Noise, neural codes and cortical organization

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Cortical circuitry must facilitate information transfer in accordance with a neural code. In this article we examine two candidate neural codes: information is represented in the spike rate of neurons, or information is represented in the precise timing of individual spikes. These codes can be distinguished by examining the physiological basis of the highly irregular interspike intervals typically observed in cerebral cortex. Recent advances in our understanding of cortical microcircuitry suggest that the timing of neuronal spikes conveys little, if any, information. The cortex is likely to propagate a noisy rate code through redundant, patchy interconnections.

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Introduction

Although it is generally agreed that neurons signal information through sequences of action potentials, the neural code by which information is transfered through the cortex remains elusive. In the cortex, the timing of successive action potentials is highly irregular [1••], and the interpretation of this irregularity has led to two divergent views of cortical organization. On the one hand, the irregularity might arise from stochastic forces. If so, the irregular interspike interval (ISI) reflects a random process and implies that an instantaneous estimate of spike rate can only emerge from the pooled responses of many individual neurons [2]. In keeping with this theory, one would expect that the temporal pattern of spikes conveys little information. Alternatively, the irregular ISI may result from precise coincidences of presynaptic events. In this scenario, it is postulated that the timing of spikes, their intervals and patterns can convey information [3–13]. According to this view, the irregularity of the ISI reflects a rich bandwidth for information transfer.

Our understanding of cortical organization and interpretation of neurophysiological data depend critically on whether neurons convey a noisy rate code or a precise temporal code. Is it reasonable to expect the average discharge rate of a neuron in the visual cortex to convey information about a visual stimulus [14–17], or should we attend to particular patterns of spikes? Is cortical circuitry organized to average out noise among redundant neurons, or to provide an expansion of temporal signaling capacity by eliminating redundancy in the pattern of inputs to different neurons? At the heart of this controversy, the critical question is why neurons spike with such irregularity. In this article, we will attempt to identify the physiological factors that may lead to irregularity in the spike train. In essence, our task is to determine whether neurons within cortical circuits behave as coincidence detectors or as integrate-and-fire devices [3].

Coincidence detectors or integrate-and-fire devices?

Given our current understanding of cortical physiology and biophysics, why do cortical neurons discharge so irregularly? This is the question recently posed by Softky and Koch [1••]. They examined spike trains from neurons in the visual cortex of the monkey, applying a clever normalization scheme that permitted them to estimate the variability of the ISI at nominally constant firing rates. They found that spiking patterns approximate a random (Poisson) process. Using a sophisticated model of a cortical pyramidal neuron and its connections [18], they argued that such irregularity is unattainable through an integrate-and-fire mechanism [1••]. Any neuron that integrates synaptic inputs with a membrane time constant of 7–20 ms should spike more regularly. The intuitive appeal of this argument is based on the following physical analogy. Imagine a Geiger counter that is wired to click only upon integration of 40 radioactive decays. Although individual decays are random in time, the modified counter clicks with great regularity because the sum of random intervals becomes reliable as the number of counted intervals increases. By analogy, a neuron that integrates random presynaptic events

Abbreviations

EPSP—excitatory postsynaptic potential; **ips**—impulses per second; **IPSP**—inhibitory postsynaptic potential; **ISI**—interspike interval; **IT**—inferotemporal; **MST**—medial superior temporal area; **MT**—middle temporal area; **PSP**—postsynaptic potential; **V1**—primary visual cortex.

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— counting to some number to reach spike threshold — cannot preserve such irregularity in its own spike output.

Fig. 1a depicts the expected output from an integrate-and-fire device; the output is nearly periodic, even though input spikes arrive at random intervals. Softky and Koch [1••] conclude that cortical neurons must perform some sort of coincidence detection, such that a particular combination of presynaptic events leads to a postsynaptic spike. This combination would occur with sufficient irregularity to account for the variable ISI. This idea is illustrated in Fig. 1b. Such a neuron would be capable of transmitting information in the precise timing of individual spikes or their temporal pattern.

On the other hand, it has long been known that a balance of excitation and inhibition will yield an irregular ISI from the standard integrate-and-fire neuron. The idea was first proposed by Gerstein and Mandelbrot [19] and subsequently developed by Calvin and Stevens [20] in their seminal work on synaptic noise in spinal motoneurons. These models are often referred to as random walk, or diffusion processes, and they have a rich theoretical base [21–29]. The idea behind this model is that the membrane potential undergoes a random walk between resting potential and spike threshold (Fig. 1c). EPSPs (excitatory postsynaptic potentials) drive the potential toward spike threshold and IPSPs (inhibitory postsynaptic potentials) drive the potential toward E_{Cl} (chloride reversal potential), beyond which there can be no further hyperpolarization. With an appropriate balance of excitation and inhibition, the ISI can be highly irregular.

