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a0005

# Hippocampus: Computational Models

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s0005

## Introduction

p0005 The hippocampus appears to be involved crucially in the acquisition and intermediate term maintenance of novel episodic event memories. For example, in the famous case of patient H.M. the anterior hippocampus and adjacent structures were bilaterally removed surgically. H.M. was consequently unable to form new event memories, but event memories prior to the surgery were preserved. H.M. also retained the ability to converse and to perform computations when uninterrupted. In order to understand the functions of the hippocampus and the specific properties of memory acquired and maintained there, it is necessary to understand intrinsic properties of neurons and the complex interactions in networks of neurons. The search for such understanding is greatly aided by computational modeling, due to the ability to make explicit and precise observations in each component of a simulation and the ability to exert similarly precise and explicit control over model structure and parameters.

p0010 The following article reviews neural models of hippocampal memory function. (1) We present an anatomical summary of the neural circuitry that is involved. (2) We compare attractor network models of memory retrieval with computational models that achieve memory retrieval in terms of sequences of activity patterns. (3) We discuss recent models of spatial navigation. (4) We highlight the significance of the 'theta' brain rhythm in recent models of hippocampal function, especially during the sequential readout of memory. This includes a recent model mechanism that achieves rapid switching between memory encoding and memory retrieval, thereby enabling specific hippocampus-dependent memory tasks. (5) This leads to the discussion of a model that proposes a mechanism for temporal context dependent retrieval of episodic memory. (6) We present advances in computational models of proposed short-term buffering in parahippocampal regions, which provide the buffer requirements for associative synaptic storage in the hippocampus. (7) We explicitly state the importance of context for recognition versus recall in memory tasks. (8) We conclude by reviewing models that address the transfer and consolidation of memories stored in the hippocampus into long-term memory and semantic memory.

s0010

## The Standard Model Based on Anatomical Structure

p0015 Recent models have directly addressed data from human cognitive memory tasks using representations based on extensive physiological and anatomical data concerning the hippocampal formation. These hippocampal models utilize many features discussed in priormodels of the hippocampus. Individual stored items such as words are represented as patterns of active and inactive neurons in the entorhinal cortex, which provides input to the hippocampus and which in turn receives converging input from a broad range of neocortical structures. Activity spreads from this input layer into subregions of the hippocampus, including a structure with extensive excitatory recurrent connections – region CA3. Strengthening of the recurrent synapses connecting active neurons within region CA3 provides a mechanism for associating different components of each stored pattern. The experimental phenomenon of long-term potentiation provides support for this mechanism of synaptic modification. Associative storage in region CA3 has been utilized in most models of episodic memory function, which differ primarily in details of the model dynamics. These models allow behavioral features of memory to be related to specific neural substrates.

p0020 The dentate gyrus (DG) receives input from entorhinal cortex (EC) and sends output to CA3. Connections diverge from a small number of EC neurons to a large number of DG neurons, resulting in a sparser pattern of activity in DG and CA3 which allows more effective associative storage. In addition, mossy cell and granule cell layers of the dentate gyrus together form a second recurrent network in the hippocampus, which may allow associative encoding in DG. Encoding of novel information may be facilitated by extensive neurogenesis observed in the human adult DG.

p0025 Region CA1 of the hippocampus receives input from layer III of entorhinal cortex (ECIII) at distal dendrites via the perforant path synapses and receives input from region CA3 at proximal dendrites through the Schaffer collaterals. Input from ECIII cannot elicit activity in CA1 independently, depending on depolarization by input from CA3. ECIII provides an active context to pyramidal neurons in CA1. By contrast, input via the Schaffer collaterals from CA3 can in some cases cause spiking in CA3 without excitatory input from ECIII. Activity in CA1 forms the output of hippocampal processing, projecting out of the hippocampus via the subiculum. In spatial tasks involving rodents, CA1 pyramidal neuron spiking has been

found to be place specific (place cells), and subiculum activity is direction specific. During theta rhythm in linear track experiments, place cell firing exhibits phase precession.

