WORKSHOP PAPER

Intraneuronal information processing, directional selectivity and memory for spatio-temporal sequences*

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Abstract. Interacting intracellular signalling pathways can perform computations on a scale that is slower, but more fine-grained, than the interactions between neurons upon which we normally build our computational models of the brain (Bray D 1995 *Nature* **376** 307–12). What computations might these potentially powerful intraneuronal mechanisms be performing? The answer suggested here is: storage of spatio-temporal sequences of synaptic excitation so that each individual neuron can recognize recurrent patterns that have excited it in the past. The experimental facts about directionally selective neurons in the visual system show that neurons do not integrate separately in space and time, but along straight spatio-temporal trajectories; thus, neurons have some of the capacities required to perform such a task. In the retina, it is suggested that calcium-induced calcium release (CICR) may provide the basis for directional selectivity. In the cortex, if activation mechanisms with different delays could be separately reinforced at individual synapses, then each such Hebbian super-synapse would store a memory trace of the delay between pre- and post-synaptic activity, forming an ideal basis for the memory and response to phase sequences.

1. A new level of computation in the brain

Dennis Bray has recently argued that the intracellular biochemical signalling pathways of *E. coli* that control its behaviour interact with each other in a manner analogous to the interactions of the (supposedly) neuron-like elements of artificial neural networks (Bray 1995). This has revolutionary implications for neuroscience: it implies that we should think of neurons not only as units that compute and make decisions by interacting with each other, but also as units that each contain decision networks within themselves. The brain is not just a very complicated hierarchy of relatively simple neural elements, but each of these elements is itself a very complicated decision network of a type that we are only beginning to understand in biophysical terms.

As an example of an intracellular computational process consider briefly how *E. coli* controls its flagellar motor. Just as direction of motion is important in vision, so the directions of changes in the concentrations of nutrients and toxins are important to *E. coli*. If a nutrient is increasing in concentration as the bacterium moves through its environment, it is moving correctly and should go on doing the same, but if the concentration is decreasing, it should stop and do something different. The appropriate actions are the reverse for increases and decreases in the concentrations of toxins. Substances in the surrounding medium bind to receptors in the bacterial membrane and these release messenger molecules

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into the cytoplasm. In order to detect whether a substance is increasing or decreasing, the bacterium has two messengers, one of which responds rapidly, the other more slowly, thus integrating the estimate of the substance concentration over a few seconds in the past. The control of the flagellar motor depends upon comparing the immediate and the time-averaged estimates, thereby making the response depend upon rate of change of concentration, not its absolute value.

Bray gives examples of proteins in *E. coli* that can act as switches and other computational elements. A pyramidal cell from the cerebral cortex receives about 10^4 synapses on spines, and each spine is about the size of *E. coli*; thus there cannot be any doubt that a single pyramidal cell might perform enormously more complicated computations than those contemplated by McCulloch and Pitts (1943) and Donald Hebb (1949) five decades ago.

It is difficult to estimate how much additional computing power these intracellular mechanisms might bring, especially in view of the reconsideration of dendritic action that is in progress (see Segev 1992, Mel 1994, Segev *et al* 1995 for reviews), but three points seem clear. First, intracellular mechanisms are in general slower than the conventional ones involving the membrane potential. Second, it is possible for there to be a very large number of different states of the variables involved in intracellular computations in each cell, and the finer spatial grain of these mechanisms increases the total computational power by a much larger factor than their slowness decreases it; the result is an overall increase by a large factor, perhaps by as much as 100 times. Third, this additional level is not a substitute for computation using membrane potentials, but an addition to it, for the results of intraneuronal computations operate through the membrane potential.

What these computations achieve will only be found out by experiments on real neurons, but theoreticians should feel challenged by the question: what *might* intraneuronal computations accomplish? In the following section of this paper I have taken up this challenge and propose one particular answer. But this is obviously not the only possible answer; the complexity of intracellular mechanisms in *E. coli* should inspire many other speculations.

2. The need for memory of spatio-temporal patterns

In taking up the challenge I have been guided partly by a theoretical concern: how does the brain store and access past information? Initially one tends to accept the hint from technology that memory requires some specialized external medium such as a magnetic tape or silicon chip. *E. coli* certainly does not have that but uses the form of intracellular short-term memory outlined above and, if *E. coli* can use the temporal pattern of its own past inputs as a basis for its decisions, it seems likely that a pyramidal cell can do so too. Hence arises the idea that each cell might beneficially store a record of the temporal patterning of its own past experience.