Although the Geiger counter model (Fig. 1a) is clearly wrong, either the coincidence detector or random walk model can account for the irregular ISIs seen in cortical neurons. However, these two schemes sanction very different strategies for cortical organization. If cortical neurons behave as coincidence detectors, then the timing of spikes can propagate through the cortex with great fidelity to convey information and to synchronize other neurons [6,10,30,31]. If an irregular ISI results from integration of excitatory and inhibitory PSPs (postsynaptic potentials), then the timing of postsynaptic spikes is random and no longer reflects the timing of presynaptic events. Precise patterns of spikes — their intervals and coincidences — would fail to propagate.

The validity of these two views rest ultimately on the behavior of neurons within cortical circuits. Which synaptic events cause a neuron to fire? The coincidence detector requires the effective set of synaptic events to occur at roughly the same frequency as the neuron spike rate. Noncoincident EPSPs must either arrive infrequently or be prevented from summating to spike threshold by a very short membrane time constant (i.e. less than a few milliseconds) [1••,32•]. The random walk model incorporates a more reasonable time constant (~10 ms or more), but the opposition of excitatory and inhibitory PSPs demands a very large number of presynaptic events to drive the neuron to threshold. Moreover, the random walk model requires roughly equal depolarizing and hyperpolarizing influences on membrane voltage to generate highly variable ISIs (MN Shadlen, WT Newsome, unpublished data). To choose between the coincidence detection and random walk models, we need answers to several critical questions. How many EPSPs arrive at the neuron during an epoch of activity, and what is their impact on the postsynaptic membrane voltage? How many IPSPs arrive during the same epoch, and what is their impact on the postsynaptic membrane? What is the balance between excitatory and inhibitory influences on membrane potential?

Evidence from synaptic physiology

How many synaptic inputs are active?

The number of synaptic contacts for cortical neurons has been estimated to be between 3000 and 10 000, depending on cortical area and species [33]. The most recent estimate for monkey visual cortex is 3900 synapses per neuron [34]. Approximately 85% of these contacts are asymmetric and, therefore, are presumed to be excitatory. The majority of these synapses are from other cortical neurons, either within the cortical column or connected to the column via horizontal axon collaterals [18,35].

It is more difficult to estimate the fraction of these excitatory synapses that are active during an epoch of excitation. Consider a pyramidal cell in V1 (primary visual cortex) that responds to an optimally oriented bar of light passing through its receptive field. How many of the neuron's inputs are active over any 30–50 ms epoch (2–3 time constants)? Many of the excitatory inputs from within a cortical column will respond under the same stimulus conditions as our pyramidal cell [36], as would most of the direct excitatory inputs from the thalamus. Inputs from horizontal connections within the cortex tend to arise from neurons with similar receptive fields [37], and cross-correlation analyses reveal that many of these neurons are active simultaneously [38,39]. Nevertheless, not all of the horizontal connections would be expected to be active at the same moment, as many arise from portions of the visual map outside the classical receptive field of the neuron they innervate [34,40] (but see [41–45]). The extent to which the map of activity overlaps the map of connectivity remains to be clarified, although optical imaging data suggest that the degree of overlap is substantial ([46]; DY Ts'o, personal communication). We are left with the impression that a large fraction of excitatory inputs ought to be active. Exactly how large a fraction remains to be determined. (We chose 10% for the simulations in Fig. 1, but the following analyses apply to any fraction over 2–3%.)

How large is an EPSP?

More important than the number of synapses is their effectiveness. How large is an EPSP in relation to the

