

- Acknowledgements**
This work was partly supported by a grant from the Health Research Council of New Zealand to W.C. Abraham and by a Fogarty Senior International Fellowship to M. Bear. We thank A. Cohen, A. Heynen and R. Sayer for helpful comments on earlier versions of the manuscript.
- 7 Larkman, A. *et al.* (1992) *Nature* 360, 70–73
 8 Izumi, Y., Clifford, D.B. and Zorumski, C.F. (1992) *Science* 257, 1273–1276
 9 Christie, B.R. and Abraham, W.C. (1992) *Neuron* 9, 79–84
 10 Christie, B.R., Stellwagen, D. and Abraham, W.C. (1995) *Hippocampus* 5, 52–59
 11 Christie, B.R., Abraham, W.C. and Bear, M.F. (1993) *Soc. Neurosci. Abstr.* 19, 1324
 12 Wagner, J.J. and Alger, B.E. (1995) *J. Neurosci.* 15, 1577–1586
 13 Bortolotto, Z.A. *et al.* (1994) *Nature* 368, 740–743
 14 Cohen, A.S., Kerr, D.S. and Abraham, W.C. (1995) *Soc. Neurosci. Abstr.* 21, 602
 15 Frey, U. *et al.* (1995) *Neuroscience* 67, 799–807
 16 Yang, X.-D. and Faber, D.S. (1991) *Proc. Natl Acad. Sci. USA* 88, 4299–4303
 17 Bashir, Z.I. and Collingridge, G.L. (1994) *Exp. Brain Res.* 100, 437–443
 18 Barrionuevo, G., Schottler, F. and Lynch, G. (1980) *Life Sci.* 27, 2385–2391
 19 Larson, J., Xiao, P. and Lynch, G. (1993) *Brain Res.* 600, 97–102
 20 Staubli, U. and Lynch, G. (1990) *Brain Res.* 513, 113–118
 21 Christie, B.R. and Abraham, W.C. (1992) *Synapse* 10, 1–6
 22 Davies, C.H. *et al.* (1991) *Nature* 349, 609–611
 23 Komatsu, Y. (1994) *J. Neurosci.* 14, 6488–6499
 24 Stelzer, A. *et al.* (1994) *Proc. Natl Acad. Sci. USA* 91, 3058–3062
 25 Ben-Ari, Y., Aniksztejn, L. and Bregestovski, P. (1992) *Trends Neurosci.* 15, 333–339
 26 Gold, J.I. and Bear, M.F. (1994) *Proc. Natl Acad. Sci. USA* 91, 3941–3945
 27 Lowenstein, D.H. *et al.* (1991) *Neuron* 6, 627–634
 28 Holmes, W.R. and Levy, W.B. (1990) *J. Neurophysiol.* 63, 1148–1168
 29 Zador, A., Koch, C. and Brown, T.H. (1980) *Proc. Natl Acad. Sci. USA* 87, 6718–6722
 30 Chard, P.S. *et al.* (1995) *Proc. Natl Acad. Sci. USA* 92, 5144–5148
 31 Bashir, Z.I. *et al.* (1991) *Nature* 349, 156–158
 32 Asztely, F., Wigström, H. and Gustafsson, B. (1992) *Eur. J. Neurosci.* 4, 681–690
 33 Clark, K.A. and Collingridge, G.L. (1995) *J. Physiol.* 482, 39–52
 34 Xie, X., Berger, T.W. and Barrionuevo, G. (1992) *J. Neurophysiol.* 67, 1009–1013
 35 Gean, P.-W. and Lin, J.-H. (1993) *Neurosci. Lett.* 158, 170–172
 36 Xiao, M.-Y., Wigström, H. and Gustafsson, B. (1994) *Eur. J. Neurosci.* 6, 1055–1057
 37 Hammond, C. *et al.* (1994) *Trends Neurosci.* 17, 497–508
 38 Selig, D.K. *et al.* (1995) *Neuron* 15, 417–426
 39 Bear, M.F. and Malenka, R.C. (1994) *Curr. Opin. Neurobiol.* 4, 389–399
 40 Lisman, J. (1994) *Trends Neurosci.* 17, 406–412
 41 Neve, R.L. and Bear, M.F. (1989) *Proc. Natl Acad. Sci. USA* 86, 4781–4784
 42 Hendry, S.C. and Kennedy, M.B. (1986) *Proc. Natl Acad. Sci. USA* 83, 1536–1540
 43 Mackler, S.A., Brooks, B.P. and Eberwine, J.H. (1992) *Neuron* 9, 539–548
 44 Thomas, K.L. *et al.* (1994) *Neuron* 13, 737–746
 45 Skene, J.H.P. (1990) *Neurosci. Res.* 13 (Suppl.), S112–S125
 46 Klee, C.B. (1991) *Neurochem. Res.* 16, 1059–1065
 47 Miller, S.G. and Kennedy, M.B. (1986) *Cell* 44, 861–870
 48 Hanson, P.I. *et al.* (1994) *Neuron* 12, 943–956
 49 Mayford, M. *et al.* (1995) *Cell* 81, 891–904
 50 Bear, M.F. (1995) *Neuron* 15, 1–4
 51 O'Connor, J.J., Rowan, M.J. and Anwyl, R. (1994) *Nature* 367, 557–559
 52 Liu, Y.B., Disterhoft, J.F. and Slater, N.T. (1993) *J. Neurophysiol.* 69, 1000–1004
 53 Dudek, S.M. and Bear, M.F. (1993) *J. Neurosci.* 13, 2910–2918

Integrator or coincidence detector? The role of the cortical neuron revisited

Peter König, Andreas K. Engel and Wolf Singer

Neurons can operate in two distinct ways, depending on the duration of the interval over which they effectively summate incoming synaptic potentials. If this interval is of the order of the mean interspike interval or longer, neurons act effectively as temporal integrators and transmit temporal patterns with only low reliability. If, by contrast, the integration interval is short compared to the interspike interval, neurons act essentially as coincidence detectors, relay preferentially synchronized input, and the temporal structure of their output is a direct function of the input pattern. Recently, interest in this distinction has been revived because experimental and theoretical results suggest that synchronous firing of neurons might play an important role for information processing in the cortex. Here, we argue that coincidence detection, rather than temporal integration, might be a prevalent operation mode of cortical neurons. We base our arguments on established biophysical properties of cortical neurons and on particular features of cortical dynamics.

Trends Neurosci. (1996) 19, 130–137

Peter König is at The Neurosciences Institute, 10640 John Jay Hopkins Drive, San Diego, CA 92121, USA, and Andreas K. Engel and Wolf Singer are at the Max-Planck-Institut für Hirnforschung, Deutschordenstr. 46, 60528 Frankfurt, Germany.

