Commentary

Simple codes versus efficient codes

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Transmission of information is an important function of cortical neurons, so it is conceivable that they have evolved to transmit information efficiently, with low noise and high temporal precision. Such precision is consistent with the output generated by various working models that mimick neuronal activity, from simple integrate-and-fire models to elaborate numerical simulations of realistic-looking neurons. But our current inability to match this data with neurons' detailed spike-generating mechanisms *in vivo* allows us a wide latitude in interpreting the significance of the various components of their spike code. One extreme hypothesis, the 'simple' model, is that each neuron is noisy and slow, performing a simple computation and transmitting a small amount of information. A competing hypothesis, the 'efficient' model, postulates that a neuron transmits large amounts of information through precise, complex, single-spike computations. Both hypotheses are broadly consistent with the available data. The conflict may only be resolved with the development of new measurement techniques that will allow one to investigate directly the properties that make a neuron efficient — that is, to be able to measure highly transient, localized events inside the thinnest dendrites, which are currently experimentally inaccessible.

Introduction

The spiking output of a single cortical neuron can be directly measured, but the cellular properties that give rise to the spikes are not well understood because these neurons receive most of their synaptic input on dendritic branches that are far too small for a recording electrode. The best that can be done, at least in a living animal, is to measure the membrane potentials as they reach their gathering point in the much larger cell body — that is, after they have been processed by the dendrites and perhaps mixed with signals from other dendrites. Therefore, in order to infer how the raw synaptic input helps fire or inhibit the neuron, one must design a working model of the neuron, for example, a numerical Hodgkin–Huxley simulation that contains assumptions about the as-yet-unmeasured properties of those thin dendrites.

Developing an accurate working model of a neuron's electrical dynamics is a crucial link in understanding how neurons communicate. However, consensus eludes us because so many questions remain unanswered. Do neurons average their inputs, or instead fire upon coincidences of synaptic events? Do they use noisy spike-rate codes, or precise spike-time codes? Are they robust to variations in the arrangement of synaptic activity on the dendrites, or sensitive to it?

These questions bedevil a recent controversy among modellers, which is to explain the irregular firing pattern of single cortical neurons, the Gieger-counter-like crackle so familiar to electrophysiologists. It turns out that wildly different (yet equally 'realistic') working models can account for the observed spiking patterns (output) of real *in vivo* cortical neurons.

This paper will critique one approach to the problem and propose another. Because both proposals are consistent with known physiology, and with insufficient experimental data to decide the issue, we must tease out the assumptions behind them.

In a recent issue of this journal, Shadlen and Newsome [1] made a masterful case for locating the genesis of firing irregularity in strong inhibitory currents (that would balance a neuron's excitatory drive), which they call 'balanced inhibition'. Their treatment of inhibitory synapses in neocortex is far more informative and complete than treatments found in competing models, including my own. But they make one, seemingly minor assertion about their simplified 'balanced inhibition' cell model