## Models Based on Attractor Network Dynamics

Many early models of the hippocampus represent memories with a single spatial pattern distributed across a population of neurons. During retrieval, activity induced by a memory cue causes activity to evolve toward one of these single spatial patterns – an 'attractor' state. This final attractor state persists indefinitely. Because of this single stable final state, these networks are referred to as fixed-point attractor systems.

Fixed-point attractors can be obtained in networks with extensive excitatory feedback connections and could therefore occur in region CA3 of the hippocampus, or in neocortical structures. One danger of such strong excitatory feedback connections is the possibility that activity can increase exponentially within the network. In early models, units were prevented from firing at rates higher than a particular maximum value, and memory states commonly involved firing at these high rates. More realistic networks obtained attractor dynamics with lower rates of firing by balancing feedback excitation with different types of inhibition, including shunting inhibition, subtractive inhibition, or normalization of total activity. Though fixed-point attractors in models can persist indefinitely, it is likely that neural circuits come under the influence of individual attractors for only brief periods. In very detailed biological models with spiking neurons, attractors require larger numbers of units to be stable, but can be obtained by using very specific point-to-point inhibitory connectivity or saturating synapses.

## Sequence Models

Memories can also be represented as sequences of activity patterns within a network. In this framework, each pattern of activity on a population of neurons such as region CA3 is associated with a different subsequent pattern during encoding. During retrieval, presentation of an early pattern then elicits a chain of different subsequent patterns in the network which could potentially be repeated in a limit cycle. Sequences provide a simple means of representing interitem associations in memory tasks, as well as pathways through the environment. Recently, models of sequence storage in region CA3 of the hippocampus have been used to address behavioral tasks, including the transitivity task studied by Bunsey and Eichenbaum and spatial navigation tasks.

An important focus of recent models concerns the phenomenon of theta-phase precession. This experimental evidence suggests sequence storage within the hippocampus. As a rat runs along a continuous track, individual neurons (place cells) in its hippocampus will fire as the rat traverses a location specific to that cell (the place field). The firing of these cells has been measured relating to the phase of a high-amplitude oscillation in the hippocampal electroencephalogram (EEG) called the theta rhythm. As the rat enters the place field associated with a particular place cell, the firing of that cell will occur late in the theta cycle. As the rat crosses and leaves the place field, the firing of the place cell will occur earlier and earlier, suggesting that the cell was initially the end of a sequence being read out in the hippocampus, and as the rat crosses the field the cell becomes an earlier component of the sequence.

Several models of theta phase precession have been published. These models all involve a readout of sequences across time, but two of them involve slow readout of sequences across the full cycle of the theta rhythm (which has a period of about 200 ms). In a model by Tsodyks, Skaggs, McNaughton, and Sejnowksi, this slow readout is obtained with very weak excitatory connections. In a model by Jensen and Lisman, this slow readout is obtained with the slow dynamics of the *N*-methyl-D-aspartate (NMDA) receptor. Recently, Lisman modified this approach by stipulating sequence readout in which the retrieval of successive items is delayed by the time taken to correct an item representation through auto-associative pattern completion. Retrieval is further delayed by feeding back the resulting activity as a cue for the subsequent readout of the next item, using the reciprocal fiber loop that is formed by the pathway from hippocampal region CA3, via the mossy cells to the dentate gyrus, and the mossy fiber pathway from dentate gyrus to hippocampal region CA3. This change in the model was motivated by data showing that NMDA antagonists did not eliminate the phase precession phenomenon.

In contrast, more rapid readout with (AMPA) receptor kinetics is used in a separate model. In this model by Hasselmo, the theta phase precession is obtained by readout of sequences to different lengths during different phases of the theta cycle, due to phasic changes in depolarization or presynaptic regulation of synaptic strength. This phenomenon could allow selective context-dependent retrieval of sequences. Finally, still other models have proposed that the theta phase

precession does not result from sequence readout, but from a precession due to theta oscillations running at different frequencies in the soma versus the dendrites of pyramidal cells. Several of these hypotheses can be tested with pharmacological investigation of the phenomenon of theta phase precession.

