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The last 10 years has seen publication of several neural models capable of performing concept formation, associative learning and recall, and pattern recognition. At the base of all these models is one or another rule for associative synaptic modification. Thus the exact modification rule seems to distinguish one model from another. Certainly specifying such a rule severely restricts the remaining degrees of freedom left to the modeler.

Our neurophysiological research has concentrated on establishing the existence of at least one such "synaptic learning rule" and, further, on specifying the properties of this rule sufficiently so that a differentital equation describing the modification rule could be reasonably proposed.

The simplest form of the equation is

$$\frac{dm_{ij}}{dt} = y_j(cx_i - m_{ij})$$

m_{ij} is the strength of the synapse formed by the afferent i and the postsynaptic cell j; y_j is the net excitation of the j^{th} postsynaptic cell; c is a positive constant; x_i is the frequency of the i^{th} afferent which by definition is nonnegative. The exact form of y is not known though it does appear to be a nonnegative function that increases with postsynaptic excitation and decreases with postsynaptic inhibition. Often y is assumed to be a linear function of synaptic excitation.

By performing the indicated multiplication it is seen that the term ycx corresponds to Hebb's predicted encoding of correlated pre- and postsynaptic activity. The other term (-ym) is needed to account for the erasable aspect of these synapses. With the linear assumption for the size of y, the equation predicts a globally asymptotically stable solution in which the value of the synapses on a cell go to the dominant eigenvector of the autocorrelation matrix of the inputs.

The initial discorvery of long term potentiation by Bliss and Lømo provides the first clear neurophysiological evidence for a cellular analog of memory storage. Today this experimental model is an even better analog since long term potentiation in the dentate gyrus of the hippocampus is known to be an associative phenomenon dependent upon the correlated activity of convergent excitatory afferents. The combined co-activity of a presynaptic input and sufficient synaptic excitation of a postsynaptic cell produces an increase of the synaptic strength of the particular synapses involved in this co-activity. Moreover, this potentiation is accompanied, at other converging synapses, by the phenomenon of long term depression an erasure-like process that decreases synaptic strength. Those synapses which are convergent to an activated postsynaptic structure but which are themselves inactive during the postsynaptic activity lose synaptic strength.

The experiments are performed using anesthetized rats. The response studied is the extracellularly recorded monosynaptic response elicited when the entorhinal cortex is stimulated and the recording electrode is in the dentate gyrus of the hippocampus. Both a synaptic waveform and, should enough synapses be active, cell firing are measured. It is the synaptic response which corresponds to the synaptic strength of the differential equation. This synaptic response takes place almost immediately after stimulation of the entorhinal cortex so there is no time for disynaptic circuitry to confuse the interpretation of the response we measure.

Critical to these experiments is the fact that both the left and right entorhinal cortices project to both the left and right dentates. This arrangement allows the insertion of two quite distant and independent stimulating electrodes. Thus one electrode is used to activate a small number of synapses which generate our dependent measure. The other stimulating electrode is used to control a very large number of converging excitatory synapses. Stimulation with this second electrode quite effectively fires the postsynaptic granule cells in the dentate. In most situations the test electrode does not activate enough synapses to fire these cells.

"Conditioning" stimulation consists of brief, high frequency trains of duration and frequency within the range that has been observed in the entorhinal cortex of behaving rats.

The initial important observation is that high frequency conditioning stimulation through the test system alone does not alter the test system itself. However, when high frequency conditioning of the test system is paired with high frequency stimulation at the other electrode (which is able to produce a powerful postsynaptic response), then long term potentiation obtains in the test system. That is, paired conditioning through both stimulating electrodes produces an increased synaptic response when the the synaptic response of the weak test system is measured alone. Importantly, high frequency conditioning of the powerful system alone depresses the size of the synaptic response of the weak test system even though the powerful system through which the conditioning stimulation is delivered is itself potentiated.

These experiments, then, show that the powerful synaptic activation is permissive for change while the exact type of change that occurs is a function of the actual activity at each particular synapse.

Although we cannot stimulate and record from a single synapse, the conclusions can be advanced and defined by using logical arguements and the natural advantages of the entorhinal-dentate system. In particular it should be realized that because of the totally bilateral nature of this system there are four responses that can be measured when recording and stimulating bilaterally. In fact the synapses of one weak pathway are totally intermingled with the synapses of the strong pathway which provides the permissive stimulus and in addition are themselves collaterals of the strong pathway terminating in the other dentate. From experiments as described above that take advantage of these facts we draw three conclusions.

1. Long term depression occurs at a synapse that is surrounded by many other synapses that have simultaneously undergone long term potentiation. Calculations show that one such depressed synapse centered within a cubic micrometer is surrounded by 20 synapses that potentiated.
2. Potentiation and depression can be differentially induced at different synapses of the same granule cell. This is deduced from experiments in which electrophysiological convergence is well demonstrated.
3. Potentiation, depression, or no change can occur simultaneuously at sister synapses of one individual afferent.

Such conclusions lead to the further conclusion that individual synapses are individually modu-

lated. In fact by extrapolation we argue that such individual modulation has practically been demonstrated. For no matter how small the weak response, so long as it is measureable, it can be potentiated by the proper paired conditioning.

Concluding that long term potentiation requires convergent co-activity gives rise to several questions including "What is the meaning of co-activity?" Varying the relative time that the conditioning stimulations are delivered through each of the two stimulating electrodes, produces a quantitative definition of co-activity. Using conditioning trains of 17.5 msec duration, simultaneous (±0.5msec) conditioning through the two stimulating electrodes produces the most potentiation of the weak test system. If conditioning of the weak test system follows immediately, or later, conditioning of the powerful input, then the test system is depressed. If the weak system is conditioned and then with a delay of 100 msec or more the strong system is conditioned, the test system is depressed. However, if the weak system is conditioned and within 20 msec of the end of this conditioning train the powerful system is conditioned, then the weak test system is potentiated. Thus co-activity is well-defined to a 37.5 (20+17.5) msec window. It might be seen that the temporal requirements have some qualitative resemblance to classical conditioning. However the result places a very specific contraint on neural models of associative learning. In particular association of external events separated by all but the shortest time requires the use of circuitry that performs as a delay line.

One final issue concerns the unit of postsynaptic integration which makes a decision about the sufficiency of converging stimulation and then goes on to permit synaptic modification. Rather than the cell body as Hebb proposes, our current evidence indicates that individual dendritic domains or branches can function independently. By taking further advantage of entorhinal-dentate anatomy, it is possible to activate synapses on different parts of the granule cell dendrites in a controlled and specific manner. When this is done with minimally sufficient postsynaptic responses, we find that it is possible to independently potentiate or depress synapses in one of the two dendritic domains. At high intensities, however, the dendritic domains show an interaction for potentiation.

If this independence is the normal functioning mode, then this adds substantial complexity to models of the nervous system, perhaps increasing the number of functional units ten-fold.

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