

**From spike frequency to free recall:
How neural circuits perform encoding and retrieval.**

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INTRODUCTION

Researchers have described numerous hypotheses of hippocampal function based on lesion data, attempting to present these hypotheses entirely in verbal terms -- using terms such as “interference”, “response inhibition”, “context”, “temporal contiguity”, “snapshot memory” etc. This method of hypothesis presentation results in an incomplete and distorted perception of the experimental data, as it is filtered through the multiple associations that each individual has with these verbal terms. Even the terms used in the title of this chapter, such as episodic memory and spatial navigation, come laden with semantic associations that may distract from the essential features of hippocampal function.

Theories of hippocampal function will only converge on a comprehensive account of a full range of behavioral data when hypotheses are directly presented in terms of physiological and anatomical data, without any distortion by verbal description. Linking these levels requires computational models which are constructed at a neural level within the constraints of physiological and anatomical data. Ultimately, linking these levels will require not only that the models of information processing proceed on a neural level, but that the input and output of the network should be defined in terms of the actual interactions with the environment. In other words, it may not be enough to build a biological model. We may only avoid the distorted perceptions of verbal hypotheses when biological models directly interact with a virtual animal moving in a virtual environment. Only then can every element of the behavioral data be tested in the context of the biological data.

This chapter will present an overview of existing models of hippocampal function, which constitute only an initial sketch of what must ultimately become a sophisticated computational framework. The first half will focus on some standard models of episodic memory function, and important open research questions. The latter half will present models of spatial navigation, including a first attempt at directly guiding navigation behavior with a neural simulation.

MODELING HUMAN EPISODIC MEMORY FUNCTION.

An extensive literature concerns the mechanisms of human episodic memory (Tulving and Markovitch, 1999). For the purpose of the modeling presented here, episodic memory is defined as the memory of an individual for a set of related events within an episode experienced by the subject within a specific delimited time period at a specific spatial location, and which the subject can access in a flexible and comprehensive manner. This is usually measured with specific laboratory tests using verbal materials. Damage to the hippocampal formation has been demonstrated to impair a number of tasks requiring memory for verbal information in a specific behavioral context. For example, damage to the hippocampus significantly decreases the percent accuracy of performance on delayed free recall of an encoded list of words, or encoding and retrieval of paired associates (Scoville and Milner, 1957; Graf et al., 1984). Selective lesions of hippocampal subregions due to hypoxia cause statistically significant memory impairments in these tasks, though the effects may be somewhat less severe in some cases (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996).

Thus, when a subject participates in a specific experiment and learns an arbitrary association between a pair of words (e.g. dishtowel-locomotive), the encoding of that association in the specific experimental context appears to depend upon circuitry within the hippocampal formation. Here we will focus on some features of a model (Hasselmo and Wyble, 1997), which demonstrates how populations of hippocampal neurons might be involved in specific human memory tasks, such as paired associate memory, free recall and recognition. This model has many features in common with other models of hippocampal memory function (Marr, 1971; McNaughton and Morris, 1987; Levy, 1996; Treves and Rolls, 1994; Hasselmo and Wyble, 1997). The model attributes particular functional roles to individual subregions of the hippocampal formation, as summarized in Figure 1.

FIGURE 1 ABOUT HERE.

Region CA3

In this model, the primary locus for encoding of associations was in region CA3 of the hippocampal formation. Two features of region CA3 make it particularly appealing as the locus for storage of episodic memory. 1.) the convergence of multimodal sensory information on this region means that strengthening of synapses here could provide associative links between distinct sensory stimuli without any strong prior associative link -- e.g. between the word "dishtowel" and the

word “locomotive”, 2.) the capacity for rapidly inducing large changes in size of synaptic potentials (long-term potentiation) at the excitatory connections between neurons in this region suggests that this region can more rapidly encode associations than many other pathways. As an initial example, we will consider the role of hippocampal region CA3 in paired associate memory function (Hasselmo and Wyble, 1997), separately considering the dynamics necessary for encoding and retrieval (though as noted below, these encoding and retrieval dynamics could occur rapidly within short time periods).

Encoding

How might the association between the words “dishtowel” and “locomotive” be stored in neural network models of the hippocampus? First, recognition of the two words activates regions of temporal lobe language cortex. Patterns of activity then spread into populations of neurons in the entorhinal cortex. Physiological and behavioral evidence suggests that the parahippocampal and entorhinal cortices provide the means for holding information about this event for a period of time (Young et al., 1997; Fransen et al., 1999; Hasselmo et al., 2000). During this period of entorhinal activity, the activity will also influence the hippocampus. A specific subset of neurons in the dentate gyrus receives input from the entorhinal cortex. These neurons do not represent the use of the words “dishtowel” and “locomotive” in all contexts, but instead represent the specific use of the words in the specific behavioral context. The same neurons will play a role in portions of a wide variety of different memories. These neurons provide the basic code for the episodic memory.

Activity in the dentate gyrus is then passed on to region CA3. In this area, widely distributed

connections give the potential for random associations between a number of disparate perceptions. Thus, even if different neurons within the inferotemporal cortex or dentate gyrus become activated the two words, region CA3 has the capability of binding together these disparate items into a unified memory for the event.

This process is summarized in Figure 2. Within region CA3, activity in a subset of neurons representing the word “dishtowel” (item #1) occurs at the same time or as activity in a subset of neurons representing the word “locomotive” (item #2). As this activity repetitively activates the neurons, the processes of synaptic modification gradually increases the efficacy of synapses between these two sets of neurons. This forms the basic trace of the event.

FIGURE 2 ABOUT HERE.

Connections within region CA3 may not be the only synapses being modified. Synapses between region CA3 and the entorhinal cortex may also be modified, forming stronger connections between each element of the memory and the patterns of activity occurring in other cortical areas. Whatever the case, this distributed change in the pattern of synaptic connectivity will allow later retrieval of the episodic memory.

Synapses constantly change in synaptic strength, under the influence of a variety of factors. The process of long-term potentiation could result from the same processes altering synaptic strength during learning, and has been studied extensively as an experimental phenomenon (Bliss and Collingridge, 1993; Levy and Steward, 1983). Several different time courses have been described, all of which may map to specific features of the decay of memory. This process of forgetting has been studied extensively on a behavioral level, but surprisingly little effort has focused

on related the specific time course of long-term potentiation to the specific time courses of behavioral forgetting.