In addition to this theoretical concern, experimental work on motion detection in vision suggests that neurons can process spatio-temporal patterns in more complex ways than hitherto supposed. It looks as though synapses can act with different delays and, if mechanisms with different delays can be separately reinforced, then each synapse could store the average time delay before reinforcement. The simplest reinforcement to consider is simply the firing of the post-synaptic neuron, from whatever cause. In that case each neuron would store, in the large set of synaptic weights corresponding to several different delays at each synapse, a record showing the average delay between activation of each synapse and activation of the cell itself. These 'Hebbian super-synapses' would place a memory

of sequence and timing in every cell and this memory would be compared constantly and automatically with the current spatio-temporal pattern of synaptic activation reaching each cell. I do not know whether such a mechanism should be called short- or long-term memory, for although the synaptic weights could persist for a long time, the maximum duration for the sequences stored would correspond to the longest synaptic delay, which could be no more than a few seconds.

3. Facts about directional selectivity

The ability to detect and respond selectively to spatio-temporal patterns is proved most directly by the existence of neurons selectively sensitive to the direction of motion of objects in the visual field. Directional selectivity in visual cortical neurons will be the main focus of this article; however, the mechanism is perhaps more open to analysis in simpler preparations such as rabbit retinal ganglion cells, and I shall also speculate about these.

First consider a psychophysical fact. It is well known that vernier misalignments can be detected down to about 6 seconds of arc, or roughly one fifth of the separation of a pair of foveal cones. Twenty years ago Westheimer and McKee (1975) made the striking discovery that this performance was maintained when the target was swept through the visual field at rates up to 2.5 deg/s, which corresponds to 300 cones/s. They used an exposure duration of 200 ms to preclude tracking eye movements, during which time the image would have been moved across about 50 cones; hence, the spatial or temporal displacement corresponding to the vernier offset could be detected when the image fell on sequences of 50 different cones just as well as when it was held stable in one position.

The system certainly integrates in time because performance improves with increased stimulus duration, but if it could *only* integrate in time, the image would be hopelessly blurred. I think the result strongly suggests that the receptive fields of cortical neurons integrate along straight trajectories in space–time (Barlow 1979) and are not fixed in retinal coordinates in the way we normally suppose. Such receptive fields cannot be represented by separate spatial and temporal weighting functions but require a combined spatio-temporal weighting function for their adequate description, as suggested in figure 1. This neuron would integrate along the trajectory in spacetime shown by the arrow, but it would preserve its very fine sensitivity to displacements with a component orthogonal to this axis, either vertically in time, or in space, or in a combination as required for moving verniers.

There are further experiments showing the same thing. Burr (1981) measured the threshold for moving spots and for lines of the same spatial and temporal extent that his spots traced out: temporal summation for the moving dots extended to much longer times than for the lines.

Burr *et al* (1986) performed ingenious masking experiments, from which they could predict receptive field shape, and came up with receptive fields similar to the well known Hubel and Wiesel type, but changing with time as in figure 1. Furthermore, the flanking regions they found show that the units not only integrate along straight spatio-temporal trajectories, but also differentiate in an orthogonal direction, explaining how positional precision can be maintained.

The first direct confirmation of such receptive fields was obtained by Emerson *et al* (1987) from a spatio-temporal analysis of the receptive fields of complex cells in cat visual cortex. Similar results have been obtained by Freeman and his colleagues on simple cells (DeAngelis *et al* 1995); as these authors put it, cortical neurons have *moving* receptive fields.

Since the masterly discussion of the problem by Adelsen and Bergen (1985) it has

**Spatio-temporal receptive field for a
directionally selective simple cell**
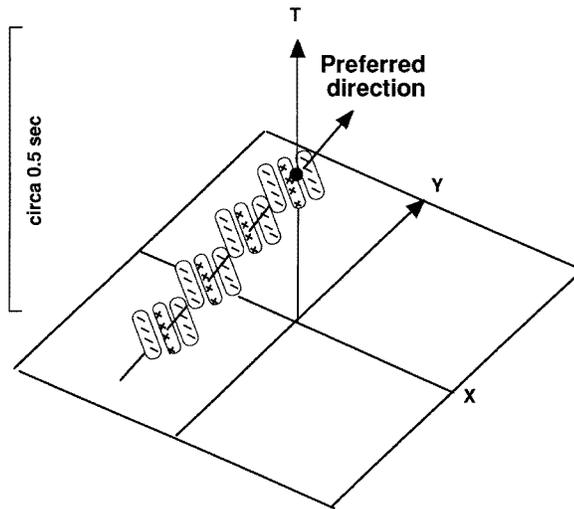
Integration occurs along a spatio-temporal trajectory,
but the cell is highly sensitive to orthogonal
displacements

