Cooperativity of unreliable neurons

Recent studies show that many presynaptic neurons must cooperate to generate a postsynaptic output, though the number is still just a tiny fraction of all the postsynaptic cell's inputs.

A typical neuron in the neocortex receives synaptic input from about 10000 other neurons, and a cerebellar Purkinje cell hears directly from more than 100 000 granule cells. What fraction of these synapses must be activated to produce a nerve impulse in the post-synaptic neuron? And, as synaptic transmission is a probabilistic phenomenon, how reliable is the com-munication link from one neuron to the next? A cluster of recent papers address these fundamental questions. Why is this news? Surely such fundamental questions must have been asked repeatedly during the history of neurobiology. The asking has been less frequent than one might think, partly because the techniques for examining individual cell–cell connections with suffi-ciently high resolution have only recently become avail-able, and partly because interest in global questions relating to how the brain computes has not been as intense in the past as it has become in recent years.

The handful of older studies in the literature that addressed these questions concluded that one neuron generally has a very small effect on its target, although this conclusion was based on data for only a few special cases. The more recent studies have confirmed and refined this earlier conclusion, and extended it to more cell types. Furthermore, the recent work has used novel methods to estimate the reliability of synap-tic connections — something that could not have been done before the advent of whole-cell recording because standard microelectrode recording does not provide a sufficiently good signal-to-noise ratio — and has found that some are quite reliable, whereas many are very unreliable, indeed much more so than had been anticipated.

By recording from granule/Purkinje cell pairs in the rat cerebellar cortex, Barbour [1] has recently estimated that transmission across the single synapse that one granule cell makes on its target Purkinje cell generally produces an increase in peak conductance of the target postsynaptic membrane that varies between 0.15 and 0.7 pS (mean 0.21 pS), and that simultaneous activation of about 30 input granule cells would be sufficient to produce a nerve impulse in the Purkinje cell. As a Purkinje cell is estimated to receive synapses from around 150000 granule cells, activity of just 0.03% of a Purkinje cell's inputs would be sufficient to produce an action potential output.

This conclusion is interesting in two respects. First, as only a tiny fraction of the neuron's inputs is suffi-cient to produce an action potential, the number of

combinations of inputs that will result in an output is vast ($\sim 10^{100}$). Second, a relatively large number of input cells contribute to a Purkinje cell output: the esti-mated number of simultaneous inputs required is about 30, but real inputs are usually not synchronous, so a much larger number — but still a tiny fraction of all inputs — would actually be required to produce an input. Furthermore, transmission at the individual synaptic contacts between granule and Purkinje cells is unreliable and of variable efficiency, tending to increase still further the number of active inputs required to produce an output.

Neurotransmitter release is probabilistic, so sometimes a nerve impulse happens, by chance, to release no quanta of neurotransmitter from the postsynaptic termi-nus — a transmission failure occurs. The reliability of a synapse is defined as being the fraction of the time that an arriving impulse produces a postynaptic response (the release probability), and the efficacy of the synapse is a measure of the postsynaptic response, when there is one. According to Barbour's observations [1], individual cells have an efficacy that varies consid-erably from one impulse to the next, and a reliability that is well less than unity (perfect reliability), although the question of reliability was not extensively investi-gated. The cerebellar circuits thus must use algorithms that tolerate unreliability and variable efficacy of indi-vidual inputs. As no single input produces a very large effect, presumably simply averaging over a relatively large population of input neurons — of the order of 100 — gives sufficiently consistent response properties.