Abbreviations

EPSP—excitatory postsynaptic potential; **IPSP**—inhibitory postsynaptic potential; **NMDA**—*N*-methyl-D-aspartate.
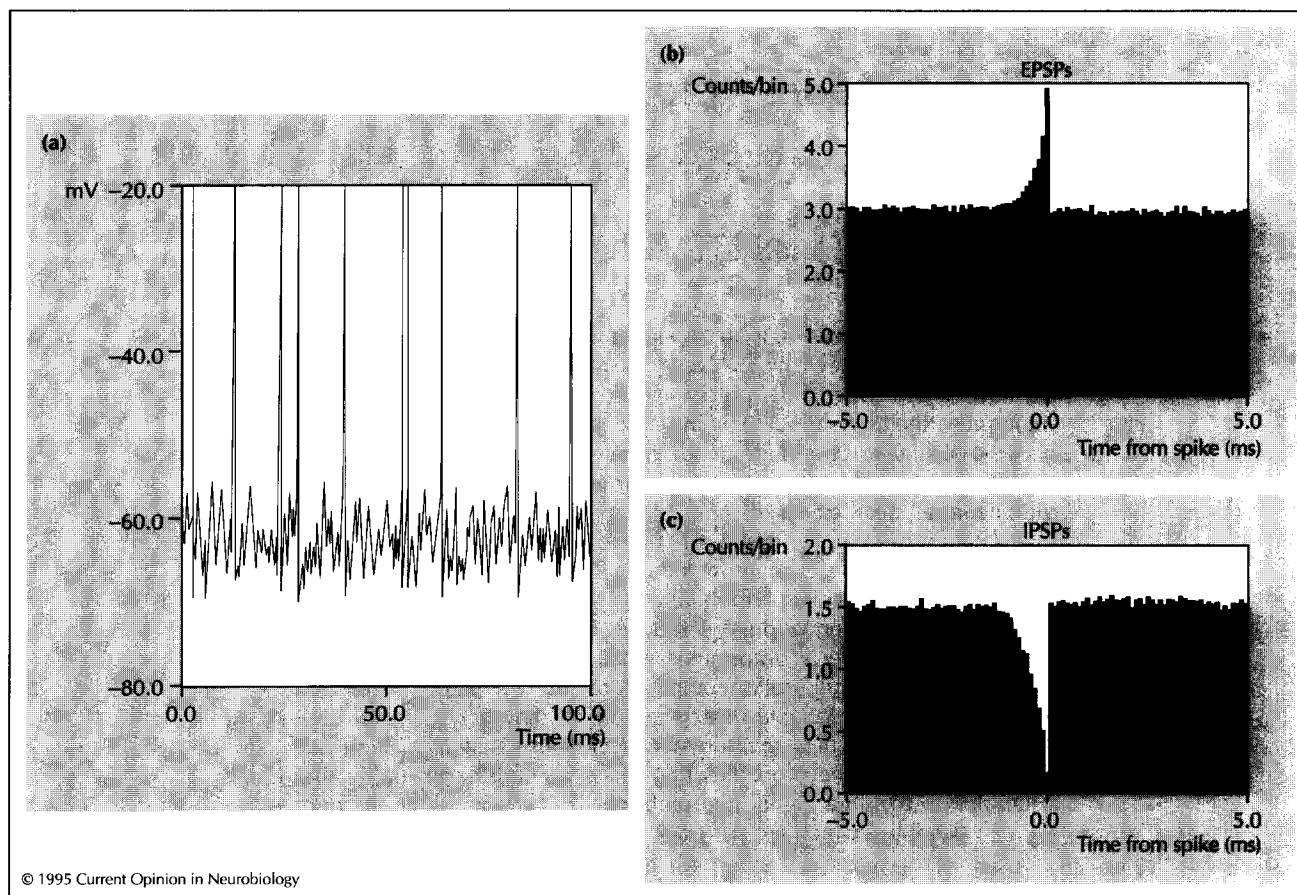
Fig. 1. Analysis of sub-millisecond temporal sensitivity in Shadlen and Newsome's balanced inhibition cortical cell model. (a) A sample trace from a single compartment, leaky-integrator neuron, using roughly balanced amounts of random excitatory and inhibitory synaptic input. Shadlen and Newsome [1] claim that such a simulation creates spikes whose timing does not reflect the timing of presynaptic events (see Fig. 1c of [1]). (b) A cross-correlogram of all EPSPs and (c) IPSPs, as triggered by output spikes ('reverse correlations'), shows that typical spikes do indeed result from deterministic combinations of presynaptic events. In particular, a typical output spike requires that there be about 60% more EPSPs than average, and about 90% fewer IPSPs than average, within the preceding millisecond. The fast timescale of this deterministic fluctuation detection can be understood, in part, by considering the inhibitory conductance as creating an effectively fast membrane time-constant (see equation 2 in the text). Although this simulation used only random input events, such a model is capable of making the fine temporal discriminations necessary to implement a spike code having orders of magnitude more information-transmitting capacity than the traditional, noisy, average-rate codes.

— that it is insensitive to the fine temporal structure of its inputs — which I believe is erroneous. The error is simple, but has strong implications for understanding cortical physiology and function.

Brains process information, and information transmission is as quantifiable a measure of performance as muscular strength or metabolic energy efficiency. Therefore, it is logical to assume that neurons use their spikes as a means of efficiently transmitting information. While we do not yet understand their spike code (i.e. the significance of spiking time, correlations, and rates), it has long been recognized that trains of irregular spikes can carry vastly more information in their precise spike times than in their noisy average rates [2,3]. This 'efficient' coding strategy has not been much explored, partly because there is very little evidence for precisely timed action potentials, and partly because of the assumption that cortical neurons are not sensitive enough to use precise spike times.

Cortical cell models that fire realistically (i.e. irregularly), however, seem to do so *because of* their sensitivity to precisely timed inputs (in some extreme cases, such as the 'hand-tuned' model discussed below, the 'neuron' can completely gate its firing in response to sub-millisecond discriminations of its input). So the crucial questions are whether cortical neurons in fact make use of that temporal sensitivity — and its potentially huge payoff in efficiency — and what kind of experiments are needed to discover it or rule it out.