ALTHOUGH OUR KNOWLEDGE about the morphological and physiological features of cortical cells has increased substantially over the past 20 years, the basic operational mode of cortical neurons has remained controversial. The traditional view, which still predominates in cortical physiology and most neural network models, considers the cortical neuron as an integrate-and-fire device. This view was advocated first by Sherrington¹ and later supported by evidence obtained from the spinal cord². An alternative concept, proposed about a decade ago^{3,4}, suggests that

neurons in the cortex operate primarily as detectors for the temporal coincidence of synaptic inputs. This proposal is motivated by the assumption that correlated activity of neurons is of crucial importance for cortical processing and that synchrony might, in particular, contribute to solving the so-called binding problem, that is, the problem of integrating distributed information into coherent representational patterns^{3–8}. Such a temporal code can only be employed by the nervous system if neurons are sensitive to coincidence. Otherwise, it would be impossible to convey

information in the temporal structure of activity propagating through the cortical network.

Recently, it has been argued that under physiological conditions coincidence detection by cortical neurons is limited by the passive membrane time constant to a time scale of about 15 ms, and therefore the average firing rates are the relevant coding dimension to cortical processing⁹. In this article, we shall review arguments supporting the opposite view, that coincidence detection is physiologically plausible on a time scale of a few milliseconds and has considerable functional potential in cortical processing.

Two competing concepts

The criterion distinguishing coincidence detection from temporal integration is the relationship between the integration time (over which neurons can effectively summate synaptic potentials) and the mean interspike interval. If the integration time is short compared to the mean interspike interval, coincidence detection prevails, whereas if the reverse is true, temporal integration dominates. Obviously, there is no sharp boundary that would permit an unambiguous distinction between the two modes of operation. Coincidence detection requires the evaluation of temporal simultaneity on a millisecond timescale, whereas temporal integration allows for summation of synaptic events over extended intervals. Yet a crucial difference between both concepts is apparent in the conversion of postsynaptic potentials (PSPs) to actual output (Fig. 1). The temporal integration model implies that most, if not all, incoming PSPs contribute to the generation of action potentials. Coincidence detection, by contrast, implies that most PSPs do not actually contribute to the generation of output signals, and that the number of relevant PSPs is small compared to the total number of PSPs impinging on a neuron.

These two modes of operation differ fundamentally with respect to the processing dynamics that they support within complex neuronal networks. If temporal integration prevails, precise timing of afferent signals is irrelevant for processing because the response of neurons is hardly affected by the temporal patterning of inputs. On a longer timescale, variations of the afferent input are faithfully copied to the output. However, as differences in the temporal structure of the input are not translated into differences in the level of the output, no actual detection of coincidences takes place. All relevant information is encoded in average firing rates and, according to this

