Dynamics of Storage and Recall in Hippocampal Associative Memory Networks

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Abstract. A major challenge to understanding cortical function is the complexity found both at the single cell and microcircuit levels. This review covers theoretical studies aimed at elucidating dynamic signal processing within hippocampal pyramidal cells. This processing involves both the intrinsic pyramidal cell properties as well as the microcircuit of inhibitory interneurons that synapse onto the cell. These factors are considered within the framework of associative memory function in areas CA1 and CA3 of the mammalian hippocampus.

1 Introduction

Considerable detail is now known about the individual neuronal cell types found in the cortex, and the circuits they form. However, mathematical models and computer simulations typically concentrate on a particular level of detail, either the single cell, or networks with simplified cellular descriptions. It is both possible and desirable to try to formulate functional models of cortical networks that include known details of all cell types and their detailed microcircuitry. This review considers theoretical modelling studies that cover aspects of the function of the mammalian hippocampus. Firstly, details of the microcircuitry formed by pyramidal cells and the variety of inhibitory interneurons in regions CA3 and CA1 of the hippocampus are given. Then single cell studies of hippocampal pyramidal cells are introduced. Finally, certain network-level models that treat these hippocampal areas as associative memories are described. Only models that attempt to include biophysical details of the cell types and realistic microcircuitry are included here. The emphasis is on providing an overview of a breadth of work that is not usually considered together, at the expense of depth in any particular aspect.

Associative memory is one of the oldest artificial neural network (ANN) paradigms. More than any other ANN, it is also plausibly a model of how certain brain regions may operate. Of particular interest here is the mammalian hippocampus, in which regions CA3 and CA1 have been proposed to be auto- and heteroassociative memories, respectively [80]. This has led to the formulation of biophysically realistic network models of associative memory based on

the architecture and operation of these hippocampal areas [55, 82]. A number of factors must be considered when moving from an ANN model to a biophysical model, including:

- how are patterns of information coded by neuronal spikes?
- what, if anything, constitutes a rhythmic clock cycle?
- how are storage and recall modes separated in space and time?
- what roles do the different neuronal types play?

The work described here makes the premise that gamma frequency rhythms (30-80Hz) may constitute a basic clock cycle [9, 45, 55]. A slower theta frequency rhythm (5-12Hz) is superimposed on this clock cycle and controls phasing of storage and recall [23, 26, 82]. This is based on the hippocampal activity seen in rats exploring a novel environment, absorbing and storing new spatial information [60]. These models do not attempt to include all behavioural states in rats, such as associated with sharp waves [7], nor necessarily any states found in other animals, particularly primates. Nonetheless, they provide explicit biophysical formulations of associative memory operation and provide an excellent viewpoint from which to try to understand neuronal cellular and microcircuit functioning in a broader context.

2 The Hippocampal Microcircuit

The dominant cell type in many areas of neocortex and hippocampus is the pyramidal cell (PC). The outputs from these cells are excitatory and the networks they form are likely to be the principal information processing structures in these brain regions. When ANNs are considered as models of the brain they are typically being equated with networks of PCs. Pyramidal cells, both in hippocampus and in neocortex, are surrounded by a variety of inhibitory interneurons (INs). These INs differ in morphology, pharmacology and connectivity [17, 46, 52]. Understanding their functional roles is a great challenge. ANN models usually contain only a single cell type (PCs) within a simple network architecture. Many of the details of the microcircuitry involving pyramidal cells and these interneurons is now known for the CA1 and CA3 regions of the hippocampus [17]. The basic hippocampal microcircuit is shown in Figure 1.

The first feature to note is the spatial segregation of excitatory input from different pathways onto a PC [34]. In CA1, the Schaffer collateral input from CA3 PCs is largely to stratum radiatum (SR), constituting the proximal region of the apical dendritic tree. Recurrent collaterals from other CA1 PCs synapse on the basal dendritic tree (stratum oriens: SO). Perforant path input from layer III of entorhinal cortex (EC) reaches the distal part of the apical dendritic tree (stratum lacunosum-moleculare: SL-M). In region CA3, input to stratum radiatum and stratum oriens is largely from other CA3 PCs. Input to the distal apical tree comes from layer II of entorhinal cortex. A third excitatory input in CA3 comes from granule cells of the hippocampal dentate gyrus which form the mossy fibre synapses in the very proximal region of the apical tree.

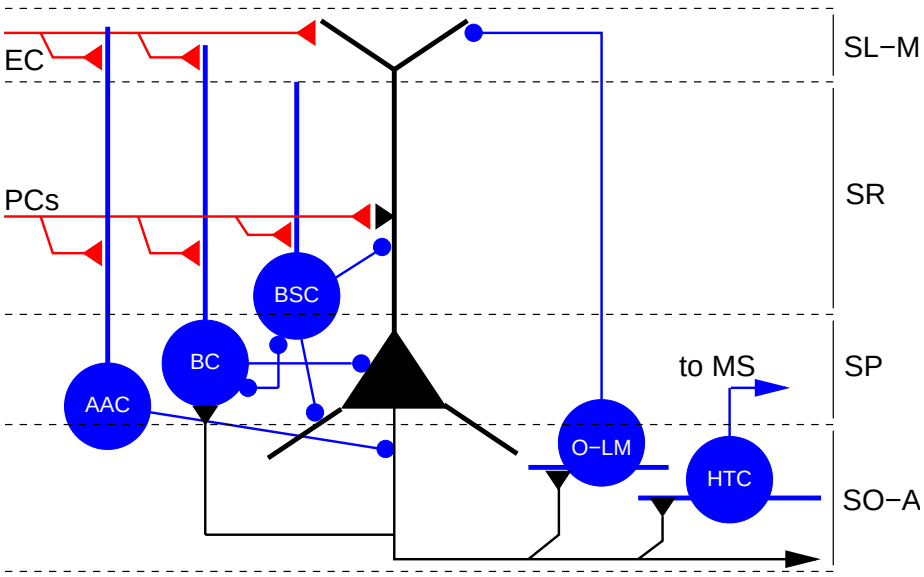

Fig. 1. Microcircuit architecture of INs surrounding a PC in the CA1 or CA3 region of the hippocampus. Small triangles are excitatory synapses and small circles are inhibitory synapses. Adapted from Paulsen and Moser [62]. See text for details.