Coincidence detection with 'balanced inhibition'

Shadlen and Newsome's balanced inhibition model (see [1]) postulates that strong inhibition causes a cortical neuron's membrane potential to fluctuate randomly. This mechanism might help account for the observed firing
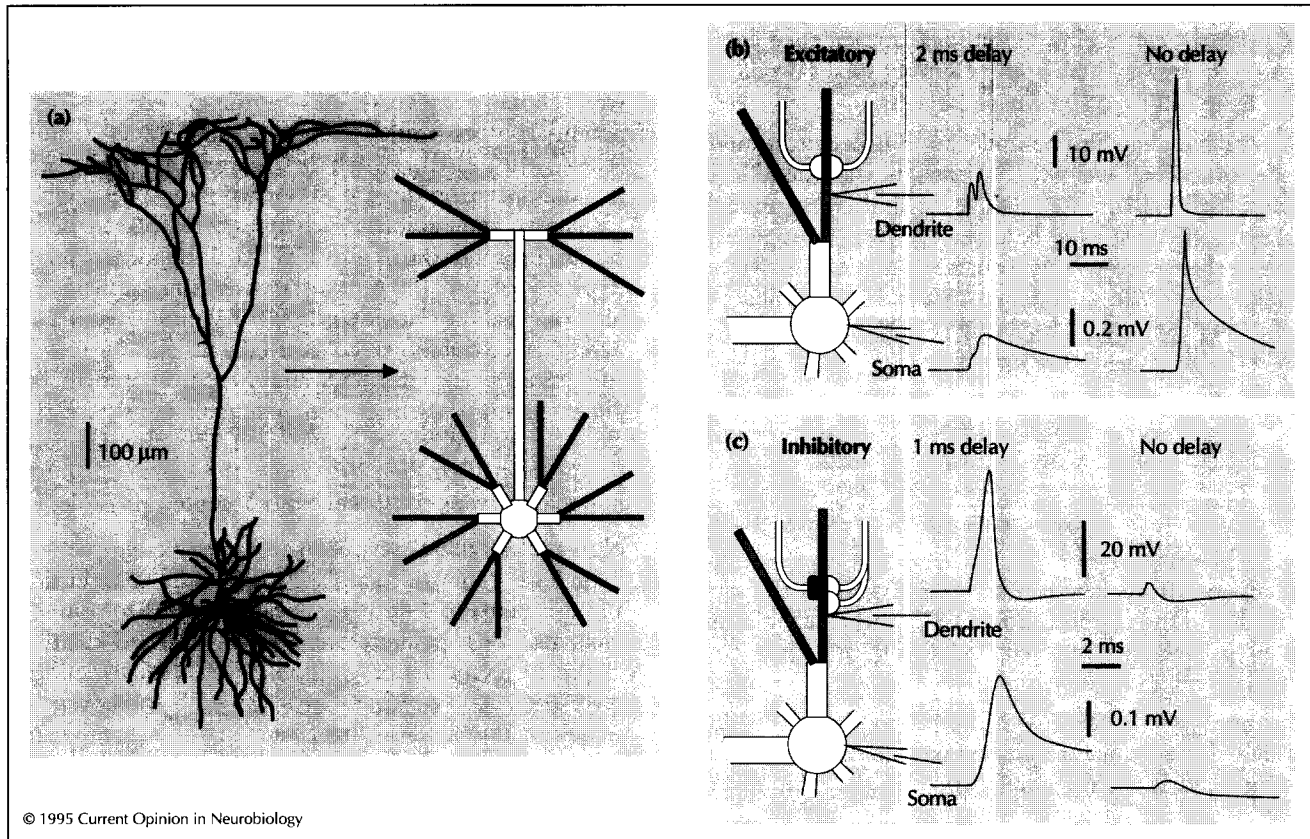
Fig. 2. Weakly active dendrites confer strong millisecond-level sensitivity on a reconstructed pyramidal cell model. (a) A layer 5 pyramidal cell, as reconstructed from cat visual cortex by Douglas and Martin (see [6]), simulated numerically. (b) If two co-localized excitatory inputs arrive two milliseconds apart, in the middle of a thin basal dendrite, they have very strong local depolarizations and fast local decays, but nonetheless produce realistically weak somatic EPSPs, which summate roughly linearly and decay with the τ_m of 20 ms. But if they arrive in coincidence, they fire a small dendritic spike that produces a threefold larger somatic depolarization. (c) A co-localized inhibitory synapse can gate such effects with fine temporal resolution. If the IPSP arrives only one millisecond after the coincident EPSPs, the dendritic spike will fire and reach the soma somewhat attenuated. But if the inhibition is coincident with the EPSPs, the dendrite will not fire, and the net effect on the soma will be negative. Such strong, transient, and highly localized non-linearities result naturally from even weak spiking conductances located in thin dendrites, but, because such non-linearities cannot occur in the popular single-compartment cell models, cortical neurons' potential for precise, high-bandwidth information transmission is often overlooked.

irregularity in cortical neurons [4]. But they claim in addition that "the timing of postsynaptic spikes is random and no longer reflects the timing of presynaptic events" [1]. A simple demonstration, using their own model and parameters (see Fig. 1c of [1]), shows that the model's spikes do in fact result from its deterministic responses to input fluctuations on a sub-millisecond timescale.