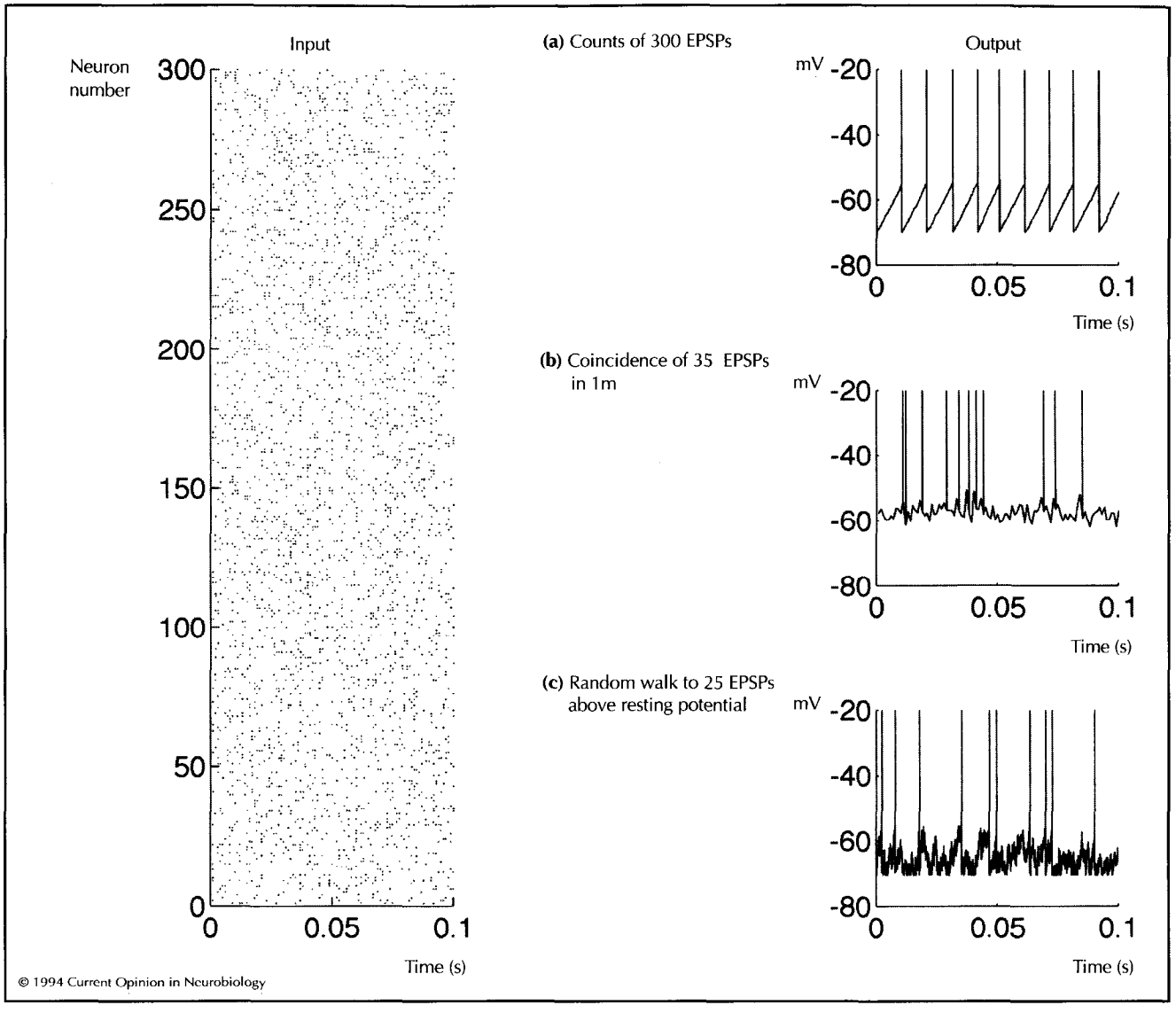

Fig. 1. Three models of synaptic integration. The response of a postsynaptic neuron over a 100 ms epoch is shown for three models. The postsynaptic neuron integrates the excitation provided by its inputs to generate a spike train. In this simulation, 300 inputs provide excitation to the neuron during a 100 msec epoch; the postsynaptic neuron is required to respond at roughly the rate of any single one of its inputs — 100 impulses per second (ips) in this simulation (in cortex, input and output neurons respond over a common dynamic range). In all models we assume a resting potential of −70 mV and spike threshold of −55 mV. For simplicity, we pretend that all EPSPs have identical amplitude, regardless of membrane potential. On the left side of the figure, the spike discharge from 300 presynaptic excitatory inputs are illustrated by rows of points. Each input neuron has a nominal spike rate of 100 ips, or 10 spikes during the 100 ms epoch shown. Spikes arrive with random ISIs. **(a)** An integrate-and-fire neuron that counts EPSPs produces a regular ISI. Each EPSP depolarizes the membrane toward spike threshold, where it remains until the next EPSP arrives. To achieve an output spike rate of 100 ips, each input must depolarize the membrane by only 1/300 of the necessary excursion to spike threshold, or roughly 0.05 mV. **(b)** A coincidence detector neuron that responds only to rare combinations of input spikes produces an irregular ISI. The membrane potential is determined by the sum of EPSPs arriving in single millisecond epochs. EPSPs from the preceding millisecond do not affect the membrane potential. To achieve an output of 100 ips the model requires 35 inputs to arrive simultaneously. Although membrane potential is reset to −70 mV after a spike, the observed potential generally lies considerably higher, due to the barrage of subthreshold presynaptic events. **(c)** An integrate-and-fire neuron that balances excitation and inhibition produces an irregular ISI. In addition to the 300 excitatory inputs, 150 additional inputs (not shown) provide inhibition. These also arrive at roughly 100 ips. As in (a), each EPSP depolarizes the neuron toward spike threshold, but each IPSP hyperpolarizes the neuron towards −70 mV. The membrane potential undergoes a random walk between an elastic barrier at −70 mV and absorption barrier at spike threshold. We have crudely implemented a balance between excitation and inhibition by setting IPSP amplitude to twice EPSP amplitude. In order to achieve a spike rate of 100 ips, EPSP amplitude is 1/25 of the excursion to spike threshold (0.6 mV). The random walk model achieves a proper dynamic range at the cost of a noisy ISI. These simulations are caricatures of more realistic biophysical models, but are intended to illustrate key points. Randomizing EPSP (and IPSP) amplitude and implementing more realistic membrane time constants (10–20 ms) has little impact on the integrate-and-fire models: (a) and (c). For the coincidence detector (b), randomizing EPSP amplitude changes the exact timing of output spikes, and the membrane time constant must be substantially less than 1 ms. Notice that although the coincidence detector and random walk models yield irregular ISIs, only the coincidence detector conveys information through the timing of spikes. The time of pre- and postsynaptic spikes is determined with millisecond precision in (b), whereas in (c) pre- and postsynaptic events are only related by rate.