Are these conclusions specific to the granule cell/Purkinje cell circuit? Not according to analyses by Gulyás et al. [2] and Otmakhov et al. [3]. Gulyás et al. [2] electrophysiologically studied pyramidal cell–inhibitory interneuron pairs in the hippocampus, and then identified the synaptic contacts responsible for the transmission of information between these cell pairs. They found that a pyramidal cell generally con-tributes only a single synaptic contact to its target inhibitory interneuron (out of the more than 1 000 synapses the cell receives). Furthermore, this synapse was found usually to release only a single quantum of excitatory transmitter (glutamate) that produces a post-synaptic depolarization of from 0.2 to 1.5 mv. Although the efficacy of synaptic transmission, like that between granule and Purkinje cells, is quite variable, the trans-mission is fairly reliable, with an average release proba-bility of 0.75 (and a range of release probabilities from less than 0.5 to over 0.9). These release probabilities

might overestimate the overall reliability of the synapse population, however, as the method for choosing cell pairs for study could well have been biased towards more reliable synapses. No estimates of the number of simultaneous inputs that might usually be required to produce an action potential in the postsynaptic neuron were given, but — assuming a threshold depolarization of about 10 mV — it would probably be in the range 10 to 30.

Otmakhov *et al.* [3] used a clever strategy to estimate the number of simultaneous inputs required to fire hippocampal pyramidal cells. They first found the threshold stimulus intensity for a projection pathway while recording extracellularly from a hippocampal neuron, and then changed to a whole-cell recording mode to find the number of synaptic inputs activated at that threshold. The required number of synchronously active synapses is again around 10 to 30. This would be approximately 0.1% of all the cell's excitatory synapses but, as noted above, such synchronous activity would normally be rare so that usually a larger number of synapses would have to be activated to yield a spike output.

All three of the studies considered above found that synaptic transmission is somewhat unreliable, and an earlier study [4] found that hippocampal synapses tend to release just one quantum of neurotransmitter with low reliability (less than 0.5). The methods used in these studies were not, however, suited to evaluating the reliability of a population of synapses. Rosenmund *et al.* [5] recently introduced a method that estimates the reliability of a large population of excitatory synapses. The idea behind their method is as follows. Apply a drug that irreversibly blocks only open postsynaptic channels, and use a concentration that will block, say, 20% of the channels at a synapse each time the synapse is activated. If every synapse releases neurotransmitter on each stimulation trial, then the size of the synaptic current would decrease exponentially at the rate of 20% per stimulus trial. If, on the other hand, stimulated synapses release transmitter only on every other trial, then the size of the synaptic response would decay more slowly, at a rate of 10% per stimulus. By careful use of this method, then, the release probability for a population of synapses can be estimated by measuring the rate at which the size of the synaptic response decreases with repeated stimulation.

A drug with the required characteristics is MK801, which blocks the *N*-methyl-D-aspartate (NMDA) class of glutamate receptor channels found at excitatory synapses if, and only if, they are open. Rosenmund *et al.* [5] carefully estimated the synaptic blocking rate for a specified concentration of MK801, and then surveyed the release probabilities for a population of synapses

on hippocampal pyramidal cells in culture. They found that the synapses could be grouped into two classes: one with a release probability of about 0.5 and another with a release probability of about 0.1 (although their observations are also consistent with a range of release probabilities from low to high). This means that at even the most reliable synapses, no transmission occurs half of the time, and at the more unreliable synapses, nine times out of ten the postsynaptic neuron receives no information when a nerve impulse arrives at a presynaptic terminal.

Is this gross unreliability of synaptic transmission just an artifact of the cell cultures used in the experiments? Presumably not, because Hessler *et al.* [6] have repeated the experiments in hippocampal slices with the same results: two populations of synapses are present, one with release probabilities of about 0.5 and another, less reliable, population with release probabilities of about 0.1.

In summary, then, these recent studies demonstrate that only a tiny fraction of all a neuron's synapses needs to be activated in order to produce a postsynaptic action potential, but a number (significantly greater than one) of presynaptic neurons must cooperate to generate a postsynaptic output. Individual synapses are, at best, unreliable, in that they pass on information only about half of the time, and many synapses are very unreliable, failing to transmit information nine times out of ten. The architecture of neuronal circuits must therefore be very different from that of the digital computers to which they are sometimes likened. In so far as these conclusions are general, they seem to place severe constraints on possible models for neural computation.

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