Figure 1 describes a model of a single compartment, leaky-integrator cell that receives 300 streams of 100 Hz random (Poisson), instantaneous, excitatory postsynaptic potentials (EPSPs) with 0.6 mV amplitude, and 150 streams of random inhibitory postsynaptic potentials (IPSPs) with 1.2 mV peak (0.9 mV mean) amplitude and reversal potential equal to the membrane resting potential, $E_{inh} = E_{rest} = -70$ mV. The cell fires an action potential upon reaching the firing threshold of −55 mV, and instantly resets to E_{rest}. Synaptic potentials and membrane decay are calculated at 0.1 ms intervals (finer than Shadlen and Newsome used), leading to an output firing rate of about 70 Hz (which is a bit slower than they observed).

With such a model, one can perform an additional 'experiment' that is not possible in a real neuron: that is, compiling a running average (cross-correlogram) of all EPSPs and IPSPs as triggered by the output spikes [5]. Those cross-correlograms have baseline values of 3.0 and 1.5 impulses per time bin, respectively, representing the average rate of synaptic inputs (Fig. 1b,c). But they also show prominent features near the triggering spikes at t =0 (Fig. 1b,c). The EPSP average shows a narrow peak of amplitude 5.0 (EPSPs/0.1 ms), indicating that in the millisecond before a typical output spike, the neuron receives 65% more EPSPs than average. The prominent dip in the IPSP average shows that a typical output spike is also preceded by a transient reduction in inhibition of nearly 90%.

This result accords with common sense because in this model, the input fluctuates randomly, and the cell tends to fire when it receives those few random fluctuations (extra excitation and missing inhibition), which drive the membrane voltage towards threshold. As those fluctuations are the simultaneous (albeit random) coincidences

and anti-coincidences of input from many different cells, the cell performs a kind of statistical coincidence detection on its inputs; therefore, the output spikes do indeed reflect the timing of presynaptic events.

This behavior can also be understood in terms of membrane time-constants (τ_m). Although the model's assigned τ_m is 20 ms, the barrage of inhibition mimicks a shorter effective time constant τ_{eff} [6]. A rough estimate of that shorter value, equating the mean inhibitory influence (dV/dt ≈ -0.9 mV/IPSP $\times$ 15 000 IPSPs/sec) and the mean inhibitory driving potential ($\Delta V \approx (V_m) - E_{inh} = 9$ mV) gives:

$$\frac{dV}{dt} \approx -\frac{\Delta V}{\tau_{eff}} \tag{1}$$

$$\dot\tau_{eff} \approx 0.67 \text{ ms}, \tag{2}$$

a factor of 30 smaller than τ_m. (τ_{eff} has about the same timescale as the features shown in Figure 1b,c, although the actual relation between peak-width and time-constant is complex [7].)

This result also accords with the proposal that plausible models that produce irregular spikes do so by discriminating fluctuations (or coincidences in their input) at a timescale much finer than the typical interspike interval [4]. If this proves true, then it implies that irregularly firing cortical neurons are capable of transmitting precise temporal codes. For example, models with strong outward currents — such as strong leaks, voltage-gated K$^+$ currents, or inhibition — meet these twin criteria of irregular firing and fluctuation sensitivity, as do models with strongly correlated volleys of EPSPs. (Models with weak outward currents do not violate the rule, because they fire quite regularly.) A possible exception could be a model with unconstrained random-walk membrane fluctuations, but such a model has an infinitely negative inhibitory reversal potential, an infinitely long memory, and a membrane voltage that drops well below physiological ranges.

A hand-tuned model

If the balanced inhibition cell model — exhibited to be so insensitive to EPSP timing (i.e. a poor coincidence detector) — nonetheless performs so sensitively, how much better might a model perform whose parameters were deliberately 'hand-tuned' to give it temporal sensitivity?

The layer 5 pyramidal cell (Fig. 2a), whose morphology was reconstructed from cat visual cortex by Douglas and Martin (see [6]), was simulated (using NEURON [8]) with a τ_m of 20 ms and with weak Hodgkin–Huxley conductances in all dendrites: that is, sodium conductance $g_{Na} = 0.006$ S cm^{-2}, about one standard deviation above the mean 0.004 S cm^{-2} reported in neonatal rat

apical dendrites [9], was barely sufficient to sustain local regenerative events in a basal dendrite; further parameters, such as $g_K = 0.0018$ Scm^{-2} and time constants, were chosen to give realistic action potentials. Action potentials were initiated in an axon initial segment (1.0 $\times$ 50 µm [10]), which had extremely strong spiking conductances ($g_{Na} = 1.0$ S cm^{-2}; $g_K = 0.5$ S cm^{-2}). Excitatory and inhibitory synapses were placed on the center of each thin, terminal basal dendritic branch (typically about 100 µm distal from the soma), with physiological reversal potentials (0 mV and −70 mV), and conductance durations (t_{peak} of 0.24 ms and 0.4 ms) and amplitudes (g_{peak} of 1.5 nS and 10 nS), chosen to produce somatic rise-times and potentials consistent with conservative published results ([11,12]; also [13]) (see the lower half of Fig. 2b). Thus, the simulation's basic ingredients were consistent with accepted physiology.

