equilibrium conditions, for the instabilities introduce essentially new features.

It may be significant that the characteristic lengths we find are of the order 10^{-2}–10^{-4} cm (equations 5, 12 and 16). Such lengths are large with respect to molecular dimensions. This justifies *a posteriori* a macroscopic treatment of the type we have applied. On the molecular scale we may speak of local thermodynamic equilibrium.

The situation is somewhat similar to that when we compare fluids in laminar or turbulent motion. Again on the molecular scale, we do not expect any difference, for the range of correlation which appears beyond the critical Reynolds number is much larger than the characteristic range of molecular interactions.

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Modifiable Synapses necessary for Learning

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Even the simplest types of synaptic modification might be the basis of memory; and both short term and long term memory may have similar mechanisms.

CHANGES in synapses in the brain may be the basis of at least some forms of memory. Several models have been put forward[1–8] to show that synapses which change in various different conditions can produce the input–output relations of learning behaviour in appropriate neuronal networks. And there has been some discussion[5,8–10] of the question of which of the many possible types of modifiable synapses could account for memory and which could not. This article shows that many of the simple types of modifiable synapses which were previously thought to be incapable of underlying memory are able to do so. The arguments that they would not be able to provide the basis of memory involved assumptions about the nature of temporal coding in the nervous system which cannot easily be justified. Thus a consideration of the logical capabilities of different types of modifiable synapses does not provide reasons for believing in the existence of some categories and not of others. But if one considers the number of anatomical structures required in a memorizing network it is possible to justify a preference for certain types of hypothetical synapses.

I shall also show here that even if the modifiable synapses tend to revert rapidly to their original states after modification, a nervous system which was suitably organized could nevertheless maintain a pattern of synaptic changes indefinitely once it had been set up. Such a process for maintaining memories could also lead the synapses to become eventually more permanently and irreversibly altered. Thus a model can be devised in which synaptic changes underlie both long and short term memory, and in which memories gradually acquire the increased stability in the face of disturbances of the brain which is characteristic of long established memories in both animals and man.

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Logical Capabilities of Modifiable Synapses

Hebb[1] provided the first carefully defined model in which synaptic modification (requiring nearly simultaneous firing of the presynaptic axon terminal and of the postsynaptic cell) could account for learning behaviour. Shimbel[2] and Rosenblatt[3] have described in more quantitative detail various models in which postsynaptic thresholds and synaptic strengths vary when there are different combinations of postsynaptic and presynaptic firing. Eccles[4] pointed out, however, that although some forms of modifiable synapse had been found in the nervous system, models such as these were postulating different and more complicated forms. He suggested that synapses showing something like prolonged post-tetanic potentiation could be responsible for learning; but he did not show in detail any configurations which could achieve in this way even the simplest forms of learning. Burns[5,10] has queried Eccles's suggestion and proposed what amounts to a principle that alterations in the influence of a modifiable cell must depend on activity in more than just the cell which is modified. This principle seems to gain rigorous support from Brindley[8], who showed that a certain class of modifiable synapses (class A), which includes simple facilitating and fatiguing synapses, cannot give rise to the input–output relations corresponding to even the simplest type of classical conditioning in nets with single spike inputs. This conclusion of Brindley's only holds, however, for nervous systems with a particular sort of temporal coding. I shall not attempt here to define rigorously the classes into which different forms of temporal coding could be divided. But I shall show that if events recorded by the nervous system are coded as bursts of impulses rather than as single spikes, then it is possible to use synapses the modification of which results only from their own presynaptic firing to devise a model of any sort of learning or conditioning.

