which the synaptic charge diffuses. This repolarization does not require a fast membrane time-constant, and indeed still occurs in the limit of zero membrane conductance. Such large, quickly repolarizing synaptic events will not occur at the soma, because the soma has a larger capacitance (hence a smaller peak depolarization), and because the thin dendrites around the soma do not provide as much of a capacitive “sink” (relative to the soma) onto which the somatic depolarization can quickly equilibrate—hence there is a less dramatic repolarization.

Rall first observed\(^{10}\) that this capacitive effect allows a faster-than-exponential EPSP decay at the soma, which could let the cell selectively fire in response to precisely timed excitatory synaptic events. Such precision in all these cases stems from his discovery that local EPSPs in branched structures always decay faster than \(\tau_{m}\) (as reviewed in Ref. 22), so that dendrites are in principle better at temporally precise computations than are somata without dendrites (all other things being equal).

What is the peak depolarization and time-course of a local EPSP inside a thin dendrite, if we assume only capacitive diffusion of charge (i.e. no leak terms)? Here we derive an approximation which gives only a very coarse estimate of the amplitude and time-scale of fast EPSPs inside thin dendrites, and we compare the approximations to simulated EPSPs.

Suppose the synaptic conductance has the traditional form of an alpha-function with peak conductance \(g_{\text{peak}}\) and time-to-peak \(t_{\text{peak}}\),

\[
\text{g}_{\text{syn}}(t) = \frac{g_{\text{peak}}}{t_{\text{peak}}} t \exp(1 - t/t_{\text{peak}}),
\]

so that \(g_{\text{in}}(t_{\text{peak}}) = g_{\text{peak}}\). We can approximate the synaptic current by assuming that the peak depolarization \(\Delta V_{\text{syn}}\) is small relative to the synaptic driving potential \(E_{\text{syn}} - E_{\text{rest}}\), so that the synaptic current is proportional to the synaptic conductance:

\[
I_{\text{syn}}(t) \approx (E_{\text{syn}} - E_{\text{rest}}) \frac{g_{\text{peak}}}{t_{\text{peak}}} t \exp(1 - t/t_{\text{peak}}). \tag{Eqn 20}
\]
The true current only reaches zero at infinite time, so we must arbitrarily choose a time at which to ignore its further effects; and we must choose a fairly brief time, to avoid excluding the fast time-scales we hope to explain. One reasonable choice is to take the end of the synaptic current pulse as occurring at time \( t = 3t_{\text{peak}} \), when over 80% of the eventual charge has passed through the synapse.

\[
Q_{\text{syn}} \approx \int_3^{t_{\text{peak}}} I_{\text{syn}}(t)dt \quad \text{(Eqn 21)}
\]

\[
= 0.8eR_{\text{peak}}(E_{\text{syn}} - E_{\text{rev}}). \quad \text{(Eqn 22)}
\]

This synapse does not pass constant current, but has a current peak at \( t_{\text{peak}} \) and a voltage peak (in simulations; Fig. 2) at about \( 2t_{\text{peak}} \). The earlier expressions for charge distribution (Eqs 9, 10) do not account for the structure of the synaptic current pulse; they only describe a pulse after it has finished. Because those expressions constrain us to predicting the EPSP after all the current has been injected, we cannot start our approximated EPSP until time \( 3t_{\text{peak}} \) (when 80% of the synaptic charge has arrived).

Those expressions also require that we pick a single moment (before \( 3t_{\text{peak}} \)) at which we pretend that all the charge arrived in a delta-function. Here we will approximate that all of the charge in Eqn 22 arrived in an impulsive pulse at the time of the actual peak current. This corresponds to \( 2t_{\text{peak}} \) before the approximation starts, so that the term \( t_{\text{rev}}/4 \) in Eqn 10 is replaced with \( 2t_{\text{peak}} \); but since in our simulation \( t = 0 \) occurs at the start of the synaptic current, our new approximation is shifted from Eqn 10 by \( 3t_{\text{peak}} \), i.e.

\[
(t + t_{\text{rev}}/4) - (t + 2t_{\text{peak}} - 3t_{\text{peak}})
\]

\[
= -(t - t_{\text{peak}}) \quad \text{for} \ t > 3t_{\text{peak}}. \quad \text{(Eqn 23)}
\]

This approximation is sketched in Fig. 13C.D.

Inside this long, thin dendrite, the charge distributes itself over a capacitance \( C(t) \) on both sides of the synaptic site. So our predicted EPSP there will be reduced by a factor of two from its value for a semi-infinite cable:

\[
V(0, t > 3t_{\text{peak}}) \approx \frac{Q_{\text{syn}}}{2C(t)} \quad \text{(Eqn 25)}
\]

\[
= 0.8eR_{\text{peak}}(E_{\text{syn}} - E_{\text{rev}})\left(\frac{1}{(\epsilon \rho d)^2}C_n(t - t_{\text{peak}})^3\right). \quad \text{(Eqn 26)}
\]

Because this approximation uses an infinitely strong current pulse, we have no way to understand the rising part of the EPSP; such a rise is not even graphed in the approximations of Fig. 2. It has many other flaws: the approximation neglects current flow out the dendrite’s end into the soma, the “real” (simulated) synapse saturates towards \( E_{\text{rev}} \), and we ignore the 20% of charge contained in the alpha-function’s tail; but Eqn 26 predicted the peak voltage and initial time-course of simulated EPSPs to within 20% (Fig. 2). The prediction worked best for short times, for which the charge was confined inside the dendrite. For times \( t > 3 \) ms, the simulated EPSP dropped off much faster than predicted by Eqn 26 because the proximal end of the dendrite was effectively grounded by the soma.