Nonetheless, these synapses had a remarkable property: their local dendritic depolarizations were tenfold faster and a hundredfold stronger locally than as measured at the soma [14,15]. Therefore, two co-localized EPSPs — in precise coincidence — could fire a small dendritic spike (Fig. 2b), which in turn caused a somatic depolarization threefold stronger than if the same synaptic events were separated in time by only two milliseconds. Furthermore, a co-localized IPSP could completely cancel such a depolarization if coincident with the EPSPs, but would have much less effect if occurring just a millisecond later (Fig. 2c), a precision also seen in models of excitable dendritic spines [16]. This model (Fig. 2) was similar to the balanced inhibition model of Shadlen and Newsome in that it gives inhibition a central role and strong magnitude (capable of roughly cancelling excitation). However, this model is also multi-compartmental, which is both more realistic and more computationally powerful than single-compartment models like Shadlen and Newsome's (see [17,18]), and is much better suited to performing fast temporal discriminations [14].

Although the parameters used in this model were conservative, the choice of which synapses to fire, and when, was highly artificial. Co-localized synapses at the center of basal branches always fired as part of a 'synaptic triplet', which is the precise pattern shown in Fig. 3a: two coincident EPSPs followed 1 ms later by an IPSP. Triplets occurred completely randomly and independently at 25 Hz on each dendritic branch (Fig. 3a). With this local ordering of synaptic events, the neuron's axon fired at a robust and realistic 55 Hz.

Whether such precise and specific connections actually exist in the cortex awaits a better understanding of synaptic formation and selectivity. This particular arrangement was chosen to highlight a specific sensitivity to the precise timing of the cell's inputs: when each triplet was perturbed by adding a slight gaussian timing jitter (of standard deviation σ) to its EPSPs and IPSP, the dendritic spikes were on average weaker or nonexistent, so that the cell as a whole fired more slowly (Fig. 3b). Even though the only independent variation
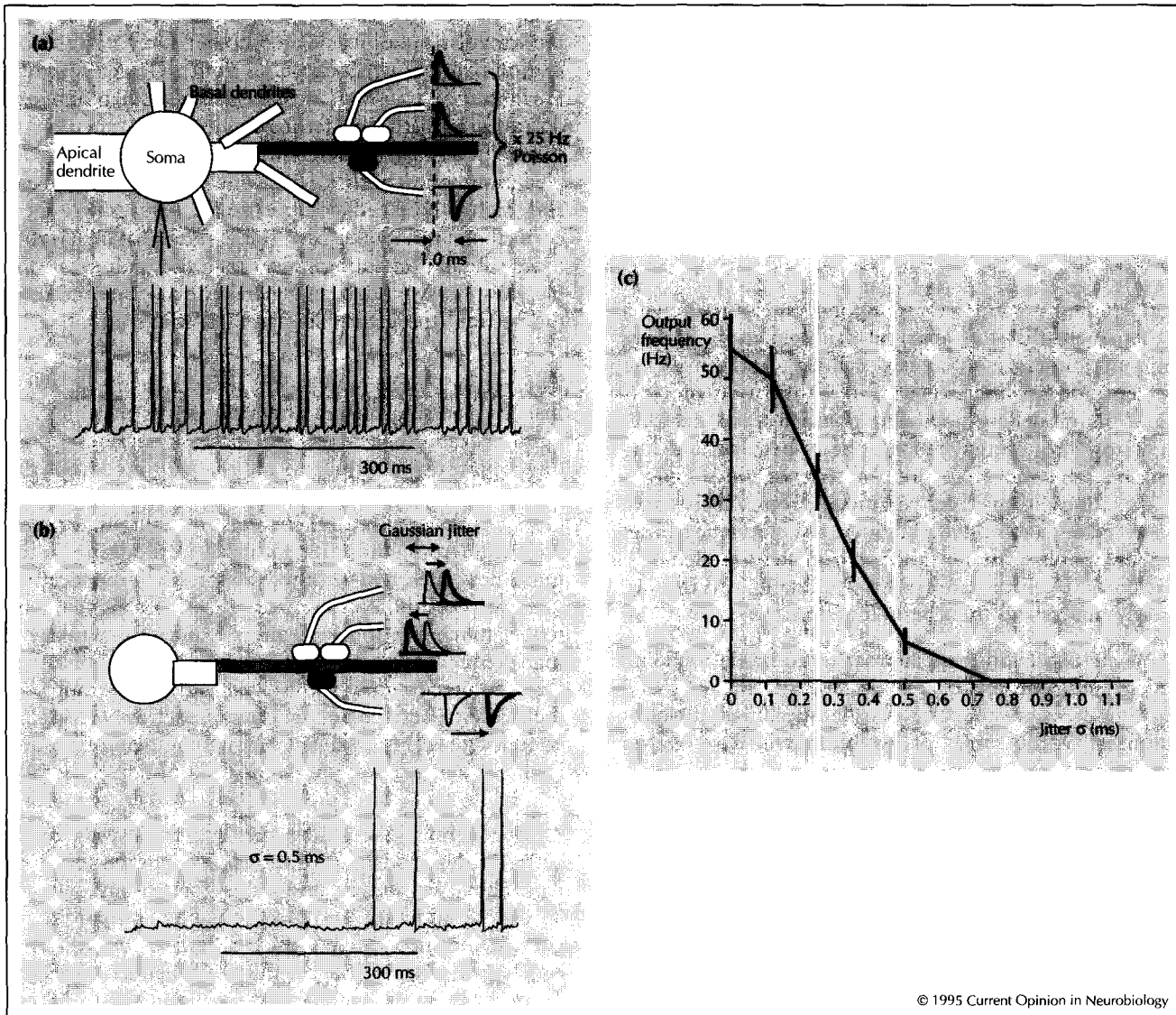
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Fig. 3. A hand-tuned (physiologically reasonable) cell model can be extremely sensitive to the temporal structure of its inputs. (a) The model in Figure 2 received its input as optimally timed triplets of two coincident EPSPs and a subsequent IPSP (as simulated in Fig. 2c), with triplets recurring randomly at 25 Hz on each basal dendritic branch, with no correlations across branches. The cell's axon fired at about 55 Hz in response to this input. (b) If only a slight gaussian timing jitter ($\sigma = 0.5$ ms) was added to the original synaptic times (thin pulses) to produce perturbed triplets (thick pulses), the cell fired much more slowly. In neither (a) nor (b) does the somatic voltage suggest the strong and sensitive non-linear interactions occurring inside the thin distal dendrites. (c) A plot of the cell's output firing rate against jitter magnitude shows that such a model has sub-millisecond sensitivity to precise input firing patterns and times. Although such delicate regimes of sensitivity may not dominate the range of physiologically acceptable models, they deserve special attention because they potentially represent information-transmission efficiencies orders of magnitude larger than the coarse, slow, noisy regimes usually considered.

