Spike timing in the mammalian visual system

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Evidence is accumulating for the existence of mechanisms that create and detect synchrony among action potentials on short time scales both within and between neurons. Progress is most rapid in the retina, the lateral geniculate nucleus, and cortical slices, where signal flow is better understood or more manipulable. The debate over the functional relevance of spike timing in cortex has gained substance from new computational models but remains unresolved.

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Abbreviations

CCG	cross-correlogram
dLGN	dorsal LGN
EPSP	excitatory postsynaptic potential
IPSP	inhibitory postsynaptic potential
LGN	lateral geniculate nucleus
MT	middle temporal visual area
RF	receptive field
RGC	retinal ganglion cell
V1	primary visual cortex
V2	secondary visual cortex

Introduction

Spike timing is important because it can reveal the functional architecture from which it arises, and it places fundamental limits on the information that neurons convey about the stimulus [1], therefore limiting what we can perceive. Because we still do not know how a set of presynaptic spike trains interacts with the sophisticated machinery within the dendrites and soma of a neuron to yield an output spike train [2], it would be unwise to dismiss the potentially rich source of information available in spike timing. This review briefly highlights some of the studies on spike timing published during 1998 and early 1999, covering synchrony in the retina, the dorsal lateral geniculate nucleus (dLGN), and visual cortex, stimulus-locked modulation in the cortex, response latency, refractory periods and bursting, temporal coding schemes, and intracellular studies that bear on coincidence detection. The retina is discussed first, followed by the LGN and cortex. At each level, spike timing is considered in terms of the information it carries about the stimulus and evidence for mechanisms to read out that information. Figure 1, which is referred to throughout the text, provides a summary of recent findings and allows comparison of time scales for the diverse set of measurements of spike timing covered here.