Fig. 1 shows a network which involves a simple fatiguing synapse, which has the basic property of classical conditioning. A burst of spikes at the output R appears every time there is an input burst along the unconditional stimulus pathway US and, if bursts along CS and US are paired, eventually also when there is a burst of spikes along the conditional stimulus pathway CS. The diagrammatic conventions (the same as those of Brindley[8]) are such that each cell requires nearly simultaneous activity in at least two excitatory synapses (hollow circles) before it will fire. Thus the cell I requires spatial summation of influences from CS and from R to fire it. The fatigable axo-axonic inhibitory synapse (black square) initially acts for long enough when it is excited by the first spike of a burst from CS that it prevents all or most of the subsequent spikes of the burst both from reaching R and from firing cell I. But if bursts along CS and US are paired, then the cell I will also fire in bursts. This results in prolonged fatigue of the inhibitory synapse activated by I, so that subsequent bursts along CS will reach R without being cut off after the first spike. Unless the input bursts are very large the network may show to a significant extent the phenomenon of "pseudo-conditioning", for repeated presentation of CS alone produces single impulses (though not bursts) in cell I and may gradually fatigue the modifiable synapse. To eliminate pseudo-conditioning it is necessary to postulate that bursts of spikes are effective at producing fatigue while spikes presented at low frequencies are not. But this does not violate the principle that the synapse is modified in a way which is determined directly by the firing only of its own presynaptic axon, and it is not physiologically implausible. Some degree of pseudo-conditioning may in any case be tolerated in the nervous system, and it could be counteracted by simple habituation in the sensory pathways. Thus a model can be derived with quite plausible assumptions in which a simple fatiguing synapse can provide the mechanism for basic classical conditioning.

To show that the simplest types of modifiable synapse can form the basis for a network which can undergo modifications of any logical complexity whatsoever, it is only necessary to construct the network shown in Fig. 2. This has the property that a burst of spikes at A will reach B if and only if the history of the net includes several bursts at some time fed into C. Such "gating" networks can be used in a quite systematic way to connect up and disconnect appropriate unmodifiable nets when any complex conditions resulting in outputs from separate unmodifiable nets have been satisfied. Disconnexion is achieved straightforwardly by arranging that a connexion is originally made through a relay cell which is

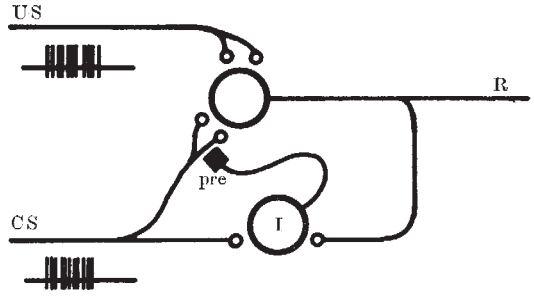

Fig. 1. A network showing the basic property of classical conditioning when it receives inputs of bursts of spikes. Two or more excitatory synapses (hollow circles) impinging on a cell must be active nearly simultaneously for the cell to fire. Thus cell I fires only if both R and CS are firing. The black square represents a (presynaptically) fatigable axo-axonic inhibitory synapse which after activation by a single spike prevents the adjacent excitatory synapse being effective for a period comparable with the length of an input burst. The inhibitory synapse fatigues if its axon from cell I fires several bursts. A burst of spikes at CS produces only one spike at R unless bursts at CS have previously been paired with bursts at US so as to fatigue the modifiable synapse.

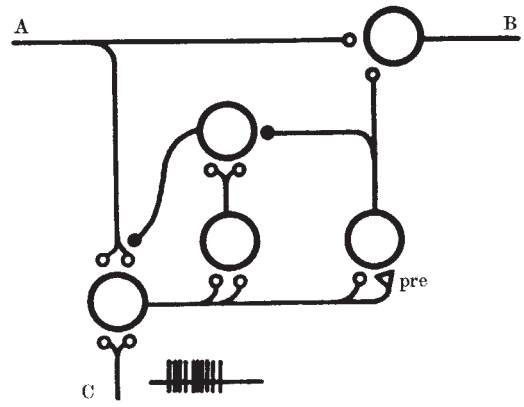

Fig. 2. A "gating" network in which presentation of bursts of spikes at the gating input (C) modifies the network in such a way that the output (B) begins to transmit bursts of spikes from the input (A). Two unmodifiable inhibitory synapses are used (solid circles), one of which is an axo-axonic synapse rendering the adjacent excitatory synapse ineffective for a prolonged period, comparable with the duration of an input burst. The hollow triangle is a (presynaptically) facilitating excitatory synapse which is initially ineffective but which becomes effective after its axon terminal has received several bursts of spikes.

subject to "gated" inhibition. There will obviously usually be more economical ways of constructing a net with complex logical requirements; but this is a possible way.

