Research Focus

Spike times make sense

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Many behavioral responses are completed too quickly for the underlying sensory processes to rely on estimation of neural firing rates over extended time windows. Theoretically, first-spike times could underlie such rapid responses, but direct evidence has been lacking. Such evidence has now been uncovered in the human somatosensory system. We discuss these findings and their potential generalization to other sensory modalities, and we consider some future challenges for the neuroscientific community.

Choosing your holds as you climb. Heeding predator cries in the wild. Recognizing friend from foe in a fast-paced popular video game. These are examples of sensorimotor tasks that appear to be performed too quickly, given the architecture of the corresponding sensory systems, to depend on the most widely assumed neural code: the firing rate of neurons, estimated over extended populations and/or time windows. The idea that information might be encoded in the precise timing of spikes, rather than in neuronal firing rates, is one that has attracted increasing attention over the past 15 years or so. But a large part of this effort has concentrated on the role of synchronous discharges [1]. Another option, suggested by one of us in 1990, is that under strong temporal constraints neurons could perform with only one spike per neuron [2], using time-to-first-spike as an information carrier (Figure 1). Although this idea was supported by theoretical studies [3], it received scarce consideration, and meager substantiation in experimental investigations. Now Johansson and Birznieks [4], consistent with previous work in rats [5], report the first direct evidence in humans of first-spike relative time coding at the population level in a sensory system, suggesting after all that we might have been, indeed, 'right on time'. How can these new findings be generalized to other sensory systems? What are the key features to look for in neuronal data? And what should keep us all busy for the 15 years to come?

First-spike times code fingertip events

To investigate neuronal coding in the human somatosensory system, Johansson and Birznieks [4] recorded from different afferents (FA-I, SA-I and SA-II) in the median nerve within the upper arm while they varied the direction of force and the shape of a stimulus applied to the fingertip. But instead of using the mean firing rate as a dependent variable, they focused on spike timing relative to stimulus onset. They found that the stimulus direction

systematically influenced first-spike latency for all these afferent types. First-spike time could even yield a reliable directional tuning curve, similar to those usually obtained with firing rates. However, for two of the afferent types (FA-I and SA-I), the direction preference obtained with first-spike latency did not correspond to that estimated with firing rates (derived from the first interspike interval). Spike time and mean firing rate codes can thus be used independently to represent different aspects of a stimulus variable.

Rank-order coding at the population level

Because recordings were not obtained simultaneously across the various afferents, it is difficult to understand how this first-spike time information is used at the population level. One possibility would be to rely on the specific order of firing among the afferents (a 'rank order' or 'recruitment order' code). Because first-spike latency jitter from trial to trial was <1 ms (median value) in all cases (i.e. much smaller than the variance in latency between afferents of one type), this code is potentially highly reliable. Using clever Monte Carlo simulations, Johansson and Birznieks showed that the rank of activation of the various afferents in one simulated trial could lead to correct discrimination within 40, 60 or 70 ms of stimulus onset (for FA-I, SA-I and SA-II, respectively). Firing rates needed on average 10–20 ms longer. Similar
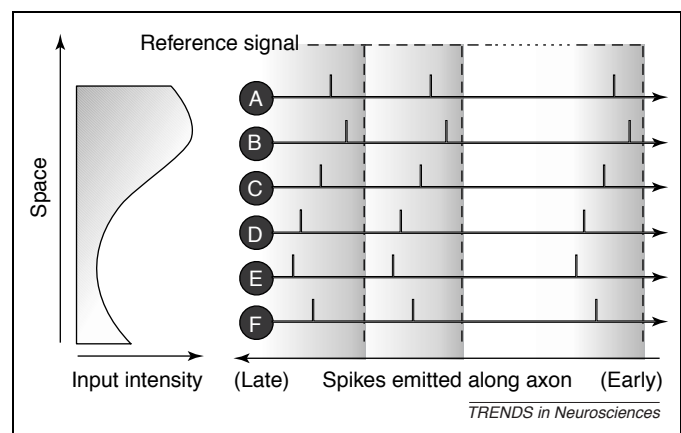