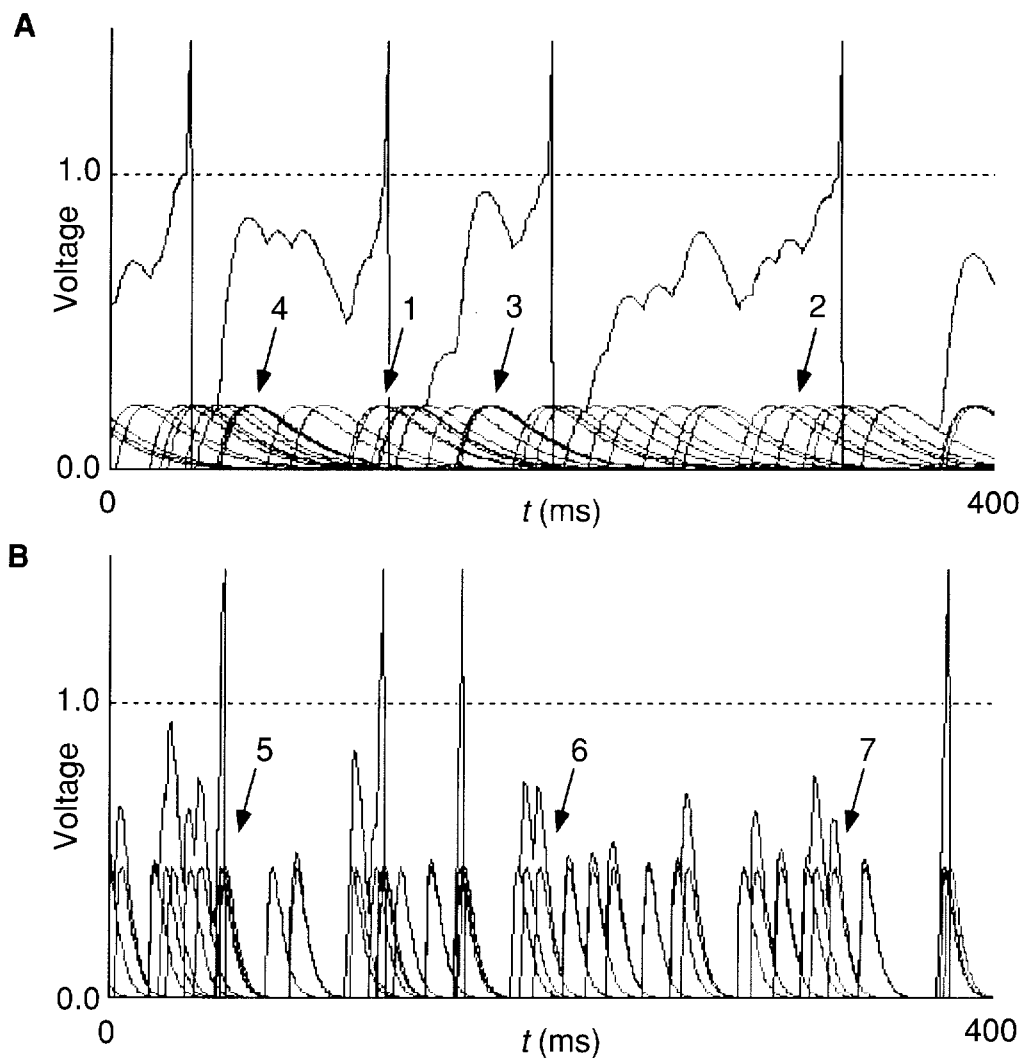


Fig. 1. Postsynaptic potentials (PSPs) are processed differently in the coincidence-detection and the temporal-integration schemes. (A) Temporal integration of a train of excitatory PSPs by a simulated neuron. The excitatory PSPs were simulated by an alpha function with a time constant of 15 ms. When the membrane potential (black) reaches threshold (broken line at value 1.0; arbitrary voltage scale), an action potential is triggered and the membrane potential undergoes reset. The majority (75%, red) of all PSPs contribute to a subsequent action potential. The remaining PSPs (25%, blue) do not affect the output of the simulated neuron. In this regime, both nearly coincident PSPs (1) and temporally distributed PSPs (2) can trigger an action potential. However, simultaneously arriving PSPs do not necessarily trigger an action potential immediately (3) and, in some epochs, they might have no effect at all (4). **(B)** Coincidence detection operating on the same train of excitatory PSPs, with the integration time constant reduced by a factor of five and the size of the PSPs increased by a factor of two, leads to a qualitatively different behavior. Synchronously arriving PSPs (red) trigger an action potential nearly instantaneously (5). Furthermore, most PSPs have no effect on the output (68%, blue), even if they contributed to an action potential in the temporal integration scheme (6,7). To improve clarity of the simulation shown in panels A and B, the number of PSPs has been kept small and their size large. The value of both parameters is not crucial for the qualitative difference observed.

concept, no information can be carried by the precise timing of action potentials. Correlations between the discharges of different neurons might arise as an epiphenomenon of circuitry, but have no functional meaning on their own⁹. By contrast, neurons operating as coincidence detectors allow for much richer dynamics of the system and can convey more information (for example, see Ref. 10). In this case, the precise temporal structure of the afferent activity is decisive for the effect on the postsynaptic neuron, and the generated output reflects temporal patterns in subsets of the inputs. This concept assumes that temporal correlations among spatially separate neurons are crucial for processing as part of the information is coded in the temporal structure of activity patterns³⁻⁸.

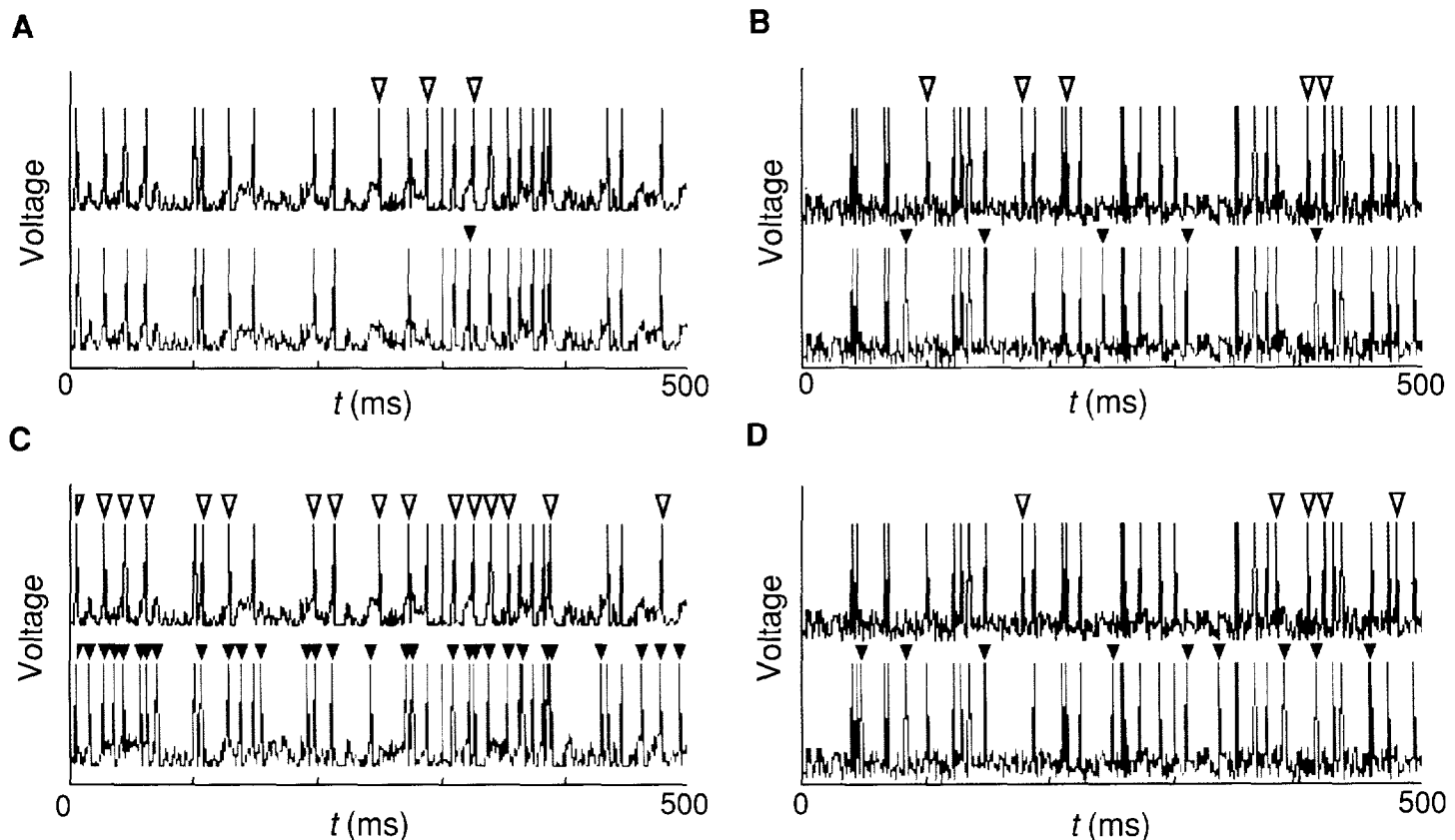


Fig. 2. Interfering noise has different effects in the temporal-integration and the coincidence-detection schemes. (A) The upper trace shows the membrane potential and action potentials of a simulated neuron performing temporal integration of postsynaptic potentials (PSPs). The input is simulated on average as a balanced distribution of excitatory and inhibitory PSPs (uniform distribution with a range of 35 PSPs; PSP magnitude, 0.25 mV; resting potential, -70 mV; threshold, -55 mV). The lower trace shows the result of perturbing the system by the addition of a second signal (magnitude, 10% of the dominant input) which also has a balanced distribution of excitatory and inhibitory PSPs. This perturbation does not change the total number or the timing of the action potentials in a significant way. An action potential is deleted (unfilled arrowheads in upper trace) or added (filled arrowheads in lower trace) in only a few instances. (B) A simulated neuron performing coincidence detection while receiving input without (upper trace) or with the interfering signal (lower trace) shows a moderate distortion of the spike train (resting potential, -70 mV; adaptive threshold with a time constant of 100 ms). (C) Using a purely excitatory interfering signal (magnitude again 10% of the dominant input) leads to a gross distortion of the original spike train with both deletion (unfilled arrowheads) and insertion (filled arrowheads) of action potentials. Note that the average firing rate increases by more than 50%. Thus, the temporal integrator is very sensitive to interfering noise with an unbalanced distribution of excitatory and inhibitory PSPs. (D) The same interfering signal applied to the coincidence detector has much less-pronounced effects (lower trace). The timing of the majority of the action potentials is preserved, although the perturbing signal gives rise to a few additional action potentials (15% increase in the firing rate). Thus, the representation of the original input is largely preserved.

