

## The enigma of the brain

Information may be coded in neuronal firing patterns in other ways than the instantaneous action-potential frequency; but proving that the brain uses a particular alternative code will not be easy.

Sometimes forward progress looks like backwards progress — recent work on the question of how the brain encodes information provides a good example of this. For many years, ever since the experiments of Lord Adrian two-thirds of a century ago, neurobiologists agreed that neurons communicate by means of a frequency (or rate) code, in which nerve impulse frequency is used to specify the variable in question — for example, light intensity. But recently a number of neurobiologists have, based on new observations, proposed that the frequency code is insufficient, and that other properties of spike (action-potential) trains are used to encode information. We used to think we understood the neural codes, but now we are not so sure.

The classical theory, in its modern formulation, holds that a given nerve cell transmits information only by the 'instantaneous' frequency of its nerve impulses, and that the output of one neuron can be interpreted without reference to the output of its neighbors. Neither the exact times at which the individual spikes occur, nor the detailed correlations between two spike trains, carries extra information that the brain uses. Of course, because of the graininess of a pulse code, one could have a high temporal resolution only with a large population of neurons, all of which were sending the same signal. Given a sufficiently large population, any time-varying signal can be encoded with arbitrary fidelity, permitting reconstruction (after the appropriate decoding step) with arbitrarily small error. One particularly simple encoding strategy is based on a population of 'integrate and fire' neurons, each of which integrates its inputs up to a threshold and then 'fires' a spike. It can be shown that the instantaneous firing frequency of a population of such neurons — the average obtained by dividing the number of spikes occurring in the population over some short interval by the number of neurons — is identical to the signal driving the population [1]. The frequency code works best with a population of neurons; but even an individual nerve cell can represent a rapidly fluctuating signal by its impulse frequency with high fidelity [2].

New observations on the behavior of central neurons have provided the impetus for re-examining the traditional view of neural coding. Although no particular proposal can be said to have strong support now, neuroscientists have recently been discussing the 'nature of the neural code' with great vigor (see [3,4], for example). Two broad classes of alternative theories have emerged: temporal-coding theories, and synchrony-coding theories. Both

posit that spikes should be regarded as more than merely expressions of some underlying instantaneous rate; they hold that individual spikes matter. The two proposals differ with respect to where the extra information is contained.

In a temporal code, information is contained in the timing of the spike train. The timing could be defined relative to some other spike produced by the same neuron, or to the stimulus, or — as Hopfield [5] has recently suggested — to the ticks of a local master clock. Hopfield's proposal offers perhaps the clearest instance of this class: in his theory, the relevant variable is the time a spike is produced by a neuron relative to the phase of an oscillatory wave present locally in a population of nerve cells. For example, intensity of an odor might be coded as the time of a spike relative to a local high frequency electroencephalogram (EEG), and a second spike in the same EEG cycle could represent a different variable, like some aspect of odor quality. A variant of this type of temporal code might represent information as the time at which spikes are produced relative to the onset of a stimulus, rather than using the ticks of a master clock; Richmond and Optican's [6] measurements of single neuron responses in the inferior temporal cortex of the monkey suggest that the elapsed time since the onset of the stimulus affects the encoding of visual form.

In its purest form, one that probably no one believes, a synchrony code would be one in which nerve impulse frequency was completely irrelevant: all information would be specified by the particular subset of neurons that, at some particular time, are producing nerve impulses synchronously. With time, this population would shift so that the temporal progression through the cortex of the subset of synchronously active neurons would constitute the time-changing representation. What would be represented in this way might be an image, or a sentence to be spoken, or a mathematical idea. In this extreme form of synchrony-coding theory, a neuron could fluctuate rapidly, according to which other neurons it synchronized with, from one representation to another, and it could generate any number of 'wasted' spikes that happened not to 'bind' it by synchrony to any neuronal 'assembly'. A less extreme form of synchrony-coding theory would hold that the neuronal representation consists simultaneously of the traditional frequency code and a synchrony code of the type just described. This latter view is closest to the one advocated by Singer and Gray [7]. Note that a synchrony code necessarily

involves neuronal populations, and will not work with a single nerve cell.

The main evidence for these proposals is found in experiments suggesting either a temporal precision in brain function that is higher than would be predicted from frequency coding, or a temporal modulation of the spike train that cannot be accounted for by temporal modulation of the stimulus. In considering these experiments, it is useful to distinguish two frames of reference relative to which the timing of a spike is defined. In the first, an extrinsic stimulus serves as the 'reference' event; in the second, it is the intrinsic activity of other neurons that provides the reference.

There are many examples of neuronal responses that are tightly locked to external stimuli. *In vitro*, spike transduction is essentially deterministic: current injected into a cortical neuron can reliably and repeatedly drive spikes with very little jitter [8]. In the intact cochlea, firing is phase-locked to better than one millisecond precision. The firing of cortical neurons can also show precise stimulus locking, as in the often-overlooked case of the onset-transient that follows a light flash. These results show that the possibility of a code based on timing precision is not precluded by the biophysical substrate.

There is also evidence for temporal modulation of the neuronal response to a static stimulus. Neurons in the monkey inferior temporal cortex respond to a one-second presentation of a complex spatial pattern with a time-varying spike rate, and the temporal details of the response depend on which shape in the ensemble is presented [6]. The temporal details of the response thus could be used to provide 'extra' information about the stimulus. While such modulation may at first appear surprising, a simple form of temporal modulation — adaptation — has been recognized since Adrian. The temporal coding suggested by these experiments may perhaps be seen as a generalization of the classical theory.

Examples of timing precision in one neuron relative to another are less abundant, perhaps because use of the multi-unit recording techniques required to detect them is still not in wide use. In the retina, the correlated activity in ganglion cells far exceeds that expected by stimulus

locking [9]. In the cortex, Abeles and colleagues [10] have found correlated firing between neurons in the monkey cortex. That is, a spike in one neuron sometimes reliably predicts the spike in another, to a temporal precision of one to three milliseconds; sometimes the second spike occurs more than a hundred milliseconds after the first. Similarly, Gray and Singer [7] have found synchronous firing that depends on the animal's attentional state.

There is thus ample evidence that, at least under some circumstances, the timing of spikes cannot be accounted for by a simple frequency code, and that there is potentially useful 'extra' information contained in spike trains. It is much harder to show that this extra information is actually used in the neural code. There are other interpretations for the experimental deviations from the instantaneous frequency hypothesis. They might arise, for example, as by-products of cortical architecture, the results of shared inputs. Alternatively, they might improve the performance of cortical processing, without actually providing an additional information channel. Designing experiments to distinguish these possibilities is emerging as the critical next step in this debate.

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