The two networks of Figs. 1 and 2 involve two different sorts of simple modifiable synapse: a fatiguing inhibitory synapse, and a facilitating excitatory synapse. This simplifies the diagrams as does the inclusion (Fig. 2) of a cell the axon of which has both inhibitory and excitatory collateral terminals on different cells. But it is always possible to replace a simple modifiable inhibitory synapse with an excitatory synapse and vice versa, or to swop a facilitating synapse for a fatiguing one, just by adding to the network one or more unmodifiable interneurones. This corresponds to the fact that any of Brindley's class A synapses can replace any other sort of class A synapse in a net with the same input–output relations[8]. The restriction of Brindley's analysis to nets with single spike inputs is not relevant in the present argument; for if one synapse can replace another for single spikes, it can replace it for every spike of a burst provided, in some cases, that time constants are chosen suitably.

We can say more than that any of the simple modifiable synapses can form the basis for any modifiable net, and show that any modifiable synapse at all can form the basis for any net. For even in the conditions of Brindley's paper[8] both his class B and class C synapses can replace class A synapses. Replacement of class A synapses by class B synapses could not be achieved in networks without transmission delays. But Fig. 3 (devised independently by Brindley and myself) shows how it can be achieved in a network with delays, however small these are. An excitatory synapse which becomes effective only if the postsynaptic cell has fired often (class *B*) is used to replace a simple facilitating synapse (class *A*) which becomes effective only when its own axon has fired often. Every possible type of modifiable synapse belongs to one of Brindley's three classes[8], and so they can all be used to replace class *A* synapses and can therefore be used to construct nets which make possible manipulations of any logical complexity on inputs which are bursts of spikes.

Arguments could be produced in favour of assuming either bursts of impulses or single spikes as the signals in a physiologically relevant network. Neither assumption can necessarily provide a valid basis for generalizing about the nervous system. But it is hard to exclude the use of bursts of spikes as necessarily irrelevant.

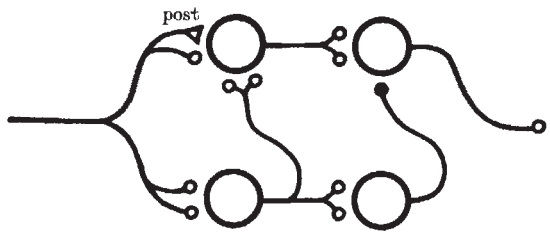

Fig. 3. A network equivalent to a simple facilitating synapse which becomes effective only when its input has been activated frequently. The inputs may be single spikes or (provided the inhibitory synapse (solid circle) results in only brief inhibition) bursts. It uses a postsynaptically facilitating excitatory synapse (hollow triangle labelled "post") which becomes effective only when the cell on which it acts has fired often. In the terminology of Brindley's paper[8] it is a class *A* network made with a class *B* modifiable synapse.

Thus claims that particular sorts of modifiable synapse are incapable of providing the basis for particular sorts of learning in networks of unrestricted size must be based on rather more complex arguments than attempted so far if they are to be of physiological relevance.

Temporal Requirements

There are at least two senses in which long term memories may be consolidated in the nervous system. First, a memory after it has been established may come to be stored in a form in which the changes in the nervous system are intrinsically longer lasting than they were initially. Second, a memory may, and in fact does, become stored in a form which is more resistant to abnormal influences on the brain than it was initially. The evidence that the second form of consolidation takes place is good, and comes from the phenomenon of retrograde amnesia. Memories which are relatively weak in influencing behaviour, but longer established, can be more resistant to concussion, electro-convulsive shock or spreading cortical depression than more recent memories which before the disturbance were stronger and may have been contradictory (for example, ref. 11). Consolidation defined in this way is probably, but not necessarily, associated with the first sort of consolidation I described, in which the changes underlying the memory become intrinsically longer lasting. It might alternatively, for example, be associated with the memory being duplicated and made more redundant.