Temporal integration and coincidence detection differ substantially with respect to their coding capacities and dynamic performance. Of particular interest is the speed of cortical processing. The parameter that is crucial for processing speed is the delay between the arrival of relevant afferent inputs and the generation of an output. By definition, neurons operating in the temporal integration mode have a processing time that is of the same order of magnitude as the interspike interval of their output. For neurons operating as coincidence detectors, this processing time is much shorter. Because only a small subset of all afferent PSPs are relevant (namely those which actually coincide and trigger an action potential), the mean time-lag between relevant input and output signals is very short – only a fraction of the interspike interval. Thus, at identical interspike intervals neuronal systems utilizing coincidence detection can process information much faster. Considering the adaptive value of processing speed, this provides a teleological argument in favor of coincidence detection¹¹.

The two modes of neuronal operation also differ with respect to error propagation. Such errors can be due to stochastic processes in the environment or within the neuronal system itself, as well as to systematic influences originating in the interaction of

different signals. In the visual system, for example, the absorption of photons by rods and cones in the retina is a probabilistic process introducing stochastic errors. An additional source of noise is the low reliability of synaptic transmission^{12,13}. Moreover, as cortical connectivity is characterized by a high degree of convergence and divergence and as, under natural conditions, a large number of neurons will be activated simultaneously, systematic errors are likely to arise from interactions among responses to unrelated stimuli. The two modes of neuronal operation behave quite differently with respect to these sources of errors (Fig. 2). Neurons operating in a temporal integration mode will, by definition, integrate all incoming activity, including noise and potentially misleading signals. Whereas the stochastic errors have a limited effect on the overall firing rate, and tend to average out (depending on the correlation of the noise in different neurons¹⁴), the systematic influences are transmitted to other neurons and potentially accumulate along processing pathways as the information is integrated. In colloquial terms: if every PSP is important for the cortical neuron, it is difficult to separate the wheat from the chaff. Thus, a system that uses neurons operating as temporal integrators, and exclusively relies on rate coding might be robust with respect to

stochastic errors, but will be highly susceptible to crosstalk.

In the coincidence-detection scheme these two kinds of errors have quite different consequences. Erroneous excitatory PSPs, whether stochastic or systematic, will have an effect only if they happen to coincide with a sufficient number of other PSPs which alone would not have reached threshold. Erroneous inhibitory PSPs, on the other hand, affect the processing only if they coincide with a number of excitatory PSPs which for themselves would just reach threshold. At present, a rigorous quantitative argument can hardly be developed because the distribution of excitatory and inhibitory PSPs in cortical neurons is not known under natural conditions. However, numerical simulations of artificial neuronal networks employing coincidence detectors indicate that a substantial fraction of erroneous PSPs will be discarded⁴. If this holds true, a system of coincidence detectors could actually operate with considerable fault tolerance, like a digital computer in which small deviations of the voltage on a signal line do not affect processing. However, for very low signal-to-noise ratios it is to be expected that the coincidence detection scheme is at a severe disadvantage, as no temporal averaging is performed. Moreover, networks exploiting coincidence detection are by definition much more susceptible to variations in timing of the PSPs. Therefore, any condition leading to changes in the speed of propagation of neuronal signals, such as altered temperature or demyelination, will have deleterious effects on coincidence detection.

Another difference between the two competing concepts relates to the 'grain' of neuronal representations. The argument rests on the relative contribution that single PSPs make to the postsynaptic response. In the temporal integration mode, this contribution is small. A decrease in the activity of a particular presynaptic fiber influences the postsynaptic neuron only in so far as the next action potential will be somewhat delayed – it will take longer until the summing PSPs will drive the membrane potential above threshold. Assuming, for example, that 10% of 3000 synapses estimated to converge on a cortical neuron supply the dominant source of input⁹, silencing one of these synapses will increase the mean interspike interval only by about 1/300. Thus, even if one of the presynaptic neurons ceases to fire altogether, the effect on the average firing rate of the postsynaptic cell will be rather limited. The implication is that an effective modulation of output activity can only be achieved if a substantial number of highly connected neurons change their discharge rate together. In contrast, in a network employing coincidence detection the contribution of individual PSPs to the propagation of activity is much higher, because fewer inputs are needed to drive a cell if they arrive in synchronous volleys^{15,16}. As has been argued for the case of so-called synfire chains⁴, small ensembles of synchronously firing neurons can easily sustain activity and exert a decisive influence on neurons at later stages of processing. Thus, the size of functionally effective neuronal populations (and, hence, the 'grain' of cortical representations) can be smaller. In this way, the coincidence detection scheme is able to reduce redundancy in distributed activity patterns and to make better use of the resources of the brain.

The most important difference between the two models, however, is that coincidence detection makes the timing of neuronal discharges available as an additional coding dimension⁵⁻⁸. This additional dimension could complement a code based on the average discharge rate and could provide an elegant and highly economic way to bind distributed neurons into functionally coherent assemblies, and to select subsets of responses for further joint processing⁴⁻⁸. Although the selection of sets of neurons is also possible by increasing the average firing rates (and there is experimental evidence for such a mechanism¹⁷), binding by synchronization is advantageous in at least two respects. First, it avoids confounding the amplitude code for stimulus features with the marker that allows for the selection of responses for further processing. Second, temporal binding permits the co-activation of multiple object representations in the same neuronal network without running the risk of forming erroneous conjunctions, because different groups of cells can engage in independent synchronous discharges⁵⁻⁸. Both aspects are of crucial importance for establishing coherent object representations and for handling relationships between different objects.

Experimental support for coincidence detection

Although available results do not prove that cortical neurons operate as coincidence detectors they let it appear at least physiologically plausible. Synchronous inputs are more effective in driving a neuron than asynchronous inputs because PSPs decay rapidly and their amplitude is small compared to the depolarization needed to reach firing threshold. Thus, neurons are naturally sensitive to coincident inputs. This is particularly so, if the mean interspike intervals are longer than the effective decay constants of the PSPs. Thus, taking a value of 8–15 ms for the passive membrane time constant into account^{3,18}, we can safely assume that in all neurons which fire at rates of 25 Hz or lower, coincidence detection is the prevailing mode.