Retrieval

What processes allow retrieval of this association? In the paired associate memory task, the experimenter gives the first word (e.g. “dishtowel”) as a cue. First this information must activate language representations in my auditory cortex. The activity will evoke some activity in the entorhinal cortex, which can activate the episodic representation of that word formed within the dentate gyrus. Activity spreads from the dentate gyrus into region CA3. Within region CA3, the population of neurons associated with the word “dishtowel” becomes active.

As shown in Figure 3, once the population of neurons in region CA3 associated with the word “dishtowel” becomes active, then the activity spreads across the previously modified synapses into a specific separate population of neurons. These are the neurons representing the word “locomotive.”

FIGURE 3 ABOUT HERE.

One or more passes of activity through the hippocampus could retrieve other aspects of the episodic event -- the expression on the experimenter’s face, or the layout of furniture in the room. Each of these pieces of information can be extracted from different overlapping sequences all of which together constitute the episodic memory for that event. The interitem associations necessary to construct this memory depend upon the flow of activity across sets of synaptic connections, allowing specific populations of neurons in region CA3 to evoke activity in other specific

populations of neurons. See Figure 4 for description of flexible retrieval within an associative network.

FIGURE 4 ABOUT HERE.

Once the activity has been evoked in region CA3, it will spread along backprojections into neurons of the entorhinal cortex, and subsequently neurons of the parahippocampal cortex, temporal cortex and frontal cortex. An important function for these regions is to receive specific items evoked within sequences in region CA3, and to hold memory for these specific items until the time when the response is necessary. In this way, a full narrative of the event can be generated, or individual specific questions can be answered without requiring repeated access to the original memory.

Free recall and recognition

The same model was used to simulate hippocampal involvement in free recall and recognition (Hasselmo and Wyble, 1997). In free recall experiments, subjects are presented with a list of words during encoding. In a separate retrieval phase, they are asked what words were on the list, and retrieve them in arbitrary order. No specific cue elicits the retrieval of each word. Instead, the general experimental context must serve as a cue for retrieval of each word. Thus, in the simulation of free recall (Hasselmo and Wyble, 1997), region CA3 provides a network in which the memory for individual words then takes the form of associations between a single episodic representation of the context and the episodic representation of the individual word items.

In this simulation, activation of the context attractor state causes activity to spread to multiple

different item attractors. These item attractors compete, allowing only one item attractor to pre-dominate and be retrieved. After a period of activity, a wave of inhibition shuts off all attractors (porribly analogous to the oscillatory inhibition associated with theta rhythm oscillations). Subsequently, activation of the context attractor state again causes activity to spread to multiple item attractors, but the previously retrieved item has sufficient residual adaptation that it cannot be retrieved repetitively.

Recognition memory for individual words has been proposed to involve two different processes: 1.) explicit remembering of the episode when the word was encoded, and 2.) the fluency of activation of single items, regardless of an association to context. The first type of recognition was modeled in conjunction with free recall (Hasselmo and Wyble, 1997), simply using activation of the item as a cue, and evaluating whether the context can be activated by spread along strengthened associative synapses. The second type of recognition probably does not involve hippocampal circuits, but may instead be located in the neocortex (O'Reilly et al., 1998).

This description focused on simple sequential activation of separate populations of neurons, but the extensive excitatory connections within the network could allow explosive growth of activity. Thus, there must be some mechanism for preventing continuous explosive growth. A simple mechanism for controlling excitatory feedback uses subtractive inhibition (Wilson and Cowan, 1972; Hasselmo et al., 1995; Hasselmo and Wyble, 1997). Other mechanisms for preventing explosive growth of activity include shunting inhibition providing division of activity (McNaughton and Morris, 1987; Levy, 1996; Treves and Rolls, 1994) saturation of excitatory synaptic transmission (Fransen and Lansner, 1995), or imposing a “k-winners-take-all” scheme (O'Reilly et al., 1998), in which only a set number of neurons can be active. Whereas most existing models have focused on

obtaining a stable activity level, it may be sufficient to utilize cycles of inhibition on the time course of gamma or theta rhythm oscillations, which will initially allow a spread of activity which is then curtailed (Wallenstein and Hasselmo, 1997).

Problem of differential dynamics during encoding and retrieval.

In addition to the potential for causing explosions of activity, excitatory recurrent connections also have the potential to interfere with the encoding of new patterns. This would cause severe proactive interference in episodic memory, and would prevent construction of useful associative links for spatial navigation (see Figure 7 below). Because of this, most associative memory models have had separate dynamics during encoding, with clamping of activity to the desired input pattern (Kohonen, 1984; Amit, 1988). In those models, spread of activity along excitatory connections between units within the network is only allowed during retrieval.

What physiological mechanisms could provide these separate dynamics for encoding and retrieval? In a number of models, I have proposed that these separate dynamics can be obtained by selectively regulating the relative strength of three variables: 1.) excitatory synaptic transmission within the hippocampus, 2.) excitatory input from entorhinal cortex, and 3.) long-term potentiation (Hasselmo et al., 1995; 1996; 2001). Modulatory input from the medial septum can potentially cause these changes in network dynamics on different time scales, causing fast changes in dynamics through effects at GABA receptors during theta rhythm (Hasselmo et al., 1996; 2001), and causing slow changes in dynamics through effects at muscarinic acetylcholine receptors (Hasselmo et al., 1995).

Appropriate encoding dynamics require strong afferent input from entorhinal cortex. At the same time, the internal connections of the hippocampus (including both recurrent connections in region CA3 and the Schaffer collaterals from CA3 to CA1) would undergo strong synaptic modification, but weak synaptic transmission. In contrast, retrieval dynamics would have weaker afferent input, with strong internal synaptic transmission, but weak synaptic modification. Previous research has not emphasized these requirements, but existing physiological data demonstrates these changes during theta rhythm oscillations in the EEG. Theta rhythm appears when animals are actively exploring the environment or attending to behaviorally relevant stimuli (Buzsaki et al., 1983; Chrobak and Buzsaki, 1994). Physiological data shows that theta is associated with sequential phases of strong entorhinal input to region CA1, followed by strong CA3 input to region CA1 (Ruddell et al., 1981; Brankack et al., 1993; Bragin et al., 1996; Wyble et al., 2000). The dynamics described above have the paradoxical requirement that long-term potentiation of the connections from region CA3 should be strongest when the synaptic transmission at these connections is weakest. Surprisingly, previous physiological data already supports this paradoxical requirement, showing that induction of LTP works best at the peak of local theta -- when synaptic transmission is the weakest (Huerta and Lisman, 1993; Holscher et al., 1997). Thus, theta rhythm dynamics could provide rapid switching between encoding and retrieval dynamics (Hasselmo et al., 2001). The encoding phase would also be enhanced by strong input from the dentate gyrus. Physiological data demonstrates that stimulation of septum enhances dentate gyrus response to entorhinal input, possibly through inhibition of the dentate interneurons (Mizumori et al., 1989; Fantie and Goddard, 1982; Bilkey and Goddard, 1985) and reversible inactivation of the

medial septum reduces spontaneous firing of neurons in dentate gyrus (Mizumori et al., 1989).