excursion in membrane potential necessary to produce an action potential? The resting potential of cortical neurons lies between –60 mV and –75 mV in slice [47–49,50••,51•], but may be closer to –60 mV *in vivo* [52–54]. Recently it has become possible to measure the postsynaptic depolarization caused by single EPSPs [49,51•,55–57,58•,59•]. Simultaneous intracellular recordings from pairs of pyramidal cells in cortical slice revealed a range of single-axon EPSPs from 0.05 mV to greater than 2 mV (e.g. mean 0.55 mV in [49]). In all cases, the size of a single-axon EPSP was highly variable. Single spikes from the same neuron may cause a large depolarization or may affect the postsynaptic neuron negligibly.

Interestingly, the size of an EPSP may be unrelated to its position on the dendritic tree. Synapses near to or far from the soma, as judged by EPSP shape, share largely overlapping distributions of PSP amplitudes [49,56]. Moreover, even electrotonically distant synapses can influence the somatic membrane potential, presumably by active dendritic conductances [50••,60••, 61••]. Cauller and Connors [62•] have recently demonstrated that synapses of layer 1 neurons to layer 5 pyramidal neurons yield measurable somatic EPSPs. Presumably, a balance between active dendritic conductances and cable properties yields a fairly stereotyped EPSP at the soma [62•]. Thus, the available data suggest that the entire dendritic tree may be capable of influencing somatic membrane potential in steps of approximately 0.5 mV. If so, just 10–40 excitatory inputs can depolarize the membrane from resting potential to a spike threshold of about –55 mV [47,49], yet hundreds of excitatory inputs probably bombard the postsynaptic cell during very brief epochs (see preceding section).

These insights raise substantive problems for both the coincidence detection and integrate-and-fire models. The bombardment of EPSPs would contaminate with extraneous inputs the set of coincident events carrying information. Coincidence detection can be saved if the membrane time constant were exceedingly short (< 1 ms) and the coincident events carrying information occur within a single millisecond of each other. Extraneous events would not sum to threshold and postsynaptic spikes would reflect specific combinations of presynaptic events, maintaining precise temporal fidelity (as in Fig. 1b). Unfortunately, this solution is unrealistic as membrane time constants are typically 8–20 ms [49,50••,58•,59•]. To our minds, this problem appears fatal for the coincidence detection model. By this we do not deny that coincidences of EPSPs exert greater influence over membrane potential than the same number of EPSPs arriving sequentially. Any neuron with a finite membrane time constant possesses this property, but this would not confer any of the enticing properties of a coincident code. The hypothesis that information may propagate via specific patterns of spikes (in time — like Morse code — or across neurons) demands that postsynaptic spikes and the presynaptic events that cause them coincide on a time scale well short of the average ISI. Coincidence detection on the time scale of the membrane time constant would confer little advantage as it would necessitate intolerably low spike rates.

An integrate-and-fire device is prone to firing rate saturation in the face of a massive excitatatory bombardment, but this problem is easily solved if roughly equal amounts of excitation and inhibition influence the postsynaptic neuron. Note that this is the same stratagem that produced variable ISIs in the integrate-and-fire model (Fig. 1c). To evaluate the integrate-and-fire model rigorously, it is vital to learn the relative influence of excitatory and inhibitory inputs on cortical neurons.

What is the balance between excitation and inhibition?