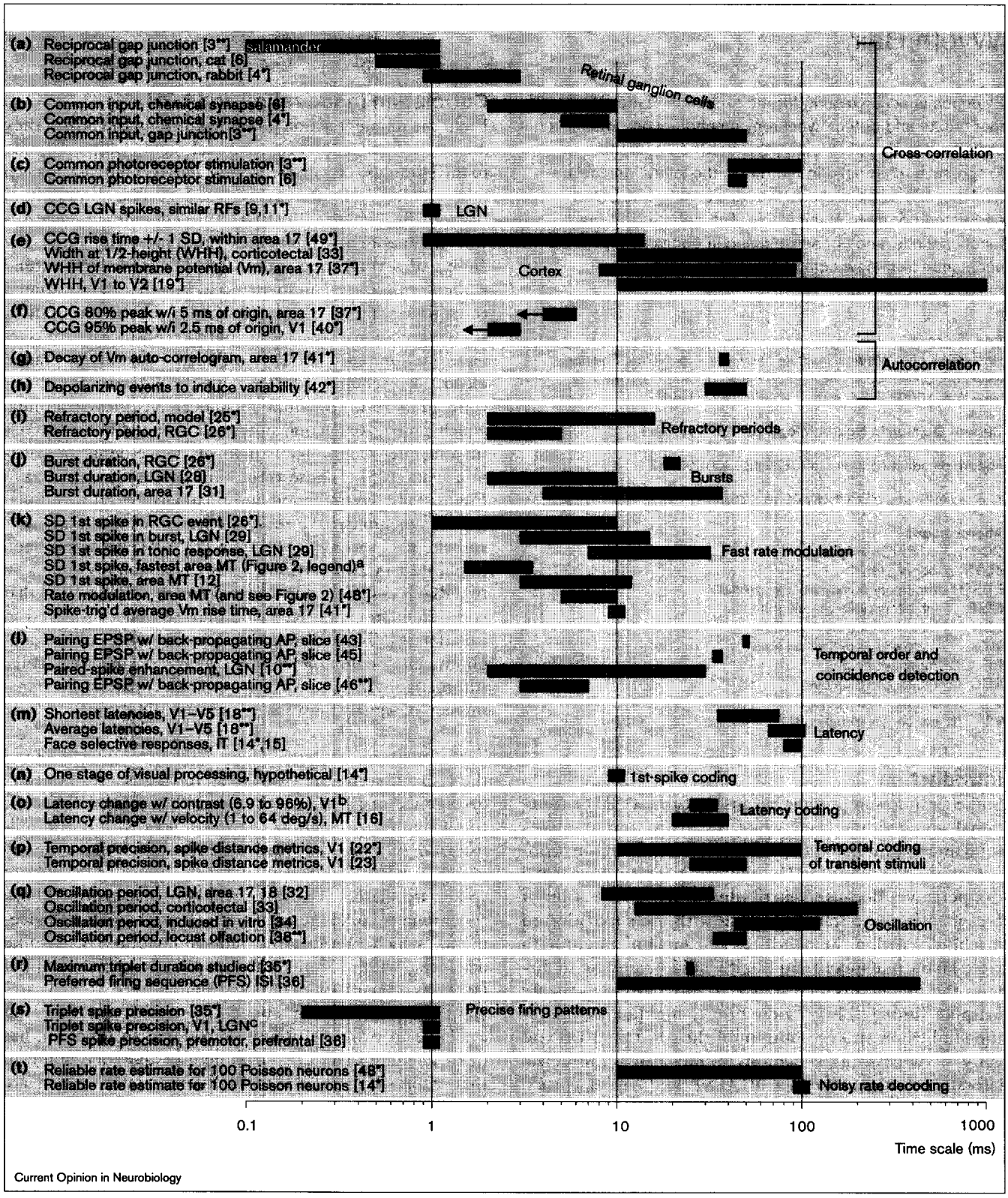
Correlation in the retina and LGN

From the moment action potentials arise in the retina, they are intertwined in precise temporal relationships not only to the stimulus (i.e. photoreceptor activity) but also to each other ([3••,4•,5,6]; for a review, see [7]). The outputs from the retinal ganglion cells (RGCs) are not random processes with independently modulated firing rates, but show synchrony at several time scales. Recent results [3••] extend earlier work in cat (summarized in [6]) that demonstrated three time scales of correlated firing in retinal output: first, slow correlation driven from photoreceptor activity; second, medium correlation resulting from common graded electrical or chemical [4•] synaptic input; and third, fast correlation resulting from reciprocal electrical coupling, which propagates action potentials to neighboring RGCs (in a manner that probably involves active dendritic backpropagation [5]). These three time scales are depicted in Figure 1a–c. Examination and pharmacological manipulation of synchrony have revealed properties of the neurons and circuits in which it was found [3••,4•], and it has been implicated in two possible roles. Synchronous spikes in two RGCs could encode a spatial receptive field (RF) that is different from the RFs of either neuron considered in isolation [8]. This RF might reflect properties of the ganglion cells' common inputs, such as amacrine cells. Alternatively, synchrony may serve to enhance the transmission of signals for weak visual stimuli [4•,8].

Tight synchrony is established again at the next stage of the visual system, the LGN (Figure 1d), as a result of the divergence of ganglion cell axons [9]. Target LGN cells fire a significant fraction of their spikes within one millisecond of those of nearby neurons that have nearly identical RFs. Within one such pair, typically 20–40% of spikes are shared. It now seems likely that many of those synchronous spikes result from a 'paired spike enhancement', which elevates the relay probability of a spike occurring within 30 ms after a spike in the same fiber [10••], and the capacity of the synchronous spikes to carry additional information about the visual stimulus, not available in two spike trains considered in isolation, has been documented [11•]. It is conceivable that some of that information relates to high firing rates, which are lowered by relay failure but re-coded as synchrony by paired spike enhancement. It was previously shown that the tight LGN synchrony attributable to RGC divergence has a supra-linear effect on cortical target neurons [9], providing evidence that this information can be read out. For more details on the implications of synchrony in the retina and LGN, see [7].

Spike timing in visual cortex

Theories of temporal coding in the cortex are more diverse, and the discussion below will begin with studies



of temporal structure that is locked to and driven by the visual stimulus and will progress, with some exceptions, to those that analyze timing that is shaped largely by the intrinsic dynamics of cortical neurons and networks.

