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Computational Models of Memory Formation in Healthy and Diseased Microcircuits of the Hippocampus

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What is Associative Memory?

Memory is important in our lives. Without a memory we are unable to remember our past experiences and our loved ones, while still being able to think about the future. Without memory we cannot learn anything. Associative memory is the ability to learn and remember the relationship between unrelated items, events, and/or objects (Suzuki, 2007). When we try to find a specific piece of information in our memory sometimes we do not retrieve it immediately. Our brain, which contains aspects of the present situation and contextual information pointing at the missing information, starts then a sequential process of associations from one item to the next that eventually leads to the missing piece. Once this piece of information is found, we immediately recognize it as the one we have been searching for.

Associative memory has been one of the oldest artificial neural network (ANN) paradigms. The concept of the associative memory was first introduced by the formalism of a correlation matrix (Kohonen, 1978; Palm, 1982, 1991; Palm & Sommer, 1996; Steinbuch, 1961; Willshaw, Buneman, & Longuet-Higgins, 1969), where memory patterns were encoded as the activity patterns across a network of computing units. Pattern storage was accomplished by Hebbian modification of the connections between the computing units. A memory was recalled when an activity pattern that was a partial or noisy version of a stored pattern was instantiated in the network. Network activity then evolved to the complete stored pattern as appropriate units were recruited to the activity pattern, and noisy units were removed, by threshold setting of unit activity. Memory capacity for accurate recall was strongly dependent on the form of patterns to be stored and the learning rule employed (Palm & Sommer, 1996).

An example of an associative memory comprising six input channels interacting with six output channels forming a matrix of 36 elements is depicted in Fig. 24.1. Activity in a channel is represented by 1 and inactivity by 0. Associations between the input and output patterns (x^i, y^i), $i = 1, 2, \ldots$, are formed via a Hebbian learning rule, where co-activation of the input and output units results in an irreversible transition of synapses from 0 to 1. Such associations between binary stimulus events are then stored in a 6×6 connectivity matrix, C. Special cases of associative memory are the auto-association, where $x^i = y^i$ for all pairs i, and the hetero-association, where $x^i \neq y^i$, $i = 1, 2, \ldots$ (Palm, 1991). In Fig. 24.1A three associations are stored: $x^1 \rightarrow y^1$, $x^2 \rightarrow y^2$, and $x^3 \rightarrow y^3$. The resulting C matrix represents the three sets of paired events.

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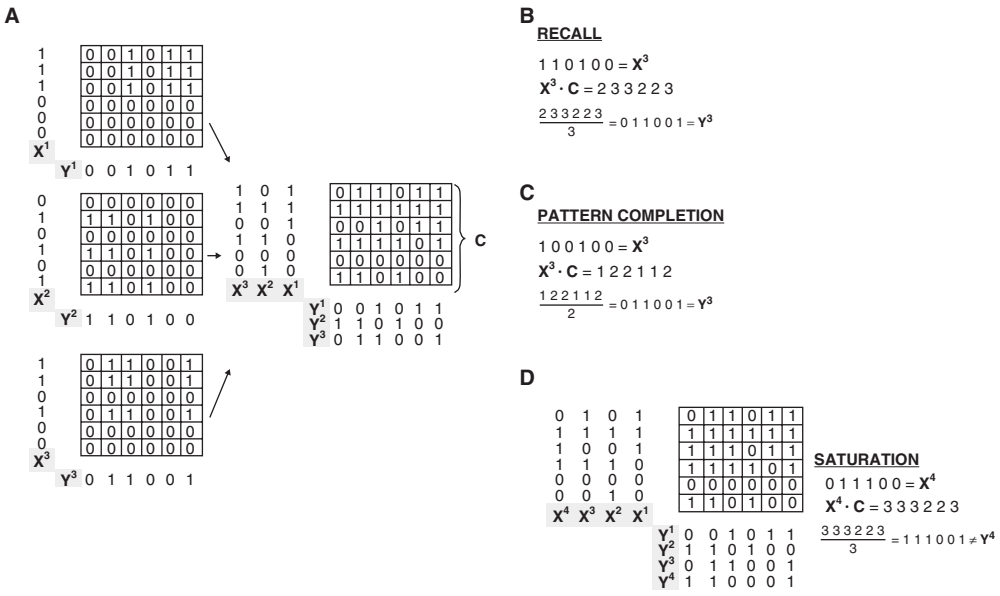