Cholinergic innervation from the medial septum could provide slower changes between encoding and consolidation dynamics. Acetylcholine reduces the strength of synaptic transmission at excitatory recurrent connections in region CA3 (Hasselmo et al., 1995) and from region CA3 to region CA1. Cholinergic modulation also serves to directly enhance modification of synaptic strength, as demonstrated in experiments showing enhancement of long-term potentiation by cholinergic agonists (Huerta and Lisman, 1993). This direct enhancement of changes in synaptic strength ensures that new learning only occurs at the time that the other cholinergic effects are present to set appropriate dynamics for new encoding (Hasselmo and Linster, 1999).

This theoretical role of medial septum in regulating encoding dynamics through cholinergic and GABAergic effects is consistent with data on drug effects, which demonstrate that encoding can be seriously impaired by two types of drugs: 1.) drugs which block muscarinic acetylcholine receptors (e.g. scopolamine), and 2.) drugs which enhance GABAergic receptor effects (e.g. diazepam or midazolam). Both of these types of drug impair the encoding of words for subsequent free recall, but do not impair the free recall of words encoded before administration of the drug (Ghoneim and Mewaldt, 1975).

Sequence storage models

Fixed patterns of activity in networks can be used to model storage of individual items, or simultaneously presented pairs of items, but these fixed patterns do not effectively represent sequential storage of associations between multiple different items, such as the interitem associa-

tions which could cause a higher probability of retrieving words which were adjacent on the list.

These interitem and cross-temporal associations can be more effectively represented by storage of multiple patterns in a sequence rather than a single pattern. The storage of a sequence of activity patterns has been proposed as an alternative function of the excitatory recurrent collaterals in region CA3 (Marr, 1971; McNaughton and Morris, 1987; Jensen and Lisman, 1996; Levy, 1996; Wallenstein and Hasselmo, 1997).

Encoding of multiple overlapping sequences runs into the problem of interference between stored sequences. Theta rhythm oscillations induced by cholinergic and GABAergic input from the medial septum could assist in disambiguating overlapping sequences (Sohal and Hasselmo, 1998). Encoding of sequences provides the flexibility necessary for relational processing in the hippocampus, including both the flexible goal directed retrieval of episodic memories, and the flexible choice of specific pathways during spatial navigation described below.

Relational processing in an associative net.

Extensive data suggests that the hippocampus is particularly important for flexible retrieval of relational information about recent events (Cohen and Eichenbaum, 1993). That is, rather than being locked into a particular stereotypical pattern or sequence of patterns, the hippocampus appears to mediate flexible access to causal relationships within a large network of interitem associations.

This framework corresponds to a case of multiple overlapping sequences encoded in region CA3, which can be accessed not only in a rigid manner specific to individual sequences, but with

flexible transitions across the elements of the network, picking out different components in different sequences.

As an example, imagine an event in which I observe my Siamese cat knock a bowl of cantaloupe off the table. One aspect of episodic memory is the sense of flexible access to multiple different components of the memory, as if a full video of the sequence were available and we could play through segments of it forward and backward with pausing and focused inspection of different elements. This flexible retrieval of different events within an episode, or different relational features could be obtained if the recurrent connections of region CA3 set up an associative network, within which specific subsequences of activity could be evoked depending upon the conditional features of the retrieval cue. This type of flexible access is schematized in Figure 4. If I look at my cat, I might be reminded of the cat knocking the bowl off the table. But if I eat a cantaloupe, I might be reminded of the cantaloupe pieces falling on the carpet after the cat knocked them off the table.

Dentate gyrus

Most theories and models of hippocampal memory function include an important functional role for the dentate gyrus. In these models, the dentate gyrus serves to reduce the overlap between different patterns of activity stored within region CA3 of the hippocampus. The dentate gyrus activity then strongly activates region CA3 pyramidal cells via the mossy fibers.

This problem of reducing overlap relates to the problem of interference between patterns encoded within an associative memory. A simple means of preventing this type of interference

between encoded pattern involves pre-processing the patterns to make their representation less overlapping when they activate region CA3. This requires two processes: 1.) a mechanism for automatically reducing overlap between multiple sequentially presented patterns, and 2.) a mechanism for mapping the altered, less overlapping representations in region CA3 back to the original input patterns in association neocortex. The overlap between stored patterns can be reduced by allowing modification of the perforant path inputs from entorhinal cortex to dentate gyrus. This results in self-organization of the dentate gyrus representation due to competition between encoded representations.

Many models of episodic memory have proposed self-organization of input to dentate gyrus, but have utilized interleaved presentation of different patterns (O'Reilly et al., 1998; Rolls et al., 1997). These networks can obtain competitive self-organization without modification of inhibition, but the requirement of interleaved learning may be unrealistic for encoding of episodic memories, unless these memories are repeatedly reactivated and utilized to refine the dentate gyrus representation (see discussion of McClelland et al., 1995). By definition, episodic memories are encoded at one point in time. This means that any representation for the initial encoding of this memory must be formed on the basis of that single presentation. The afferent input could persist for a period of time (see discussion of the possible role of entorhinal cortex as a buffer), but it is not intermixed with the reactivation of other encoded memories. Thus, the encoded memories are not interleaved during learning. This presents a special problem for models of the dentate gyrus in episodic memory, as most models of self-organization and competitive learning utilize interleaved learning of a large set of input patterns.

Sequential self-organization of representations in the dentate gyrus has been obtained by utilizing modification of inhibitory connections (Hasselmo and Wyble, 1997). In the model, individual representations in dentate gyrus are initially activated due to random divergent input. At this point, excitatory feedforward connections undergo Hebbian modification to strengthen the drive on that dentate representation. This would allow smaller entorhinal patterns to activate dentate gyrus, but this excitatory modification is offset by enhancement of inhibitory feedback connections within the dentate gyrus (Hasselmo and Wyble, 1997). These can then prevent any patterns which do not strongly resemble the initial input pattern from activating the same representation.