However, with carefully chosen and optimized stimuli as used in physiological experiments, it is possible to drive cortical neurons at sustained rates that are much higher than 25 Hz, occasionally even exceeding 100 Hz. In these highly active neurons, the interspike interval is shorter than 10 ms and one might ask whether the sensitivity for coincidence is sufficient to detect precise synchrony among afferent inputs, that is, coincidence within time intervals as short as a few milliseconds (<5 ms). The crucial parameter is the time constant of the PSPs as it limits the temporal resolution with which different inputs can be segregated from one another. In a variety of preparations, time constants of the order of 10 ms have been reported for excitatory PSPs in cortical neurons^{3,18}. Recent theoretical work indicates that shorter values are probably even more realistic. Thus, it has been shown that the time constant of a PSP is dramatically affected by the background activity in the respective neuronal network and can shorten considerably in highly active cells¹⁹. In addition, theoretical studies of signal propagation in dendritic trees of cortical neurons suggest that the effective time constant in fine branches of the dendritic tree might actually be one order of magnitude smaller than the membrane time constant at the soma²⁰. Active dendritic processes might even push

the temporal resolution into the sub-millisecond range²¹. Although these studies need to be substantiated by further physiological measurements, they suggest that the biophysical properties of cortical neurons allow for coincidence detection with a precision in the millisecond range.

In addition, there is evidence to suggest that the time constant of the effect of a PSP can actually be much shorter than the decay constant, as measured for an isolated event. Thus, correlated excitatory and inhibitory influences can, in a similar manner to a push-pull mechanism, drastically shorten the effective time constant of excitatory PSPs (Ref. 18). Moreover, when considering time constants, it is important to differentiate between the time constant of transmitter binding and that of the actual conductivity. That the actual conductivity can be quite fast is demonstrated by a recent study in rat visual cortex showing that the excitatory synaptic currents mediated by kainate (AMPA) receptors have average time constants of about 2 ms (Ref. 22). It seems likely that such kinetics would be sufficiently fast to achieve coincidence sensitivity with a precision in the range of a few milliseconds. Even in the case of NMDA receptors, where the time constant for ligand binding can be quite long, the time constant of the actual current might be as short as a few milliseconds due to the voltage gating²³.

Taken together, these arguments indicate that the effects of individual PSPs might be sufficiently short-lived to make cortical neurons sensitive to precise temporal coincidence. This conclusion is supported by recent simulation studies which have investigated the effects of input synchrony on the firing behavior of cortical neurons^{15,16,19}. These studies, in which realistic estimates of physiologically relevant parameters were incorporated into compartment models, confirm the assumption that synchronous inputs are more effective than asynchronously arriving signals.

Considerations of neuronal dynamics at the systems level also suggest that the precise timing of neuronal signals can be used to encode information. A particularly impressive case is the location of sound sources by evaluating interaural latency differences²⁴. In the barn owl and echo-locating bats central neuronal circuits are able to detect and utilize timing differences of the order of microseconds. Although these circuits employ neurons with specialized morphology, the fact that their sensitivity to coincidences is at least three orders of magnitude better than the time constant postulated for coincidence detection in the cortex (<5 ms) suggests that one should be cautious when judging what cortical neurons, with their delicate morphology, can or cannot do.

Psychophysical data on visual perception support the notion of high temporal precision. Differences in timing of afferent signals in the range of a few milliseconds can induce drastic perceptual effects. A classical example is the so-called Pulfrich phenomenon, that is, the generation of an illusory depth effect by introducing interocular delays. Here, timing differences of the order of 1 ms can be sufficient to produce the effect²⁵. More recent experiments have extended this classical demonstration to a wide variety of paradigms and show that the visual system can readily use small timing differences to discriminate successive stimuli²⁶, determine temporal order²⁷, achieve vernier

acuity²⁸ and perform figure-ground segregation^{29,30}. In all of these cases, the temporal threshold delays between discriminanda are of the order of 3–5 ms. Although the neural mechanisms underlying these perceptual capacities have not yet been identified, it seems likely that some sort of precise coincidence detection is used²⁴ in order to exploit at such high resolution the temporal structures present in the external input.

There is also ample evidence for an internal temporal patterning of neuronal activity suggesting that temporal relationships among the discharges of neurons might be relevant for processing. The most prominent and best documented example of such patterning is the EEG. Since the pioneering studies of Berger³¹, it is established that the brain generates oscillatory electrical potentials which are so large that they can be picked up even with scalp electrodes (for reviews, see Refs 18,32). This implies a precise synchronization of the respective potential generators in the brain because otherwise the tiny transmembrane currents of the myriads of neurons contributing to the EEG would not summate effectively but cancel out⁴. The analysis of the spectral composition of this intrinsically generated neuronal synchrony has become an important tool for the diagnosis of functional states, supporting a close relationship between temporal patterning and function. More recently, it has also become possible to evaluate the coherence of the potential fluctuations across different cortical areas. This has led to numerous demonstrations of close relationships between behavioral performance and neuronal synchronization^{33–37}.

Experiments performed with microelectrodes add to the abundant evidence for internal synchronization of neuronal activity. They show, at the cellular level, that neurons in cortical and subcortical centers can synchronize their discharges with a precision in the millisecond range (for reviews, see Refs 6–8). So far, most of the data have come from studies in the visual system of cats and monkeys, where synchronization has been observed within and between cortical areas, between thalamic nuclei and corresponding cortical areas and even across the cerebral hemispheres. Similar observations have been made in the auditory, somatosensory and motor cortex, and in association areas of the prefrontal cortex (for review, see Ref. 8).