Figure 1. Neural coding using spike-firing times. An input activation pattern (left) is converted into a spatiotemporal spike sequence (right): the most activated of the six neurons (A–F) tend to fire with shorter latencies. Spikes are represented as tick marks along the corresponding axon (spikes emitted earlier have traveled farther from the cell body, towards the right). The input does not necessarily reflect stimulus intensity or contrast, but rather any 'feature' to which the neuronal population is sensitive, including temporally defined features. The brain can decode this spike sequence using a particular external (e.g. stimulus onset) or internal (e.g. local field potential oscillation) reference signal. Additionally (but non-compulsorily), the reference signal and spike sequence can be refreshed cyclically: this is illustrated on the figure by two repetitions of the output spike sequence.

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observations were made for the ability to discriminate surface shape (flat versus curved).

Importantly, correct discrimination could be obtained when only a small percentage of the afferents had been recruited. For the fastest afferent type (FA-I), only 6 ms of integration was needed after the first spike within the population. Although this is already quite impressive, note also that the Monte Carlo simulation tends to underestimate the reliability of the rank-order coding, because it assumes that latency jitter from trial to trial is independent among the various afferents. Clearly, if first-spike times tend to vary together on each trial (which can be decided only on the basis of simultaneous recordings from multiple afferents), then the rank-order code could prove to be even more powerful.

Johansson and Birznieks [4] do not show that first-spike time rank-order information is actually used by the somatosensory cortex, nor even that it reaches there. They simply show that it is available within a time frame compatible with known behavioral constraints. And this makes it one of the few serious candidate codes to date. Two questions remain. What is the evidence for similar coding schemes in other systems? And how might this information be interpreted by upstream neurons?

Origins of spike asynchrony and the need for reference signals

First-spike time differences across neurons ('spike asynchrony') arise in neuronal systems in two non-exclusive situations (not counting stochastic effects in spike generation processes): either because of stimulus dynamics (different receptors activated at different times), as in visual motion processing [6,7], or because of differences in stimulus features (because the time to threshold directly reflects feature strength and optimality [2,8–10] (Figure 1). At the next level, however, decoding spike asynchrony is a comparable problem in these situations.

Talking about spike times – and in particular first-spike times – makes sense only with respect to a reference event: the first spike after stimulus onset, or after a particular event in a dynamic stimulus. It is almost ubiquitous in sensory systems that 'first spikes' following clearly defined stimulus events (e.g. onset) are much more temporally reliable than the following ones [5–7,9–11]. But this might be due, in part, to a form of experimenter bias: a spike that would be precisely timed with respect to an internal event to which the experimenter does not have access will be considered, by default, as unreliable. In what follows, we briefly review spike-time coding schemes and possible internal and external reference signals in various sensory systems.

Reading out spike asynchrony: internal and external reference signals

In laboratory situations, stimulus onset is generally clearly defined and can serve as an obvious reference signal (as in the study by Johansson and Birznieks [4]), but it requires further assumptions to be used explicitly: whereas the experimenter knows precisely when a stimulus is turned on, the subject still has to acquire this information from the sensory input itself. For example, periods of neuronal silence preceding stimulus onset, together with synaptic adaptation properties, might allow neuronal populations to reset between successive, well-separated stimuli.

A further difficulty arises in natural situations where stimulus onset is not necessarily well defined. A more robust alternative in this case might be to use relative spike-firing times – that is, to exploit other spike times as the reference signal. Numerous studies in the past decade have focused on situations where spikes occur in concert among a subset of neurons within a reasonably short delay [1]. In theory, synchronous firing can be considered a special case of relative spike-time coding. In general, a particular time difference between spikes from two different neurons can be interpreted as valuable information regarding the features encoded by these neurons [12]. This is a well-known coding strategy in auditory cortex [10]. In practice, this is revealed as a phase advance in cross-correlograms from simultaneously recorded cells. As suggested by Johansson and Birznieks, decoding this information might be implemented by delay lines feeding into coincidence detectors, although less costly alternatives exist [13].