## Models of Spatial Navigation

p0060 The hypothesis that pathways through the environment are stored as sequences of place cell activity gives rise to another prediction, that as a pathway becomes familiar, place fields should expand and move backward along the path. This prediction has recently been confirmed in experimental measurements. Recent models by Burgess, Sharp, Hasselmo, Koene, and Gorchctchnikov have proposed that representations of neural space involve learning of multiple different pathways within that space, which can then be effectively integrated in a flexible relational structure. Many models start with an array of simulated place cells which encode the environment, and then modify the connections between these cells to learn gradients toward specific goals. This can be viewed as instantiating the assumption that space is the dominant parameter for neuronal response, although it is possible that place cells arise from a generic sparse conjunctive coding scheme. One recent model by Samsonovich and McNaughton assumes that generic two-dimensional maps of space are precoded in region CA3, and learning of a new environment involves modification of excitatory input to individual maps, rather than modification of recurrent connections within a map. In contrast, models which start with individual sequences can draw on a range of features in each sequence, building a response to task elements beyond just the spatial layout. Most models use a particular goal to influence the activity of other neurons in order to direct network activity toward a particular location. This remains an important issue, as experiments have not demonstrated 'goal cells' in any particular structure. Functional models of navigation provide an important means of interpreting available physiological evidence from this important experimental paradigm.

## The Significance of Hippocampal Theta Rhythm

p0065 Recent computational models address the role of the hippocampal theta rhythm. During the peaks and troughs of the theta rhythm, differential modulation of membrane potential and synaptic transmission results in phasic changes in the magnitude of synaptic currents induced in region CA1 by input from EC and CA3 during different phases of theta rhythm. Empirical data show that the phase of theta rhythm in hippocampal regions also affects the strength of synaptic modification by long-term plasticity (LTP). The strongest LTP is elicited by stimulation at the peak of theta rhythm, as recorded in the hippocampal fissure. Combined, these modulatory effects led to the presupposition that opposing phases of theta rhythm may impose rapidly alternating modes that differentially favor encoding (strong input from EC, strong LTP) and retrieval (strong internal spread arising from CA3, weak LTP) in subregions of the hippocampus.

p0070 Computational models that propose a mechanism of ongoing alternating encoding and retrieval during task performance allow encoding of new information, interleaved with retrieval of prior knowledge to perform the task. Recent simulations of spatial navigation behavior used a mechanism of alternating encoding and retrieval within each theta cycle. These simulations were based on the hypothesis that information needed to perform the task is retrieved during each theta cycle in hippocampal region CA1. It was proposed that retrieval activity in CA1 is elicited by a convergence of excitatory input from pyramidal neurons in entorhinal cortex layer III through the perforant path and of excitatory input from pyramidal neurons in hippocampal region CA3 via Schaffer collaterals. The models suggested three important uses of theta rhythm. (1) Theta modulation enables rapidly alternating encoding and retrieval modes. (2) Offset phases of theta modulation in the connected networks of the entorhinal cortex and hippocampus enable synchronous operations. For example, the readout of buffered activity in the entorhinal cortex can occur reliably for presentation as input during the encoding phase of activity at the recurrent fiber synapses of hippocampal region CA3. (3) The modulation of membrane potential at theta rhythm in layer II of the entorhinal cortex may be an essential component of a nonsynaptic buffer that can maintain short sequences of spiking activity.

p0075 Recent computational modeling proposes explicit mechanisms for the retrieval of episodic memory in a specific temporal context. This effectively models data from Wood and Eichenbaum showing that units fire in a selective context-dependent manner in region CA1 of the hippocampus. Inputs representing forward retrieval could be gated by inputs representing temporal context via convergence in region CA1. Simulations demonstrated performance in a delayed spatial alternation task in which temporal context-specific retrieval is necessary for successful performance of the task.