This model was also accurate in predicting the time-scale of EPSP decay. We can quantify the EPSP duration by the time \( t_{\text{1/2}} \) from its peak to half its peak amplitude. The approximate model decays by 1/2 when

\[
\sqrt{\frac{2t_{\text{peak}}}{t_{\text{1/2}} + 2t_{\text{peak}}}} = \frac{1}{2} \quad \text{(Eqn 27)}
\]

\[
t_{\text{1/2}} = 6t_{\text{peak}}. \quad \text{(Eqn 28)}
\]

This very narrow pulse-width matches almost exactly the \( t_{\text{1/2}} \) of EPSPs with fast \( t_{\text{peak}} = 0.05 \) and 0.1 ms (Fig. 2), and agrees within 25% for the longer \( t_{\text{peak}} \). This decay-time depends only on the time-course of synaptic current—but not on the dendritic properties—as the simulation showed (Section 2.1). In addition, this approximation shows that for fast synaptic currents, the local peak amplitude of an EPSP scales as \( \sqrt{t_{\text{peak}}} \), rather than linearly as the total charge does, so that briefer synaptic currents have a larger peak local amplitude in relation to the charge they carry.

3.3. Active dendritic terminal branches

What happens when active conductances in one of those distal terminal branches create a dendritic spike? Simulations have shown the most trustworthy answer (Section 2.1); here we will only describe a very approximate explanation of this dendritic spiking.

Let us suppose that one entire terminal branch—but not the dendritic trunk, other terminal branches, or the soma—is homogeneously coated with HH-like channels, which can spike in response to synaptic currents (the black areas in Fig. 1B). Suppose that this terminal branch is connected directly to the soma (as is only one terminal branch in the reconstructed cell), and that the soma remains near resting potential. How much of the terminal branch will depolarize above threshold? How much current and charge will the spiking branch deliver to the soma, and to the other terminal branches? On what parameters do these results depend?

First, we must ask which properties of the terminal branch itself will dominate: capacitive or resistive? Given a strong peak sodium conductance (during spiking) of \( G_{\text{Na}} = 0.2 \) S/cm², we can calculate a temporarily fast membrane time-constant

\[
t_m = C_m/G_{\text{Na}} \quad \text{(Eqn 29)}
\]

\[
= 1 \mu F/0.2 \text{ S} \quad \text{(Eqn 30)}
\]

\[
t_m = 0.005 \text{ ms}. \quad \text{(Eqn 31)}
\]

This time-constant is far faster than the closing time-constant of the sodium channels [\( t(h) = 0.5 \) ms],
suggesting that the capacitance of the terminal branch membrane itself will not seriously attenuate the spike's local voltage. Furthermore, the passive membrane conductance (due to a simulated \( R_0 \) of 30 k\( \Omega \) cm\(^2\)) is so much less than the peak active conductances that passive terms can be ignored; the only terms we will need inside the spiking branch are the axial resistance \( r_0 \) and peak membrane conductance \( G_m \).

However, the capacitance of the soma and other terminal branches together will be substantial enough that those areas will not depolarize very much during the single dendritic spike, as we saw in the simulations of Section 2.2 and Fig. 4. So we ask: in what manner will the terminal branch sustain a spike, given the boundary conditions that the proximal end of it is effectively well below spiking threshold, and the distal end is saturated near +50 mV? How much charge will it deliver to the soma during the spiking event?

Simulations show that the actual behavior of a simulated dendritic spike is very complex: a strong synaptic event in the center of the terminal branch initiates positive feedback depolarization in nonlinear sodium and potassium conductances, which propagates away from the synaptic site in both proximal and distal directions. As a result, the amplitudes and time-courses of both currents vary dramatically from one end of the terminal branch to the other.

To represent the somatic effect of these complicated interactions we can use several strikingly simple approximations. First, we can suppose that instead of a propagating action potential we have a single canonical HH-type event, in which peak conductances may vary along the branch, but all conductances reach their peak values simultaneously. Then, we replace the complicated and temporally overlapping conductance curves \( G_n(t) \) and \( G_m(t) \) with two non-overlapping triangular functions, whose peak value will be uniform over the entire active portion of the dendrite and whose duration is the conductance's simulated time-constant \( (\tau_h, \tau_K) \). This approximation is a very crude one, failing to account well for the sodium conductance's time course (Fig. 14), but it will prove sufficient to explain many of the spike's influences. Because the sodium and potassium conductances are approximately not to overlap in time, the peak somatic depolarization occurs before any potassium current flows, and should be nearly independent of \( G_m \) (as simulations showed in Section 2.2 and Fig. 6).

Now we will estimate the peak sodium current into the soma, by calculating the total current through the "active" membrane during the conductance peak. The voltage profile \( V(x) \) and membrane conductance \( g_m(x) \) of this terminal branch are clearly inhomogeneous, \( V \) being near rest (e.g. ~75 mV) at the soma end and near \( E_n = +50 \text{ mV} \) at the distal end. A brief transmembrane current into the soma results from the sodium conductance. That conductance is open only above the threshold voltage \( V_{1.2} \), so that the transmembrane current should not depend on \( E_n \), but only on the driving potential over which sodium channels are open, i.e. \( E_n - V_{1.2} \). Thus the peak current is calculated only from the region of dendrite in which sodium channels are open, and the proximal end of that region occurs wherever \( V(x) = V_{1.2} \).

To find that current we will crudely characterize the active portion of the dendrite by a single input conductance in series with a battery of strength \( E_n - V_{1.2} \). That input conductance—the single-resistor replacement for the entire active dendrite—is roughly given by two cable properties: (i) the intracellular axial resistance \( r_0 (\Omega \text{cm}) \) and (ii) the mean sodium conductance \( \approx 0.5 G_m \text{m} d (\Omega \text{cm})^{-1} \) (i.e. the average membrane conductance over the voltage range \( E_n \) to \( V_{1.2} \) is about half its peak value). So the total peak current across the membrane, and hence the current into the soma, will be approximately

\[
\begin{align*}
\mathcal{I}_n & \approx (E_n - V_{1.2}) \left( \frac{G_m \frac{\pi d^2}{4}}{r_0} \right)^{1/2} \quad \text{(Eqn 32)} \\
& = (E_n - V_{1.2}) \left( \frac{G_m \frac{\pi d^2}{8}}{R_m} \right)^{1/2} \quad \text{(Eqn 33)}
\end{align*}
\]

This can be considered a "current-source" (es) approximation (Fig. 15), because the open-channel region of dendrite always has its border wherever \( V(x) = V_{1.2} \). The rightmost term is the input conductance of a semi-infinite cable with "leak" \( G_m / \pi d \).