Region CA1

If the associations encoded in region CA3 require a transformation in the dentate gyrus to make them less overlapping, then there must be some means of reversing the transformation in order to map the encoded patterns back to the activity patterns associated with sensory processing in association cortex. However, there are no direct connections from region CA3 to neocortical structures such as the entorhinal cortex. How can this mapping back to neocortical sensory activity take place?

Region CA1 appears well suited to this putative mapping function (McClelland and Goddard, 1996; Hasselmo et al., 1995; Hasselmo and Wyble, 1997). However, in addition to simple remapping, region CA1 could play an important role in determining whether the reconstructed pattern in region CA3 satisfies criteria for remapping to neocortical structures, based on a com-

parison of the region CA3 output with the current sensory input relayed through entorhinal cortex (Gray, 1982; Eichenbaum and Buckingham, 1989; Hasselmo and Wyble, 1997). This process is summarized in Figure 5.

FIGURE 5 ABOUT HERE.

This matching function could be very important for ensuring that incorrect retrieval does not propagate back to entorhinal cortex. For example, if the input pattern has not been previously encoded, the immediate retrieval from region CA3 will not have any useful information. In addition, if there is severe interference of the new pattern with previously stored patterns, the immediate retrieval from region CA3 will contain additional undesired information which should be restricted from passing back to entorhinal cortex.

Region CA1 has the appropriate anatomical connectivity for this type of comparison function. The output from region CA3 pyramidal cells arrives via the Schaffer collaterals and synapses in stratum radiatum of region CA1. The direct input from entorhinal cortex arrives via the perforant path and synapses in stratum lacunosum-moleculare of region CA1. The output of region CA1 pyramidal cells flows back to entorhinal cortex, either directly or via the subiculum.

Thus, the activity of region CA1 pyramidal cells reflects the convergence of Schaffer collateral input from region CA3 and perforant path input from entorhinal cortex (see Figure 5). If region CA1 pyramidal cells would require inputs from both pathways in order to fire (or would require the inputs to match if there is perforant path input), then only matching patterns would activate region CA1 and only matching patterns could spread back to entorhinal cortex.

Region CA3 actually contains direct afferent input from the entorhinal cortex in stratum

lacunosum-moleculare, but the longitudinal association fibers (laf) only contact region CA3 pyramidal cells and interneurons, and the Schaffer collaterals only contain region CA1 pyramidal cells and interneurons. Thus, even if region CA3 performs a comparison function, all output must pass through the potential comparison function of region CA1 as well. Having a separate comparison stage might be important in that it can allow region CA3 to settle into an attractor, without immediately vetoing this attractor or sequence on the basis of input from entorhinal cortex. Thus, region CA3 has the flexibility to generate multiple associations and region CA1 sorts through these to pick out valid retrieval candidates.

The theory of a comparison function in region CA1 has been described verbally in a number of locations (Gray, 1982; Eichenbaum and Buckingham, 1989), but only in a few publications have the actual mechanisms of such a comparison been described in detail and analyzed mathematically or simulated (Hasselmo and Schnell, 1994; Hasselmo et al., 1995). In some simulations, the sum of region CA1 activity was utilized to regulate levels of modulatory input from the medial septum (Hasselmo and Schnell, 1994; Hasselmo et al., 1995). Regulation of cholinergic and GABAergic modulatory input from the septum could also determine the capacity for information to flow back to entorhinal cortex.

As shown in Figure 5, retrieval in region CA3 generates predictions which are evaluated by matching in region CA1. This same basic function could be applicable to neocortical function, with supragranular layers II/III playing the same retrieval role as CA3, and holding these predictions in working memory until converging input from layer II/III and other sources (thalamus or lower cortical areas) generates matching activity in infragranular layers (V/VI). This matching

criteria would then allow activity to spread to other cortical or subcortical regions. This amounts to a gating process, in which predictions in working memory are matched with current input cues, and matching allows progression to new state. For example, in a simulation of counting, a working memory representation of zero would predict the first presentation of an object. When the object is seen, this match of cue and prediction would cause activation of a gate which would activate the representation of “one.” This would then predict the second presentation of input from the exact same object representation. The second presentation of the object would only activate the neuron receiving predictive input from “one”, and the activated gate would only activate the new representation for “two.” In this manner, matching of prediction and cue could allow gating functions which could form the basis for rule representations in neocortical circuits.

The general process of comparison between retrieval and input plays an important role in a more abstract class of models described with the term: Adaptive Resonance Theory (ART). The connectivity of ART networks has not been explicitly mapped to physiological structures, but these networks regulate the formation of new representations on the basis of a comparison between the current input and the representations formed in response to previously presented input (Carpenter and Grossberg, 1993).

Entorhinal cortex

In many models of hippocampal memory function, the entorhinal cortex plays a simple role as the source of input and recipient of output from the hippocampus. The entorhinal cortex certainly fits this role with regard to anatomical data. As summarized in Figure 1, input from neocor-

tical association cortices converges on the entorhinal cortex, which provides the primary afferent input to the dentate gyrus as well as providing input to stratum lacunosum-moleculare of region CA3 and region CA1. On the output side, efferent connections from region CA1 and subiculum provide a major projection to the deep layers of entorhinal cortex, which send divergent projections to association neocortex.

The entorhinal cortex can be seen as the gateway to the hippocampus. In this role, it could play an important functional role in regulating whether particular sensory input reaches the hippocampus. The limited capacity of episodic memory storage can be used more efficiently if only important information is relayed. In this context, the modulatory state of entorhinal cortex could be very important. This structure exhibits changes in physiological state associated with different behavioral states, including theta EEG oscillations which appear to be regulated by the medial septum to provide input to region CA1 which is out of phase with the region CA3 input (Mitchell and Ranck, 1980; Alonso and Garcia-Austt, 1987).

An important means by which entorhinal cortex could regulate input to hippocampus is by acting as a buffer for incoming information, holding behaviorally relevant information for a period of time longer than the presence of the sensory input itself. This potential role is supported by evidence that lesions of the entorhinal cortex and perirhinal cortex impair performance in delayed non-match to sample tasks in non-human primates (Zola-Morgan et al., 1994) and rats (Otto and Eichenbaum, 1992). In these tasks, a stimulus is presented at the start of the trial, and after a delay period the animal must respond to the object which they did not see at the start of the trial. This lesion effect suggests that entorhinal cortex may retain activity during the delay period.