Though a complete catalogue of interneuronal types remains to be determined, several classes can be distinguished on anatomical and pharmacological grounds [17, 46, 52]. These include basket cells (BC), bistratified cells (BSC), axo-axonic (chandelier) cells (AAC) and oriens lacunosum-moleculare (horizontal) cells(O-LM). These INs are all inhibitory GABAergic cells. As illustrated in Fig. 1, like excitatory afferents, different IN types target specific spatial regions on PCs. They also receive excitatory input from particular pathways and may form synaptic (inhibitory) and gap junction (excitatory) connections with other INs. Other cell classes include horizontal and radial trilaminar cells and INs that only synapse onto other INs [17]. A subclass of horizontal trilaminar cells (HTC) send axon collaterals out of the hippocampus to the medial septum (MS). There may also be inhibitory projections between hippocampal subfields (CA1 to CA3).

In addition to targetting specific dendritic localities on PCs, different classes of IN also exhibit a specific spread in their network connectivity across cells. Typically, an IN makes synaptic connections within a defined local area, unlike PCs that make widespread connections. Total IN numbers may be only 10% of the total cell population, with a single PC innervating hundreds of INs and an IN innervating several thousand PCs [17]. The spread of IN connections may be highly focussed. For example, a single O-LM cell makes connections in the distal dendritic tree of PCs with a spread that exactly matches the spread of excitatory input from a single entorhinal cell onto the same PC dendritic location

[17]. The nature of the inhibitory connections also differs with IN class. Basket and axo-axonic cells make several powerful connections onto the perisomatic and axon initial segment regions of a single PC, respectively, indicating the ability to strongly influence spike generation and output in the PC. In contrast, bistratified cells make more diffuse connections, with no more than one connection on a particular dendritic branch [17].

There is not a one-to-one correspondence between morphology, pharmacology and electrical activity in INs, making classification very difficult [17, 46, 52]. Basket cells, in particular, include at least two types that are distinguishable on pharmacological grounds and appear to have distinct functional roles within the hippcampal microcircuit [16]. In the associative memory models to be described later in this paper, the basket cells are likely the parvalbumin (PV)-containing cells. Recent data indicates that certain cell types may be distinguished by their firing patterns in different brain states [41].

What does the microcircuit do? Most well studied, both experimentally and with mathematical modelling, is the contribution of the microcircuit to generating and stabilising oscillatory activity at different frequencies [78]. Though the mechanisms that produce oscillations are not the focus here, two different oscillations, the theta and gamma rhythms, play an important part in certain models of associative memory function in the hippocampus. The precise mechanisms underlying theta (5-12Hz) are complex and include extra- and intrahippocampal sources [8, 61]. Gamma (30-80Hz) is strongly determined by the intrinsic cellular and synaptic properties of the hippocampal microcircuit [83] and may be controlled by external inputs to the hippocampus [13]. Here we are concerned with the possible functioning of the microcircuit as an *information processing* construct. In the final sections of this paper we will consider the possible role of this microcircuit in controlling storage and recall within associative memory networks.

3 Signal Processing in Neurons

Neurons integrate synaptic input from other neurons for the end purpose of producing their own output signals for propagation to receiving neurons. The synaptic input also results in signals that are internal and localised within a neuron and determine synaptic plasticity. The integration of synaptic input involves the spatial and temporal summation of signals from different synapses and the interaction of these summed signals with the intrinsic membrane properties of the neuron. These properties are determined by the typically heterogeneous distribution of different types of ion channels throughout the dendritic tree.

3.1 Intrinsic Properties of Pyramidal Cells

Increasingly detailed knowledge is being obtained about the spatial distribution of ion channels in different neuronal types, as recently reviewed in Migliore and Shepherd [59]. CA1 pyramidal cells are amongst the most well characterised in

this regard. Sodium and calcium channels maintain a relatively uniform density out into the apical dendritic tree, though sodium channel characteristics and the type of calcium channel may change with distance [38, 50]. The fast A-type potassium channel and the mixed cation H channel increase in density roughly 6-fold over several hundred micrometers distally in the apical tree [30, 47].

Voltage-activated ion channels are characterised by the membrane voltage range over which they open (activate), and the time course of their opening and closing. Certain channel types will remain open while the membrane voltage is within the appropriate range. Other channels inactivate with a certain time course, that is they will close some time after they have opened, even though the membrane voltage may still be within the range at which these channels first open. Many ion channels activate when a cell is depolarised, that is, when the membrane potential moves towards zero from rest. Such channels include sodium, calcium, delayed rectifier (DR) and A-type (A) potassium, and the mixed cation M channels. Other types, such as the H channel are activated at hyperpolarised potentials. Sodium, calcium and the DR and A potassium channels activate quickly with millisecond kinetics. The M and H channels activate with time courses in the tens of milliseconds. These channel types will be more extensively discussed than others in what follows. Slower channels, such as the calcium-activated slow-after-hyperpolarizing-potential potassium channel (AHP), have activation dynamics in the range of hundreds of milliseconds to seconds, and contribute to spike frequency adaptation.

Functionally, these voltage-activated ion channels may be classified as *amplifiers* or *suppressors* of changes in membrane voltage. Ion channels whose reversal potential and activation range are in the same direction as a change in membrane potential away from rest act as amplifiers. The current generated by the opening of these channels will move the voltage further from rest. Sodium and calcium channels are amplifiers. In contrast, various potassium and mixed cation (M and H) channels are suppressors of voltage change. Movement of the membrane potential away from rest into the activation range of these channels is in the opposite direction to their reversal potential. Consequently the current generated by the opening of these channels will tend to nullify the original change in potential. The action potential (AP) is the classic example of the interaction of amplification by sodium channels and suppression by potassium channels. Fast channels such as these, with dynamics in the millisecond range, are responsible both for generating action potentials and shaping synaptic voltage responses (EPSPs) as they travel through the dendritic tree to the soma. Slightly slower channels, such as M and H, that are suppressors of voltage change, act as high pass filters and contribute to electrical resonance in neurons, as will be described below.