Using relative spike times can avoid the problem of an absolute reference signal, but there remains the difficulty of resetting the system during a continuous train of stimulation. Simple integrate-and-fire neurons cannot do this without further assumptions. An internal signal shared by at least a local neuronal population –for example local field potential oscillations at a particular frequency [14] – can circumvent this reset problem, allowing the population to fire only within particular phases and shutting down all activity at other phases. In the olfactory system of locusts, a barrage of inhibition from a structure called the lateral horn, arriving in the mushroom body shortly after each wave of excitation, acts together with intrinsic properties and oscillatory synchronization to limit odor representations to a particular temporal window, which is refreshed cyclically [15]. A similar fast inhibition creates a sharp 'window of excitability' in rat barrel cortex [16], where whisker deflection patterns are likely to be encoded by first-spike firing times [5]. Likewise, the location of a rat within its environment is reflected in the precise phase relationship of spikes emitted by 'place' cells with respect to a hippocampal theta oscillation [17,18].

Finally, an external, periodic sampling or 'exploratory' signal could also play the role of a temporal reference for spike-time codes. An example is the periodic whisking movement in rats, which has been linked with oscillations in somatosensory cortex (although the correspondence is far from direct [19]). Similarly, saccades or microsaccades might play an equivalent role in vision [20,21], sniffing in smell, and so on. Such exploratory behavior, parsing the input stream into discrete events, would turn each successive sample into a new stimulus with its own 'onset' time, followed by its proper sequence of 'first spikes'…In other words, this closes the loop, and brings us back to the well-known laboratory conditions.

Table 1. Recent experimental evidence for precise spike-time coding in various neuronal systems, with postulated reference signals[a]

System	Preparation	Recording site	Coding	Information	Reference signal	Refs
Somatosensory	Human	Peripheral nerve fibers	First-spike time	Direction of force, surface shape	Stimulus onset	[4]
	Rat[b]	Barrel cortex	First-spike time (inhibition barrage)	Stimulus location	Stimulus onset	[5,16]
Olfactory	Locust	Mushroom body	Sparse and/or binary, phase-locked (inhibition barrage)	Odor identity	20–30 Hz oscillation	[15]
Auditory	Marmoset	Auditory cortex	Spike time	Auditory event (when)	Stimulus transients	[22]
	Cat[b]	Auditory cortex	First-spike time	Peak pressure	Stimulus onset	[10]
	Marmoset[b]	Auditory cortex	Relative spike time	Auditory features (what)	Other spikes	[23]
	Rat[b]	Auditory cortex	First-spike time (binary)	Tone frequency	Stimulus onset	[24]
Visual	Macaque monkey, fly and salamander	MT, H1 and retina	Precise timing	Visual event (when)	Stimulus onset and transients	[6,7,11]
	Macaque monkey[b]	V1	Precise timing	Visual features (what): contrast, orientation	Stimulus onset	[8,9]
	Cat[b]	V1	Phase and/or latency shift	Line orientation	Other spikes and/or LFP gamma oscillation	[12,25]
	Macaque monkey	V1	Bursts	Line orientation	Microsaccades	[21]
Hippocampus	Rat[b]	CA1 and CA3	Phase	Place	Theta oscillation	[17,18]

[a]Abbreviations: CA1 and CA3, cornu ammonis fields 1 and 3; H1, horizontal-motion-sensitive neurons type 1; LFP, local field potential; MT, middle temporal area; V1, primary visual cortex.
[b]Some of the corresponding studies used anesthetized preparations.

How general is spike-time coding?

Over recent years, there has been a host of experimental discoveries in various systems – some of them mentioned here – that hint to the sophistication of neural codes employed in the brain (Table 1). Spike timing comes up almost systematically as a highly reliable coding dimension, at least insofar as the relevant reference signals are available to the experimenter. In our opinion, exploring these reference signals might turn out to be one important key to solving several outstanding problems in neuroscience. In addition to stimulus onset, internal oscillatory and external exploratory signals appear to be used as temporal reference for spike-time codes in the somatosensory, olfactory, auditory and visual systems, as well as in the hippocampus. In other words, spike times might turn out to be the general unit of sensory representation. One important question for the future will be to understand how (and whether) this information embedded in relative spike times at the population level can be decoded and used by the brain. Theoretical proposals exist [3,13] but further experimental evidence is badly needed. We hope that the study by Johansson and Birznieks will open the way for a massive awakening to these issues.

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