Although the presence of synchrony does not, *per se*, prove its functional relevance, recent results suggest that coincident firing might indeed play an important role in information processing. First, several studies have demonstrated that neural synchrony in the visual system of cat and monkey depends crucially on the configuration of the stimuli used to activate the neurons. Spatially separate cells show strong synchronization only if they actually respond to the same object. If they are activated by different stimuli, which cannot be perceived as coherent, the cells fire in a less correlated or even an uncorrelated manner^{38–40}. In all these cases, changes in the global configuration of stimuli are reflected only by changes in synchronization patterns, but not by changes in the average firing rate of the recorded neurons. Second, recent studies performed in strabismic cats have revealed that perceptual deficits encountered in those animals are closely related to alterations of the synchronization behavior of visual cortical neurons but

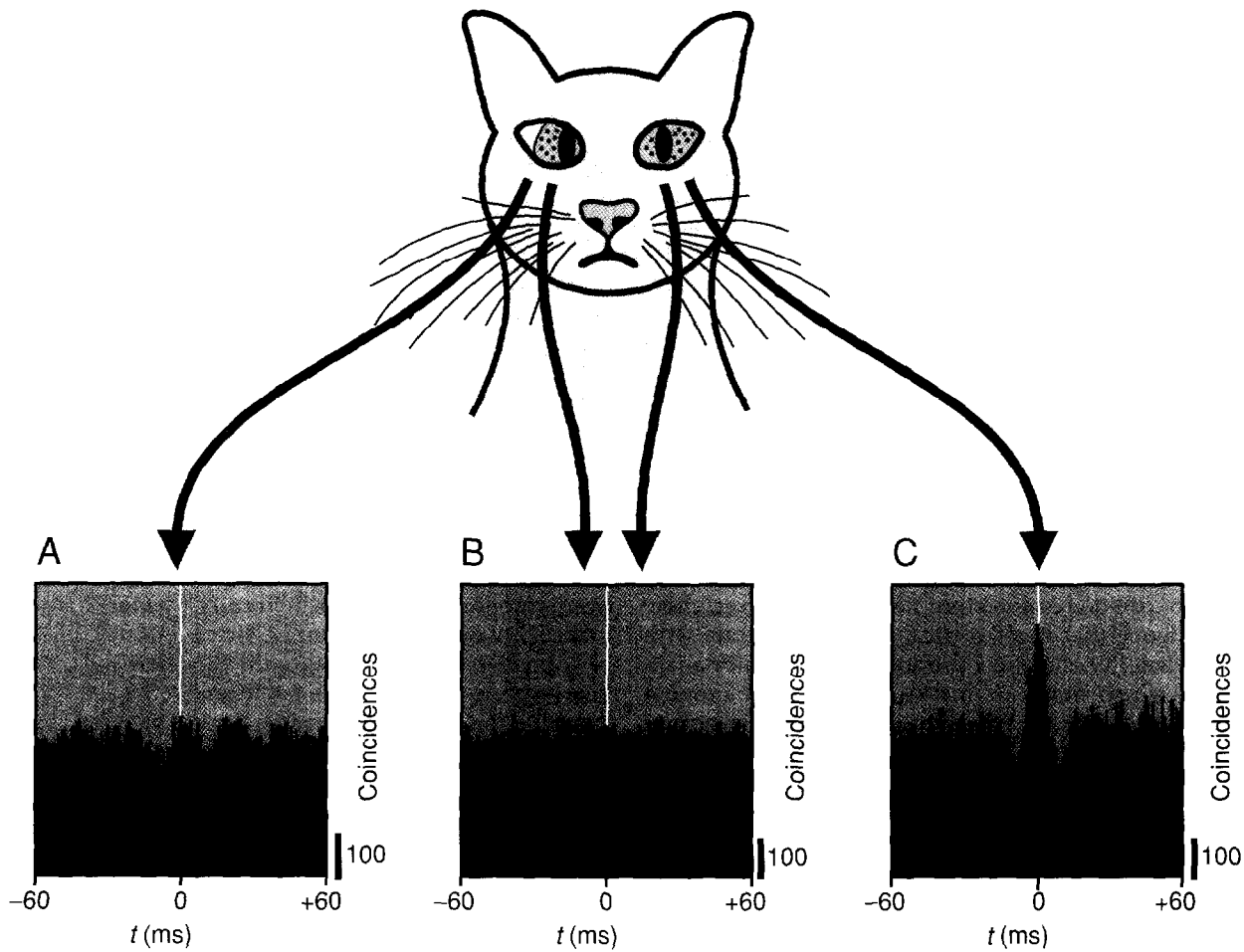


Fig. 3. Experiments in strabismic cats provide evidence for the functional relevance of neuronal synchrony. Data are taken from a correlation study in cats with a convergent squint which has been induced surgically early in development⁴². Typically, these animals use only one eye for fixation. The non-fixating eye then develops a syndrome of perceptual deficits called strabismic amblyopia. In the visual cortex squint induction leads to a breakdown of binocularity and, thus, the vast majority of neurons respond to stimulation of just the left or just the right eye. Interestingly, neurons driven by the amblyopic eye do not show a loss of responsiveness and have essentially normal response properties. However, the amblyopia is accompanied by a selective impairment of the intracortical interactions. The lower panel shows representative examples of cross-correlograms between cells driven by the amblyopic eye (A), by the normal eye (C) and between cells dominated by different eyes (B). Note that the temporal correlation is strong if both recording sites are driven by the normal eye. Synchronization is, on average, much weaker between cells dominated by the amblyopic eye and is, in most cases, negligible if the recording sites receive their input from different eyes. These observations agree well with the perceptual deficits encountered in these animals that show an impairment of perceptual integration through the amblyopic eye and, in addition, are completely unable to bind features detected by different eyes into a single percept. This correspondence between perceptual malfunction and selective disturbance of synchrony suggests that temporal correlations on a fast timescale are essential to normal visual processing. Figure modified from Ref. 42.

not to changes in their individual response properties^{41,42} (Fig. 3). Third, data from the frontal cortex of monkeys show that temporal correlations between spatially distributed neurons can exhibit a consistent relationship to the behavior of the animal, even if their overall activity does not change⁴³.

Taken together, these studies are consistent with the hypothesis that synchronization might serve as a mechanism to associate flexibly and select subsets of distributed neuronal responses⁶⁻⁸ for further joint processing. If, however, synchronization is indeed exploited to select responses and to bind them together for joint evaluation, this implies that neurons must be sensitive to precise temporal coincidence. Actually, the mere occurrence of precisely synchronized discharges already provides an argument in favor of coincidence detection. It is highly unlikely that the observed synchrony is due to spurious coincidences because it occurs with near-zero phase-lag irrespective of the distance between neurons, and shows a systematic dependence on the

configuration of stimuli without being phase-locked to them⁶⁻⁸. In order to generate synchrony with the observed precision, however, neurons have to be sensitive to coincidence and capable of reliably transmitting temporal patterns.

A recent objection

In a recent publication, Shadlen and Newsome⁹ have challenged the view that coincidence detection on a millisecond timescale is a physiologically plausible concept. Their objection is based on a heuristic model of integrate-and-fire neurons. The assumption is that cortical neurons receive a balanced input of excitatory and inhibitory PSPs which causes random fluctuations of the membrane potential. Thus, the membrane potential undergoes a 'random walk' to the threshold value and any temporal structure in the input to the neurons is lost. Based on the model, Shadlen and Newsome conclude that the summation properties of cortical neurons are too imprecise to support coincidence detection. They argue that the

temporal patterning of activity cannot be used to convey information, thus leaving as the only coding dimension the firing rates of neurons. However, we believe that several of the assumptions underlying Shadlen and Newsome's simulation can be questioned and, hence, that this model is not sufficient to refute the possibility of coincidence detection by cortical neurons.