A detailed exposition of the different ion channel types found in hippocampal pyramidal cells and their dynamic characteristics is given by Borg-Graham [6].

3.2 Signal integration

The dynamic characteristics of different ion channels and their spatial distribution within dendritic trees gives them specific functional roles for synaptic signal integration. Ion channels contribute to the time course and summation of synaptic input. Here we consider work that addresses how excitatory inputs that are widely distibuted across the apical dendritic tree of PCs summate to affect cell output in the soma. Do such inputs sum linearly? Will distant inputs have as much influence on cell output as those close to the cell body?

Synaptic scaling One consequence of synapses being spatially distributed across a dendritic tree is that those synapses that are more distant from the cell body may have less impact on the voltage response at the soma than more proximal synapses, due to membrane current leakage as signals travel through the dendrites. Either distal synapses need to produce larger local EPSPs or signals need to be amplified as they travel along the dendrites to overcome this disadvantage. There is experimental evidence that the synaptic AMPA conductance does increase with the distance of the synapse from the soma in the apical dendrites of CA1 pyramidal cells [2, 49].

Temporal summation The rising density with distance from the soma of A and H channels in the apical dendritic tree of CA1 PCs may in part determine the temporal summation of synaptic inputs. In a series of experimental and modelling studies, Magee [47, 48] has demonstrated that deactivation of the H current may act to shorten the time course of distal EPSPs. This has the effect that the temporal summation of trains of EPSPs is independent of their spatial location within the dendritic tree.

In a modelling study, Migliore [57] has demonstrated that activation of the A current and deactivation of the H current are instrumental in restricting the temporal integration of distal and proximal inputs to a time window of around 20msecs within which the distal input precedes the proximal input.

Spatial summation For a pyramidal cell to produce an output it typically needs to receive a number of contemporaneous inputs. These inputs are likely to be spatially distributed across a portion of the dendritic tree. Their spatial locations, in combination with the local membrane characteristics, will determine how the different inputs summate.

Various functional scenarios depend on the mathematical form of input summation. In a study of pattern recognition by CA1 PCs, Graham [19] considered a situation in which a pyramidal cell needed to be able to accurately distinguish the number of simultaneous excitatory inputs arriving at random locations within the *stratum radiatum* portion of the apical dendritic tree. The amplitude of the voltage response in the soma was used as the criterion for measuring the number of inputs. Different spatial distributions of the same number of inputs produced

slightly different voltage amplitudes, introducing noise into the measurement that limited the discrimination that could be made.

Different characteristics of the synaptic input and the membrane properties of the dendritic tree were explored. The basic case consisted of all inputs (in the form of single APs) arriving at exactly the same time onto a dendritic tree containing only a leak conductance (passive membrane). A comparison was made between the distributions of voltage amplitudes for 200 compared with 100 inputs to synapses at different random spatial locations. Amplifying mechanisms at each synapse and in the dendritic membrane that boosted distal inputs all acted to improve the signal-to-noise ratio between the amplitude distributions of 200 and 100 inputs. This equates with an improvement in the cell's discrimination of the number of simultaneuous inputs reaching its dendritic tree. The amplifying mechanisms included (1) scaling of the synaptic AMPA conductance so that the EPSP amplitude at the soma of a single input was independent of synaptic location, (2) an NMDA component of the synaptic EPSP, (3) a uniform distribution of persistent (noninactivating) sodium channels in the dendritic membrane, and (4) a uniform distribution of low-voltage-activated calcium channels. These mechanisms improved input discrimination when included individually and in combination.

Two extra sources of noise were included. Firstly, rather than the APs arriving synchronously at all the synapses, the arrival times were uniformly distributed across a short interval of 20msecs. Secondly, a random variation in the maximum synaptic conductance was added to each synapse to simulate quantal variance. As might be expected, discrimination ability was reduced by quantal variance. Intriguingly, the temporal variance of arrival times actually increased discrimination ability. This was presumably due to a reduction in nonlinear summation at nearby synapses and a randomisation of EPSP arrival times at the soma.

Linear and nonlinear summation Using a very detailed model of a CA1 pyramidal cell, Poirazi et al. [64, 65] investigated the impact of the relative spatial location of synapses on the summation of their EPSPs. They considered the cellular response to active synapses clustered locally on a dendritic branch, with a number of clusters on different branches. The computer simulations demonstrated that the clustered inputs on a single branch summed nonlinearly due to amplification by NMDA, sodium and calcium currents. The peak voltage output from a dendritic branch was a sigmoidal function of the number of active inputs on that branch. However, the voltage signals propagating from separate branches summed linearly in the trunk of the apical dendritic tree due to rectification by the A current. Thus they characterised the pyramidal cell as a two-layer network in which the input at the soma consisted of the linear sum of a set of sigmoidal units, corresponding to the dendritic branches.

3.3 Resonance

The dynamics of neuronal membrane and ion channels causes electrical resonance in neurons. The membrane capacitance and resistance (or leak conductance) provide low-pass filtering of electrical signals. This is most clearly seen if a neuron is driven by a subthreshold oscillatory current. The amplitude of the voltage response gradually decreases as the current frequency increases, for the same current amplitude. In contrast, relatively slowly activating ion channels that act as suppressors of voltage change provide high-pass filtering. These channels do not activate sufficiently fast to attenuate high frequency changes in membrane potential, but will act to suppress lower frequency changes. This combination of low- and high-pass filtering results in resonance. For stimulation by a subthreshold oscillating current of some fixed amplitude, the neuronal voltage response will have a maximum amplitude at some frequency of oscillation intermediate to the range of low- and high-frequency attenuation. Ion channel currents that amplify voltage changes can provide an amplification of the resonance peak. An introduction to neuronal resonance is provided by Hutcheon and Yarom [33].