The striking ability of dynamic visual stimuli to entrain cortical responses, commonly observed as spikes locking to video displays at 60 Hz and occasionally up to 100 Hz, has been used as a tool to study the limitations of information

Figure 1 legend

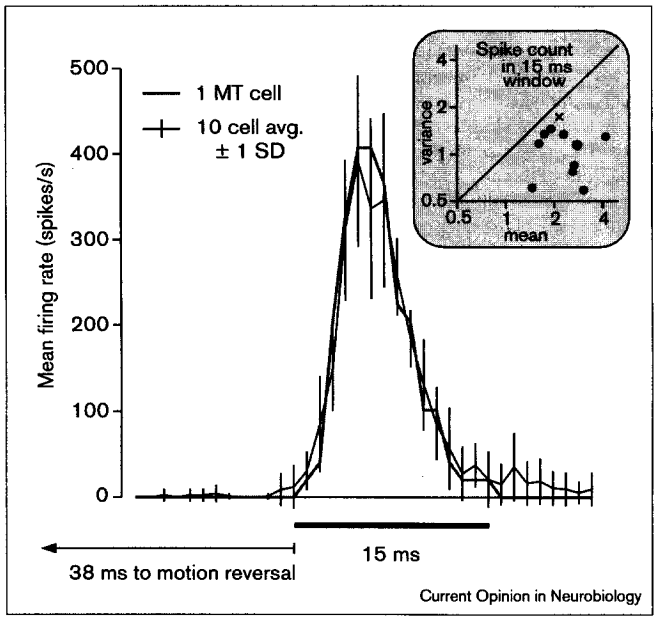
Time scales for spike timing measurements and putative coding schemes in the visual system. There are several caveats. These values (horizontal bars and descriptions on left) were extracted from papers discussed in this review. Most were derived from data in those papers; some were merely cited. The boundaries are not hard, and bar centers deserve more attention than boundaries. These data, from a limited set of recent studies, may represent neither the most accurate nor the most complete measurements available; however, most are typical. Several main trends are apparent. **(a–f)** The time scale of spike train cross-correlation varies widely in the visual system. For tight correlation, circuits are known and involve direct coupling between cells (a,e) or direct common input (d). When the common signal is several synapses away, correlation is broader: (c) and some of (e). Peaks in cortex, even when broad, are often centered to an accuracy of several milliseconds (f). Refractory periods (i), bursts (j), and fast stimulus-locked rate changes (k) are on the order of milliseconds. **(l)** This is also the time scale on which intracellular *in vitro* studies have identified mechanisms sensitive to the temporal structure of neuronal inputs. **(n–t)** Time scales for several coding schemes, other than synchrony, which use spike timing (n–s) or spike rate (t) to carry information in the visual system are shown. For these schemes, with the exception of (n), reading the code takes on the order of tens of milliseconds. [a]W Bair, JR Cavanaugh, JA Movshon, *Soc Neurosci Abstr* 1998, 24:1745; [b]MC Wiener, MW Oram, BJ Richmond, *Soc Neurosci Abstr* 1998, 24:1258; [c]MW Oram, R Lestienne, MC Wiener, BJ Richmond, *Soc Neurosci Abstr* 1998, 24:1258.
AP, action potential; ISI, inter-spike interval; SD, standard deviation.

transmission in the motion pathway [12] and to probe the temporal dynamics of direction selective neurons (W Bair, JR Cavanaugh, JA Movshon, *Soc Neurosci Abstr* 1998, 24:1745). Figure 2 shows responses of direction-selective cells in the middle temporal cortical area (MT/V5), which represent what is currently thought to be typical of the fastest stimulus-locked modulation of firing rate that can be achieved in the visual cortex — on the order of several to 10 ms. This time scale is consistent with related measurements from other studies of the visual system, as shown in Figure 1k. The observation that sudden changes in the visual scene elicit precisely timed, strong responses that are often more reliable than a Poisson process (see inset in Figure 2; but also see [13•] for a perspective on the fly's visual system) supports speculation that latency is an important form of temporal coding in the visual system [14•,15]. Response latency encodes stimulus contrast independent of response strength in primary visual cortex (V1) (MC Wiener, MW Oram, BJ Richmond, *Soc Neurosci Abstr* 1998, 24:1258) and depends on the speed of a moving stimulus in direction selective neurons in areas V1 and MT ([16]; W Bair, JR Cavanaugh, JA Movshon, *Soc Neurosci Abstr* 1998, 34:1745). Latency codes usually rely on the transient nature of visual stimuli or saccades to provide a reference signal [14•,15].

