Synaptic transmission: **Noisy synapses and noisy neurons**

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The finding that the synapses relaying sensory input to the cortex may have different properties than intracortical synapses has implications not only for sensory processing, but for the role of noise in neural computation as well.

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In order to make sense of a visual scene, the brain must process a continuous stream of input from more than 10^6 photoreceptors. How does the brain cope with what would seem to be a massive case of information overload? In one view, it simply does not — the brain resigns itself to processing only a fraction of the data it receives and tosses away the rest. An alternative view is that the brain is rather more crafty, and compresses the signal rather than discarding it [1]. The sensory signals coming in from the outside world are highly redundant, and in the course of evolution organisms have learned that some signals occur more often than others. Studies on the earliest peripheral stages of sensory processing suggest that they are particularly well adapted to exploiting such redundancies so as to encode naturalistic stimuli efficiently (for example, see [2]).

Such high coding efficiency requires reliable, low-noise biological 'wetware', and indeed the peripheral nervous system seems to have evolved a variety of specialized mechanisms to provide just that. It is less clear, however, whether central circuits employ such high-fidelity encoding strategies [3]. In particular, it appears that communication between cortical neurons is often highly unreliable and noisy. Recent findings raise the possibility that this stochastic variability may not be so much a flaw as a feature that the brain puts to good use.

Messages are passed between most neurons *via* chemical synapses, at which an all-or-none electrical action potential from the presynaptic neuron causes one or more neurotransmitter-filled vesicles to release their contents onto the surface of the postsynaptic cell [4], where receptors turn the chemical message back into an electrical signal. In the course of working on the neuromuscular junction — the synapse between a motoneuron and a muscle fiber — Katz and collaborators discovered more than forty years ago that individual release sites act in a stochastic fashion: when an action potential invades the motoneuron terminal, a given site releases a vesicle of neurotransmitter only some small fraction of the time. In spite of its underlying stochastic mechanism, transmission at the neuromuscular junction is reliable, because the response of the muscle fiber is the average over a very large number (>1000) of individual release sites.

In the cortex, individual synapses seem to be extremely unreliable: the probability of transmitter release in response to a single action potential can be as low as 0.1 or lower [5]. In other words, as many as nine out of ten presynaptic stimuli fail to trigger transmitter release. The critical difference between these cortical connections and those at the neuromuscular junction is that, in the cortex, the synaptic connection between a pair of cells is often made up of only a few release sites, sometimes only one [6,7]. In the cortex, then, the postsynaptic response to a single presynaptic action potential is highly variable, because it is the average over a small and unreliable population. As might be expected, this input variability in turn causes fluctuations in the timing and number of spikes in the postsynaptic cell [8].

In the periphery, reliability is achieved by averaging over many release sites. In the cortex, rich interconnectivity within a restricted volume limits the possible number of such redundant connections. Is unreliable transmission then an inevitable consequence of the biophysics of cortical circuits? Or is this apparent 'noise' somehow used by the cortex to enhance its processing power? In other words, is this apparent 'bug' really a 'feature'?

The notion that noise might be a feature seems at first implausible — what possible advantage could there be, for example, to leaving out nine of every ten words from a telephone conversation? Early work on the neuromuscular junction, however, suggests an important role for low-probability release. Release probability depends on the history of presynaptic activity [9]. At some synapses, if a pair of spikes occurs in rapid succession, the probability of transmitter release is dramatically higher for the second spike; at other synapses, pairs of spikes occurring at particular intervals can cause depression of the response to the second spike. This short-term plasticity effectively turns each synapse into a temporal filter. Probabilistic transmission might thereby provide the dynamic range required for rapid modulation of synaptic efficacy.

A first step to demonstrating a functional role for synaptic variability is to show that different populations of presynaptic cells form synapses with different probabilities of release and undergo different forms of short-term modulation. Just such a set of connections has recently been described by Stratford *et al.* [10]. Using techniques to activate single-fiber inputs onto layer 4 spiny stellate cells in cat visual cortex, they distinguished three distinct synaptic populations differing in their connection strength, failure probability and response-amplitude variability. Using anatomical techniques, they identified these three synaptic populations with: first, inputs from other layer 4 cells; second, inputs from layer 6 pyramidal cells; and third, afferent axons bringing sensory input from the outside world *via* the obligatory relay of the thalamus.

Although the observation that probabilistic transmitter release is modulated in different ways at different synapses is suggestive of a functional role for synaptic variability, the critical question is whether the preponderance of unreliable synapses in the cortex is due to biophysical constraints. To show that it is not requires a counter example: a reliable central synapse which achieves reliability by having a constant release probability close to unity, rather than by averaging over large numbers of individual release sites. It appears that Stratford *et al.* [10] may have found just such a counter example. They report that the two strong inputs — those arising within layer 4 and the putative thalamic inputs — show very few release failures and a low response variability. Volgushev *et al.* [11] have described a connection with similar properties in rat visual cortex.

Stratford *et al.* [10] did not set out to find a reliable synapse. Instead, their goal was to understand how the basic local circuit in the cortex performs primary sensory processing. To this end, the fact that thalamic synapses differ, regardless of how, from their intracortical counterparts has strong implications for the nature of sensory processing in all systems. The fact that the putative thalamic input is stronger and possibly more reliable than some of its intracortical counterparts suggests a privileged role for feed-forward input from the outside world in ongoing cortical information processing.

Before concluding definitively that unreliable synaptic transmission is not a bug, several further steps are required. The most important is to determine whether reliable transmission can be sustained during the persistent activity encountered *in vivo*. Yet the fact that some synapses can be reliable under at least some conditions raises the prospect that synaptic unreliability may be part of information processing, not information loss.

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