A recent experimental and modelling study has demonstrated resonance in CA1 PCs [32]. Resonance at both depolarised and hyperpolarised potentials was evident, with a resonance frequency of around 7Hz in both cases. This corresponds to the theta frequency range. At depolarised potentials, high-pass filtering resulted from activation of the M-current, with the resonance peak being amplified by a persistent sodium current. At hyperpolarised potentials, high-pass filtering was provided by the H-current and little amplification was evident.

Different neuronal types have different resonant characteristics. In hippocampus, horizontal cells have a similar resonance frequency to PCs, while fast spiking interneurons resonate in the beta-gamma range of 10-50Hz [63]. This is indicative of different ion channel distributions in different cell types. Subthreshold resonance also translates into the spiking regime. An oscillating current amplitude that does not normally produce spiking activity will result in neuronal spiking around the resonant frequency.

The functional implications of intrinsic neuronal resonance are not yet clear. One possibility is that it acts to accentuate and stabilise network oscillations, particularly at theta frequencies.

Multiple roles for the H-current The hyperpolarisation-activated mixed cation H-current has potentially multiple roles in regulating neuronal activity [69]. The work of Magee [47, 48] and Migliore [57] demonstrates that deactivation of the high density of H channels in the apical dendritic tree of PCs can act to shorten the time course of distal EPSPs and so normalise temporal summation of inputs.

In contrast, activation of the H-current results in theta frequency resonance. The same effect that produces resonance can also result in PC spiking following hyperpolarising inhibition due to rebound depolarisation through H-current activation. The H-current thus plays a role in entraining PC firing to rhythmic network inhibition and promoting network oscillations at theta frequency [11].

3.4 Synaptic plasticity

Internal signals As well as determining the spiking output of a neuron, synaptic input, in combination with the intrinsic membrane properties, determines voltage and calcium signals that are internal to the neuron. Such signals play a role in synaptic and cellular plasticity.

The standard scenario of Hebbian learning requires a measurement of both pre- and postsynaptic activity at a synapse to drive plasticity. The postsynaptic activity may be signalled by back-propagating action potentials (BPAPs), which in turn affect the calcium concentration at a synapse. The calcium concentration determined by both pre- and postsynaptic activity may be the signal which is most directly related to the magnitude and direction of synaptic change. This standard scenario is considerably complicated by the possibility of active processes contributing to local dendritic calcium spikes that are not associated with BPAPs. Goldberg et al. [18] discuss the consequences of such spikes for cellular plasticity.

Action potentials originating at the soma, or axon initial segment, may be actively propagated back into the dendritic trees of pyramidal cells [75, 76]. This is due to the high density of sodium channels found in at least the main trunk of the apical dendritic tree. The rising density of A-channels with distance from the soma, and sodium channel inactivation kinetics, result in an attenuation in back-propagating action potential (BPAP) amplitude with distance [30, 56, 58]. Block of the A-channels results in a significant reduction in the BPAP attenuation and may allow the emergence of slow calcium spikes in the dendrites [30]. These phenomena are neatly summarised in the online supplement to Poirazi et al. [64, 65], whose model is able to reproduce the effects.

Mechanisms that alter BPAP amplitude and propagation will also affect synaptic plasticity [74]. Thus the A-current in the apical dendrites provides one such mechanism for regulating the signals underlying synaptic plasticity. Switching off the A-current effectively switches on plasticity. Appropriately timed synaptic input that precedes a BPAP achieves this by inactivating the A-current for the time window of BPAP propagation [58]. The A-current may also be reduced by neuromodulators such as acetylcholine, which acts to shift the A-channel activation kinetics to more depolarised potentials [29].

Models of synaptic plasticity A number of recent models [40, 71, 70] have attempted to capture the basic interaction between internal and external signals in driving synaptic plasticity. These models seek to reproduce data demonstrating spike-timing-dependent plasticity (STDP) [5]. If postsynaptic activity occurs within a small time window of around 20msecs following presynaptic activity, then the synapse increases in strength (long-term potentiation: LTP). If, however, the postsynaptic activity precedes the presynaptic activity within a similar temporal window then a reduction in synaptic strength (long-term depression: LTD) occurs.

In these models, synaptic strength is altered as a function of calcium entry [40, 71] or the rate of voltage change at a synapse [70]. Calcium entry occurs

through NMDA channels and voltage-gated calcium channels. A BPAP with an after-depolarising potential is required to reproduce the temporal characteristics of STDP. Saudargiene et al. [70] investigated the significance of BPAP shape and demonstrated that fast BPAPs, as seen in the proximal apical dendritic tree, produce STDP with both LTP and LTD components. However, slower BPAPS, as seen the the distal tree, result in only LTP during the time window of STDP.

3.5 Neuromodulation and metaplasticity

As apparent from the discussion above, signal integration and generation in pyramidal cells, and other neuronal types, is a function of external input and the intrinsic membrane properties of the neuron. Any alteration in synaptic and extrasynaptic membrane properties will change the input-output functionality and plasticity of a neuron. Pyramidal cells in the hippocampus receive a wide range of so-called neuromodulatory inputs that alter ion channel properties, rather than contribute directly to voltage signals. Neuromodulators alter the membrane characteristics by blocking or enhancing specific ion channels and by altering their dynamics. Such changes may cover the entire cell, or be directed to specific spatial locations, such as the pre- or postsynaptic membrane. The end result is a change in the voltage response of the neuron to synaptic input. Such neuromodulators include acetylcholine, dopamine and serotonin, amongst others.

Modulatory changes may be directed at synaptic plasticity. As indicated by the STDP models, synaptic calcium levels [85] are a major determinant of synaptic plasticity. Alterations in the calcium response to voltage signals, or the relationship between calcium level and changes in synaptic strength will modify the *learning rule* employed by the neuron. This is known as *metaplasticity* and can be effected by neuromodulators and by the history of activity at a synapse [1, 10, 67]. For example, acetylcholine may reduce the A current in CA1 PC dendrites, allowing large amplitude BPAPs to reach much of the dendritic tree [29], potentially enhancing calcium entry and thus synaptic plasticity.