This input conductance assumptions (inaccurately) that the entire active portion of the dendrite contains uniform, half-open sodium channels, although clearly the most proximal channels are fully closed, and the most distal ones fully open; but more importantly, this approximation preserves the scaling properties, showing how input conductance would change in response to changes in dendrite diameter, peak membrane conductance, or intracellular resistivity.

As a test, this expression predicted that the 1.0 \( \mu \text{m} \) diameter dendrite simulated in Fig. 3 would pass a current of 3.15 nA; the simulated value, as measured from the maximum proximal slope \( dV/dx \), was 3.0 nA (Section 2.2.1). No free parameters were needed to get this agreement between approximation and simulation.

Because the voltage characteristics of spiking sodium channels are similar across various cell types, the driving voltage of about \( E_n - V_{1.2} \approx 100 \text{ mV} \) should not vary. However, the other parameters (dendrite geometry, intracellular resistivity, and peak sodium conductance) are more germane to the scale-dependence of dendritic spiking. In particular, this approximation shows that the current injected by the dendrite into the soma is relatively insensitive to changes in peak sodium conductance, but is more sensitive to dendritic terminal branch diameter \( d \),
which affects both sodium conductance (per cm) and intracellular axial resistance:

\[ i_{Na} \propto \left( \frac{G_{Na} x d}{8 r_g} \right)^{1/2} \quad \text{(Eqn 34)} \]

So

\[ i_{Na} \propto (G_{Na})^{1/2} \quad \text{(Eqn 35)} \]
\[ i_{Na} \propto d^{1/2} \quad \text{(Eqn 36)} \]

The above approximation was made for a dendritic terminal branch directly connected to the soma, so that its proximal end was held low, near \( E_{rest} \) (in this section, \( E_{rest} \) often approximates \( V_{soma} \), since their difference is usually much smaller than the potentials which dominate current flow); but if there were a length of passive dendritic trunk with high resistance \( R_d \) between the terminal branch and the soma (Fig. 15B), would the peak current to the soma be reduced below \( i_{Na} \)? The answer is yes. In the preceding discussion, \( i_{Na} \) can be interpreted as resulting from a resistance \( R_{sep} \) between the location where
the sodium conductances begin to open (i.e. where $V(x) = V_{1/2}$) and $E_{Na}$ (Fig. 15A):

$$R_{eff} = \frac{E_{Na} - V_{1/2}}{i_{Na}}. \quad \text{(Eqn 37)}$$

However this second model of spiking current is of two resistances, $R_{tk}$ and $R_{na}$ in series from $E_{Na}$ to $E_{rest}$ (Fig. 15B), so the resulting current from the above-threshold dendrite is better approximated by a "resistive-dendrite" expression,

$$i_{Na} = \frac{E_{Na} - E_{rest}}{R_{na} + R_{eff}}. \quad \text{(Eqn 38)}$$

We now have two separate models for the current from a spiking dendrite arriving at the soma: the current-source model (Eqn 33) and the resistive-dendrite model (Eqn 38). We can interpolate between them by noting that each model tends to overpredict current in the region in which it is not valid (e.g. $i_{Na}$ is too large as $R_{na} \ll R_{tk}$, and $i_{Na}$ is too large when $R_{na} \approx R_{eff}$). So a simple approximation is to calculate both currents for a given
terminal branch, and then to choose the minimum of the two:

\[ i_n = \min(i_{\text{apical}}, i_{\text{soma}}) \]  

(43)

This is the predicted peak spiking current from an active dendrite to the soma, the basis for the predicted somatic potential. It is compared with simulations in the next section.

3.4. Somatic depolarization from a spike

The net depolarization at the soma imparted by this dendritic current pulse can be estimated by knowing the time-dependent capacitance of the soma and of its basal terminal dendrites. As a very rough estimate, we can pretend that the terminal branches (which dominate this capacitance, and are much easier to characterize than the thicker, shorter intervening parent dendritic trunks) are directly connected to the soma, and that each of those branches contributes capacitance \( C_{\text{soma}} \lambda(t) \). The current pulse from a dendritic sodium spike has duration about \( \tau(h) = 0.5 \text{ ms} \), so the lengths of dendrite charged just after the pulse will be about \( \lambda(t) = 70 \mu \text{m} \) for the distal basal dendrites and \( \lambda(t) = 150 \mu \text{m} \) for the apical dendrite. We can then assume that the charge is evenly distributed over the soma (of area \( 1250 \mu \text{m}^2 \)), over the proximal 70 \mu m of each of the 43 other (non-spiking) terminal branches (mean diameter about 0.88 \mu m), and over the 150 \mu m of the apical dendrite (diameter 4.5 \mu m), for a total capacitance charged of

\[ C_{\text{soma}} \approx \frac{17.23 \mu \text{m}^2 + 43(0.88 \times 70 \mu \text{m}^2)}{4} + 4.5 \times 150 \mu \text{m}^2 \pi \times 1 \mu \text{F/cm}^2 \]  

(40)

\[ \approx 1.1 \times 10^{-10} \mu \text{F}. \]  

(41)

In addition to ignoring the variation in dendritic size and branching structure, we assume that each dendritic spike will create a voltage peak \( V_{\text{peak}} \) in accordance with the definition of \( \lambda(t) \) (Eqn 17), so that a dendritic spike delivering charge \( Q \) should give

\[ V_{\text{soma}} \approx \frac{Q}{C_{\text{soma}}}. \]  

(42)

For the highly idealized triangular sodium conductance function outlined above (which will produce an axial current with similar time-course), the net (integrated) charge \( Q \) deposited on \( C_{\text{soma}} \) will be the area under the triangle: half the product of the peak current and the current's duration. So the approximate net depolarization of the cell and dendrites due to the single dendritic spike will be given by

\[ Q \approx i_n \tau(h)/2, \]  

(43)

\[ V_{\text{soma}} \approx \frac{\tau(h)i_{\text{apical}}}{2C_{\text{soma}}}. \]  

(44)

This prediction was tested for each of the 44 terminal branches separately, at both high and low peak sodium conductances ("strong HH" and "weak HH"). Fig. 4 shows the simulated somatic depolarization plotted against its value predicted from branch diameter and trunk resistance (Eqn 44), so that a good match lies on the line with unit slope. Most depolarizations lie within 20% of predicted values, showing the inherent soundness of the approximations. Again, no free fitting parameters were necessary for this agreement.