It is easy to imagine that if synaptic changes are to constitute the mechanism of a memory they must last for at least as long as the memory. Eccles, for example, has argued[9,12] that postulated changes in synaptic efficacy must be "of very long duration—days or weeks". Although this is probably true there is no good evidence that it is so. A careful argument might show that a nervous system in which it were not so would have to be implausibly large. But a mechanism with only short lasting intrinsic synaptic modifications is certainly capable of forming the basis for prolonged memories; and it is possible that such a mechanism is the means by which memories are initially stored while the process of consolidation acts to make the synaptic modifications more permanent. In this way the need to postulate a separate mechanism for short term memory (such as the circulation of impulses in loops) can be avoided. A very crude mechanism by which memory can be maintained and consolidated will be described for the simple network of Fig. 1.

For a relatively short lasting synaptic modification to form the basis for a long term memory it is necessary that the occurrence of the modification should result in the repetition of the local conditions within the nervous system which led to the modification. In a simple network this is simple to arrange. If in the network of Fig. 1 the fatigue of the axo-axonic inhibitory synapse lasts only for some minutes or hours, then the CS must be presented within this length of time or else the conditioning will be "forgotten". To prevent this forgetting we can arrange that there is a source of bursts of spikes within the network which occasionally presents a "pseudo-stimulus" to the conditioning network. We need to interrupt the CS pathway with a relay cell which can be excited either by the real CS or by the "pseudo-stimulus"; and we need to arrange that the output R is inhibited during the "pseudo-stimulus" so that there is no spurious output from the net. The overall arrangement is shown in Fig. 4.

If the time constant of "forgetting" of the modifiable synapse becomes longer and longer the more often the conditions for its modification are repeated, rather in the way that the time constant of post-tetanic potentiation becomes longer with longer periods of tetanus[13], then the network shows memory consolidation.

It is interesting that the model of Fig. 4 has a very striking superficial resemblance to the organization of the nervous system during sleep. During paradoxical sleep there are sporadic bursts of activity in the sensory relay cells of the lateral geniculate nucleus[14,15] and there is steady postsynaptic inhibition of motoneurones[16]. The analogy is not so straightforward in detail, however, for in a nervous system capable of learning on the basis of many different patterns of sensory stimulation it is not easy to see how the memories could be maintained by the injection of "pseudo-stimuli" into a sensory pathway so early. The hypothesis that sleep is important for memory consolidation is directly testable.

Economy

As I have shown, almost any sort of modifiable synapse, even if it does not undergo a long lasting modification, can in principle be the mechanism underlying memory in a network similar (within the limits of present knowledge) to the nervous system. It is obviously true, however, that in very simple networks some sorts of synapse permit particular input–output relations to be obtained with fewer cells and fewer synapses than do others. It is probably true that arguments about the number of elements required would favour certain types of synapse in complex networks as well; but this is hard to prove.

One simple argument does favour some types of synaptic modification on very basic grounds. There is evidence that the number of synapses in the mammalian cerebral cortex exceeds the number of neurones by a factor of something like 10^4, and that one neurone on average has

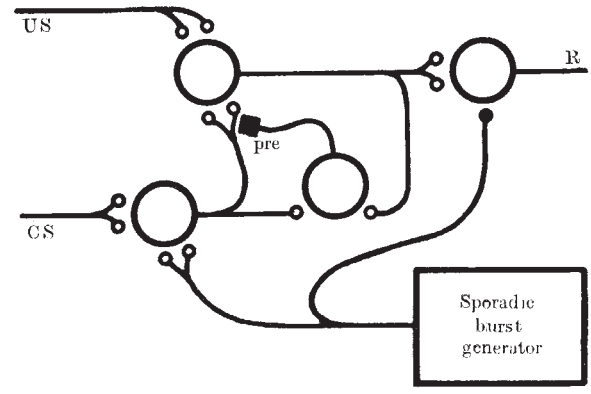

Fig. 4. A network in which a synapse with a short-lived modification produces long term memory. An element which sporadically generates bursts of spikes is added to the basic classical conditioning network of Fig. 1 so as to maintain the fatigue of the modifiable synapse after it has been initiated by the conditioning procedure (pairing of CS and US bursts). The sporadic bursts must occur at intervals shorter than the time in which the intrinsic change of the modifiable synapse would disappear. If the fatigue of the modifiable synapse becomes less and less reversible the more often its axon is made to fire bursts, then the network shows memory consolidation.

synapses on at least 10^2 other neurones[17]. If we accept this last figure, then any mechanism which permits independent modification of the synapses between different pairs of neurones automatically has a maximum possible information storage capacity 10^2 times larger than a mechanism in which all the synapses from or to a particular cell are modified together. This argument would favour the kind of modification conditions (near coincidence of pre and post-synaptic firing) proposed by Hebb[1] and Griffith[7], rather than the change in postsynaptic threshold proposed by Shimbel[2], the gating mechanism proposed by Burke[6], or the facilitating and fatiguing synapses discussed here. But unfortunately we do not know to within a factor of 10^2 what, in any relevant sense, the storage capacity of the brain is. So the argument is hardly conclusive.