Figure 1. Three-dimensional representation of a receptive field that could resolve moving verniers in the experiments of Westheimer and McKee (1975). The spatio-temporal weighting function is not separable in space and time, but allows integration along a linear spatio-temporal trajectory.

been widely accepted that directionally selective neurons have receptive fields in which spatial and temporal integration are not separable; we now see that this inseparability takes the specific form of integration along straight spatio-temporal trajectories. But how is this achieved physiologically? It could be achieved by having delayed inputs to each cell, rather as suggested by Mitchison (1989), and the lagged inputs from the LGN (Saul and Humphrey 1990) might serve such a role. But, in accordance with my goal in this article, I want to explore new possibilities.

4. Possible delay mechanisms

What is needed is a mechanism for collecting together information with different delays for different inputs. Table 1 shows some possible mechanisms for delaying the effect of an input to a neuron. The first mechanism was suggested 100 years ago by Sigmund Exner when he proposed a very modern-looking explanation for motion after-effects; conduction times are also the main component of the delay in the reverberating circuits proposed by Lorenté de Nô (1938) and taken up by Hebb (1949) to account for persistent activity in his cell assemblies. The electrotonic properties of dendrites have been extensively discussed recently (see for instance the thorough review by Mel (1994)); thus, to pursue my goal I shall again ignore these two possibilities and discuss the last two.

   Calcium-induced calcium release (CICR) is fascinating because it propagates quite

Table 1. Possible delay mechanisms.

Mechanism	Comments	Possible Examples	References
Impulse conduction time	Difficult for long delays	Visual motion detection	Exner (1894)
		Cerebellum	Braitenburg (1961)
Dendrites act as an electrotonic delay line	Even worse for long delays	Starburst amacrines of rabbit retina	Rall (1964) Borg-Graham and Gryzywacz (1991)
Calcium-induced calcium release (CICR)	Propagates along endoplasmic reticulum at $40~\mu s^{-1}$	Another possibility in starburst amacrines of rabbit retina	Jaffe and Brown (1994)
Second messenger production, phosphorylation, methylation, etc	Delays occur because active molecule must first be synthesized	Movement control in *E. coli*	Bray (1995)
		Variable delay in rods	Baylor *et al* (1979)

slowly inside the cell, along the surface of the endoplasmic reticulum, without influencing the cell membrane directly. The results on the membrane potential are indirect and are the consequence of flooding the cytoplasm with Ca^{++} ions. This can have many effects, but these are likely to include the opening of K^+ channels with consequent stabilization of the membrane potential near its resting value, i.e. inhibition. Since directional selectivity in the rabbit retina seems to depend upon a spreading inhibitory effect, CICR is a likely candidate.

Figure 2 shows a modification of a scheme originally proposed (Barlow and Levick 1965) for the ON–OFF type directional selectivity in the rabbit retina. Since then the morphology of these ganglion cell dendritic trees has been described by Oyster *et al* (1993), the cholinergic 'starburst' amacrine cells involved in directional selectivity have been found by Masland and Mills (1979), further described by Famiglietti (1983) and Masland and Tauchi (1986) and incorporated in a mechanism fitting many of the facts by Vaney (1991). But there are discordant features and none of the proposals fits all the elegant experimental results of Yang and Masland (1992, 1994).