Figure 24.1 Example of a correlation matrix (adapted with permission from Cutsuridis & Wenneckers, 2009). (A) Associations of three memory patterns X^1->Y^1, X^2->Y^2, X^3->Y^3 using the mechanism of the correlation matrix. The resulting *C* matrix represents the three sets of paired events. (B) Perfect recall of an input pattern. (C) Pattern completion of an input pattern. (D) Saturation. Errors in recall start to occur as the matrix approaches saturation.

Recall of an input pattern is accomplished by multiplying the matrix *C* by a corresponding input pattern, e.g. $X_3 = (1\ 1\ 0\ 1\ 0\ 0)$ and performing an integer division analogous to a variable threshold, the value of which is equal to the number of ones in the cueing pattern (i.e., $\theta = 3$). Perfect recall can be achieved by this division process even if the patterns share common active elements, provided that not too many different patterns have been presented (Fig. 24.1B and C). Errors in recall will begin to occur as the matrix approaches saturation (Fig. 24.1D).

Early Views of Associative Memory in Hippocampus

David Marr (1969, 1971) was the first computational scientist to formulate a neural implementation of the correlation matrix in the hippocampus. His network consisted of N principal neurons, one inhibitory neuron, and two types of inputs. All neurons were modeled as simple threshold neurons (McCulloch & Pitts, 1943) with a resting threshold equal to one. Each of the Y inputs strongly depolarized a principal neuron and caused it to fire. All X inputs contacted all principal neurons. Their synaptic weights were initialized to zero and were strengthened according to a Hebbian rule. The X inputs also excited the inhibitory interneurons, which in turn inhibited the principal neuron's somata. The produced inhibitory signal was proportional to the total number of nonzero elements in the input pattern and performed a division operation in the principal neuron's soma allowing this way the neurons that learned the pattern to recall it accurately.

Although Marr's model was a successful one in predicting that the hippocampus works like a content-addressable memory (CAM) system, it was very rudimentary because the types of neurons used in this scheme were simple threshold neuronal nodes and the synaptic weights were updated according to an iterative time quantized update scheme, providing a very rough insight into the dynamical processes in the hippocampus. Since then

a dramatic accumulation of knowledge about the morphological, physiological, and molecular characteristics, as well as the connectivity and synaptic properties of excitatory and inhibitory neurons in the hippocampus have been witnessed (Cutsuridis, Graham, Cobb, & Vida, 2010b). Excitatory neurons are primarily pyramidal neurons and they constitute 90% of all neurons in the hippocampus, whereas the remaining 10% are interneurons, primarily inhibitory, which are classified according to their morphological, physiological, molecular and synaptic characteristics into other numerous subclasses (Somogyi & Klausberger, 2005). Collections of thousands of such cells then interact in cell assemblies (microcircuits), with each microcircuit being individual machinery, which receives, processes, and transmits information. In the next section, I will briefly review the experimental literature of the hippocampus regarding the different families of neurons and their operations in memory formation and rhythm generation. In the section on "Computational models of hippocampal microcircuits," I will review representative examples of simple and detailed spiking neuronal models of associative memory. In the final section I briefly discuss practical issues and difficulties involved in realistic biophysical modeling of (micro)-circuits of associative memory and discuss future challenges.