Inhibitory synapses constitute approximately 15% of the synapses on cortical neurons [34,35,63]. Most of these synapses arise from smooth stellate neurons within 400 microns of the target cell [64–66,67•], but some are from basket cells as far as 1–1.5 mm away [67•,68•]. For many years, intracortical inhibition was thought to shape the receptive field properties of sensory neurons, such as orientation and direction tuning [69–74]. Theoreticians contemplated interesting computational properties for inhibition, such as veto power (gating) and dendritic multiplication [75,76]. Surprisingly, intracellular recordings in V1, *in vivo*, have shown that IPSPs tend to occur when EPSPs occur [52,53,77,78]. For orientation-selective neurons, therefore, EPSPs and IPSPs both occur most frequently in response to optimally orientated stimuli [53,77]. This puzzling observation becomes sensible in light of the current conjecture that a primary role of inhibition is to control the gain, or amplification, of neural signals [18,78]; inhibition must balance the excitatory bombardment to prevent the neuron's firing rate from saturating.

The requirement of equal excitatory and inhibitory inputs appears at first blush damning for the integrate-and-fire model, as excitatory synapses on cortical neurons outnumber inhibitory synapses by roughly 6 : 1 [34,35,63,66]. Despite this morphological inequity, we suggest that physiological balance could be achieved in at least four ways: firstly, IPSPs may have a larger impact on membrane polarization; secondly, a larger fraction of inhibitory synapses may be active during any temporal epoch; thirdly, inhibitory interneurons may fire more rapidly than excitatory neurons; and, fourthly, inhibitory synapses may be more secure than excitatory synapses. Physiological evidence exists in favor of three of these mechanisms. Inhibitory synapses are concentrated near the soma [35,66,79], and are known to have relatively large conductances and long durations, suggesting that IPSPs have a greater impact on the postsynaptic membrane potential ([18,55,80]; A Thomson, D West, J Deuchars, *J Physiol (Lond)* 1993, 473:173P). In addition, it seems likely that inhibitory interneurons fire at higher rates than do excitatory neurons in the same cortical column [81–83]. Finally, many excitatory impulses may simply fail to depolarize the postsynaptic

neuron. Such synaptic failures have been demonstrated in hippocampal cell culture and slice [84•,85,86•], and are thought to reflect a presynaptic failure to release neurotransmitter. Although this phenomenon is just beginning to receive attention in the neocortex ([57,58•,59•,87•]; D Smetters, S Nelson, *Soc Neurosci Abstr* 1993, 19:628), preliminary evidence suggests that inhibitory inputs are more secure than excitatory synapses (A Thomson, D West, J Deuchars, *J Physiol (Lond)* 1993, 473:173P). Inhibitory neurons tend to make multiple contacts with their targets [64,68•], whereas (excitatory) pyramidal neurons tend to make single synapses [40,86•]. Although the available data are inconclusive, it seems entirely plausible, if not probable, that excitation and inhibition on cortical neurons are much more closely balanced than the anatomy would suggest.

With these data in mind, let us return to Fig. 1. To produce this figure, we assumed 300 presynaptic neurons are active (~10% of the excitatory input to a pyramidal neuron) during a 100 ms period. Each input neuron provides about 10 spikes, which arrive at irregular intervals during this epoch. The postsynaptic neuron is not allowed to saturate, so a good rule of thumb is to find conditions that allow it to fire about 10 spikes. To do this with the simple counting device (Fig. 1a), we had to assume an EPSP amplitude of 0.05 mV (1/300 of the excursion from reset to spike threshold), which is clearly incorrect. In any case, we can exclude this model because it produces a regular ISI. To model the coincidence detector (Fig. 1b), we had to assume an EPSP amplitude of about 0.4 mV. Unfortunately, we also had to mimic a membrane time constant of under 0.5 ms. Basically, there can be no summation of EPSPs beyond an interval of 1 ms or less. There is no plausible basis for this conjecture (but see [32•]). Finally, we considered a simple random walk mechanism (Fig. 1c). Here the average EPSP was 0.6 mV and we mimicked a long time constant (greater than 10 ms). However the model assumes a strong source of inhibition. In this rendition we added 150 inhibitory presynaptic neurons, each providing roughly 10 spikes, arriving randomly. Each IPSP hyperpolarizes the membrane toward −70 mV in steps twice as large as an EPSP. This is a crude approximation to a balance between hyperpolarizing and depolarizing forces on the membrane. This idea seems to be most consistent with synaptic physiology. In essence, the random walk model with balanced excitatory and inhibitory inputs allows the neuron to behave as an integrate-and-fire device and maintain a reasonable response rate. The cost, however, is an irregular ISI. If this conjecture is correct, then the timing of output spikes is stochastic and can convey little, if any, information.