Arguments which took account of the means by which the memories were to be stored and retrieved might show discrepancies far larger than 10^2 between the memory capacities available with different types of modification mechanism. But such arguments have yet to be formulated.

Relevance of Experiments

Theoretical arguments about what sorts of synapses may and may not be present in the brain will perhaps turn out not to be essential to physiology, for the question of which types of synapse are actually present may be settled directly by experiment. Bliss, Burns and Uttley[18] have described relevant experiments which suggest that there are synapses which increase their influence when the postsynaptic cell fires without the presynaptic axon, and which decrease their influence if the presynaptic axon fires. But even fairly direct experiments such as these are hard to interpret without ambiguity. If we consider the possibility that inhibitory pathways could be facilitated as well as excitatory ones, then the evidence of Bliss Burns and Uttley[18] is quite consistent, for example, with there being only synapses which require coincidence of pre and post-synaptic firing to increase their strength.

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Conformation of Cholinergic Molecules relevant to Acetylcholinesterase

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Crystal structure analyses of several cholinergic molecules, combined with their relative rates of hydrolysis by acetylcholinesterase, allow one to determine the conformation of labile cholinergic molecules relevant to their interaction with the enzyme.

THE nervous system is a pulse communication system. For most of the peripheral systems acetylcholine [$(CH_3)_3N^+CH_2CH_2OCOCH_3$] is released at the end of one cell, diffuses across a synaptic space of approximately 2×10^4 pm, stimulates the next cell, either another nerve cell or a motor cell, and is hydrolysed by the enzyme acetylcholinesterase to choline [$(CH_3)_3N^+CH_2CH_2OH$]. In this article we describe the conformation of the labile molecule acetylcholine on interaction with the hydrolysing enzyme acetylcholinesterase on the basis of a correlation between the crystal structures of several different molecules and the relative rates of their hydrolysis.

Acetyl-α-methylcholine is rapidly hydrolysed by bovine erythrocyte acetylcholinesterase, the L(−)S-enantiomer at 97 per cent of the rate of acetylcholine and the D(+)R-enantiomer at 78 per cent[1]. The L(+)S-enantiomer of acetyl-β-methylcholine is hydrolysed at 54 per cent of the rate of acetylcholine and the D(−)R-enantiomer is a weak inhibitor of the enzyme[1]. Acetylthiocholine is hydrolysed at about the same rate as acetylcholine[2] by acetylcholinesterase, as is also acetylselenocholine[2]. The recent analyses of the crystal structures of these and other cholinergic molecules, aided by model building with CPK space-filling and MRC wire atomic models, make it possible to determine the optimum conformation of labile substrates interacting with the enzyme and to explain in a logical way the variations in the rates of hydrolysis.

We have analysed the crystal structure of D(+)R-acetyl-α-methylcholine iodide[3] and found two different conformations of the molecule in the asymmetric unit. Torsion angles of both enantiomers of the two conformations are given in Table 1. (The torsion angle τ of the bonded group A–X–Y–B is the angle between the planes AXY and XYB. Viewed from the direction of A it is positive if clockwise and negative if anticlockwise. Values of $\tau = 0°$, 60°, 120° and 180° are termed syn-planar, syn-clinal, anti-clinal and anti-planar, respectively.)

One conformation is syn-clinal[4] at C5–C4, as are most cholinergic molecules[5]. The other conformation has τ O1–C5–C4–N = 148°, midway between anti-clinal and anti-planar. This conformation is unusual for N^+–C–C–O– groups[6] and indicates the lability of these molecules and the possibility of multiple stable conformations with very nearly equal energies. The rates of hydrolysis of acetyl-α-