The dependence of somatic depolarization on peak sodium conductance appears in Fig. 3B. For both dendrites simulated, \( V_{\text{soma}} \) varied as \( \sqrt{C_{\text{soma}}} \), the weak dependence predicted by Eqn 34 above. These theoretical and simulation results are not consistent with the naive idea that the somatic amplitude of dendritic spikes depend linearly on peak sodium conductance.

3.5. Pulse widths

As simulated in Section 2.3, the delayed-rectifier currents from a dendritic spike can completely repolarize the soma after the spike. Such a somatic voltage pulse is very brief. In fact, we can expect that the entire duration \( t_{\text{rise}} \) of the somatic depolarization—approximately as a triangle—will be only the sum of its rise time and its fall time. We have already approximated that the inward current duration (and thus the somatic voltage rise-time) is \( \tau(h) \). Likewise, we can assume that the outward potassium current \( i_n \) has duration \( \tau(K) \). So the somatic voltage transient's full-width at half maximum \( t_{1/2} \) should be about half the sum of those two times:

\[ t_{\text{rise}} \approx \tau(h) + \tau(K) \]  

(45)

\[ t_{1/2} \approx \frac{\tau(h) + \tau(K)}{2} \]  

(46)

\[ t_{1/2} \approx 1.2 \text{ ms}. \]  

(47)

The previous simulations (Section 2.3) show this to be the case (Fig. 7). The widths of most simulated somatic current pulses were near 1.2 ms, and a few wider pulses (1.3–1.6 ms) occurred when one dendrite recruited others in firing, so that several sequential dendritic spikes appeared at the soma as one broader spike. This broadening was more prominent in the "strong HH" case, where stronger depolarizations caused more frequent recruitment.

3.6. Capacitance of dendritic spines

The primary influence of dendritic spines—which were not included in the above simulations—is to increase the membrane's effective capacitance and leak conductance by a factor of two to three. Leak conductance has proved unimportant at the fast timescales of this study, but a change in membrane capacitance can be critical.

In the case of an isolated EPSP inside a dendrite (Section 2.4), a doubling of membrane capacitance should increase \( C(t) \) by \( \sqrt{2} \) (Eqn 17), so that the local peak voltage is decreased by a factor of \( \sqrt{2} \), or about 30%. Using this factor to attenuate the previously simulated amplitude of 19 mV, the dendritic EPSP simulated in Section 2.4 is predicted to peak at only
13.5 mV with the doubled membrane capacitance; the newly simulated value was 14.4 mV, a difference of 7% from the prediction.

A similar test was made for the somatic depolarization $\Delta V_{\text{soma}}$ due to a spike in that dendrite. The predicted effect on $C_{ic}$ is similar, with the dendrites' effective capacitance increased by $\sqrt{2}$ [through $C(t)$] and the soma's capacitance doubled. The somatic peak earlier had been $\Delta V_{\text{soma}} = 8.3 \text{ mV}$, which when corrected by the new capacitance values would yield a predicted 5.45 mV—which differed from the newly simulated peak, 5.6 mV, by only 3%. We can conclude that dendritic spines’ extra capacitance will decrease all peak depolarizations from the values simulated in rough accordance with these predictions, and by reducing $\lambda(t)$ will further isolate different parts of the dendritic tree.

4. DISCUSSION

Can a cortical cell perform millisecond computations, or only much slower temporal averaging? Many researchers believe that single-cell cortical computation must be inherently slow, because of the enormous attenuation of high-frequency signals in thin dendrites and because of the high spiking variability (near-Poisson “noise”) associated with single-unit cortical firing. However, both of these influences can instead be interpreted as facilitating single-spike computation instead of hampering it.

4.1. Requirements for millisecond computation

While the dominance of truly random “noise” in spike times would certainly preclude reliable computation at the single-spike level, the very existence of highly variable (and possibly non-random) spike trains suggests that the single neurons generating them are not performing much temporal integration of multiple EPSPs. In fact, such strong interspike-interval variability is not consistent with current models of temporal integration of EPSP’s, and might be effective instead at fast information transmission.

In addition, even the weakly correlated spikes recorded between pairs of neurons seriously diminish the ability of a population of such neurons to carry information in their averaged responses, although those correlations are potentially useful for coincidence-detection.

So the argument that high variability precludes high-frequency computation can be turned on its head: the high variability might indicate that the cell does use and transmit high-frequency information. In fact, a binary pulse code of precisely timed (but irregular) spikes has a dramatically higher information capacity than a code using an average firing rate of irregular spikes. So instead of using an average rate code heavily contaminated by irregularity, the brain might instead be using a optimum binary code in which each spike's unpredictable but precise timing lets it carry the maximum possible information. While there is scattered indirect evidence for millisecond precision in spike patterns, we so far lack evidence that such precision plays a perceptual role outside the auditory system, where submillisecond computations are routine. (There is one example of temporal precision in vision: Burr showed that human observers perceived a vernier offset in a moving bar when its two halves were flashed as little as 1.5 ms apart.)

The other argument against high-frequency computation is that dendritic capacitance would filter out the high frequencies. This view suggests that cortical neurons are effectively single, slow computing units, limited in temporal precision because passive dendrites “smooth out” transient events en route from synapse to soma. However, that argument can also be inverted, since any passive properties which “bottle-up” fast events inside distal dendrites necessarily make those events locally strong and quickly repolarizing, and in addition make those dendrites isolated from each other at high frequencies, so that they might carry out nearly independent fast computations.

If such computations occur, then the cell does not act as a single slow unit, but as tens or hundreds of semi-independent fast units. As an example of the computational enhancement such a scheme might provide, imagine that each of about 100 distal dendritic branches were a separate computational unit acting with 1-ms resolution. The cell would then have a 100-times as many computing units as a single undifferentiated cell, each one operating about 20-times faster than the membrane time-constant. So it would have roughly 2000-times the computational power of a traditional single-compartment leaky-integrator neuron.