Implications for cortical organization

Our understanding of the sources of ISI irregularity has fundamental implications for our views of cortical organization. If the variable ISI reflects a precise temporal code that must be propagated through the cortex, the pattern of cortical connectivity should emphasize divergence, and redundancy should be avoided. Moving downstream in a cortical pathway, therefore, we would expect fewer neurons to covary their responses under similar stimulus conditions, a view that probably demands reduction, if not outright elimination, of redundancy in the form of columnar organization. In fact, we would expect to see progressively less spike rate modulation at all, as rate modulation can only muddle a temporal code with spurious coincidences [88•,89]. Alternatively, if synaptic integration produces a truly random ISI, the neural code consists simply of modulations in spike rate. As any one neuron provides a poor estimate of the instantaneous spike rate, the cortex must use ensembles of neurons to represent the same information. This view demands a reiterated organization of redundant, column-like modules, even in higher cortical areas.

Clustering of neurons with similar response properties (redundancy) is a well-established principle in primary sensory and motor areas of the cortex, and is beginning to receive attention from investigators working on higher cortical areas as well. By analyzing patterns of connectivity revealed by local biocytin injections, Amir *et al.* [90•] found a patchy organization of horizontal connections reiterated in striate, extrastriate, and parietal cortex of the macaque monkey. Similar observations have been made in inferotemporal (IT) [91•], frontal and limbic cortex [92], suggesting common organizational principles that are consistent with a redundant coding strategy [93•]. Recent physiological data from IT cortex also support this point of view; nearby neurons, probably organized in the form of columns, appear to share preferences for similar features of visual objects [94,95] and faces [96] (but see [97•]).

Size of fundamental signaling units in cerebral cortex

If clusters of functionally similar neurons carry information in the form of noisy, redundant rates, how many neurons are needed to estimate firing rate precisely? Simple statistical considerations reveal that the instantaneous rate from an ensemble of 100 or so neurons can be estimated reliably within a single ISI[1]. We suggest that

[1] For example, the estimated spike rate from 100 neurons over any 10 ms epoch, each spiking at 100 impulses per second (ips) with random ISI, is 100 ips $\pm\sqrt{10}$. By contrast, one of the chief disadvantages of neural codes that rely on temporal patterns of spikes is that such patterns may take a long time to propagate. To take advantage of the information capacity rendered by an irregular ISI, the nervous system may have to wait a long time for critical spikes and intervals.

neuronal pools of this size may comprise the fundamental signaling units of cerebral cortex.

Interestingly, the existence of common noise within cortical columns suggests that pool sizes exceeding 100 neurons confer little or no signaling advantage. The noisy spike rates of adjacent cortical neurons elicited by repeated presentations of a particular stimulus are not independent, but covary weakly with an average correlation coefficient of roughly 0.12 [97•,98]. Correlated noise (presumably arising from common input) shared by all members of a neuronal pool places fundamental limits on signaling power because the common noise cannot be eliminated by averaging among neurons within the pool. Monte Carlo simulations indicate that the signaling advantage gained by averaging asymptotes at roughly 100 neurons [17,98,99], further supporting the notion that ensembles of this size may comprise the fundamental signaling units of cortex.

Objections to the random walk model and rate-coding hypothesis

The biophysical support is weak

This objection to our point of view is fair enough. The random walk model for generating variable ISIs depends critically on an approximate equality of excitatory and inhibitory influences on membrane voltage, but the actual state of affairs is simply unknown. We have cited fragmentary physiological evidence indicating that inhibition has a more substantial impact than suggested by morphology, but little direct evidence is available on the critical issues of single IPSP size, relative firing frequencies of excitatory and inhibitory neurons, and relative failure rates for EPSPs and IPSPs. We note, however, that this caveat does not argue against the random walk model (and, by extension, the rate-coding hypothesis), but rather clarifies the type of biophysical data that will ultimately permit a truly informed choice of models.

Reliable temporal spike patterns exist in cortex

Abeles and colleagues [88•,89] have demonstrated repeating temporal patterns of spike discharge among ensembles of neurons in frontal cortex. In visual cortex, synchronous patterns of discharge have been observed in anesthetized and awake animals under a variety of conditions (see [10] for review). If the ISI is truly random, then these observations must be attributed to co-modulation of spike rate, imposed by some common input such as the thalamus. They do not necessitate coincidence detection; nor do they imply a precise temporal code.

In a somewhat different vein, Optican, Richmond and colleagues [8,9,100] have shown that temporal patterns of spikes convey more information about visual stimuli than the spike rate does in single neurons of areas V1 and IT. It is unclear whether the type of temporal encoding proposed by these investigators would necessitate a deterministic ISI. Modulation of the average response rate might suffice. Interestingly, Tovee *et al.* [101••] have shown that brief (20–50 ms) estimates of rate from IT neurons convey nearly as much information as the 300–400 ms components of a putative temporal code.

The acid test for any theory of the neural code is to establish a connection to behavior. In cortical areas MT and MST, fluctuations in spike rate have been shown to correlate with an animal's decisions in a motion discrimination task [99,102,103••]. Examples abound in the motor cortex for a connection between neural discharge rate and behavior (see [104]). To our knowledge, however, there is no evidence that a temporal pattern of activity (beyond rate modulating) in cortex has any consequence for behavior.