In their model, the average number of incoming independent PSPs determines the magnitude of the membrane potential fluctuations and, thus, the output of the neuron. The assumption is that a neuron receives about 30 000 PSPs per second (that is, an average activity of 100 Hz in at least 10% of a total of 3000 input neurons). If one considers that most of the studies from which such estimates can be inferred have used highly optimized stimuli, it is not clear whether, under more natural conditions, such a large fraction of the afferents would be active at such high rates. Furthermore, the model assumes that the activity level of the output neuron is in a similar range to the firing rates of the dominant input neurons. However, there is evidence that most cortical synapses operate with low reliability and show pronounced frequency adaptation which might dramatically reduce the number of effective PSPs. *In vitro* studies in the hippocampus have revealed that the probability of neurotransmitter release can be as low as 10% for a large proportion of synapses^{12,13}. Furthermore, the inputs to a cortical neuron are not necessarily independent because of synchronization. Because synchronized PSPs appear as a single synaptic event, this further reduces the number of inputs that effectively contribute to the generation of noise fluctuations of the membrane potential. All these factors will result in a discrepancy between the amplitude of the input and the expected output, thus clashing with one of the model's basic assumptions. Taken together, these considerations suggest that several quantitative assumptions of the model might require modification which, in turn, might lead to rather different simulation results.

Another central assumption of Shadlen and Newsome's model is that excitatory and inhibitory inputs are exactly balanced. Several reasons suggest that this might not necessarily be so. In neurons of the visual cortex, excitatory and inhibitory postsynaptic responses often have a similar preference for stimulus orientation but inhibitory influences are more broadly tuned⁴⁴. Even if excitatory and inhibitory inputs are balanced during presentation of the optimally oriented stimulus, addition of a second stimulus would skew the balance towards inhibition if its orientation is within the tuning range of the inhibitory, but not within that of the excitatory, input. In addition, there is evidence for systematic changes in the balance between excitation and inhibition during the response of a neuron. Often neuronal responses are oscillatory^{6–8} and, hence, characterized by an alternating predominance of excitatory and inhibitory influences. Under these conditions, the neurons in Shadlen and Newsome's model would tend to generate regular firing patterns, which is in conflict with their assumption that input and output activity have Poisson statistics.

Finally, in a recent analysis using the same set of parameters as Shadlen and Newsome, Softky⁴⁵ came to the conclusion that neurons can perform coincidence detection on a millisecond timescale despite the apparently long time constants of PSPs. The reason is

that the bombardment with inhibitory inputs shortens the effective time constant of the model neuron to the sub-millisecond range. Taken together, the arguments considered here suggest that the heuristic model proposed by Shadlen and Newsome is not sufficient to demonstrate that the coincidence detection scheme lacks physiological plausibility.

Concluding remarks

The aim of this article was to discuss arguments for and against the notion that cortical neurons could function as coincidence detectors. It is our view that there is, as yet, no compelling evidence against this possibility while both theoretical considerations and experimental data seem to support the coincidence detection scheme. It should be emphasized that our conclusion is not in conflict with the assumption that average firing rates are carriers of information in the nervous system. Even if individual neurons do not act as integrators, effective rate codes can be propagated by assemblies of neurons which carry the information in a highly distributed manner. However, the concept of coincidence detection extends this view in important respects since it makes additional temporal codes available for cortical processing.

Clearly, most of the current experimental evidence is indirect, and further studies are needed to corroborate the hypothesis that the cerebral cortex exploits precise temporal patterning of neuronal activity to convey information. The effects of synchronous versus temporally dispersed synaptic inputs will have to be compared in *in vitro* studies to test the coincidence sensitivity of neurons. In addition, simulation studies are required that use more-sophisticated single neuron models and examine how large assemblies of coincidence-detecting neurons behave if they receive temporally structured input. Finally, experiments are required that establish direct relationships between changes in the synchronization of neurons and an animal's sensory-motor performance.

Selected references

- 1 Sherrington, C.S. (1906) *Integrative Action of the Nervous System*, Yale University Press
- 2 Eccles, J.C. (1957) *The Physiology of Nerve Cells*, Johns Hopkins Press
- 3 Abeles, M. (1982) *Isr. J. Med. Sci.* 18, 83–92
- 4 Abeles, M. (1982) *Local Cortical Circuits*, Springer
- 5 von der Malsburg, C. and Schneider, W. (1986) *Biol. Cybern.* 54, 29–40
- 6 Engel, A.K. et al. (1992) *Trends Neurosci.* 15, 218–226
- 7 Singer, W. (1993) *Annu. Rev. Physiol.* 55, 349–374
- 8 Singer, W. and Gray, C.M. (1995) *Annu. Rev. Neurosci.* 18, 555–586
- 9 Shadlen, M.N. and Newsome, W.T. (1994) *Curr. Opin. Neurobiol.* 4, 569–579
- 10 Stein, R. (1967) *Biophys. J.* 7, 797–826
- 11 Thorpe, S. and Imbert, M. (1989) in *Connectionism in Perspective* (Pfeifer, R., Schreter, Z. and Fogelman-Soulie, F., eds), pp. 63–92, Elsevier
- 12 Rosenmund, C., Clements, J.D. and Westbrook, G.L. (1993) *Science* 262, 754–757
- 13 Hessler, N.A., Shirke, A.M. and Malinow, R. (1994) *Nature* 366, 569–572
- 14 Zohary, E., Shadlen, M.N. and Newsome, W.T. (1994) *Nature* 370, 140–143
- 15 Bernander, Ö., Koch, C. and Usher, M. (1994) *Neural Comput.* 6, 622–641
- 16 Murthy, V.N. and Fetz, E.E. (1994) *Neural Comput.* 6, 1111–1126
- 17 Lamme, V.A.F. (1995) *J. Neurosci.* 15, 1605–1615
- 18 Creutzfeldt, O.D. (1995) *Cortex Cerebri*, Oxford University Press
- 19 Bernander, Ö. et al. (1991) *Proc. Natl Acad. Sci. USA* 88, 11569–11573