This hypothetical high-speed computational ability is enhanced in cells—like cortical pyramidal cells—which have multiple branchings and long, thin dendrites. However, this scheme requires some method of delivering the results of the brief, isolated computations from dendrites to the soma; passive dendrites cannot do it.

However, active dendrites can; and the most effective active conductances for maintaining isolation among dendrites would be fast (e.g. sodium rather than calcium) and totally repolarized (e.g. strong $G_{Na}$), so that no persistent depolarization could couple the dendrites or allow temporal integration. Jascove argues that such active conductances are necessary to overcome the very short length constants of thin dendrites (an assertion which depends strongly on his choice of small $R_{in}$, about a tenth the value simulated here). Experimental evidence relating to active conductances on terminal branch is discussed in the next section.

While this paper explores some possible functions of fast EPSPs and distal dendritic HH conductances, it does not treat the many other conductances—voltage-dependent and otherwise—thought to
operate in distal dendrites of cortical and hippocampal pyramidal neurons [e.g., Ca\(^++\)] and N-methyl-D-aspartate (NMDA)-mediated. The present work suggests that such postulated nonlinearities may be greatly strengthened by two additional mechanisms. Firstly, the inclusion of strong, active outward currents (like \(I_{\text{Na}}\)) can shorten the effective time-window for the cell's response to synaptic input. Secondly, when synaptic events are quickly repolarized—whether by active repolarization or by passive charge-equalization—the cell moves away from the linear, additive regime of temporal integration and into the nonlinear, multiplicative regime of coincidence-detection. Nonlinearities are much stronger at fast time-scales.

The two mechanisms proposed here for fast membrane repolarization (which is necessary for coincidence-detection) are more energy-efficient than the traditional approach of fast passive membrane time-constants. A strong passive membrane conductance draws a relatively large, constant amount of metabolic power in order to maintain the cell's resting depolarization, even when the cell receives no input. But the fast repolarization through capacitive charge-equalization requires no especially strong membrane conductance, and repolarization by delayed-rectifier conductances only demands a large membrane conductance (and the resulting power drain) just after a dendritic spike, but not while the cell is unexcited. The two mechanisms proposed here for fast membrane repolarization (which is necessary for coincidence-detection) are more energy-efficient than the traditional approach of fast passive membrane time-constants. A strong passive membrane conductance draws a relatively large, constant amount of metabolic power in order to maintain the cell's resting depolarization, even when the cell receives no input. But the fast repolarization through capacitive charge-equalization requires no especially strong membrane conductance, and repolarization by delayed-rectifier conductances only demands a large membrane conductance (and the resulting power drain) just after a dendritic spike, but not while the cell is unexcited.

4.2. Problems with sub-millisecond computation

There are many reasons why sub-millisecond processing seems unlikely, in addition to the fundamental question of whether a single cell can respond with such precision. Foremost is the issue of preserving precise spike times as they propagate along axons. The absolute difference in the lengths or propagation speeds of different axons need not be a problem, since cortical connectivity might be arranged (e.g., through selective myelination, synapse growth and pruning) so that only spikes with the same mean time-delay (both monosynaptic and polysynaptic) would impinge upon the same cell. A more critical problem is the scatter or dispersion in spike latency relative to its mean value, which can be up to 10%, depending on the axon’s average firing rate. This would limit the fastest computations to nearby regions, where the axons are shortest and thus the scatter in time is least in absolute terms.

A more systematic influence on single-spike latencies is the temperature of the axon. If temporally precise processing is to take place, then maintaining each axonal connection at a fixed delay would require the cortex to be kept at a tightly regulated temperature, as it is in mammals and birds; but of course there are many other physiological reasons for exact body-temperature regulation.

Another potential problem is the exact nature of this hypothetical coincidence-detection coding. There is no evidence in brains for a central synchronizing clock in the brain, as one finds in digital computers, and little reason to think it might exist; but the
absence of a single central timing-reference does not mean that relative spike-times are unimportant; Abeles’ proposed “synfire chains” use only relative spike times.

Perhaps the trickiest issue is whether millisecond-scale coding would be an exact, deterministic process—in which even a single synaptic or branch-point failure could seriously modify the cell and network response—or whether the process would be more distributed and robust, like population-encoding at a very fast time-scale (where the “population” would contain binary variables, i.e. single spikes, rather than a population of temporal averages of spikes). Such questions involve the probabilistic nature of synaptic or quantal inputs\(^6\) and single-channel conductances,\(^6\) the ability of networks of coincidence-detecting cells to perform more precise or reliable computations than isolated cells, and the desirability of whatever functions arise. These issues are well beyond the scope of this exploratory work.

4.3. Plausibility of critical assumptions

4.3.1. Submillisecond synaptic currents. Part of this paper postulates that submillisecond synaptic currents exist inside cortical dendrites. Measurements of EPSCs in the somata of cortical cells are consistent with fast dendritic EPSCs. Spike-triggered averaging reveals subthreshold monosynaptic potentials with amplitudes in the 50–400 μV range and rise-times from 0.5–1.0 ms (10–90% rise-time in rat visual cortex slice\(^6\) to 0.8–2.4 ms (0–100% rise-time in cat visual cortex slice\(^6\) to 0.8–2.4 ms (0–100% rise-time in hyperpolarized rat cingulate and sensorimotor cortex cells\(^6\)). Ferster also shows shock-induced EPSCs with rise-times as low as 0.5 ms.\(^6\) Although these researchers did not directly measure synaptic currents, we can assume (to first order) that the dendritic EPSC duration cannot exceed the somatic EPSC rise-time, because the somatic potential integrates the current (which has been additionally smoothed by the intervening dendritic capacitance). So the submillisecond EPSC rise-times reported by those researchers are probably due to synaptic currents lasting less than a millisecond (e.g. \(t_{\text{rise}} \leq 0.3 \text{ ms}\) ). However, the activation of NMDA-mediated conductances at moderate depolarizations might prolong the local EPSCs,\(^6\) thereby reducing the temporal precision of single synaptic events.