Spike timing is critical in some neural systems

Clearly, some neural structures convey information in the timing of successive spikes. The best examples are probably from brainstem auditory pathways, where spikes may be time-locked to peripheral events (e.g. primary-like neurons of the cochlear nucleus [105]). So long as synaptic contacts are multiple and, hence, secure, spikes can propagate reliably from one neuron to the next, preserving a temporal code. In cortex, however, we argue that many inputs affect the neuron, and a single presynaptic spike has little bearing on the exact timing of a postsynaptic spike. This is not true, however, if certain inputs have privileged contacts. For example, a single spike from thalamus may induce a time-locked spike in visual cortex consistent with monosynaptic excitation ([106]; J Alonso, R Reid, T Wiesel, *Soc Neurosci Abstr* 1993, 18:425). Within cortex, such time-locked spikes are exceptional [38,39,107,108•].

Spike rates may be time-locked to stimulus change

The inability to preserve information about the time of a spike would seem to imply that the discharge rate cannot modulate in a time-locked fashion to external inputs. This is not true. In a random walk mechanism, the discharge rate follows the activity of inputs; but given a base rate, the time to the next spike is (nearly) random. Consider the spike train recorded from an MT neuron responding to successive presentations of an identical pattern of moving dots (Fig. 2). The average discharge rate fluctuates in a time-locked fashion to the moving dot display. Yet the exact time of any one spike within any 10–20 ms epoch is nearly random from trial to trial. The neuron approximates a random (Poisson) point process with non-stationary rate. The variance of the spike count tallied for each trial actually exceeds the mean. Nevertheless, the average instantaneous discharge rate is consistent from trial to trial, as is apparent in the raster's vertical structure (Fig. 2a). Presumably, this rate maintains temporal fidelity with changes in the stimulus. If instead of successive trials, we imagine that the