Neuronal Diversity, Microcircuits and Rhythms in the Hippocampus

The hippocampus has been studied extensively yielding a wealth of data on cell types and their passive and active properties, network architecture, and synaptic plasticity (Cutsuridis et al., 2010b). Hippocampus contains principal excitatory neurons (granule cells (GCs) in DG and pyramidal cells (PCs) in regions CA3 and CA1), and a large variety of inhibitory interneurons (Freund & Buzsaki, 1996; Somogyi & Klausberger, 2005). Neurons in the hippocampus receive external inputs via different pathways from the cortex and the extrahippocampal areas. In the dentate gyrus, GCs receive inputs directly from layer II of the entorhinal cortex (EC). In CA3, inputs come from the EC layer II to the distal apical tree of the PCs. Inputs to proximal and basal dendrites are largely from other CA3 PCs. Another excitatory input to CA3 comes from the GCs of the dentate gyrus, which form the mossy fiber synapses in the very proximal region of the apical tree of the PCs. In CA1, the Schaffer collateral excitatory input from the CA3 PCs impinges to PC proximal dendritic regions. Recurrent collaterals from other CA1 PCs synapse on the basal dendritic tree, whereas perforant path inputs from EC layer III reach the distal region of the apical dendritic trees of PCs.

Cells in the hippocampal regions compute information differently. The DG is implicated in pattern separation (Hasselmo & Wyble, 1997; Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Wilson & McNaughton, 1993), CA3 in pattern completion (Marr, 1971; McNaughton & Morris, 1987), and CA1 in novelty detection (Vinogradova, 2001) and mismatch of expectations (Hasselmo & Schnell, 1994). In addition, regions CA3 and CA1 have been proposed to be auto- and hetero-associators for the storage of declarative memories, respectively (Treves & Rolls, 1992). Computation in each hippocampal region takes time creating temporal windows of excitability, which are evident by local field potentials (LFPs) (Buzsaki, Anastasiou, & Koch, 2012).

Theta rhythm (4–10 Hz) is one such LFP (Alonso & Garcıa-Austt, 1987; Vanderwolf, 1969) and it has been shown to play an instrumental role in the coordination of neuronal firing in the entorhinal–hippocampal network (Buzsaki, 2002). Theta oscillations have also been implicated in the encoding and retrieval of episodic and spatial memories (Cutsuridis, Cobb, & Graham, 2008; Cutsuridis, Graham, & Cobb, 2010a; Cutsuridis, Graham, Cobb, & Hasselmo, 2011; Cutsuridis & Hasselmo, 2012; Cutsuridis & Poirazi, 2015; Cutsuridis & Wenneckers, 2009; Hasselmo, 2005; Jensen & Lisman, 2005; Kunec, Hasselmo, & Kopell, 2005) and disruption

of them results in behavioural deficits (Winson, 1978). Theta rhythm in hippocampus is paced by the MS and the diagonal band of Broca in the basal forebrain (Stewart & Fox, 1990; Winson, 1978), although several theta generators and theta dipoles seem to work independently in the hippocampus (Buzsaki, 2002; Montgomery, Betancur, & Buzsaki, 2009).