Electrophysiological recording demonstrates that some neurons in this region do maintain stimulus selective activity during delay periods in a DNMS task (Young et al., 1997). This sustained activity may depend upon induction of self-sustained activity on a cellular level due to effects of acetylcholine (Klink and Alonso, 1997; Fransen et al., 1999; Hasselmo et al., 2000). This retention of activity could be very important for providing a sustained source of afferent input for a time period sufficient to induce synaptic modification within the dentate gyrus and hippocampal subregions.

In addition to its potential role in holding input during encoding in the hippocampus, the entorhinal cortex may play an important role in regulating the flow of output from the hippocampus. This could take place both during interaction with the environment and during quiet waking and slow-wave sleep. During interaction with the environment, the validity of retrieved information needs to be compared with sensory input (see discussion of region CA1 above). During quiet waking or slow-wave sleep, this output does not play a direct role in guiding behavior, but could mediate the consolidation of memory function (Hasselmo, 1999).

SPATIAL NAVIGATION MODELS

This section focuses on modeling the mechanisms of spatial navigation -- the process of encoding spatial locations and following paths between different locations. Nothing about the mechanisms of cortical or hippocampal function requires that there be a distinction between episodic memory function and spatial navigation. Given that both these functional categories appear to depend upon hippocampus, an effective model of hippocampus should account for both sets of data.

However, at this point in time there is a clear set of empirical data and computational modeling of memory function which specifically focuses on spatial memory function. In particular, many studies of hippocampal function in rats focus on behaviors involving memory for specific locations, and rats provide a greater opportunity for electrophysiological and neurochemical measurements in awake, behaving animals.

Physiological data

Considerable physiological data relevant to rat spatial navigation has been obtained. The responses of many neurons in hippocampus have been defined as “place cells”, which respond selectively to a specific location within the environment (O’Keefe and Recce, 1993; Skaggs et al., 1996; Wilson and McNaughton, 1993). This definition of place cell implies a specific role in spatial coding, but these responses could be a specific manifestation of a more general property of encoding events in an episode (Eichenbaum et al., 1999).

In behavioral tasks, hippocampal and entorhinal neurons demonstrate responses to most behaviorally relevant components. For example, in operant conditioning tasks hippocampal neurons respond to task elements including approaching and obtaining water reward (Wiener et al., 1987; Otto et al., 1992; Young et al., 1997), sampling an odor stimulus (Wiener et al., 1987; Otto et al., 1992), sampling local features of the environment such as texture (Shapiro et al., 1997) and making incorrect or correct responses (Wiener et al., 1987; Otto et al., 1992). In addition, during performance of delayed nonmatch to sample tasks, neurons show specificity for match or non-match trials in hippocampus (Otto et al., 1992) and entorhinal cortex (Young et al., 1997). Neu-

rons show activity during the delay period of the task in entorhinal cortex (Young et al., 1997). In hippocampus, studies of single neurons do not show distinct delay activity (Otto et al., 1992) whereas the ensemble code appears to maintain information across the delay (Hampson and Deadwyler, 1996). This response to all behaviorally relevant variables suggests that hippocampal neurons are not constrained to any specific sensory dimension but encode a range of events which constitute individual episodes (Eichenbaum et al., 1999).

In recent experiments, it has been explicitly shown that place cells show responses more suggestive of episodic memory function than pure spatial encoding (Frank et al., 2000; Wood et al., 2000). These experiments used tasks in which rats would run along a single central arm of the maze in the same direction, but on different trials they would have to turn either left or right at the end of the central arm. Some neurons recorded in these tasks would show differential responses on “go--left” versus “go-right” trials. Thus, the response depended on the past and future trajectory of the rat, despite the fact that the rat had exactly the same external cues and movements along the central arm.

Computational modeling of spatial navigation

A number of models of spatial navigation have utilized the basic connectivity structure of region CA3. In these models, individual spatial locations are encoded as a pattern of activity across a sub-population of place cells, and the strengthening of synaptic connections between these place cells allows activity representing one location along a path to evoke the neuronal activity representing the next location along the path. During retrieval, neuronal activity elicited

by one location can spread to adjacent locations dependent upon the prior strengthening of excitatory recurrent connections during encoding.

These models can be categorized on the basis of differences in the process of encoding the environment. Some models involve encoding of individual paths through the environment, with a global representation built from these pathways, whereas others start with a two-dimensional representation of the full environment which is then modified to encode goal location. Here, these different categories will be termed “path-based” and “grid-based” models.

Path-based models versus grid-based models.

The encoding and retrieval of specific pathways through the environment has been modeled in recurrent networks representing region CA3 (Levy, 1996; Wallenstein and Hasselmo, 1997; Hasselmo et al., 2001). In the Levy laboratory, simplified models of region CA3 have been developed with neurons represented by units with binary output states. In these models, the encoding of a path is modeled with sequential activation of different sets of units, for example, pattern A, B, C, D and E. Application of an asymmetric Hebbian learning rule strengthens connections where the activity of a presynaptic unit precedes the activity of a post-synaptic unit, consistent with neurophysiological data (Levy and Steward, 1983). Retrieval is then obtained by providing input to units in pattern A, and allowing the activity to sequentially spread across modified connections to activate units in pattern B, then pattern C, then D, then E.

These models deal with the problem of overlapping components of sequences by allowing strengthening of connections across multiple time-steps. For example, synaptic modification can

allow units not receiving afferent input to become associated with specific segments of the stored paths. Levy calls these local context units. The local context units enhance the capacity for disambiguating sequences, as well as allowing activity later in the sequence to influence earlier activity.

This type of path based framework was used in a network of compartmental biophysical simulations of region CA3 pyramidal cells (Wallenstein and Hasselmo, 1997; Wallenstein et al., 1998). This network demonstrates many of the pathway encoding properties of the Levy model using a more biologically realistic framework. Theta rhythm oscillations in the model greatly enhanced the encoding of new sequences.

More recent models developed in my laboratory have focused on the selection of specific pathways dependent upon the current goal location. In these models, activity spreads backward from the goal location along associative circuits strengthened in the entorhinal cortex. This activity then cues the spread of activity in region CA3 representing the forward spread from current location. The convergence of the forward and backward representations in region CA1 allow selection of the first pathways receiving convergent activation from goal and current location, which usually results in selection of the shortest pathway, as described in the simulation below (Gorchetchnikov and Hasselmo, 2001).

In grid based models, place cell representations are also assumed to be present when an animal initially encounters a new environment. However, in contrast to the pathway based models, these representations are assumed to be laid out in a full two-dimensional interconnected grid, presetting the nature of place cell interconnections without any role of context. The grid-based

models are proposed to set up a representation which can guide subsequent behavior. In this framework, the simulated rat performs multiple traversals through the environment, and recently activated connections are modified when the rat reaches the goal location. Eventually, the connections form a two-dimensional gradient of responses which are directed toward the goal location in the network (Blum and Abbott, 1996; Gerstner and Abbott 1997).