Acetylcholine has been given a central role in biophysical models of associative memory [22, 21, 55]. Pyramidal cells and interneurons in the hippocampus are subject to multiple effects from acetylcholine via two broad classes of acetylcholine receptors (muscarinic and nicotinic), that have distinct spatial locations and dynamics [66]. The effects of acetylcholine include reducing various intrinsic potassium currents, including the A current, and high-threshold calcium currents, whilst increasing low-threshold calcium currents [55]. Presynaptic receptors result in presynaptic inhibition of transmitter release at certain pathway-specific glutamatergic and GABAergic terminals [27, 28, 16]. NMDA currents may be increased [66]. These effects combine to significantly alter cellular activity and plasticity, and overall network dynamics. The possible functional effects for associative memory are considered in the following section. A review of computational modelling of various forms of neuromodulation has been conducted by Fellous and Linster [12].

3.6 Summary

This section has covered a range of work dedicated to understanding the signal integration properties of individual neurons, particularly hippocampal pyramidal cells. Synaptic input impinging on the PC dendritic tree is filtered by the intrinsic membrane properties of the dendrites. The resultant voltage signals determine the cell's spiking output as well as synaptic and cellular plasticity. Amplification and suppression of voltage changes by the heterogeneous population of voltage-gated ion channels in the PC membrane clearly modify the effect of synaptic input on cell output. Interneurons also exhibit particular populations of ion channels that contribute to their distinctive firing patterns [46, 52], and presumably their functional roles.

4 Associative Memory Neural Networks

4.1 Associative memory

The associative memory paradigm involves the storage of information so that it is content-addressable rather than index addressable. That is, a partial or noisy cue pattern is used to recall a pattern stored in the memory, rather than the index, or address, of where the pattern is stored. Such a memory is called *autoassociative* if the cue pattern results in the completion of that pattern during recall. The memory is *heteroassociative* if a cue results in a different pattern being recalled with which it was associated during pattern storage.

Neural networks can act as associative memories in which memory patterns are represented by neuronal activity. Storage takes place via some form of Hebbian synaptic learning rule. A basic rule that strengthens the connection between two neurons that are coactive (like LTP) is sufficient. A rule that includes synaptic LTD when pre- and postsynaptic activity is anticorrelated increases memory capacity [84]. During recall, the initial network activity determined by a cue pattern will result in those neurons that belong to the relevant stored pattern receiving, on average, the strongest synaptic input. By the setting of a suitable threshold, through network inhibition, only those neurons belonging to the pattern should remain active, completing the recall process.

A network containing recurrent connections between a single pool of neurons can act as an autoassociative memory. A pattern of neural activity is associated with itself by the strengthening of the recurrent connections between the active neurons. Such a network can also be used to heteroassociatively store a sequence of patterns. If the sequence is presented to the network in a temporal order, with some short time between each pattern, then a temporal Hebbian learning rule can associate the activity of one pattern with the next pattern in the sequence. A two-layer network in which one (input) layer of neurons sends connections to a second (output) layer can act as an heteroassociative memory. Hebbian plasticity of these feedforward connections can associate activity in the input layer with activity in the output layer.

Biophysical models In this section we consider models that examine the implementation of associative memory function in biophysical networks of spiking neurons. The models are based on regions CA1 and CA3 of the mammalian hippocampus. They treat CA3 as an autoassociative memory or heteroassociative sequence learner. The CA3 to CA1 pathway is considered as an heteroassociative memory. Similar functional subdivisions of the hippocampus have a long history, dating back to the work of David Marr [44, 51, 53, 80]. Attempts have been made to specify the nature of the information stored in each hippocampal stage, including the dentate gyrus, and how the information is transformed from stage-to-stage [44, 80]. We are more concerned here with the precise workings of individual stages, rather than the hippocampus as a whole.

In this construction [27, 28] certain synaptic pathways are modifiable and form the site of memory formation. Other pathways provide an external synaptic drive that selects certain PCs to be active. These pathways determine the patterns of PC activity to be stored associatively. The mossy fibre input from dentate gyrus granule cells onto the proximal dendrites of CA3 pyramidal cells acts to select which CA3 PCs are active for a particular pattern to be stored in the CA3 autoassociative (or sequence) memory. Synaptic modification by Hebbian learning of the recurrent connections between CA3 PCs stores this pattern. A pattern of activity in layer II of the entorhinal cortex is heteroassociated with a CA3 activity pattern by Hebbian learning at the perforant path synapses in the CA3 PC distal dendrites. Input from entorhinal cortex subsequently can act as a recall cue for the CA3 autoassociative memory. Similarly, in CA1, Hebbian learning of the Schaffer collateral input from CA3 PCs onto the CA1 PCs heteroassociates a CA3 pattern with a CA1 pattern. The active PCs in a CA1 pattern are selected by perforant path input from layer III of entorhinal cortex onto the PC distal dendrites. Subsequently, a recalled pattern in CA3 acts as a cue for pattern recall in CA1.

Binary patterns are represented by the synchronous emission of single action potentials by the relevant pyramidal cells. These active cells can be equated with a binary one, whereas the silent PCs correspond to a binary zero. Gamma frequency (around 40Hz) network activity constitutes the basic clock cycle [9, 45, 55], so that a pattern is represented by the spiking activity on a single gamma cycle. Recent experimental data indicates widespread synchronous PC activity on this time scale [20], supporting this construction. The slower theta rhythm (around 5Hz) is used as the frequency of pattern presentation for storage and pattern cuing for recall [55, 82]. Storage and recall may take place on opposite phases of a single theta cycle [23, 26].