The starburst amacrines have long dendrites radiating from their cell bodies and these might transmit waves of CICR, as Jaffe and Brown (1994) have shown occurs in hippocampal dendrites. In the current scheme it is proposed that bipolar cells normally transmit activity to the ganglion cells through about the outer third of the dendrites of the starburst amacrine cells; that is to say bipolar cells depolarize these amacrine dendrites which in turn excite the underlying ganglion cell dendrites. The amacrine cell dendrites are postulated to have another input nearer the cell body which initiates a wave of CICR propagating centrifugally. As this reaches the region interposed between bipolar cells and ganglion cell dendrites, the Ca^{++} increase opens K^+ channels, stabilizes the membrane potential and vetoes the normal transmission of activity from bipolar terminals to ganglion cell dendrites through the amacrine cell. The inputs and outputs to the amacrine fit these requirements quite well (Famiglietti 1983) and this is the kind of mechanism that our new knowledge of cell physiology opens up; however, there is no other evidence for or against it that I know of.
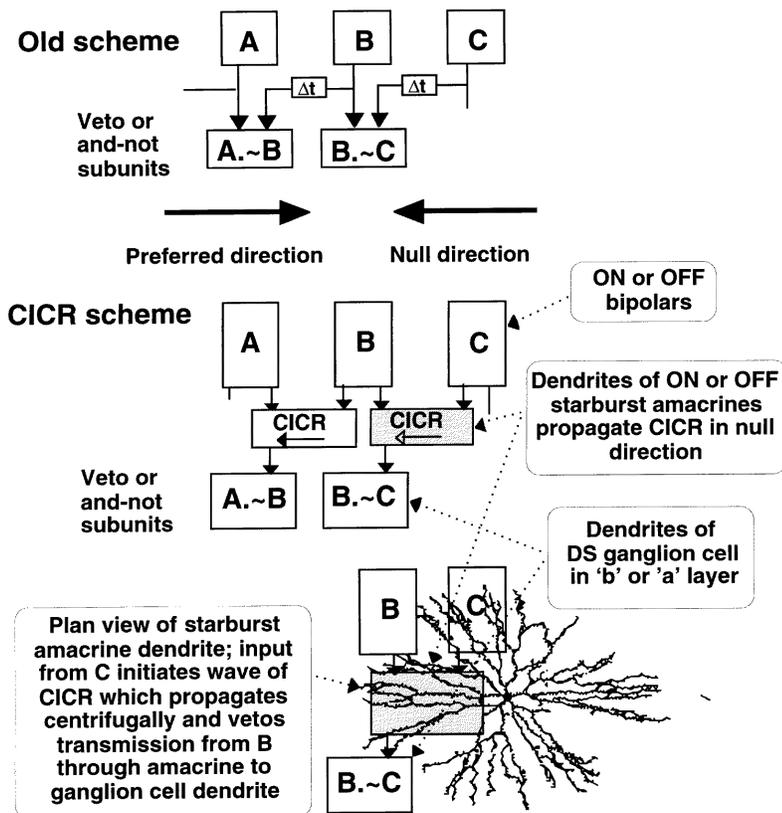
DIRECTIONAL SELECTIVITY

Figure 2. Calcium-induced calcium release (CICR) may provide the veto mechanism for ON–OFF directional selectivity in ganglion cells of the rabbit retina. The top version is the scheme originally proposed by Barlow and Levick (1965): delayed (or more persistent) inhibition is conducted in the null direction, so if C is excited first it vetoes responses that would have been elicited by B, and likewise for B and A. In the CICR scheme it is proposed that the bipolar B normally excites the underlying dendrites of the ganglion cell through the tips of the dendrites of the starburst amacrine cell, but this is vetoed if a wave of CICR has been initiated more centrally along a starburst amacrine's dendrite by excitation at C. Similarly oriented dendrites of another amacrine conduct CICR initiated by B and veto transmission from A to the ganglion cell. The other dendrites of each amacrine veto motions in other directions.

5. Temporally sensitive Hebbian super-synapses

Turning to cortical neurons, figure 3 shows an idea that would make these into enormously powerful elements for storing and responding to spatio-temporal patterns or 'phase sequences'.