Excitation and inhibition in the hippocampus come in different flavors and support different functions (Freund & Buzsaki, 1996; Somogyi, Katona, Klausberger, Lasztoczi, & Viney, 2014). Inhibition sculpts the activities of excitatory cells (GCs in DG and PCs in CA3 and CA1), allowing them to fire at particular temporal windows and phases with respect to external network oscillations (Mizuseki, Sirota, Pastalkova, & Buzsaki, 2009; Somogyi et al., 2014). At least 25 different types of inhibitory interneurons have been identified in regions DG, CA3, and CA1 of the hippocampus (Fuentealba et al., 2008a; 2008b, 2010; Jinno et al., 2007; Somogyi et al., 2014; Somogyi & Klausberger, 2005; Vida, 2010). These include axo-axonic cells (AACs), the perisomatic basket cells (BCs) and the dendritic bistratified cells (BSCs), ivy (IVY), neurogliaform (NGL), oriens lacunosum-moleculare (OLMs), molecular layer interneurons with axons in perforant-path termination zone (MOPP), hilar perforant path-associated cells (HCs), hilar interneurons with axons in the commissural/associational pathway termination zone (HICAP), and the interneuron-selective cells (IS) in the DG (Capogna, 2011; Fuentealba et al., 2008a; 2008b, 2010; Somogyi & Klausberger, 2005). AACs innervate exclusively the initial axonal segment of the DG GCs and the CA3 and CA1 PCs, whereas BCs innervate their cell bodies and proximal dendrites (Somogyi & Klausberger, 2005; Vida, 2010). CA1's BSCs and IVYs innervate the CA1 PC basal and oblique dendrites, whereas OLM and NGL cells target the apical dendritic tuft of CA3 and CA1 PCs aligned with the EC input (Capogna, 2011; Somogyi et al., 2014). The DG HC cells target the apical dendrites of the DG GCs (Vida, 2010), whereas the MOPP cells feedforwardly inhibit the DG GCs. HICAP cells inhibit the proximal GC dendrites, near where MC axons terminate and provide feedback inhibition. IS cells inhibit exclusively other interneurons and modulate the excitability and synchrony of the network. Long range INs, such as the somatostatin- and mGluR1α-positive neurons in stratum oriens project to the subiculum, other cortical areas, and the medial septum, whereas somatostatin-negative ones and trilaminar cells project to the subiculum and other cortical areas but not to the septum (Jinno et al., 2007; Somogyi et al., 2014; Somogyi & Klausberger, 2005).

DG, CA3, and CA1 cells discharge at different phases of theta oscillations (Capogna, 2011; Fuentealba et al., 2008a; 2008b, 2010; Mizuseki et al., 2009; Somogyi et al., 2014; Somogyi & Klausberger, 2005). CA1 OLMs, BSCs, IVYs, and PCs fire at the trough of theta recorded in the CA1 SP, whereas CA1 AACs, BCs, and NGLs fire at the peak of theta recorded in the CA1 SP (Fuentealba et al., 2008a; 2008b, 2010; Somogyi & Klausberger, 2005). CA3 AACs fire rhythmically around the peak of the theta oscillations recorded locally in CA3 (Viney et al., 2014), whereas CA3 BCs and PCs fire around the trough of the local CA3 theta with the PCs firing leading the BCs firing by few degrees (Tukker et al., 2013). CA3 OLMs, which are recurrently excited by the CA3 PCs should fire at the trough of CA3 theta right after the CA3 PCs. In addition to hippocampal cells, MS cell activities are theta modulated (Borhegyi, Varga, Szilagyi, Fabo, & Freund, 2004; Dragoi, Carpi, Recce, Csicsvari, & Buzsaki, 1999; Stumpf, Petsche, & Gogolak, 1962). GABAergic MS neurons form two distinct populations exhibiting highly regular bursting activity that is coupled to either the trough or the peak of hippocampal theta waves (Borhegyi et al., 2004).

In addition to theta oscillations, cells in the hippocampus fire at different phases of other rhythms, such as gamma (30–80 Hz) and sharp wave-associated ripples (SWRs) (100–200 Hz). Gamma oscillations constitute a basic clock cycle (Graham, 2003) and are embedded in theta oscillations

(Colgin, 2015). SWRs occur during the offline replay and consolidation of previous experiences (Somogyi et al., 2014). In CA1, during sharp wave ripple oscillations, BCs and BSCs strongly increase their discharge rates in phase with the ripple episode. In contrast, axo-axonic cells fire before the ripple episode, but pause their activities during and after it. OLM cells pause their firings during ripples. On the other hand, during theta oscillations, OLM cells, BSCs, and PCs increase their firing rates at the troughs of the extracellular theta, whereas BCs and AACs fire at the peaks of it. During gamma oscillations, the firing rates of BCs, AACs, and BSCs correlate with the extracellular gamma in different degrees, whereas OLM cells do not correlate at all with gamma oscillations.