4.2 An autoassociative memory model

Menschik and Finkel [55] implemented an autoassociative memory network model based on the CA3 region of the mammalian hippocampus. In this model, patterns are represented by the spiking activity of a set of 64 pyramidal cells. The recall dynamics of the PCs is controlled by 8 basket cells (BCs) and 64 axo-axonic cells (AACs; chandelier cells), giving a network of 136 neurons in total. The network

architecture consists of recurrent excitatory connections between the PCs; BCs receive excitatory connections from all PCs and send inhibitory connections to each other and back to the perisomatic region of the PCs; each AAC receives an excitatory connection from one PC and sends an inhibitory input back to the axon initial segment of that same PC. Excitatory connections are modelled as AMPA and NMDA synapses; inhibitory connections are $GABA_A$ synapses. The relatively detailed compartmental models of Traub and colleagues [77, 79] are used for both the PCs (66 compartments) and interneurons (51 compartments). Synapses are modelled as simple single or dual exponentials, with no voltage dependence for the NMDA current.

Only the dynamics of pattern recall is examined with the model. The basket cell network provides gamma-band synchronized oscillations which form the clock cycle of recall. Theta-band $GABA_B$-mediated inhibition from the medial septum is modelled as a 6Hz square-wave current injection in the soma of the basket cells. Thus the BCs are inhibited (hyperpolarised) on one phase of theta, and excited (depolarised) on the opposite phase. This allows one half of a theta cycle for pattern recall by PC activity before BC inhibition becomes sufficiently strong to silence PCs and thus reset the network for the next cue pattern. Each new recall cue is presented at the start of a theta cycle in the form of entorhinal input to AMPA and NMDA synapses in the distal dendrites of those PCs that are to be active.

Pattern storage takes place by using the connection weights of a Hopfield artificial neural network autoassociative memory [31] to scale synaptic conductances in the biophysical network model. Positive weights scale the maximum conductances of the AMPA and NMDA receptors at the PC recurrent collateral synapses. Negative weights scale the maximum $GABA_A$ receptor-mediated conductances at the AAC to PC synapses. For the results presented in [55], 5 random 64-bit binary strings were stored in the Hopfield net to produce the connection weights.

Recall performance was tested for various levels of cholinergic modulation of the network. Cholinergic input to PCs and BCs is modelled as a constant concentration that reduces the maximum conductance of intrinsic membrane AHP and calcium (Ca) currents, and reduces the amplitude of AMPA and NMDA-mediated EPSCs from recurrent collaterals. Diffuse cholinergic depolarization of PCs and BCs is modelled by a constant somatic current injection (which sets the DC level of the theta-band square wave injection to the BCs). Increasing cholinergic input switches pyramidal cells from bursting to spiking mode due to a decrease in the AHP and Ca currents that underly bursting. The spiking mode is used for associative memory recall. Menschik and Finkel [55] hypothesize that PC bursting mode is suitable for inducing the synaptic plasticity underlying learning. Calcium entry in the dendrites is far higher during burst firing, compared to regular spiking. As mentioned earlier, calcium levels may be the dominant signal driving synaptic plasticity. This distinction between storage and recall modes has similarities to Buzsáki's *two stage* memory model [7]. Menschik and Finkel's role for cholinergic modulation differs from Hasselmo's proposal

(see below) that the decrease in recurrent excitation induced by acetylcholine is ideal for the learning phase of associative memory [22, 21].

Computer simulation of the model demonstrated that even highly noisy cues provide accurate retrieval of a stored pattern within half a theta cycle (around 9 gamma cycles or recall steps, given a high gamma frequency of around 100Hz) under conditions of normal cholinergic modulation. Decreasing cholinergic input, as in Alzheimer's disease, slows the gamma frequency and increases the strength of recurrent excitation. Gamma frequency is slowed due to a lowering of cell excitability and an increase in the AHP and Ca currents that leads to an increase in interspike intervals. Both effects result in recall performance deteriorating due to a reduction in the number of gamma cycles available for recall and interference from other stored patterns through the strong recurrent connections.

4.3 Phasing storage and recall

The autoassociative memory model of [55] only considers network dynamics during recall of stored patterns. A complete neural model of associative memory should include the dynamics of both storage and recall and mechanisms for switching between these phases of operation.

The dynamics of recall requires the suppression of synaptic plasticity or a weight control mechanism that stops excessive changes in synaptic strengths during the recall of previously stored patterns. Principal cell activity must also be suitably thresholded by inhibitory interneurons so that the cells belonging to the stored pattern, which are also receiving the strongest excitation, are the only ones to become active.

Storage, on the other hand, requires synapses to be plastic, but excitation in the plastic pathway should not contribute to principal cell activity. For example, if the recurrent connections between principal cells in an autoassociative memory were allowed to contribute to excitation during storage, then previously stored patterns would become confused with new patterns, whose representation is driven by external activity.

The role of cholinergic neuromodulation in setting appropriate conditions for pattern storage has been explored in a series of models by Hasselmo and colleagues [22, 21, 27, 28]. In experimental work with rat piriform cortex and hippocampus, they have demonstrated that cholinergic input selectively suppresses layer-specific or recurrent excitation, while promoting plasticity in the same pathway [4, 24, 27, 28]. Using rate coded, as opposed to spiking, models of CA1 [27] and CA3 [28], they have explored how these cholinergic effects improve storage in associative memories.

These same models [27, 28] also explore how feedback regulation of cholinergic input can effectively switch the memory network between storage and recall modes. In the hippocampus, the major source of cholinergic input is from the medial septum. Specific interneurons in CA1 and CA3, that are excited by pyramidal cells, send long-range inhibitory connections to the medial septum [17]. In the models, excitatory drive to the pyramidal cell network by a novel pattern on the pattern-determining pathway results in low activity in the PC network.

Consequently, inhibitory feedback to the medial septum is low and cholinergic input from the septum is high, setting conditions for pattern storage. In contrast, excitation (cueing) from a previously stored pattern leads to high PC activity as recall proceeds. Feedback inhibition to the septum then also increases, reducing cholinergic input and promoting the conditions required for pattern recall.