This depends upon synaptic mechanisms with different time courses at a single synapse, perhaps triggered by a single neurotransmitter. At the top are shown the synaptic potentials that would be produced by each of four postulated post-synaptic processes, if each occurred alone. In fact, they are triggered together, so the rather complex EPSP shown in the second
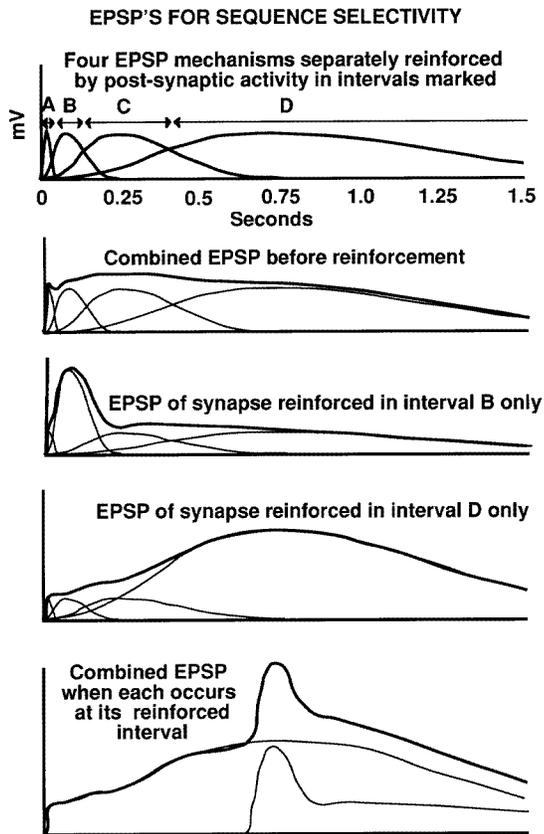
EPSP'S FOR SEQUENCE SELECTIVITY

Figure 3. Hebbian super-synapse capable of storing the delay between pre-synaptic activity and reinforcement by post-synaptic activation. The top panel shows four postulated synaptic mechanisms with different time courses for their EPSPs. These are separately reinforced if post-synaptic activity occurs in the time intervals marked and increase in amplitude when this happens; otherwise they decrease. The second, third and fourth panels show the combined EPSP before reinforcement, after reinforcement in interval B and after reinforcement in interval D. The last panel shows the EPSP from two synapses, one reinforced in B and one reinforced in D, when the D-reinforced synapse is activated first followed by the B-reinforced one at the appropriate interval. A large combined EPSP results, whereas for other sequences and timings the EPSP is smaller and often little larger than for each alone. A neuron provided with such synapses would become selectively sensitive to spatio-temporal input patterns that succeed in causing post-synaptic activity and would thus be an ideal mechanism for storing and detecting phase sequences.

panel is produced. But this is a Hebbian synapse, so if a post-synaptic action potential occurs it will increase the potency of one or more of the mechanisms; it is assumed that each mechanism is reinforced in this way when the post-synaptic action potential occurs near its peak. Any mechanism not so reinforced becomes weaker.

The third and fourth panels show what happens to the combined EPSPs at a synapse or group of synapses if there is reinforcement in the second or fourth interval only. The EPSP is changed in shape and peaks at the interval of the reinforcement.

Now, if two groups of synapses have been reinforced at different intervals and then receive pre-synaptic activation in the right sequence and separated by the right interval,

their peaks will coincide, producing the combined EPSP of the bottom line. With any other sequence or interval a smaller EPSP will be produced, often little bigger than each could produce by itself. Figure 3 shows only four excitatory mechanisms peaking at 25, 75, 250 and 750 ms, but it is possible that there might be more of them covering a larger range; inhibitory mechanisms are also possible and would improve the resolution of the system.

A network of such units would form a sparse representation based on commonly occurring spatio-temporal patterns of input. As with the network proposed by Földiák (1990) it would require anti-Hebbian inhibitory interconnections to decorrelate units that shared a large proportion of their inputs. Changing the units to make them capable of handling spatio-temporal as well as purely spatial patterns would create a network well suited to the task of sorting out the commonly occurring patterns in, for example, auditory speech inputs, or visual images of motion through an environment.

In his book, Hebb (1949) attached great importance to the brain's ability to respond to spatio-temporal patterns, which he called 'phase sequences', and invoked reverberating cell assemblies as a mechanism of short-term memory that would make this possible. The intracellular mechanism proposed here meets both the spatial and temporal requirements for selective response to phase sequences and thereby provides an ideal mechanism for them.

6. Conclusions

From this discussion the general conclusion is that important computational mechanisms exist at the intraneuronal level and that cellular physiology provides the key to understanding these. Specifically, it seems possible that a single synapse could store the time delay between arrival of transmitter from pre-synaptic terminals and post-synaptic activity. The fact that temporally sensitive Hebbian super-synapses have not already been described is not good evidence against them, for you do not find such mechanisms without looking specifically for them. But I must admit that when you *do* look for such things, you very often find something a little different; thus, we must be prepared for disappointments and surprises. Nevertheless, I am convinced that computation in the sub-synaptic cytoplasm is a rich field to explore.

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