was the timing noise of individual events, the cell was quite sensitive to that noise: for example, $\sigma = 0.25$ ms reduced the output rate by half, and $\sigma = 0.8$ ms shut off firing entirely (Fig. 3c).

There was little indication in the somatic voltage trace (Fig. 3b,c) of the very strong and transient dendritic signals that gave rise to this remarkable sensitivity. Because such temporally precise mechanisms can be nearly 'invisible' to somatic recording electrodes, great care will be needed in searching for them experimentally.

There are many cellular properties not included in this model, which could have affected these results: for example, slow currents, due to Ca^{2+} or tonic NMDA mediated conductances, would probably have decreased

the model's temporal sensitivity. Other properties might have made the cell even more sensitive, such as strong inhibition of the axon initial segment [19] and soma [20], fast Ca^{2+}- and voltage-gated K^+ currents, and correlations in synaptic input across dendrites and across time.

In any case, this model — like any simulation of a neocortical cell — is not 'realistic', because we do not yet know realistic input patterns or the detailed intracellular and synaptic properties of mature neurons in vivo (and especially of the thin dendrites where most input arrives). Nor do the familiar concepts borrowed from passive cable theory (time constant, electrotonic length, compactness) adequately describe the intricate non-linearities occurring in active dendrites at fast timescales [14].

Simplicity versus efficiency

The hand-tuned model is remarkably sensitive to input timing, but it is manifestly artificial as it was specifically designed to show this sensitivity. What is the point of hand-picking parameters to demonstrate a model unsupported by direct experimental evidence? Because evolution sometimes works the same way, picking out and building upon useful parameter regimes against tremendous odds.

Hand-tuning a model for temporal precision shows a bias, namely that the apparent randomness of spiking and our ignorance of *in vivo* cellular details mask an efficient and specific structure of information processing. This modelling approach postulates and explores such structure, even when it appears peculiar and implausible. But the more popular style of modelling — that is, choosing 'average' parameters from widely varying estimates, and only evaluating a few simple responses to a few simple stimuli — also incorporates a hidden bias: that cortical neurons are (relatively) simple, and that we already understand their basic functions.