The starting conditions of these models are very similar, in that they both assume some initial mapping of sensory features to specific place cell representations. Other models explicitly model the formation of place cell representations through self-organization of afferent input to the hippocampus (Sharp et al., 1996; Burgess et al., 1997). The path based models assume that as an animal passes through different locations along a path, specific place cell representations are activated (implicitly assuming these place cells are initially only connected with the standard default connection strengths). The grid based models assume a network with homogeneous connectivity except where the animal has actually traversed the grid and modified connections. Thus, venturing into an area without paths is initially similar to going onto a portion of the grid that has no modified connections. However, if you have a gap and then cross it in one direction, left to right, then later cross it right to left, in the path based model the initial path would be direction selective, context properties would cause it to have a representation distinct for each direction. These direction selective responses could then be associated together to provide a non-directional response (Kali and Dayan, 2000). In contrast, in grid based models the place cell representations are already multidirectional and any directionality would have to involve later modification based on context, i.e. choosing of different grids on the basis of context. Thus, they make different pre-

dictions about the initial directionality of place cell representations.

Because grid-based models do not focus on the episodic, context-dependent components of individual pathways, they would be difficult to utilize for showing how separate representations can be set up in the same environment. The use of a single two-dimensional grid results in loss of episodic features which are preserved in a path-based model. Thus, a path-based model would more effectively account for a change in place cell representations when a rat is switched from a broad exploratory task to a specific directional traversal of the same space (Markus et al., 1997), and could account for differential responses in the stem of a T-maze before a rat makes differential responses in a spatial alternation task (Wood et al., 2000).

Guiding a virtual rat with a hippocampal simulation.

Many of the hypotheses described above make strong assumptions about the nature of behavioral input during a task and the output required for guidance of movement. These additional assumptions about the input and output can be reduced if the network directly interacts with an agent moving through an environment. This section presents a recent simulation developed in java, in which a hippocampal simulation directly guides movement of a virtual rat through a virtual environment, and receives its sensory input on the basis of those movements.

This simulation was developed within a general purpose neural simulation package developed by Robert Cannon under the name “catacomb” (DeSchutter, 2000; Cannon, 2000). This package allows flexible creation of multiple different environments including arbitrary barrier locations, and arbitrary locations for individual objects. A virtual rat can be placed into a given

virtual environment, and its movements can be controlled in one of three ways: 1.) according to pre-determined trajectories, 2.) with random choice of direction and speed of movement, and 3.) with output from a neural simulation. Numerous parameters of the environment and rat can be adjusted within the simulation.

The hippocampal simulation developed within this package contains the essential features of the simulations described in the preceding sections of this chapter. But the guidance of a rat in an environment required multiple additional functional components of the network. The structure of the network and its interaction with the virtual rat in the virtual environment is summarized in Figure 6.

FIGURE 6 ABOUT HERE.

Navigation in this model depends upon encoding and retrieval of pathways through the environment, in the form of strengthened excitatory synapses between individual place cell representations. The network receives direct sensory input representing location within the environment from the “place” node shown in Figure 6. Thus, place cell representations are assumed de facto, similar to other simulations (Blum and Abbott, 1996; Redish and Touretzky, 1998) -- the model does not explicitly model processes which could set up place cell representations, such as self-organization of the excitatory input from entorhinal cortex (Sharp et al., 1996; Burgess et al., 1997), or the self-organization of excitatory connections arising from region CA3 pyramidal cells (Levy, 1996; Wallenstein and Hasselmo, 1997).

Encoding

During encoding, the network receives input from precoded trajectories covering the full T-maze. This causes sequential activation of neurons in entorhinal cortex layer II. The activity spreads from entorhinal cortex layer II into region CA3 and entorhinal cortex layer III, and from entorhinal cortex layer III to region CA1. As place cells are sequentially activated, excitatory connections between these place cells are strengthened according to a brief window of Hebbian synaptic modification corresponding to the relative timing of pre and post-synaptic spiking necessary for induction of long-term potentiation during paired cell recording (Levy and Steward, 1983; Bi and Poo, 1998). Those experiments showed that long-term potentiation would be induced if a pre-synaptic spike preceded a post-synaptic spike by less than 100 msec, and long-term depression would be induced if a presynaptic spike followed a post-synaptic spike by a similar time window. In the simulation, we focus on a single step function which causes synaptic strengthening for any post-synaptic spike falling within a 70 msec period after a presynaptic spike. As can be seen in Figure 7, this results in strengthening of connections in the network between adjacent place cells, but not between non-adjacent place cells.

This aspect of the simulation already raised an important problem not discussed in other simulations. The window of induction for long-term potentiation (Bi and Poo, 1998) is too small relative to the average interval between activation of individual place cells. Rats take seconds or more to cover the distances in the maze, and often pause to investigate individual locations. This slow movement and frequent pausing causes difficulties in forming associations between adjacent locations, unless there is some mechanism for buffering place information to bridge across delays

between individual locations. To address this problem, I incorporated a simplified representation of intrinsic afterdepolarization mechanisms which have been modeled previously in greater biophysical details (Fransen et al., 1999; 2000; Hasselmo et al., 2000). In these simplified representations, generation of a single action potential initiates dual exponential time courses to cause a period of afterhyperpolarization followed by afterdepolarization. This results in repetitive firing of a neuron at about theta frequency for 3 to 4 spikes. This repetitive self-sustained intrinsic activity assists in ensuring that activity is sufficient to allow strengthening of all connections between adjacent locations, as shown in Figure 7 above.

Retrieval

During retrieval dynamics, network activity guided by the location of food reward (goal) and the current location converges within the simulation to activate the appropriate next location for movement toward the chosen goal. The activity within individual regions during this phase is shown in Figure 8, and summarized below.

FIGURE 8 ABOUT HERE.

Entorhinal cortex layer III:

This region is activated by the goal location in prefrontal cortex. Each time this goal location is activated, the activity spreads backward from the goal location across the connections of the network, as shown in the row showing entorhinal cortex in Figure 8. The broad spread of activity within this network results in a much larger place field representation for individual cells in the

entorhinal portion of the model, consistent with data from recordings of the entorhinal cortex (Barnes et al., 1990; Quirk et al., 1992; Frank et al., 2000). The pattern of activity in entorhinal cortex layer III causes subthreshold activation of layer II and region CA1.