These rate coded models do not make use of gamma or theta rhythms to clock storage and recall. Further, the phasing between storage and recall by regulation of cholinergic input is relatively slow, in accord with the time constant of seconds for the neuronal effects of acetylcholine via muscarinic receptors [25, 26]. However, assuming a relatively constant level of acetylcholine, rapid phasing between storage and recall within a theta cycle is possible via $GABA_B$ mediated network effects [25, 23]. In this scenario, the waxing and waning of $GABA_B$ inhibition provides a concurrent waxing and waning in the strength of layer-specific or recurrent excitatory connections via presynaptic inhibition. This provides conditions suitable for pattern storage or pattern recall on opposite phases of a theta cycle. This is explored in a spiking model of sequence memory [82], described below.

4.4 A model of sequence storage and recall

Wallenstein and Hasselmo [82] developed an associative memory model of sequence storage and recall using spiking neurons. Their network contains 1000 pyramidal cells (PCs) and 200 interneurons (INs) in a spatial grid with connectivity determined by Gaussian probabilities over distance, such that PCs connect with 15% of PCs and 20% of INs. INs contact 30% of PCs and 20% of INs. The INs are putative basket cells, and no other IN type is explicitly represented. PCs and INs are represented by five-compartment multi-ion-channel models. PCs contain a range of ion channels (fast Na, KDR, Ca, KAHP, KCa, KA), whilst INs contain only fast Na and K channels. Both cell types receive synaptic AMPA, NMDA, $GABA_A$ and $GABA_B$ input. PCs receive recurrent excitation from other PCs and slow $GABA_B$ inhibition on apical dendrites, with perisomatic fast $GABA_A$ inhibition from the INs. INs receive excitation on the soma from PCs, with fast inhibition on soma and proximal dendrites and slow inhibition on distal dendrites from other INs. All synapses are assumed to have presynaptic $GABA_B$ receptors. During network activity, an estimate of external GABA concentration at each cell is made over time and used to downregulate all synaptic connections to implement the effect of these receptors.

Theta oscillations are induced by rhythmic GABAergic input from the medial septum expressed as IPSPs on the somata and proximal dendrites of INs. Septal cholinergic input is modelled as a sustained steady-state excitation due to a partial reduction in leak current in the distal dendrites of PCs and INs. This level of modulation is set to give random activation of around 15% of PCs and INs at any one time. Within a theta cycle, INs fire bursts of APs at gamma frequency, whilst PCs fire one or a few spikes at a particular phase of theta.

Whereas Menschik and Finkel [55] considered the storage and recall of discrete patterns, Wallenstein and Hasselmo [82] use their network to store and

recall a sequence of patterns. Each pattern within a sequence to be stored is delivered as entorhinal afferent AMPA input to the apical dendrites of selected PCs for 20msecs at the start of a theta cycle, with a new pattern delivered on each theta cycle (every 100msecs). A sequence is 30 patterns long and is delivered five times during learning. Learning is implemented by a temporal Hebbian rule applied only to NMDA conductances on the recurrent collaterals of PCs. Before learning, the NMDA conductances are set to random values. During learning, changes in conductance are proportional to the product of presynaptic activity (average presynaptic firing rate over the last 50ms preceding postsynaptic activty) and postsynaptic activity (difference of postsynaptic membrane voltage above a threshold value of -30mV). This gives only LTP as changes are zero if the postsynaptic voltage is below threshold. This rule incorporates elements of STDP but is different in detail from the STDP models considered above.

At the start of each theta oscillation the PCs belonging to a particular pattern in the sequence fire APs due to the external afferent input. In addition, 15% of other PCs fire randomly due to background excitation (cholinergic depolarization) at different times during the theta cycle. Due to the 50msec time window of the temporal Hebbian learning rule, the connections between the active PCs of one pattern and the active PCs of the next and subsequent patterns in a sequence are not strengthened, as each pattern is separated by 100msecs. Instead, connections between pattern PCs and randomly firing PCs are strengthened. After a number of learning trials certain non-pattern PCs start to fire gamma frequency trains of APs that span in time several of the sequence patterns. These *context sensitive* cells are the glue that binds the sequence together (see Levy [43] for a different model of how context sensitive cells may form).

Presynaptic inhibition via $GABA_B$ receptors is vital to the accurate storage and recall of patterns in this network. During the first half of a theta cycle, $GABA_B$ inhibition is high. This suppresses recurrent excitation so that PC firing strongly reflects entorhinal afferent input which specifies the current pattern in the sequence. Without this reduction in recurrent excitation, activity due to previously stored patterns occurs early in a theta cycle and interferes with the formation of context sensitive cells that encode the correct ordering of patterns in a sequence. Later in theta, $GABA_B$ decays, and PCs start firing due to recurrent excitation, reflecting stored patterns. In this second half of a theta cycle, the network effectively shifts from storage to recall modes. Afferent input that arrives in the latter half of theta acts as a recall cue. Recurrent excitation results in the rapid (gamma frequency) replay of the subsequent section (5 or so patterns) of the stored sequence over the remaining part of the theta cycle.

The context sensitive cells can be likened to the so-called *place cells* found in rat hippocampus. If a rat is moving through an environment, then PCs firing early in a theta cycle reflect the rat's current location, whereas later firing PCs are predicting where the rat is going. As the rat moves through the place field of a PC, that PC's firing occurs earlier in the theta cycle. Such phase precession of spike firing is a characteristic of experimentally-recorded place cells [60]. This

is analogous to the partial sequence recall following the appropriately timed presentation of a cue pattern in this model [82].

4.5 Other models

A number of other modelling studies have considered the theta/gamma rhythm associative memory operation of networks of spiking neurons. Lisman and Idiart [45] introduced the idea of a short-term memory buffer in which memory patterns are represented by the activity on each gamma cycle. During each theta cycle around 7 of these patterns are replayed, with repetition on subsequent theta cycles. Jensen, Idiart and Lisman investigated how NMDA receptor dynamics could account for this short-term memory buffer, and also considered how short and long-term memory may interact for sequence storage and recall [36, 37, 35]. Sommers and Wennekers [72, 73] examined how stored patterns could be recalled within single gamma cycles, allowing a new pattern to be recalled on each such cycle. These models do not explicitly include features of the interneuronal microcircuit. Fránsen and Lansner [15] considered cortical columns as the basic representational units in a model of neocortical associative memory, with each column consisting of a small network of PCs and INs.