Understanding the functional roles of these cells in encoding and retrieval of memories and rhythm generation currently poses a great challenge. Computational and mathematical models play an instrumental role in exploring such functions and facilitate the dissection of operations performed by the diverse interneurons. The aim of the next section is to provide a snapshot and a résumé of the current state of the art of the ongoing research avenues concerning computational models of hippocampal microcircuits with particular emphasis on the functional roles of the various inhibitory interneurons in memory formation in the hippocampus in health and in disease.

Computational Models of Hippocampal Microcircuits

Of paramount importance in memory research is the ability of any system to learn new things and acquire new memories, while at the same time not forgetting what it had previously learned. Such a memory system ought to be capable of determining which is new, requiring a distinct memory to be formed (pattern separation), and which details need to be recalled from incomplete or noisy information (pattern completion). In the next two sections I will review some of the most prominent microcircuit models of the hippocampus in relation to memory formation, storage, and recall, in both health and disease.

Models of the Healthy Hippocampus

Sommer and Wennekers (2000, 2001) extended the original hippocampal CAM model (Marr, 1971; Palm, 1980; Willshaw, Buneman, & Longuet-Higgins, 1969) to investigate its memory capacity and robustness of efficient retrieval under varying memory load and type of external stimulation (tonic and pulsed). For learning they used the clipped synaptic modification rule of the Willshaw model (Willshaw et al., 1969). Memory patterns were sequences of binary numbers (1 or 0). Each pattern was presented to a fixed number of cells in the network and each cell was active in more than one memory pattern. Inhibition worked as a global nonconstant threshold. With tonic stimulation, the addressed memory was an attractor of the network dynamics. The memory was displayed rhythmically, coded by phase-locked bursts or regular spikes. The participating neurons had rhythmic activity in the gamma frequency range (30–80 Hz). If the input was switched from one memory to another, the network activity followed this change within one or two gamma cycles. With pulsed stimulation, memories were no longer attractors and they were retrieved within one or two gamma cycles. Burst of firing became relevant for coding and its occurrence was used for discriminating related processes from background activity.

Hunter, Cobb, and Graham (2008) compared and contrasted the performance of the Sommers and Wennekers model with previously published recall results of the Willshaw model (Graham & Willshaw, 1995, 1997). They tested how well the network can recall a pattern when there is full (100%) or partial (10%) connectivity or corruption due to noise and how the global inhibitory threshold could implement the winner-take-all (WTA) recall of a stored pattern. Biophysical implementations of three separate WTA recall methods were used: (1) standard WTA implemented by intrinsic PC thresholding (increases in Na^+

density and membrane resistance) and global inhibition; (2) normalized WTA implemented by localized inhibition proportional to the excitation a cell could receive, the range of EPSPs, and the dendritic sums produced; and (3) amplified WTA via a nonlinear increase of EPSP summation, so that the cells that reached a certain membrane potential increased their summed EPSP amplitude via a persistent Na^+ current. Recall was tested by tonically stimulating a subset of principal neurons in the network using an injected current of varying strength. Recall performance was tested by storing 50 random patterns, each consisting of 10 active cells, in the network and then using five of the 10 cells of a stored pattern as a recall cue. Recall quality with 10% connectivity was: (1) 61% in standard WTA, (2) 64% in normalized WTA, and (3) 65% in amplified WTA.

Kunec, Hasselmo, and Kopell (2005) advanced a detailed CA3 model of the hippocampus using biophysical representations of the major cell types including pyramidal cells (PCs) and two types of interneurons (BCs and OLMs) to dissect the operations performed by the various types of interneurons in and inputs to the network as well as investigate how variations in biophysically meaningful and experimentally measurable parameters affect the simulated encoding and retrieval. Inputs to the network came from MS, which paced the theta rhythm in the CA3 model into two half subcycles (one for storage and the other one for recall), and the EC (directly and via DG). Their model reproduced experimental results showing that the various cell types fire at a preferred phase relationship with respect to the underlying theta rhythm and to each other, and offered distinct functional roles of the various cells in storage and recall of memory patterns in CA3.