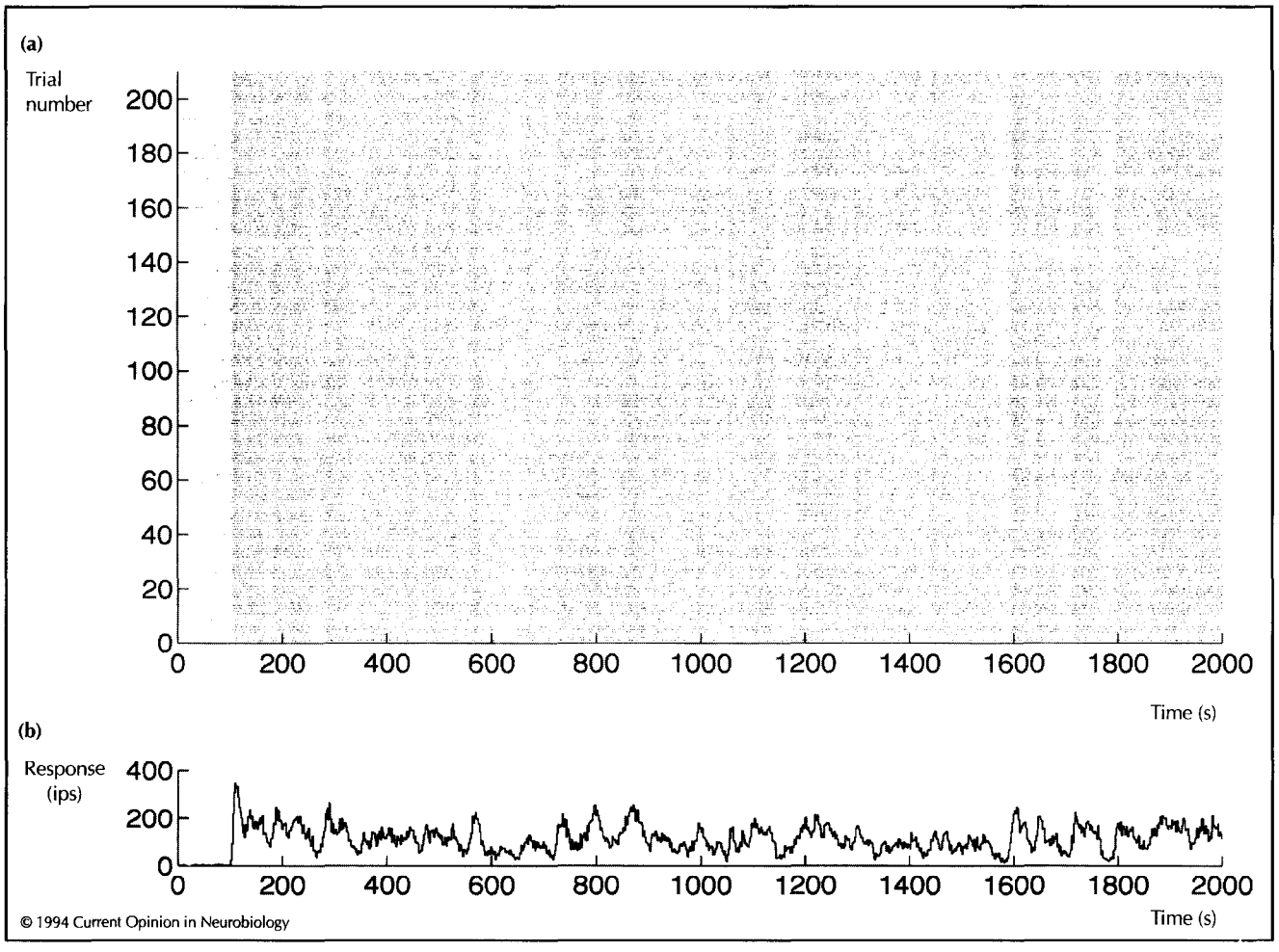

Fig. 2. Responses of a neuron from area MT of monkey extrastriate visual cortex to 210 presentations of an identical pattern of dynamic random dots. **(a)** Response rasters show time of individual spikes on each trial (row). The response varies systematically during each two second trial, producing an appearance of vertical contours throughout the raster. **(b)** Peristimulus time histogram. The instantaneous spike rate is computed in 2 ms bins. The response rate undergoes fluctuations over coarse and fine time scales. Power spectral density analysis of this waveform reveals reliable changes in instantaneous rate at up to 80–100 Hz. Although the instantaneous rate reflects changes in the visual stimulus, the exact timing of spikes is random. Each row in (a) provides a very noisy estimate of the waveform in (b). The spike trains have the characteristic of a non-homogeneous random (Poisson) point process, consistent with Fig. 1c.

raster rows represent the response from individual neurons, then the ensemble would be capable of transmitting changes in spike rate with an effective sampling rate of 5–10 ms. A more sophisticated analysis of this sort has been performed by Bialek and colleagues [11,109] on motion-sensing neurons in the fly.

Conclusions

This survey leads us to a tentative view of cortical information processing that unifies diverse experimental observations concerning synaptic physiology, neural coding and cortical organization. We argue that the biophysics of synaptic integration provides a critical key to understanding the nature of neural codes and how cortical circuitry is organized to propagate those codes. Individual cortical neurons receive a plethora of synaptic input, presumably to provide computational power. The neuron avoids saturation by balancing excitation and inhibition in a random walk along membrane potential, thus preserving a rate code that reflects its inputs. The neuron pays a price for this stratagem, however, adopting a (nearly) random ISI and thereby sacrificing a precise temporal code. The instantaneous spike rate is variable, analogous to a Poisson process, but can be represented more precisely by pooling the spike discharge from many neurons. This cries for redundancy in the neural code: multiple neurons must provide estimates of the same information. To achieve redundancy, however, neurons must receive some common input which, in turn, limits the accuracy of the rate code: pooling cannot average out correlated noise [17,99]. Signal-to-noise reaches asymptotic levels by the time 100 neurons are included in the pool; adding more neurons is futile. Thus, the fundamental signaling units of cortex may be pools on the order of 100 neurons in size — approximately the number of neurons in a cylindrical column

aligned with the dendritic field of one layer 5 pyramidal cell [110,111•]. On this view, pieces of cortex must exert influence over other pieces of cortex as small signaling units of redundant and weakly correlated neurons. As the fundamental motivation for this point of view rests ultimately in synaptic physiology, we see no reason that the same principle should not apply at any location in neocortex, where thousands of inputs influence a neuron's output.

A central implication of this point of view is that the organization of cortical connectivity should remain coarse. Downstream neurons are unlikely to draw input from a special neuron here and another one there, but instead probably receive redundant input from a pool (50–100) here and another pool there. If we are correct, then the search for information in temporal patterns, synchrony, and specially labeled spikes is unlikely to succeed. On the other hand, there is reason for optimism because the secrets of the brain's messages may be revealed by the analysis of single neurons acting in concert with others of similar ilk. Thus, the activity of single neurons may be connected to behavior by virtue of redundancy, raising hopes that probing the brain with tungsten will continue to yield important knowledge.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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This theoretical paper makes two important contributions to our knowledge about neural signals. The authors analyzed single unit data from monkey visual cortex and found that ISIs are highly irregular. This is a tricky analysis and the authors perform it commendably. The bulk of the paper focuses on models of synaptic integration. The authors conclude that neurons cannot behave as integrate-and-fire devices, as is classically thought, but that they act as coincidence detectors. We believe they have underestimated the importance of inhibition (see text).

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