All of the distal dendritic EPSCs simulated here—even the fastest ones with \(t_{\text{rise}} = 0.05 \text{ ms}\)—produced longer somatic rise-times (at least 0.5 ms), due to smoothing by dendritic capacitance. Thus the simulated somatic rise-times are in the same range as the experimental recordings. Direct measurements of EPSC duration in cortex at low membrane potentials (<75 mV) with low-impedance electrodes, combined with realistic cell models to infer the synaptic currents on the dendrites from the somatic rise-times, might better determine the speed of dendritic EPSCs. Such models are necessary because highly transient events in distal dendrites cannot be voltage-clamped, as direct EPSC measurements require.\(^3\)

One provocative possibility is that the measured somatic EPSCs result from sodium spikes in dendritic spines. The 0.5-ms time-course of a sodium spiking current is about the right duration to produce the observed somatic EPSC rise-times; and the currents flowing through a synapse with \(g_{\text{syn}} \approx 5 \text{ nS}\) (which simulate the right EPSC amplitude) are comparable to those which would flow through a spine stem with diameter 0.1 μm, length 1.0 μm, and resistance 200 MΩ (or 5 nS),\(^4\) whose head was briefly held near \(E_{\text{syn}}\).

4.3.2. Active dendritic conductances. The two types of coincidence-detection discussed here—detection of coincident EPSCs inside dendrites, and of coincident dendritic spikes at the soma—both require the existence of strong HH-like conductances inside thin terminal dendrites. Such conductances have not yet been unambiguously observed.

There is some evidence for active conductances in the thick apical dendrites of both hippocampal\(^3\) and cortical neurons.\(^3\) However, such conductances may not be sufficiently strong to sustain spikes, and may consist primarily of calcium conductances, which might be triggered by fast coincidences without preserving their precise timing; but the thick apical dendrite is morphologically very different from the narrow basal branches, so it may serve a different function, and its conductances may not reflect conductances on the narrowest distal branches. At present there are no direct recordings from the distal basal dendrites of cortical cells, because those dendrites are far too thin to be impaled with a recording electrode; and it does not yet seem practical to record optically voltages or sodium concentrations in single thin dendrites at the millisecond time-scale of interest here.

If fast dendritic spikes do exist, they might be visible at the soma as potentials which have much greater amplitude than solitary EPSCs and repolarize much faster than the (presumed) membrane time constant. Ferster shows (but does not discuss this interpretation of) traces of such “small spikes” in visual cortical cells which meet these criteria: they have amplitudes of 8–15 mV (greater than single EPSCs, but weaker than full-fledged action potentials), submillisecond duration (full-width at half-maximum), and repolarization to \(E_{\text{rest}}\) within 1 ms.\(^{10,16}\) These small spikes result from electrical shocks to the lateral geniculate nucleus (LGN) (i.e. due to many coincident synaptic events, rather than to the monosynaptic events used in spike-triggered averaging), but the mechanism producing them is unclear.

Such dendritic spikes might also be inferred from intracellular potentials in cells driven by natural (e.g. sensory) synaptic excitation. As Mel has reported\(^3\) and these simulations confirm, dendritic sodium spikes might only produce somatic potentials of
1 nV, so that individual spiking events could be nearly "invisible," blending together to appear as high-frequency "synaptic noise." A power-spectrum analysis of the subthreshold potential between spikes might help quantify this effect, and an autocorrelation analysis could show whether the observed fluctuations are mostly due to self-repolarizing events (e.g., dendritic spikes) or to other less structured currents.

However, dendritic spikes might be sufficiently strong that a single one could fire the cell (e.g. in the "coincidence-of-EPSPs" model). Under sensory stimulation, such a dendritic spike might be inferred from a somatic spike which rises from a voltage below the somatic firing threshold. (A dendritic EPSP could reach its local "firing threshold" while the soma was still well below threshold, so that the resulting somatic spike would appear to arise "out of nowhere" from below threshold voltage. For an example, see the difference in apparent thresholds between traces A and B of Fig. 8.) A practical test would be to compare the "firing threshold" as measured by d.c. current injection with the threshold inferred from firing due to natural synaptic stimulation.

4.3.3. Coincidence detection in cortical cells. There are other types of neurons—usually auditory neurons—which operate even faster than the sub-millisecond regime discussed here. For instance, individual spikes in the auditory system of barn owls can phase-lock to tones of frequency up to 5-9 kHz (the cells responsible are morphologically very different from cortical pyramidal cells). Spikes from cells in the monaural nucleus of the echolocating big brown bat can lock to stimuli with a precision of 30 μs. Also, single-EPSP coincidence-detection without temporal integration can take place in the cochlear nucleus of mice, although in this case the excitation comes from very large somatic synapses (rather than from dendritic spikes) and the repolarization comes from a fast membrane leak and inhibitory currents (rather than from active potassium conductances).

Regardless of mechanism, a role for coincidence-detection is consistent with published cross-correlation histograms (CCHs) between cortical cells. Abeles2 shows many examples of millisecond-level precision preserved over hundreds of milliseconds. In addition, narrow features have appeared in the work of Nelson et al.,9 where about 10% of cell pairs across cat visual areas 17 and 18 have centered CCH peaks a few milliseconds wide (which they dub "towers"). Other reports show wider and smaller cross-correlation peaks between cells in the same orientation column,3 or as far apart as several mm.

The most dramatic reports come from Toyama et al.'s recordings of nearby cortical cells of similar response type in cat visual cortex.57 They report that about 60% of CCH's between pairs of cells have prominent, narrow peaks at zero. Those peaks typically contain over 30% of the cell's spikes, meaning that about 30% of a pair's spikes are coincident (within 0.1 ms in many cases; see their figures 1, 3, and 4); but both of the recording electrodes might have actually recorded spikes from the same cell, making the narrow peak an artifact.

