INTEGRATION IN THE NEURONS
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When I was in graduate school in the late '30s the neuron was known as an all-or-none mechanism; the synapse was the only point of lability and graded potentials were unknown. Even well into the '40s, during my postdoctoral years, the local, graded potential in the axon due to a just subthreshold stimulus was not generally accepted, although clearly demonstrated by Hodgkin in 1938. Graded response in single units became known at the neuromuscular junction (Eccles et al. 1941) having been anticipated by implication in sympathetic ganglia (Eccles 1935), but for some time these peripheral situations were not regarded as predicting central physiology. The great simplifying concept of the neuron doctrine was well appreciated, in contrast to the alternatives, lumped under the rubric of reticularism. The idea of a continuous reticulum was not dead, in spite of Cajal's spirited argument in his last book (1933); few doubted Cajal but we lacked the convincing evidence of the electron microscope. The model proposed by McCulloch and Pitts (1943) of assemblies of all-or-none elements was only oversimplified to a certain degree.

One of the several quiet revolutions that has swept over neuroscience has been increasing appreciation of the many labile parameters within and among neurons, the multiplicity of extrasynaptic sites for molecular participation in determining neuronal activity and response, the combinatorial possibilities of the numerous dimensions of integration, even at the single cell level. Nevertheless, my reading of current literature indicates a continuing tendency to forget these facts. Model neural networks, which of course must simplify, are just one expression of this tendency, when they are based at all upon the biological reality. Graded signals, not only graded intervals, are seriously overlooked in the common working notion of brain operations. Coding in an information machine should be a first order subject of inquiry; yet it is almost missing from textbooks, meeting programs and research agendas, with some notable exceptions. Reliability of neurons is generally regarded as low. They are treated as inevitably noisy or sloppy, without consideration of the known facts that they can be highly reliable or of the possibility that they might show jitter and stochastic behavior for deterministic or adaptive reasons. "Noise" is more accurately called unexplained fluctuation. The amazing discovery that neural connectivity in real circuits can be worked out has sunk in, but not the realization that this is insufficient to lead to understanding how nervous tissue works. Redundancy is rightly recognized as widespread, though not general; but it is greatly overrated. Many authors underline the dozens, even hundreds of different kinds of neurons, using one or a few criteria, but precious few take into account all the known criteria. With an essay on each of these six topics, the thesis of this group of chapters and of the selected papers, is that a dose of realism is needed, even for modelers who can justify a reasonable degree of simplification.

My interest in integrative mechanisms began with simple experiments on nerve nets in real animals [40-1, 40-2], leading to the conclusion
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that there are probably unpolarized synapses. New evidence, 40 years later, indicates that some, but not all of these are in fact sets of reciprocally polarized terminals (Mackie 1967, 1990). The heuristic suggestions of Gesell (1940; Gesell et al. 1954) led me to confirm his prediction that pacemaker neurons can be altered in their rhythm by weak, imposed direct current [43-3], as already strongly suggested by Auger and Fessard (1929).

Impressed by the curious phenomenon of giant fibers [44-1], I began looking for preparations to exploit the single unit advantages of these systems. The classic anatomy of the squid giant system by Young (1936, 1939), which had led others to study the last third order giant axon, led me to try for the synapse between it and the second order giant endings in the stellate ganglion. This preparation succeeded [46-2, 48-2], the first junction after the neuromuscular junction to be locally studied. It made a striking contrast with the unpolarized electrical synapses in the annelid giant system, which I also studied [45-1, 48-1, 53-2]. It also made obvious the fundamental difference between excitability and responsiveness [52-1, 52-2] and their independent fluctuation. When Susumu Hagiwara joined me and we revisited the squid synapse [57-4] with two intracellular electrodes, one in the pre- and one in the postsynaptic side, it became possible for the first time to say that a synapse could not be electrical. No sign of the arriving pre-spike could be detected in the post-unit at high gain during the one millisecond synaptic delay. It must be chemical, by exclusion.

Even richer in integrative properties proved to be another preparation, also chosen for its access to single units, although not giant in this case—the lobster cardiac ganglion, with its 9 cells. My student, Donald Maynard, started this line (Maynard 1955, 1961); Hagiwara and I [57-6] penetrated and distinguished intracellularly the pacemaker and follower cells. With Otani [59-3] and Terzuolo [56-5, 57-6, 58-4] the integrative parameters were explored further. Watanabe and I [60-1] discovered the modulation of activity in pacemakers by injecting subthreshold slow potentials, but not spikes, in a follower cell. This was perhaps the first case of subthreshold electrical interaction between cells millimeters apart, by contacts of fine processes that cannot conduct impulses. This ganglion was one of the main inspirations for the synthetic essay [61-1] on the various ways that patterned nervous discharge can arise, whether episodic as in a sneeze or iterative as in locomotion, emphasizing the centrogenic capacities, at that time underplayed by major authors. Pattern became the theme of several studies that showed neurons are sensitive to specific temporal sequences, given the same mean frequency (Maynard 1955; [63-3, 67-2, 69-3]).

Several other preparations were studied in this laboratory that have special interest in revealing integrative properties. I refer to sensory receptors, which often model neurons or are neurons (see Section II). Here I mention only two. The frog retinal ganglion cells discovered by Maturana et al. (1960), that only respond to complex stimuli such as small, dark, moving objects, fascinated me and, with the Grüssers, we confirmed and extended their study. One feature, for example, is the memory these cells show, for a number of seconds; also the erasability of that memory, given a new stimulus, shown by some subtypes and not others, presumably via heterosynaptic facilitation or defacilitation [63-1, 63-2, 64-3]. The other preparation I will mention here was the branch of the lateral line nerve in electric fish that proved to carry fibers from electoreceptors, for which we were stimulated to look by the elegant behavioral experiments of Lissmann (1958). One of the surprising features we found was that these receptors manifest a variety of spike codes. The most insightful were those that encode stimulus intensity without change in firing frequency but only in phase relative to other neurons. They were sensitive to shifts of microseconds [61-4, 65-5, 68-5, 86-9]. A selection of the papers on these two preparations will be found in Sections II and III, below.
I. Integration in the Neurons

References

Citations without names, in the form: [year-number], are found in the author's bibliography, page 633 et seq.


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