- 20 Agmon-Snir, H. and Segev, I. (1993) *J. Neurophysiol.* 70, 2066–2085
- 21 Softky, W.R. (1994) *Neuroscience* 58, 13–41
- 22 Hestrin, S. (1992) *Neuron* 9, 991–999
- 23 Bekkers, J.M. and Stevens, C.F. (1990) *Cold Spring Harbor Symp. Quant. Biol.* 55, 131–135
- 24 Carr, C.E. (1993) *Annu. Rev. Neurosci.* 16, 223–243
- 25 Rogers, B.J. and Anstis, S.M. (1972) *Vision Res.* 12, 909–928
- 26 Georgeson, M.A. and Georgeson, J.M. (1985) *Vision Res.* 25, 1729–1733
- 27 Westheimer, G. (1983) *Vision Res.* 23, 759–763
- 28 Burr, D.C. (1979) *Vision Res.* 19, 835–837
- 29 Fahle, M. (1993) *Proc. R. Soc. London Ser. B* 254, 199–203
- 30 Fahle, M., Leonards, U. and Singer, W. (1993) *Invest. Ophthalmol. Vis. Sci. Suppl.* 34, 785
- 31 Berger, H. (1929) *Arch. Psychiatr. Nervenkr.* 87, 527–570
- 32 Steriade, M. et al. (1990) *EEG Clin. Neurophysiol.* 76, 481–508
- 33 Jokeit, H. and Makeig, S. (1994) *Proc. Natl Acad. Sci. USA* 91, 6339–6343
- 34 Lutzenberger, W., Pulvermüller, F. and Birbaumer, N. (1994) *Neurosci. Lett.* 176, 115–118
- 35 Joliot, M., Ribary, U. and Llinás, R. (1994) *Proc. Natl Acad. Sci. USA* 91, 11748–11751
- 36 Desmedt, J.E. and Tomberg, C. (1994) *Neurosci. Lett.* 168, 126–129
- 37 Tiitinen, H. et al. (1993) *Nature* 364, 59–60
- 38 Gray, C.M. et al. (1989) *Nature* 338, 334–337
- 39 Engel, A.K., König, P. and Singer, W. (1991) *Proc. Natl Acad. Sci. USA* 88, 9136–9140
- 40 Kreiter, A.K., Engel, A.K. and Singer, W. (1992) *Soc. Neurosci. Abstr.* 18, 12
- 41 König, P. et al. (1993) *Eur. J. Neurosci.* 5, 501–508
- 42 Roelfsema, P.R. et al. (1994) *Eur. J. Neurosci.* 6, 1645–1655
- 43 Vaadia, E. et al. (1995) *Nature* 373, 515–518
- 44 Ferster, D. (1986) *J. Neuroscience* 6, 1284–1301
- 45 Softky, W.R. (1995) *Curr. Opin. Neurobiol.* 5, 239–247

Acknowledgements
It is our pleasure to thank our colleagues at the Max-Planck-Institute for Brain Research and at The Neurosciences Institute for valuable discussions, and William Newsome for helpful comments on an earlier version of the manuscript.

LETTERS TO THE EDITOR

Directional motor control

The recent review by Georgopoulos¹ highlights the prodigious output of the small army of researchers who have taken to summarizing the activity of motor-cortical units as a population vector in coordinates of polar extrapersonal space. In order to treat this paradigm as a hypothesis, as claimed, the author must clarify what the hypothesis actually states.

Georgopoulos does provide some necessary conditions for any population vector to describe a set of reaching movements, but these actually hold equally well for population vectors in myriad co-ordinate systems, including those based on intrinsic co-ordinates of the limb (for example, muscle and joint velocities) with no components related directly to the end point of the limb. Mussa-Ivaldi² has already provided a formal statement of the necessary conditions and a general proof that the cortical activity that actually represents muscle-based co-ordinates can be used to construct accurate population vectors in extrapersonal space.

The proponents of the population-vector hypothesis are really inviting the reader to infer the truth of another, more interesting, hypothesis, namely that the activity of individual neurons and columns of the motor cortex is invariantly related to the direction of movement of the end point of the limb, as represented in an extrinsic co-ordinate frame, that is, extrapersonal space. The problem is that this hypothesis has been tested and shown to be false. If the motor cortex is actually organized in extrapersonal space co-ordinates, then making the same set of movements of the hand in different postures of the arm should not change the

tuning vectors of individual motor-cortical cells, but it does³. Dismissing this finding by recomputing population vectors (Fig. 1 in Georgopoulos¹) is simply a retreat into the uninteresting hypothesis. Stating that the 'preferred direction [of individual units]...can change...when the posture of the arm change[s]' reduces the 'hypothesis' to curve fitting.

There is no question that somewhere between the eyes and the limb muscles, there must be a transformation between the visually encoded targets in extrapersonal space and the motoneuronal recruitment to reach such targets. The problem is to identify the actual steps in the transformation and where and how they are computed. What do we actually know about this?

As Georgopoulos points out, motor cortex does not appear to compute the control signals to individual muscles. This is hardly surprising, given the fact that almost all of the pyramidal-tract activity is filtered through a phalanx of spinal interneurons before reaching any motoneurons. These interneurons are remarkably divergent in their output projections and convergent in their inputs from somatosensory afferents and extrapyramidal descending systems⁴. On the other hand, the organization of sensorimotor-cortical areas might reflect more of the organization inherent in the sensory feedback that is shared with the spinal cord. This information is necessarily closely related to the topology of the musculoskeletal apparatus and skin; there is little possibility or reason for it to be transformed into extrapersonal space co-ordinates en route through the dorsal column and thalamic nuclei⁵. The most

salient sensory feedback for unobstructed reaching would be kinesthesia, which appears to be derived largely from muscle-spindle primary endings that have precisely the sorts of direction and velocity tuning that have been found in motor-cortical cells⁶. These signals have an orderly relationship to hand movement because of the mechanical linkage imposed by the musculoskeletal apparatus of the arm. More importantly, in a kinematically redundant system, the preferred direction in extrapersonal space of the individual signals might rotate with the origin and posture of the movement, whereas extrapersonal-space vectors based on the end point of the movement should not. Furthermore, there is at least the possibility that a co-ordinate frame constructed from intrinsic sensors might produce an orderly topical map for motor cortex, which is conspicuously lacking in population-vector theories.

This is not to say that motor cortex computes in a reference frame that is defined by muscle spindles, but is rather to show how little can be said about this computational problem by creating and displaying population vectors in any arbitrary co-ordinate frame. The 'top-down theory of computation' approach to the visual system is useful because the hypotheses that are derived from a theory about perception can be tested psychophysically. A 'top-down' theory of sensorimotor control must be integrated 'bottom-up' with musculoskeletal mechanics and spinal circuitry in order to understand whether any particular hypothesis actually offers a test of the theory or simply the inevitable consequences of trigonometry and newtonian mechanics.

Gerald E. Loeb
Ian E. Brown