These are two conflicting approaches to model-building with insufficient data: the hypothesis of efficiency and the hypothesis of simplicity. Broadly speaking, efficiency assumes that the forces of evolution will have shaped the operating regimes — however unlikely they may seem — so as to optimize an organism's performance. Examples outside the brain abound: the aerodynamic efficiency of soaring birds, the quantum efficiency of photoreceptors [21], the nanosecond acuity of echolocating bats [22].

Simplicity, on the other hand, is the traditional scientific hypothesis, as embodied in Occam's Razor: one chooses the most simple explanations consistent with the observations. A simple model will only seek to explain existing data with a minimum number of assumptions, and will contain no assumptions about the significance of parameters or mechanisms that we do not understand.

Not only is the hypothesis of efficiency strictly unscientific, but it presents two special problems when applied to understanding how information is efficiently transmitted in the brain. The first is that in the special case of computing and processing information, efficiency is the *opposite* of simplicity. Just as a computer's power depends on the number of its possible internal states (memory) and its clock speed, so the potential power of a single cortical neuron depends on its structural complexity (the number of functionally independent compartments) and its temporal resolution. Crude estimates suggest that a pulse code of irregular spikes is a hundredfold more efficient than an analog rate code [3,23], because the rate

code's noise serves as the pulse code's information[1] (e.g. the irregular pulses inside a computer carry more information than the irregular pulses from a Geiger counter). Furthermore, transients at that fast single-spike timescale do not propagate very far inside a branched membrane, so a neuron's many different dendrites are nearly de-coupled from one another [14]. This combination of fast and highly localized computation gives a single neocortical neuron potentially three orders of magnitude more overall computing power than the traditional simple, slow, noisy models. In general, the more complicated the neuron, the greater its potential efficiency[2].

The second problem with the efficiency hypothesis is that, by favoring electro-chemical events that are very tightly localized in space and time, it ascribes to nature a powerful incentive to use the very properties that are beyond the resolution of our instruments. For example, synaptic amplitude excursions are strongest, briefest, most numerous, and most localized in the thinnest terminal dendrites, and yet, these are precisely the locations that are most difficult even to see using a light microscope, much less measure directly and unintrusively at high frequencies. And the sensitivity of those tiny dendrites to precise input patterns depends very strongly on their fastest electrical non-linearities, such as Na^+ spiking conductances [14], which are now only being measured in the much wider apical dendrites, in brain slices [9].

As a benchmark, consider the task of investigating a better-understood kind of information processor: a silicon chip. We already know that for reasons of space, power consumption, and speed, the best computer chips contain the most densely packed, fastest, tiniest transistors (0.5–2 μm, a bit larger than thin dendrites). Could we probe them in the same way we probe brains? Not by 'electrophysiology' — touching the chip with an external electrode — for the two reasons outlined above. First, the electrode is bigger than a typical transistor or inter-transistor distance, so it would be hard to record from just one. In addition, a single transistor, designed only to drive its small fellows at high speeds, cannot in addition drive the much larger capacitance of the probe, as the probe would load and disrupt the circuit under study. Because of these limitations, the simplest state-of-the-art method for bringing a chip's single-transistor output to the lab bench requires first designing a large, dedicated amplifier circuit for each transistor of interest, then fabricating from scratch a new chip with the transistor-amplifier pairs, and finally measuring the amplifier's output during circuit operation (see [26] and references therein). The clumsiness of this process illustrates the difficulty of probing, from the outside, the inner workings of an efficient information processor.

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[1]Information efficiency might be measured in bits-per-second, bits-per-spike, or bits-per-calorie. The estimate only requires knowing the strengths, timescales, and probabilities of the signal and noise in the code; it does not require knowing how the brain uses information.
[2]Some efficiency-related measures have already been applied to perceptual processing, such as 'info-max' [24] and redundancy reduction [25]. But both these measures assume average-rate coding rather than precise temporal coding.

Existing evidence, and the lack of it

A serious short-coming in the hypothesis that living brains transmit information using single spikes is a lack of experimental evidence. There is no evidence that single spikes in visual cortex have any precise timing in relation to their input stimuli (J Heller *et al.*, personal communication); even much weaker stimulus-related temporal modulation at much slower timescales is in dispute [27,28]. But unlike inputs to simple stimulus-driven transducers, most inputs to a cortical neuron do not come directly from the 'stimulus', but rather from other cortical neurons. Furthermore, cortical neurons may use their spikes in ways beyond simply encoding the experimental stimulus.

When both the input source and the general function of some neuron are evident, as they are in signal transduction — such as in the fly eye [21] or the cricket cercal system [29,30] — then information-theoretic analyses relating spike trains to stimuli give a fairly complete description of the neuron's capabilities: such neurons can transmit up to 3–4 bits of information per spike about a simple stimulus, such as local velocity or air movement. But a realistic 'stimulus' for mammalian cortex is not an air puff, but rather a complex situation involving on-going patterns of full-field vision and other modalities. Likewise, the 'output' of cortex may be a complex behavior including gesture, locomotion or vocalization. The fact that some cortical neurons do respond to simple, localized stimuli does not circumscribe their role in interpreting the much richer and more complex inputs that brains encounter outside the lab.