s0035 ## Short-Term Buffers

p0080 Experimental observations and computer modeling by Alonso and Fransen demonstrated that certain pyramidal neurons in the entorhinal cortex exhibit afterdepolarization and the ability to maintain a stable pattern of intrinsic spiking even after input has terminated. In layer II of the entorhinal cortex (ECII), the intrinsic spiking frequency is similar to the frequency of the theta brain rhythm. The persistent firing behavior of those neurons led to proposals for short-term buffers of spike sequences, which can allow the acquisition and encoding of novel input in the parahippocampal and hippocampal regions. The buffer of spike sequences could allow (1) time compression between patterns of spikes to enable spike timing-dependent potentiation, (2) multiple cycles of spike pattern reactivation to repeatedly strengthen active synapses, and (3) maintenance of sequence order for the encoding of episodic memory. Another important element of these models is network-wide competitive inhibition, which serves to suppress activity following a pattern of spikes and thereby guarantee the separation of successive buffered spike patterns. This competitive inhibition and the detection of spiking at a phase of the theta rhythm that indicates a full short-term buffer are the proposed components of a mechanism that enables first-in first-out replacement of buffered spike patterns with novel spiking input patterns. In addition to its role during sequence encoding, a short-term buffer for short sequences of representative spike patterns may gather and time compress a short sequence of spikes elicited by input that provides a temporal context cue for episodic retrieval in the hippocampus.

s0040 ## Recognition versus Recall

p0085 Most humans are familiar with the difference in effort required for recognizing a name versus recalling a name. Recall is more sensitive than recognition to injections of the acetylcholine receptor blocker scopolamine before encoding, and the cellular basis of this sensitivity has been analyzed in a model. In this model, neurons in entorhinal cortex represent the subject's memory for experimental context – i.e., the testing room and apparatus – while separate neuronal populations in this area represent individual items – i.e., words on a list. During encoding, activity spreads through the dentate gyrus into region CA3, where connections are strengthened among the neurons representing context, among the neurons representing individual words, and between the context and word neurons. The experimentally demonstrated effects of scopolamine were represented by reducing the rate of synaptic modification, reducing the depolarization of neurons, and increasing feedback excitation.

p0090 Simulation of scopolamine effects impaired subsequent recall but not recognition. During free recall, a subject is asked, "What words were on the list?" In the model, this is simulated with activation of entorhinal context units, which activate the context representation in region CA3. This context representation then sequentially activates the representations of individual words via strengthened connections (competition between words prevents simultaneous recall). During recognition, subjects are presented with individual words. In the model, neurons representing individual words are activated. If spread of activity across strengthened connections is sufficient to evoke activity in the context neurons, then the item is counted as correctly recognized. Because the context is present more frequently than the words during encoding, it has stronger excitatory feedback and is easier to activate, allowing recognition to persist even when slower synaptic modification during encoding prevents effective recall. This model suggests specific parameters of memory function which should be affected by specific drugs. Drug effects on conditioning phenomena in rats have also been modeled, but space does not allow review of neural models of conditioning.

p0095 The model of recognition described previously used one representation of recognition processes – but humans may use two different processes in recognition: (1) a process of rich recollection, in which the details of the specific item are recalled in a specific context, and (2) a general sense of familiarity based on component features of an item. The rich recollection process may depend on the hippocampus, whereas the familiarity sense may depend on other cortical structures, including parahippocampal structures. Experimental data on these differences have been addressed in a recent paper which models the dynamics of recollection in a simulation of the hippocampal formation. The activation of representations in region CA3 of this model depends upon a conjunction of cues in the entorhinal cortex. This requirement of a specific conjunction of features prevents recollection from being induced by items containing only a portion of the features of a particular memory. For example, the model was trained on patterns representing word pairs such as 'window-reason' and 'car-oyster' and then tested on repaired lures such as 'window-oyster.' The model was able to recollect studied word pairs and reject many re-paired lures by retrieving the correct pair. The simulation also demonstrated the experimentally observed property that recollection-based recognition decreases with

number of words on a list, whereas there is an increase in false alarms due to the more vague familiarity-based recognition. This familiarity-based recognition may take place outside the hippocampus and contribute to many aspects of memory function. Lesions of the hippocampus alone cause significant impairments in episodic memory tasks including recognition memory, but research indicates that lesions including structures adjacent to the hippocampus cause stronger overall memory impairments.

s0045

## Consolidation

p0100 Lesions of the hippocampal formation do not appear to impair pre-existing semantic memory, but there is some loss of episodic memories from the time before the lesion, and more recently stored information appears to be affected more strongly – a phenomenon termed temporally graded retrograde amnesia. This suggests that the hippocampus mediates the gradual formation of neocortical memory representations. Models of the formation of semantic memory demonstrate that gradual, interleaved learning of new episodic information with existing semantic representations is essential to prevent distortion of previously stored semantic representations. Thus, the hippocampus may provide a temporary store for associations which then gradually modify neocortical representations.