Such centered monosynaptic CCH peaks (with monosynaptic width) are traditionally interpreted as resulting from direct "common input" to the two recorded cells: spikes from shared presynaptic neurons cause the coincident output spikes. However, the fraction of inputs which must be coincident in order to create the observed output coincidences depends very sharply on the particular neuron assumed. For an integrator-type model,12 the two recorded cells must share a fairly large portion of strong excitatory input in order to fire in concert, because integrators preserve and use every input pulse, and thus do not require a large total number of them. On the other hand, a coincidence-detecter model can exhibit synchronous firing with a far smaller fraction of shared excitatory synapses, because such a cell requires many more large, brief EPSPs in order to fire upon the occasional coincidence of a few. In general, integrator-models are much harder to cause to fire in coincidence, because an individual integrator's firing is primarily determined by the time of its previous firing rather than by the state of its present input.

The coincidence-detection model also accounts more easily for the relative absence of CCH peaks with monosynaptic temporal offset,29 a fact which would seem to indicate that while many cell pairs share common input, the source of common input is somehow seldom recorded. (To solve this paradox, Nelson et al. postulate a tiny subset of "driving" cells which induce synchrony by means of exceptionally strong synaptic excitation to a whole cell population.) However, if cortical cells are like those proposed here, responding primarily to coincidences from multiple independent sources (each source driving both recorded cells), then no source cell would correlate well with a recorded cell—leading to the observed deficit of off-center peaks—while the recorded cells would still correlate strongly with each other.

As a possible test of how individual synapses contribute to a cell's firing, one might compare directly the EPSP magnitude and time-course (as measured intracellularly by spike-triggered averaging) with the CCH, as measured for the intracellularly recorded action potentials. Such a comparison using motoneurons has already yielded results substantially in agreement with the theory of temporal integration of EPSPs.14 It remains to be seen whether cortical cells conform as well.

Another possible example of fine correlation structure can be seen in CCHs observed between LGN cells and the visual cortical cells they drive;53 the off-center peaks (about 4-6 ms wide), corresponding to excitatory LGN input to the target cell, seem to have millisecond-scale structure in the form of "dips" at about 2-2.5 ms after triggering (see their figures 3,
5.6, and 7; but in any single one of those seven traces the dip might result from statistical noise, and even taken together they only suggest that further investigation and better statistics are desirable. Statistically significant millisecond-level structure in CCH “noise” could indicate that a cell is driven both mono- and polysynaptically, with the precise timing of its synaptic input preserved. However, even the absence of obviously precise correlations between any given recorded pair might still hide significant structure at higher orders: if five or 10 exactly synchronous input neurons are necessary to fire a given neuron, the temporally precise input-output relation might never be noticed in a single-pair CCH recording.

4.4. Analytical and simulation results

The simulated “toy model” used here—a realistic pyramidal cell morphology endowed with simplified active conductances—demonstrates two principles: (i) that dendritic spikes can in principle approximate coincidence-detection on sub-millisecond EPSPs with little temporal integration, even when the membrane time constant is much longer (\( \approx 30 \) ms); and (ii) that some effects of dendritic spiking can be approximated by simple analytical expressions. The crucial element for coincidence-detection is the quick repolarization of the membrane after a depolarizing pulse appears. One mechanism for this repolarization is the passive voltage decay as charge from a sub-millisecond EPSC equilibrates across a dendrite’s distributed capacitance into the soma. Another mechanism is the active removal of charge from the soma of charge by a dendritic spike’s \( I_{\text{Na}} \). Either or both mechanisms might operate in real cells; the two mechanisms were simulated separately for simplicity of illustration.

A quantitative measure of a model cell’s effectiveness at coincidence-discrimination \( (E) \) compares the cell’s strong firing from optimally coincident EPSPs to its weaker response to regularly distributed EPSPs (Section 2.7). This artificial measure shows that a realistic pyramidal-cell morphology with active dendrites may discriminate fine temporal coincidences, and that the best model (the “weak HH coincidence-of-dendritic-spikes” model) is a perfect coincidence-detector at even its highest firing rates (Fig. 10).

5. CONCLUSION

The marriage of known cortical pyramidal cell morphology to postulated HH-like conductances on distal basal dendrites yields a simplified model cell which can in principle discriminate EPSP arrivals at the sub-millisecond level. Such fast computation might be complementary to the slower and better-known coding by average spike rate, because many differently patterned pulse-trains can share a common average rate, and can thus carry independent information at both fast and slow time-scales. The much higher bandwidth (kHz vs Hz) of this hypothetical single-spike computation might prove a useful alternative to the lower-frequency oscillations (40 Hz) proposed to solve some cognitive tasks, such as feature segmentation and the “binding problem” and visual awareness, because the cognitive information can be multiplexed into the average rate code while preserving its spiking character. However, it remains to be seen experimentally whether single cortical cells contain the fast synaptic conductances and active distal dendrites necessary for sub-millisecond coincidence-detection, and whether those cells actually do perform parallel nonlinear computations with kilohertz bandwidth.

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REFERENCES

6. APPENDIX A: RECTANGULAR-PULSE DIFFUSION

This appendix shows how the response of the diffusion equation (Eqn 6) to an instantaneous current impulse—a Gaussian distribution of charge which broadens with time—can be used to represent the voltage decay in a dendrite after a non-impulse current pulse is applied.

Our current pulse will begin at \( t = -t_0 \) and end at \( t = 0 \), carrying total charge \( Q \). We approximate the local dendritic potential for \( t > 0 \) and \( c = 0 \) with a function called \( V_{	ext{diff}}(x, t) \), based upon the impulse-response solution \( V_c(x, t) \) (Eqn 8).

To do this we will need to choose a moment at which a single impulse of charge \( Q \) will best represent the d.c. pulse; this moment will be \( -\Delta t < 0 \).