That process of interpretation, or perception, may involve interrelations among parts of the stimulus. And those interrelations might be coded as temporal fluctuations that are independent of the stimulus itself. The task could be visual perception by synchronizing rate-fluctuations among neurons [31,32], figure–ground separation by the phase of neural oscillators [33], visual attention modulated by oscillations [34–36], or 'binding' by preserving the precise spike times of individual inputs [37]. In all these cases, there is both a need for extra precision in cortical temporal discrimination and a reason that such responses may seem like 'noise', that is, signals unrelated to the experimental stimulus.

In most of these cases, the temporal signal is multiplexed into an average-rate signal carrying information complementary to it. A cell like Shadlen and Newsome's [1], for instance, might convey slowly changing stimulus properties by its averaging firing rate, even while its spike times carried additional information relating the stimulus to other parts of the environment. Using redundant, parallel pathways might safely allow imperfections in any single cell's response: temporal precision in the network does not necessarily require the faithful transmission of every pulse to and from every neuron [38] (after all, synaptic failure [39], and even neuronal death, are common occurrences in functioning brains).

Possible experimental tests

In the search for temporal precision, the unexpected submillisecond precision of Shadlen and Newsome's model provides an important lesson: what we find depends on what we look for. For instance, the arguments above suggest that precision will probably not be found in a single neuron's post-stimulus time histogram, but may appear only in the correlations between selected pairs or groups of neurons [38,40].

One experimental approach may be easy to implement: recording, storing, and publishing intracellular and extracellular data with as little low-pass filtering and smoothing as possible, so that signals at fast timescales are at least available for scrutiny by others.

Finding highly precise interspike interval patterns would strongly support precise-coding models [41,42], but such studies often have problems in constructing a null hypothesis — that is, the expected number of chance repetitions in a data set — relative to which the discovered pattern repetitions may or may not be significant (R Lestienne, Soc Neurosci Abstr 1994, 20:22).

Multi-electrode studies might reveal whether precise coincidences of spikes exist in primate cortex, as they do in cat [43–45]. Presently, single electrodes using thresholds or template-matching spike-sorters cannot record two exactly coincident action potentials, because the individual extracellular potentials are superimposed. But given good records, a total absence of millisecond-level coincidences would be hard to reconcile with the coincidence-detecting hypothesis.

Intracellular records of the thinnest basal and apical dendrites might resolve whether they contain the strong, fast events proposed here. Extracellular patch records ('cell attached', i.e. with unruptured membranes) might prevent the recording pipette from capacitively loading the tiny dendrite and eliminating the very effect it seeks to measure.

A better but less practical measurement would look for the scenario posed in Figure 2: whether two co-localized and coincident EPSPs on thin dendrites produce a somatic effect greater than the sum of their separate contributions. (At present, even a single such synaptic site is only visible using electron microscopy; finding two such synapses nearby on the same dendritic branch, and then finding and impaling both presynaptic neurons, is nearly impossible.)

Such tests would be more believable (but difficult) on cells with the adult complement of dendrites and conductances [46], and in awake animals, where the firing irregularity, synaptic background activity [6] and action potential repolarization [47] best match their true operating conditions.

An ideal test of the hypothesis that spike times are important would be to perturb all latencies in some area of living cortex by a millisecond or so, while observing whether behavior is affected. This might in principle be

done by changing the conduction speed of the axons in the white matter (through temperature or chemistry).

Conclusions

So far, every cortical cell model that generates realistically irregular spikes, including Shadlen and Newsome's balanced inhibition model, is also capable of discriminating its input on a fast timescale. A hand-tuned model of a reconstructed pyramidal cell, containing physiological conductances, is even more sensitive, capable of entirely shutting off its firing in response to sub-millisecond jitter in its synaptic arrival times. But its crucial properties are contained in its thinnest dendrites, and their effects are virtually invisible in the somatic voltage trace. Thus, the very properties that could make a neuron most sensitive, may also be the most difficult to measure.

Such temporal precision makes cortical neurons at least capable of implementing codes that use precise spike times. Such codes can be over two orders of magnitude more efficient at information transmission than the traditional, noisy average-rate codes. So a search for temporally precise spike codes could be motivated by the observation that evolution, having designed such wonders as flight, photosynthesis and echolocation, might also have designed neurons to process information efficiently. Although the efficiency hypothesis is only a hypothesis — in that it proves nothing, and cannot substitute for real data — it can nevertheless point the way for future experiments, so that we do not make the error of missing an important phenomenon just because we have not looked for it.

Acknowledgements

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