Drawing inspiration from the Kunec et al. (2005) model and the experimental data of Klausberger and colleagues (2003, 2004), Cutsuridis and colleagues (Cutsuridis et al., 2008, 2010a, 2011; Cutsuridis & Hasselmo, 2012; Cutsuridis & Poirazi, 2015; Cutsuridis & Wennecker, 2009) advanced a series of detailed biophysical models of the CA1 microcircuit of the hippocampus in order to investigate the memory capacity, recall performance, rate and phase coding properties, and functional roles of various types of cells in region CA1 as a function of cue loading, presentation frequency, and learning task. The Cutsuridis and colleagues modeling studies have been very influential in computational memory research and were the first to make a number of theoretical predictions regarding the roles of various types of inhibitory interneurons in the hippocampus in memory formation, which only recently have been experimentally validated:

- Theta-modulated inhibition is what separates encoding and retrieval of memories in the hippocampus into two functionally independent half-cycles of the theta rhythm (Cutsuridis et al., 2008, 2010a). This theoretical prediction has been recently experimentally verified (Siegle & Wilson, 2014).
- Theta-modulated perisomatic inhibition plays an instrumental role in the encoding of memories in region CA1 of the hippocampus by allowing the generation of dendritic calcium spikes that promote synaptic LTP, while minimizing cell output (Cutsuridis et al., 2008, 2010a). This theoretical prediction has recently been experimentally verified (Siegle & Wilson, 2014).
- Theta-modulated proximal dendritic inhibition in region CA1 of the hippocampus controls both cell output and suppresses dendritic calcium spikes, thus preventing LTPs (Cutsuridis et al., 2008, 2010a). This theoretical prediction has recently been experimentally verified (Siegle & Wilson, 2014).
- Theta-modulated distal dendritic inhibition in region CA1 of the hippocampus removes interference from spurious memories during recall (Cutsuridis et al., 2008, 2010a).
- Intra- and extra-hippocampal inhibition provide the necessary environment for the maintenance of rate- and phase-coding properties of place cells in region CA1 of

the hippocampus (Cutsuridis & Hasselmo, 2012). This theoretical prediction has been experimentally verified recently (Kaifosh, Lovett-Barron, Turi, Reardon, & Losonczy, 2013).

Recently, Nolan, Wyeth, Milford, and Wiles (2011) suggested that spike timing in the hippocampus is the mechanism capable of deciding when to learn a novel input pattern and when to recall by completing to a previously learned pattern, using a decision criterion based on patterns currently stored in the system. They advanced a novel computational model of the DG–CA3 microcircuit implicitly performing pattern-by-pattern novelty separation. The model incorporated spike timing-dependent plasticity (STDP) as the mechanism to discriminate between known and unknown patterns by switching on and off learning. This pattern-by-pattern suppression ensured that even in unfamiliar situations, already known patterns are not relearned; whereas in familiar situations, unknown patterns could be learned. Simulation results demonstrated that (1) STDP in the EC–CA3 synapses provided a pattern completion ability without recurrent CA3 connections, (2) the race between activation of CA3 cells via EC–CA3 synapses and activation of the same cells via DG–CA3 synapses distinguished novel from known inputs, and (3) modulation of the EC–CA3 synapses adjusted the learned versus test input similarity required to evoke a direct CA3 response prior to any DG activity, thereby adjusting the pattern completion threshold.

Along the lines set by Nolan et al. (2011), Hummos, Franklin, and Nair (2014) advanced a more biologically realistic model of the DG–CA3 microcircuit that included principal cells and two of the most common interneurons, basket cells (BCs) and oriens lacunosum-moleculare (OLM) cells. Both inhibitory interneurons in the model were modulated by ACh according to experimental data (Lawrence, 2008). The model suggested pattern separation and completion of the DG–CA3 circuits produce instability through different dynamics, consequently requiring different mechanisms for their stabilization. Although the recurrent connections in CA3 promote runaway excitation, OLM inhibition and short-term depression at the recurrent connections are effective in preventing this instability, whereas BC inhibition by itself is not. Also, low ACh levels enhance CA3 recurrent connections leading to more sustained bursting in PCs, and short-term depression at these recurrent connections moderates this excitatory activity, whereas high ACh levels result in very long burst sizes that are optimally controlled by OLM inhibition.