Other studies have explored possible mechanisms for sequence storage and recall. Sequence storage as continuous attractors in an autoassociative memory and how that might relate to hippocampal place cells has been the subject of a number of studies [39, 68, 81]. Melamed et al. [54] discuss the interesting problem of encoding behavioural sequences that occur on arbitrary timescales and may need to be temporally compressed to fit within the theta/gamma rhythms.

5 The Hippocampal Microcircuit Revisited

Neural network models of associative memory need to account for a number of factors. During pattern storage network activity should only include the current pattern to be stored, which is likely determined by external input to the network. Activity resulting from previously learnt patterns interferes with the storage of a new pattern and degrades memory performance. Thus mechanisms that limit such activity are necessary. Pattern recall requires that intial network activity, as the result of an externally applied cue that is a partial or noisy version of a stored pattern, evolves towards and stabilises at the appropriate stored pattern. The ability to achieve this is dependent upon appropriate synaptic plasticity (learning) during storage. Nonetheless, the activity of individual PCs must be tightly controlled by a thresholding mechanism for recall to work.

The models described in the previous section provide initial explorations into how networks of spiking neurons may act as associative memories. Storage and recall dynamics are determined by synaptic and intrinsic cellular properties and by alteration of these properties by neuromodulation with acetylcholine. Acetylcholine and $GABA_B$-mediated inhibition may serve to set appropriate conditions

for pattern storage by reducing synaptic transmission whilst promoting plasticity on the modifiable pathways [22, 21, 82]. Patterns for storage and recall cues are provided by afferent input from the entorhinal cortex [55, 82]. Basket cells provide the basic gamma rhythm clock cycle that is modulated at the slower theta rhythm. Cueing for storage and recall proceeds at the theta rhythm. PC thresholding during recall is provided by basket cells [82] with a contribution from axo-axonic cells [55]. No other interneuronal types are explicitly included in these models.

It is possible to ascribe functionality to more of the hippocampal microcircuit. Ideas concerning interneuronal network involvement in rhythm generation and control of PC networks are explored in Buzsáki and Chrobak [9]. Paulsen and Moser [62] consider how GABAergic interneurons might provide the control structures necessary for phasing storage and recall in the hippocampus. Building on their ideas, the following observations can be made concerning the roles for different interneuronal types.

Basket cells BCs provide inhibition to the perisomatic region (on and around the cell body) of PCs and are driven by feedforward pathways from entorhinal cortex, mossy fibers (CA3) and Schaffer collaterals (CA1), and in a feedback pathway by recurrent PC collaterals. They may also inhibit each other and bistratified cells. Different classes of basket cells exist that may have very different functions [16]. A likely role for PV-containing BCs is threshold-setting for PC activity during pattern recall. Many models use BCs in this way [55, 72, 73, 82]. Typically in these models the PCs receive an identical threshold-setting inhibition that is a function of average PC activity over the entire network [72, 73]. In reality each PC will receive different inhibition depending on their particular BC input and the afferent drive that those BCs are receiving. That afferent drive will be at best an estimate of overall PC activity on the basis of the sample of PCs that are driving those BCs. Thus the *threshold* signal across the whole network will be rather noisy, limiting recall accuracy. How limiting this noise actually is has not been investigated. The models considered here [55, 82] do use a population of BCs, but they do not rigorously test the memory capacity of their networks.

In addition, models typically use identical model cells for particular cell types. Recent work has demonstrated that variation in inhibitory cell properties between cells of the same type can significantly alter the effect of population inhibition on PC activity [3, 14].

Bistratified cells BSCs provide feedforward inhibition driven by Schaffer collaterals to CA1 PCs and feedback inhibition driven by recurrent collaterals to CA3 PCs. Unlike the the strong, focal inhibition of basket cells, BSC inhibition is diffusely distributed to apical and basal dendrites [17]. It seems ideally suited to controlling synaptic plasticity during pattern recall by reducing BPAP amplitude and calcium entry in the dendrites.

Axo-axonic cells AACs provide feedforward inhibition, driven by entorhinal and hippocampal PC afferents, to the axon initial segment of PCs. In constrast to their threshold-setting role in [55], they could be involved in shutting off PC output during pattern storage, when such output may not be desirable, while not interrupting BPAPs that are involved in synaptic plasticity. Stopping PC output would also stop feedback inhibition to PCs via BCs and O-LM cells, thus additionally aiding BPAP propagation into the dendrites and maximising the influence of pattern-determining input from entorhinal cortex to the distal dendrites of PCs.

However, the effect of AAC inhibition may be more selective than a simple block of APs emitted by a PC. A simulation study on the interaction of inhibition and A-type potassium channels in CA3 axons indicates that a block may be selective for the large diameter Schaffer collaterals, whilst allowing transmission to the smaller recurrent collaterals [42].

Oriens lacunosum-moleculare cells O-LM cells send focal feedback inhibition onto the distal dendrites of PCs. This provides control over pattern-determining input from entorhinal cortex. Such pattern-determining input is necessary during storage, but may not be required during pattern recall.

Horizontal trilaminar cells Some HTCs send axon collaterals outside of the hippocampus, particularly to the medial septum [17]. They are driven by PC recurrent collaterals. Feedback inhibition to the medial septum that is a function of local PC activity may act to modulate acetylcholinergic input to the hippocampus and effectively switch CA1 and CA3 circuits between storage and recall modes [27].

6 Conclusions

Neural circuitry is extremely complex and consequently it is very difficult to *reverse engineer* it to determine its function. Associative memory provides a useful computational paradigm on which to base an attempt at reverse engineering the microcircuit of the mammalian hippocampus. Mathematical models and computer simulations that investigate aspects of the hippocampus at the single cell and network levels, within the context of associative memory, have been discussed. These models are able to assign particular functions to aspects of the microcircuit. However, there is still a long way to go before we fully understand what experimental neuroscience has already told us about the cellular properties and circuit architecture of the hippocampus.

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