Like synchrony in the retina or LGN, response latency not only carries information about the visual stimulus, but also sheds light on functional architecture. Latency measurements are being used to challenge the anatomically derived hierarchy of visual areas [17] on functional grounds. Absolute latencies for responses to similar stimuli across multiple visual areas [18••] and relative spike latencies detected in cross-correlations between V1 and V2 [19•] reveal that neurons assigned to different hierarchical levels are often activated simultaneously or in the wrong order. While latency equality does indicate a lack of functional hierarchy for at least the initial responses of the neurons under study with respect to the stimulus employed, latency differences cannot be used to infer functional hierarchy (i.e. serial connectivity). This is stressed in a study by Maunsell *et al.* [20•] that provides a compelling simulation of how increasing convergence of inputs can substantially shorten response latency. Their arguments, well suited to their study of the magno- and parvocellular processing streams in which differences exist in both latency and numbers of potential inputs, are correct in principle and await experimental validation.

Another recent set of studies by Victor, Purpura and colleagues [21,22•,23] on spike timing in visual cortex took an approach reminiscent of the work of Optican and Richmond [24]. They raised the familiar question of whether spike timing carries information that spike count does not, but their approach was based on a novel set of spike distance metrics [21]. The authors conclude that there is additional information in spike timing on the scale of 10–100 ms (Figure 1p) and argue that it is not all accounted for by temporal variation in mean firing rate [22•,23]. However, the spike distance metrics are by design sensitive to stimulus-locked modulation, and it is difficult to assess directly from these reports whether other features of spike timing carry information and what those features might be. New spike train metrics developed to determine whether a neuron's response belongs to a particular class of modulated renewal processes — which includes a Poisson process with a time-varying rate function — may provide insight into how temporal information is encoded in ways not captured by mean rate variations [25•]. This and another careful study by Berry and Meister [26•], which accounts for numerous trial-by-trial statistics of retinal ganglion cell spike trains, are significant steps towards deciding whether crucial information is lost when within-trial details of relative spike timing are washed away in the computation of mean firing rate envelopes. Their contribution lies in combining temporal analysis of neuronal data with simulations that begin to incorporate fundamental properties, such as refractory periods, which cellular biophysics impose on spike trains statistics. Finally, to the extent that studies of temporal coding [21,22•,23,24] boil down to an examination of variations in the stimulus-locked firing rate, they may be viewed partly as an alternative approach to studying the same phenomena that have led to the description of many cortical neurons as spatio-temporal filters. These two views have been linked in the past [27], but few studies of temporal coding

Figure 2



With what temporal resolution can visual stimuli modulate the firing rate of a cortical neuron? Mean instantaneous firing rate is plotted for one MT neuron (thick line; average of 46 trials) in response to a brief (10 ms) motion reversal (from null to preferred and back) of a drifting sinusoidal grating optimized for the classical receptive field. The average of similar plots for 10 MT neurons is shown by the thin line (plots aligned on half-rise points before averaging). The point of half-rise occurs on average 41 ms following the motion reversal. For these 10 neurons (the most responsive to motion reversals in a database of 39), the instantaneous firing rate was modulated from zero to maximum in about 5 ms, and the standard deviation of the first spike time ranged from 1.5–3.5 ms (mean 2.4 ms; see also [12]). The latter measurement is plotted in Figure 1k with similar measurements from other studies. The inset shows that the spike count during the 15 ms period indicated by the scale bar (main panel) was less variable than that of an inhomogeneous Poisson process (see also [26•]). Filled circles plot variance, σ^2, versus mean, μ, for the 10 MT cells (log axes). On average, σ^2/μ was 0.48 (SD = 0.22). The 'x' shows values for a Poisson process (modulated by the mean firing rate shown in the main panel, thin line) that was discretized to 1 ms precision. Data recorded extracellularly in anesthetized monkeys (W Bair, JR Cavanaugh, JA Movshon, unpublished data).

have been able, or willing, to bridge the gap between new, highly sophisticated response metrics and more classical characterizations of temporal response properties.