Entorhinal cortex layer II:

This region receives subthreshold input from the current location, as well as subthreshold input from entorhinal cortex layer III. When the backward spread from the goal converges with the input of current location, this causes spiking activity corresponding to current location at the appropriate time. This activity then causes suprathreshold activation of region CA3.

Region CA3:

When region CA3 receives suprathreshold input from entorhinal cortex layer II, the spiking activity spreads forward along strengthened excitatory recurrent connections corresponding to previously encoded pathways through the environment, as shown in the row illustrated region CA3 in Figure 8. The spread of activity is terminated by activation of feedback inhibition which prevents excessive spread of excitation within the region (corresponding to the relatively small size of place fields for neurons recorded in region CA3). Synaptic output from region CA3 causes subthreshold activation of region CA1.

Region CA1:

This region receives subthreshold input from both region CA3 and entorhinal cortex layer III.

Neurons in this region only spike when they receive simultaneous input from region CA3 and entorhinal cortex layer III, as shown in the row illustrating region CA1 in Figure 8. This input is accurately timed such that it only causes spiking when the forward spread from current location matches the backward spread from goal which activated the current location. Excessive spiking activity is prevented by feedforward inhibition of region CA1 neurons by the output of region CA3. This activity in region CA1 causes spiking corresponding to the next location a rat needs to enter in order to start moving toward its goal. For each new current location, the cycle repeats to allow updating of the next desired location.

Theta rhythm modulation of network dynamics.

In the sections above, encoding and retrieval dynamics are described separately. However, a rat is presumably always able to encode new information, even in the midst of performing a learned navigation task in the maze. Thus, these phases of encoding and retrieval should not persist for long periods.

Theta frequency oscillations provide a mechanism to obtain effective encoding and retrieval in the network during continuous behavior. These theta rhythm oscillations are large amplitude 3-10 Hz oscillations which appear in the hippocampal EEG when a rat is actively exploring the environment (Buzsaki et al., 1983; Chrobak and Buzsaki, 1994). In contrast, the EEG shows irregular activity during immobility or consummatory activities such as eating or grooming.

Theta rhythm oscillations in the EEG of region CA1 result from sequential changes in the amplitude of synaptic currents in different layers of region CA1. As proposed in recent publica-

tions (Hasselmo and Wyble, 2000; Hasselmo et al., 2001), these changes in synaptic current during each cycle of the theta rhythm may correspond to successive phases of encoding and retrieval during each cycle.

During the encoding phase of the theta cycle, afferent input from entorhinal cortex is very strong, whereas the excitatory recurrent connections in region CA3, and the connections from region CA3 to region CA1 are very weak. This allows effective clamping of network activity to the afferent input, which is optimal for strengthening of excitatory recurrent connections to form an accurate representation of environmental features (such as adjacent place cells). Note that this requires that long-term potentiation of the excitatory recurrent connections and Schaffer collaterals should be maximal at the time that synaptic transmission at these connections is the weakest. This is consistent with physiological data showing that long-term potentiation is best induced at the peak of the local EEG, which is the time when synaptic currents are the weakest (Huerta and Lisman, 1993; Holscher et al., 1997).

During the retrieval phase of the theta cycle, afferent input from entorhinal cortex is at its weakest, but the excitatory recurrent collaterals in region CA3 and the Schaffer collaterals from region CA3 to region CA1 are at their strongest. This allows activity to be predominantly driven by spread of activity across previously modified synapses. Note that this retrieval will cause distortion of the pattern of connectivity unless there is no long-term potentiation at these connections during this time (thus, LTP must be weakest when synaptic transmission is the strongest.) If retrieval occurs during encoding, the spread of activity causes spiking to occur in a large number of neurons during the window for induction of LTP. This retrieval during encoding results in

strengthening of connections between distant, non-adjacent locations, causing a severe breakdown in network function, as shown in Figure 7.

Possible mechanisms of selective episodic activity.

This detailed model of the role of hippocampus in spatial navigation allows generation of multiple potential mechanisms for particular behavioral and electrophysiological phenomena. In particular, the differential firing of neurons in the stem of the T-maze during performance of delayed spatial alternation (Wood et al., 2000) could arise from a number of different network interactions during behavior, including the following potential mechanisms:

1. Modification of afferent input from entorhinal cortex could allow gradual separation of firing activity based on slight differences in the context input from neocortical structures. This mechanism would require that there are sufficient differences in neocortical activity dependent on the next turn, which are amplified by differences in perforant path connectivity to result in distinct cell firing patterns depending on the next turn.

2. Forward self-organization of excitatory connections in region CA3.

Prior location of the rat could cause gradual separation of sequence representations in region CA3. In this framework, the network would start out with a single representation of the stem, but as the task becomes more familiar self-organization of the excitatory connections within region CA3 could cause distinct activity in different paths which progressively spreads forward -- like

the unzipping of a zipper.

3. Backward self-organization of region CA3 connections.

The future location of the rat could cause activity to spread backward through the local context units described in previous work (Levy, 1996; Wallenstein and Hasselmo, 1997). This mechanism is unlikely, as activity in region CA3 associated with the end of the pathway is not consistent with the small size of place fields in region CA3.

4. Backward spread of activity from the goal could dictate which neurons in region CA1 can fire.

In the framework described for spatial navigation above, the backward spread of activity from a goal location representation in entorhinal cortex can determine which representation in region CA1 will be activated. In this framework, region CA3 neurons would tend to show nonspecific activity in the stem of the maze, but the convergence of this nonspecific spread of activity from the current location with the entorhinal input to region CA1 would allow selectivity dependent upon the future trajectory.

The detailed simulation presented here provides the opportunity to explore these multiple different mechanisms for causing selective firing in the stem of the T-maze, and for determining specific features of spike timing associated with individual hypothetical mechanisms. Thus, the interaction of a detailed spiking model of the hippocampal formation with a virtual rat moving through a virtual environment will provide a means of evaluating detailed quantitative mecha-

nisms directly with regard to both behavior and physiology, without the mediation of imprecise verbal hypotheses.