First let us find \( \Delta t \). Since we have a steady current pulse between \( t = -t_0 \) and \( t = 0 \) (Fig. 13), we can compute the actual voltage at \( x = 0, t = \Delta t \) by the convolution of the delta function with the pulse duration:

\[
V(0,0) = \int_{-t_0}^{0} dt' V_c(0, -t').
\]  
(Eqn 48)

We can find \( \Delta t \) by setting this voltage equal to the voltage which would exist at \( x = 0, t = \Delta t \) in the impulse solution:

\[
V(0,0) = V_c(0, \Delta t).
\]  
(Eqn 49)

By eliminating \( V(0,0) \) we can find \( \Delta t \) in terms of \( t_0 \):

\[
\frac{1}{t_0} \int_{-t_0}^{0} dt' V_c(0, -t') = V_c(0, \Delta t)
\]  
(Eqn 50)

\[
\frac{1}{t_0} \int_{-t_0}^{0} dt' (-t')^{-\frac{1}{2}} = \Delta t^{-\frac{1}{2}}
\]  
(Eqn 51)

\[
\frac{t_0}{\Delta t} = 4
\]  
(Eqn 52)

So a current pulse of duration \( t_0 \) ending at \( t = 0 \) is approximated by a single delta-function at \( t = -t_0/4 \), which is equivalent to just shifting the time-origin in the impulse solution by \( t_0/4 \). So we have a new \( \sigma_c \) to use in the expression for voltage in the dendrite:

\[
V_{	ext{conv}}(x, t) = \frac{2Q}{\sigma_c \sqrt{2\pi} c x} \exp\left(-\frac{1}{2} \left(\frac{x}{\sigma_c}\right)^2\right)
\]  
(Eqn 53)

where

\[
\sigma_c = \sqrt{2(t_0 + t_0/4)/t_0 c}\n\]  
(Eqn 54)

for \( t > 0 \).

7. APPENDIX B: INTEGRATOR-MODELS AS COINCIDENCE DETECTORS

This appendix calculates the “coincidence-detection effectiveness” \( E_c \) (Section 2.7, Equation 2) for three well-known integrator-models of cells (see Ref. 22, Chapter 1) and Ref. 59). These integrator models assume that all input current pulses cause identical depolarization (unity) and have vanishingly brief duration, and that the model cell fires and resets upon attaining a threshold depolarization of \( N_a \) pulses (for “number to threshold”, e.g. \( N_a \) or more coincident input pulses will fire the cell). None of these models have spatial extent or explicit membrane conductances.

The simplest model, the “perfect integrator”, is a leak-free capacitor which accumulates depolarizing pulses until it reaches threshold, at which time it instantly fires and resets. Because \( N_a \) inputs accumulated over a long time produce exactly the same depolarization that \( N_a \) coincident inputs would produce,

\[
f_c = f_m = \frac{f_m}{N_a}.
\]  
(Eqn 55)

and \( E_c = 0 \).

(Eqn 56)
Fig. 16. Input–output characteristics ($f_{\text{op}}$ vs. $f_n$) of three simple integrator models for regular input, and their effectiveness at detecting coincident inputs pulses. (A) The perfect integrator with threshold delivers an output after every $N_0$ input pulses (here $N_0 = 6$). A leaky integrator with decay constant $\tau_p$ cannot fire at input rates below $N_0/\tau_p$ (here $\tau_p = 3$ ms). A perfect integrator with absolute refractory period cannot fire again for time $\tau_r$ after firing, so $f_{\text{op}}$ saturates at 1/$\tau_r$ (here $\tau_r = 1.0$ ms). (B) For a fixed input rate $f_n$, both leaky and refractory models respond to coincident (or optimal) inputs as perfect integrators. Those stronger responses (relative to temporal integration of evenly timed inputs) give an effectiveness measure $E$, where $E = 1$ represents a model which performs no temporal integration, and $E = 0$ represents a model which cannot distinguish inputs according to coincidence. Note that the leaky integrator only serves as a good coincidence-detector ($E \approx 1$) at very low input rates.

In contrast, the leaky integrator model loses depolarization at a rate

$$\frac{dV}{dt} = \frac{V - E_{\text{rest}}}{\tau},$$

(Eqn 57)

so that inputs pulses are "forgotten" with time. This model fires in response to evenly spaced inputs as

$$f_t = \begin{cases} \tau \log \left( 1 - \frac{N_0}{f_n \tau} \right) & \text{for } \frac{N_0}{f_n \tau} < 1 \\ 0 & \text{otherwise.} \end{cases}$$

(Eqn 58)

(Eqn 59)

(Eqn 60)

But its response to optimally timed coincident inputs (in volleys of $N_0$) is the same as that of the perfect integrator model, because the cell fires instantly, before the leak term can have any effect:

'leaky':

$$f_{\text{op}} = \frac{f_n}{N_0}$$

(Eqn 61)

so

$$E_t = \frac{1}{1 + \frac{N_0}{f_n \tau \log \left( 1 - \frac{N_0}{f_n \tau} \right)}}$$

for $\frac{N_0}{f_n \tau} < 1$

(Eqn 62)

$$E_t = 1$$

otherwise.

(Eqn 63)

This expression for $E_t$ is near unity only when $N_0 f_n \tau$ is near to or greater than one, i.e. with low input rates or very strong leak terms (Fig. 16).

The third model is the perfect integrator with refractory period, which cannot be triggered during a "dead time": $\tau_r$ after each firing. The refractory period does not change this model’s response $f_{\text{op}}$ to coincident inputs which arrive outside the refractory period (i.e. as long as the input does not try to make the integrator spike more often than once every $\tau_r$),

$$f_{\text{op}} = \frac{f_n}{N_0} < f_n \tau_r,$$

(Eqn 65)

so $f_{\text{op}} = f_n/N_0$ as before (Eqn 55). But a certain portion of evenly spaced inputs will fall in the refractory period, so the output rate $f_t$ saturates for high even input rates. Thus at high rates coincident inputs are more effective than evenly spaced ones, so $E_t$ is increased:

'refractory':

$$f_t = \left( \frac{N_0 + \tau_r}{f_n} \right)$$

(Eqn 66)

$$E_t = 1 - \left( 1 - \frac{f_n \tau_r}{N_0} \right)^{-1}.$$  

(Eqn 67)

In summary, the refractory period can detect high-resolution temporal information ($E_t > 0$) only at high inputs, while the leaky integrator does so only at low rates (Fig. 16). These models in combination would be more realistic, but analysing them is well beyond the benchmark-only role they serve in this paper. In addition, a refractory period is a poor model for coincidence-detection inside cortical cells, because it operates most effectively when the cell fires regularly, which cortical cells do not do. However, a refractory period can have some computational applications.\(^{15}\)