Bursts of action potentials are one component of spike trains that could encode information in a non-stimulus-locked manner, as suggested above. Studies have directly addressed this putative role for bursts and have sought clues to how bursts are decoded postsynaptically. In the LGN relay cells, known for having explicit burst and tonic firing modes, an information theoretic analysis revealed that tonic spikes and bursts encoded very similar information about the stimulus. However, whereas a tonic spike encoded twice as much information as a burst spike, bursts taken as unitary events encoded three times as much information as a tonic spike [28]. The additional information conveyed by bursts may have to do with their response latency being less variable than that for tonic spikes [29]. In cortex, bursts are known to provide information about particular stimulus parameters such as orientation (e.g. [30]). One study measured the effectiveness of cortical bursts and found that bursts compared to single spikes are associated, on average, with double the response in nearby neurons whose cross-correlograms (CCGs) show an asymmetry consistent with a serial connection [31]. But, spikes were individually less effective in bursts than in isolation. Paired spike enhancement in LGN neurons is strongest at about 3–5 ms [10••], implying that a short burst of spikes would be more effective than predicted by linear summation. This suggests that bursts from the retina are interpreted differently from those within cortex. However, the cortical study [31] relied on shifted CCG peaks to infer serial connection, which is problematic as noted above with respect to response latency [20•].

The studies discussed so far have dealt largely with stimulus-locked modulation (Figure 1k,o and probably p) or with spike timing on relatively short time scales (Figure 1i–k), but some of the most striking forms of temporal structure and putative temporal codes are not stimulus locked and involve longer times. These include synchronized oscillations [32–34], repeating spike triplets [35•], and the 'precise firing sequences' related to synfire chains [36]. In the visual system, synchronized oscillations are still found to be prevalent by some [32] and not by others [19•,37•], whereas in other systems, the relevance of synchronized oscillations has been established [38••]. Recent accounts on solving the binding problem have relied more on synchrony (and firing rate enhancement) [39], even in the face of some compelling evidence against the idea [40•]. The theory that repeating spike triplets carry information independent of firing rate received support through the application of metrics that detect triplets in a manner nearly independent of firing rate, at least when applied to Poisson data [35•], but now some of those results are in question. It turns out that a statistical model that matches the experimentally observed variance in firing rate, which is typically greater than that for a Poisson process, can account for the excess number of triplets in LGN and V1 spike trains (MW Oram, R Lestienne, MC Wiener, BJ Richmond, *Soc Neurosci Abstr* 1998, 24:1258). With regard to precise firing sequences in frontal cortex, a recent study addressed criticism that these patterns might not have behavioral relevance by providing evidence for their correlation to behavior during visuomotor tasks [36]. The significance of these patterns of discharge remains uncertain for the visual system. Proposals for underlying circuitry (e.g. synfire chains in the case of precise firing sequences) typically involve networks of neurons and not just direct connections between two cells or the intrinsic dynamics of one cell, so verification is difficult. These temporal patterns, extending over tens to hundreds of milliseconds, are probably too long to be

codes that subserve rapid visual processing in the cortex [14•,15,22•,31]. Their time scales are plotted for comparison in Figure 1 q–s. The high precision of spikes in triplets (Figure 1s) seems out of place considering that such precision is otherwise achieved only where circuits are known to quickly propagate action potentials between directly coupled neurons (Figure 1a,d,e).

In spite of the evidence that visual stimuli can impose temporal patterns on spike trains, a large fraction of spike train variance is often not explained by the stimulus. To probe the local origin of the unexplained variance, recent studies have measured [37•,41•] and manipulated [34,42•] the intracellular potential in cortical neurons. Large, spontaneous fluctuations in membrane potential on the scale of tens to hundreds of milliseconds were found in, and were correlated between, visual cortical neurons [37•]. In single neurons in slice, injecting current that simulated Poisson EPSPs and IPSPs yielded spike trains that were substantially less variable than those observed *in vivo*, whereas injecting current that simulated large, synchronous barrages of EPSPs produced spike trains that matched *in vivo* variability [42•]. Through arguments based on the correlation of membrane potential variations within and between neurons, these studies all conclude that highly structured and synchronous input is responsible for the statistics of output spike trains [34,37•,41•,42•]. The consistency of the time scales cited in these studies is apparent in Figure 1e (third bar),g,h.

Mechanisms to detect synchrony

What mechanisms exist to read out the timing of spikes? The supra-linear accumulation of Ca^{2+} in dendritic spines, which depends on the relative timing of pre- and postsynaptic inputs on the scale of tens of milliseconds [43,44] or less [45], is one candidate. More compelling may be the account of a mechanism by which synchrony across cortical laminae on the scale of milliseconds can alter the discharge of layer V pyramidal neurons in a manner that greatly amplifies the impact of weak dendritic inputs [46••]. The applicability of these mechanisms *in vivo* and for temporal coding is speculative [2,47], but the time scales involved, plotted in Figure 1l, are consistent with most of the range over which other mechanisms produce and alter temporal structure in spike trains.