Models of the Diseased Hippocampus

Menschik and Finkel (1998) were the first to advance an Alzheimer's disease model of hippocampal CA3 region dynamics inspired by the Buzsaki "two-stage" memory model and the suggested role for interneurons (Buzsaki, 1989; Buzsaki & Chrobak, 1995) and the Lisman and colleagues model on embedded gamma cycles within the theta rhythm (Lisman, 2005; Lisman & Idiart, 1995). They used detailed biophysical representations of multicompartmental models of pyramidal cells and two types of inhibitory interneurons: basket cells and chandelier cells to study the modulation and control of storage and recall dynamics in Alzheimer's disease by subcortical cholinergic and gamma-aminobutyric acid (GABA)ergic input to the hippocampus. They showed that synchronization in the gamma frequency range can implement an attractor based auto-associative memory, where each new input pattern that arrives at the beginning of each theta cycle comprising 5–10 embedded gamma cycles drives the network activity to converge over several gamma cycles to a stable attractor that represents the stored memory. Their results supported the hypothesis that spiking and bursting in CA3 pyramidal cells mediate separate behavioral functions and that cholinergic input regulates the transition between behavioral states associated with the online processing and recall of information.

Cholinergic deprivation led to the slowing of gamma frequency, which reduced the number of "gamma cycles" within the theta rhythm available to reach the desired attractor state (i.e., memory loss and cognitive slowing seen in Alzheimer's disease).

Inspired by the Cutsuridis and colleagues (2010a) modeling study, Bianchi et al. (2014) investigated the conditions under which the properties of hippocampal CA1 pyramidal neuron altered by increasing cAMP response element binding (CREB) activity may contribute to improved memory storage and recall. With a set of patterns already stored in the network, they found that the pattern recall quality under Alzheimer's disease-like conditions is significantly better when boosting CREB function with respect to control. Their results were robust even when synaptic damage due to Alzheimer's disease progression increased, supporting the idea that the use of CREB-based therapies could provide a new approach to treat Alzheimer's disease.

Yim, Hanuschkin, and Wolfart (2015) extended an already well-established DG microcircuit model (Santhakumar, Aradi, & Soltesz, 2005) into testing the hypothesis of whether the experimentally observed intrinsic scaling of GC activity serves as a mechanism to maintain the pattern separation function of the DG network. They found that while increasing performant path (PP; direct EC input to DG) strength degraded pattern separation only gradually, slight elevation of mossy fiber (MF) sprouting severely impaired pattern separation. When the DG network was hyperexcited, then the leaky GCs ameliorated pattern separation. In some sprouting cases with all-or-none seizure behavior, they observed pattern separation to be disabled with and without leaky GCs. When MF sprouting was mild (and PP strength was increased), then leaky GCs were particularly effective in restoring pattern separation performance.

Conclusions

I hope I made evident that large-scale biophysical microcircuit models of associative memory are very important, because they allow us to run *in silico* experiments of networks of neurons, while bypassing the technical difficulties of a real experiment, in order to answer questions and uncover mechanisms related to the interaction between the local microcircuit activity and global processing to achieve the desired overall processing functionality observed in learning and memory. Several practical issues such as parameter searching, network scaling, suitable simulation environments, and computational speed, memory, and efficiency ought to be addressed in future large-scale modeling studies of memory formation (Carlson, Nageswaran, Dutt, & Krichmar, 2014; Gleeson, Silver, & Steuber, 2010; Djurfeldt, Ekeberg, & Lansner, 2008; Hasselmo & Kapur, 2000; Van Geit, de Schutter, & Archard, 2008).

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