p0105 The potential effect of the loss of hippocampal training on semantic memory has been investigated in studies of children with perinatal damage to the hippocampus. These subjects show a profound impairment of episodic memory, and as might be expected from the model, their development of semantic memory requires extensive training over a longer period – the external world must take the place of an internal mechanism for interleaved learning. The phenomenon of temporally graded retrograde amnesia does not appear consistently in all behavioral tasks, but in the case of human subjects, temporally graded retrograde amnesia appears to be particularly true for patients with damage selective to the hippocampus proper.

p0110 Potential physiological mechanisms for a two-stage model of memory formation have been proposed. The initial encoding in the hippocampus has been proposed to occur during theta rhythm dynamics, and the subsequent transfer to the neocortex to occur during sharp waves in quiet waking and slow-wave sleep. The dramatic decrease in acetylcholine levels during slow-wave sleep could contribute to these different dynamical states, as it will greatly enhance the strength of excitatory feedback in the hippocampus. This two-stage system allows rapid encoding of episodic memories, with slower consolidation of more complex semantic representations.

*See also:* Hippocampus and neural representations (00767); Declarative memory system: anatomy (00755); Animal models of amnesia (00746); Memory: computational models (00754).

## Further Reading

Burgess N, Recce M, and O'Keefe J (1994) A model of hippocampal function. *Neural Networks* 7(67): 1065–1081.

Eichenbaum H and Cohen N (2004) *From conditioning to Conscious Recollections Memory Systems of the Brain*. Oxford: Oxford University Press.

Gluck M and Myers C (2000) *Gateway to Memory: An Introduction to Neural Network Modeling of the Hippocampus and Learning*. Boston: MIT Press.

Hasselmo M, Bodelon C, and Wyble B (2002) A proposed function for hippocampal theta rhythm: Separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Computation* 14(4): 793–817.

Hasselmo M and Eichenbaum H (2005) Hippocampal mechanisms for the context-dependent retrieval of episodes. *Neural Networks* 18(9): 1172–1190.

Hasselmo M and Wyble B (1997) Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function. *Behavioural Brain Research* 89: 1–34.

Jensen O and Lisman J (1996) Hippocampal CA3 region predicts memory sequences: Accounting for the phase precession of place cells. *Learning & Memory* 3: 279–287.

Jensen O and Lisman J (2005) Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. *Trends in Neurosciences* 28(2): 67–72.

Koene R, Gorchetchnikov A, Cannon R, and Hasselmo M (2003) Modeling goal-directed spatial navigation in the rat based on physiological data from the hippocampal formation. *Neural Networks* 16(5–6): 577–584.

Koene R and Hasselmo M (2006) First-in-first-out item replacement in a model of short-term memory based on persistent spiking. *Cerebral Cortex* 17: 1766–1781.

Levy W (1996) A sequence predicting CA3 is a flexible associator that learns and uses context to solve hippocampal-like tasks. *Hippocampus* 6(6): 579–590.

Lisman J (1999) Relating hippocampal circuitry to function: Recall of memory sequences by reciprocal dentate-CA3 interactions. *Neuron* 22: 233–242.

Lisman J (2005) Hippocampus, ii: memory connections. *American Journal of Psychiatry* 162(2): 239.

Lisman J and Idiart M (1995) Storage of $7 \pm 2$ short-term memories in oscillatory subcycles. *Science* 267: 1512–1515.

McClelland J, McNaughton B, and O'Reilly R (1995) Why there are complementary learning systems in the hippocampus and

neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review* 102: 419–457.

Norman K and O'Reilly R (2003) Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. *Psychology Review* 110(4): 611–646.

Reed J and Squire L (1997) Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behavioral Neuroscience* 111: 667–675.

Rolls E and Treves A (1998) *Neural Networks and Brain Function.* New York: Oxford University Press.

Sharp P (1991) Computer simulation of hippocampal place cells. *Psychobiology* 19: 103–115.

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