Two contrasting views of spike timing

In light of results from an increasing number of spike timing studies in the visual system, it is interesting to examine two recent and quite opposed views on the use of spike timing for visual processing ([15,48•]; see also [14•]). One model is built around the conviction that spike timing reflects noise and mean firing rate alone conveys information [48•]. It successfully simulates a visual system that integrates noisy spike trains to produce equally noisy spike trains across a realistic range of mean firing rates. The other model proposes a code in which only the first spike matters — information is encoded in the rank order of discharge — and it has been implemented as a feedforward network for detecting facial features [15]. The former model grew out of experiments that measured spike trains for two seconds while monkeys made near-threshold discriminations based on signal-carrying pulses embedded like raindrops (i.e. lacking greater spatial or temporal structure) among similar random noise. The latter model was motivated by observations of short response latencies (e.g. 100 ms) for neurons eight levels into the cortical hierarchy responding selectively to high-contrast, highly structured images (e.g. faces and facial features). These models, intentionally distilled by their architects, do not begin to account for the variety of temporal structure present in the visual system, but each may contain an element of truth regarding the interpretation of action potentials when the outputs of the visual system are orchestrated for the tasks from which the models were derived.

The time scales of these coding schemes (Figure 1n and t) are compared to others (Figure 1p–s). Given the tens of milliseconds required for full and literal implementations of most of the codes, it is clear that, while they may be candidate codes for higher level neurons to tap into information in the visual system or could be used by a subset of neurons to slowly develop tuned responses, much of the communication and processing of information in the retina, LGN, and visual cortex must go on without them.

Conclusions

Studies of spike timing are beginning to reflect a gradual shift in emphasis from the soma to the dendrites and from single neurons to ensembles. It is likely that greater reward will come from examining the spatio-temporal distributions of presynaptic spikes across a dendritic arbor during brief epochs than has resulted from the scrutiny of statistical patterns within single spike trains over the course of seconds. Insight concerning functional circuitry is currently arising from studies that focus on short time scales and direct connections [3••,10••,46••,49•]. If the study of spike timing in this context does not ultimately reveal one fundamental insight into the 'neural code', it should at least lead us closer to a circuit-level understanding of the great diversity of processes that subserve visual perception.

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Membrane voltage fluctuations measured right before visual stimulus onset are correlated with those following stimulus onset and with the evoked spike count. Variations in membrane potential, changes in spike threshold, and stimulus dependent high-frequency inputs all contribute to spike variability. This paper is interesting to read in combination with [37•].

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By injecting current into neocortical neurons in slice, the authors attempt to resolve the question of whether random EPSPs and IPSPs adding passively can account for the ubiquitous observations of high variability in cortex *in vivo*. The results suggest that some structure to the input is required.

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46. Larkum ME, Zhu JJ, Sakmann B: **A new cellular mechanism for**
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An appropriately timed combination of excitation in the apical dendrites (3–7 ms delay for optimality) and a back-propagating action potential from the soma can induce a burst of 2–3 spikes at the soma in both regularly spiking and bursting layer V pyramidal neurons. The mechanism relies on dendritic Ca^{2+} spike initiation and is highly sensitive to inhibitory inputs, which can shut it off for hundreds of milliseconds.

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In this tale, the champion of spike timing, coincidence detection, starved for correlated inputs and deprived of its arsenal of intrinsic neuronal dynamics, dies an untimely death. A bleak cortex populated by undifferentiated neurons is then over-run by the 'high-input regime' in which the forces of excitation and inhibition clash to produce spike trains where noise is actually noise and signal is carried by mean firing rate. When the regime runs into trouble propagating information rapidly, it marshals ensembles of 100 redundant neurons that revive correlated input just before the end. Compare this view to that of [14•,15,42•].

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The latency and width of cross-correlogram peaks is consistent with functional connectivity from layer IV simple cells to layer II and III complex cells. The brief time scale of these peaks is plotted in Figure 1e (top bar).