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FIGURE LEGENDS

Figure 1. Left: Overview of the anatomical connectivity of the hippocampal formation. These connections include: 1.) perforant path connections from entorhinal cortex layer II to the dentate gyrus, 2.) mossy fibers projecting from the dentate gyrus and synapsing on region CA3 pyramidal cells, 3.) the longitudinal association fibers providing excitatory recurrent connections between pyramidal cells in region CA3, 4.) the Schaffer collaterals connecting pyramidal cells of region CA3 to pyramidal cells of region CA1, 5.) excitatory feedback projections from region CA1 and subiculum to deep layers of the entorhinal cortex, 6.) direct perforant path projections from entorhinal cortex layer III to region CA1. Most sensory input entering the hippocampus arrives via layers II and III of entorhinal cortex, which receives convergent input from a range of multi-modal association cortices. Output to cortical structures projects via deep layers of entorhinal cortex. Right: Summary of the basic components of hippocampal memory models. Individual subregions of the hippocampus shown on the left are modeled with populations of processing units with connections summarized on the right. Each rectangle in the figure on the right represents a population of processing units in the model. Arrows represent synaptic connectivity within the models. In addition to the connections summarized in Figure 3.1, computational models include 7.) direction perforant path projections from entorhinal cortex layer II to region CA3, 8.) connections from region CA1 and CA3 to subcortical circuits influencing the activity of neurons in the medial septum, 9.) modulatory cholinergic and GABAergic innervation from the medial septum to the hippocampus, 10.) bidirectional connections between entorhinal cortex and higher order association cortices, including perirhinal cortex and parahippocampal gyrus.

Figure 2. Left: Afferent input evokes a pattern of activity in region CA3. Filled circles represent active neurons in the network. Different inputs evoke different patterns of activity in region CA3. For example, presentation of the first word in the context of a specific memory task (item #1) might evoke activity in one set of neurons. Presentation of the second word in that task (item #2) might evoke a second pattern of active neurons. Right: Hebbian synaptic modification strengthens synapses between active neurons.

Figure 3. LEFT: A retrieval cue evokes activity in a subset of neurons in region CA3. RIGHT: Activity spreads along excitatory recurrent connections within region CA3 to evoke the full pattern of activity.

Figure 4. Example of retrieval of distinct relational properties or sequences of events from a network of encoded associations. Responses to different questions about an episodic event can result in different sequences of accessing the necessary information to answer the question.

Figure 5. Overview of comparison function. Episodic input from entorhinal cortex passes through dentate gyrus and region CA3, where retrieval based on previously encoded representations takes place. This retrieval then passes on via the Schaffer collaterals to region CA1, where there can be a direct comparison with episodic input from entorhinal cortex. If region CA3 and dentate have not previously encoded the memory, this comparison function might reveal a poor

match. B. Overview of matching function. Top two lines represent activity of synaptic input to specific neurons from different sources (EC input and CA3 retrieval). Bottom lines represents the sum of input effects on postsynaptic activity for each neuron relative to threshold. Mismatch: for unfamiliar patterns, the retrieval from region CA3 does not match with EC input, and postsynaptic activity is below threshold for most neurons. Match: for familiar patterns, the retrieval from region CA3 matches EC input and brings neurons in the pattern above threshold .

Figure 6. The essential components of the network simulation are summarized here. Input from a place representation (“place”) depend upon the location of the virtual rat in the virtual environment. This input activates entorhinal cortex layer II, which has intrinsic properties allowing self-sustained activity, and sends excitatory output to entorhinal cortex layer III and region CA3. Region CA3 and entorhinal cortex layer III send converging input to region CA1. The place representation also sends subthreshold input to a prefrontal cortex region. Sensory input for proximity to objects (“proxim”) activates a unit representing activation of ventral tegmental area by food reward. The input from ventral tegmental area enters the a prefrontal region along with input representing space. The convergence of ventral tegmental and place input to prefrontal cortex causes spiking and activation of intrinsic mechanisms maintaining working memory for reward location. During retrieval phases, the convergence of activity from entorhinal cortex layer III and region CA3 causes spiking in region CA1 indicating the appropriate next location. This spiking output guides the movements of the virtual rat toward the desired goal.

Figure 7. Pattern of connectivity within region CA3 of the integrate and fire simulation. Lines represent excitatory connections between CA3 pyramidal cells which have been strengthened during encoding. Connections in opposite directions are offset from one another to illustrate the strengthened connections are bidirectional in this simulation, though larger scale simulations should be able to function with unidirectional connections. LEFT: When encoding of sequential input from entorhinal cortex occurs at separate phases from the retrieval activity spreading along recurrent connections in CA3, then the network forms an effective representation of the T-maze, with connections (black lines) only between place cells representing adjacent locations in the maze. RIGHT: When encoding and retrieval are not separated, the spread of activity across the excitatory recurrent connections during encoding causes broadly distributed firing during encoding. This broadly distributed firing causes strengthening of connections between place cells representing locations which are not adjacent, and prevents accurate navigation of the virtual rat within the virtual environment.

Figure 8.

Spread of activity in the network during retrieval. The different rows of this figure show activity in different subregions of the simulation during retrieval (only retrieval dynamics are simulated in this example, to clarify the patterns of activity). Bottom row: Entorhinal cortex (EC). Activity spreads backward from goal location, causing sequential spiking in neurons representing locations throughout the maze. Top row: Region CA3. When the spread in entorhinal cortex reaches the current location, activity spreads forward in region CA3 from the current location of the rat (at

the start of the stem in this example). Middle row: Region CA1. Synaptic input from entorhinal cortex and region CA3 converges in this region, causing spiking of a neuron representing the next desired location (at the T-junction of the maze).

FIGURES

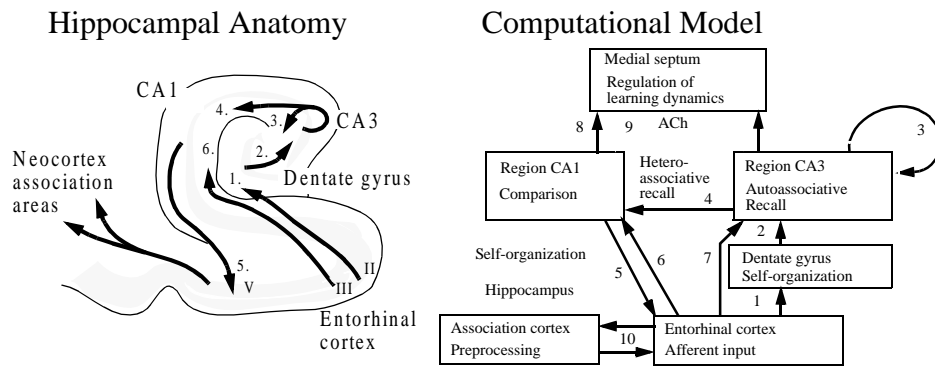


Figure 1

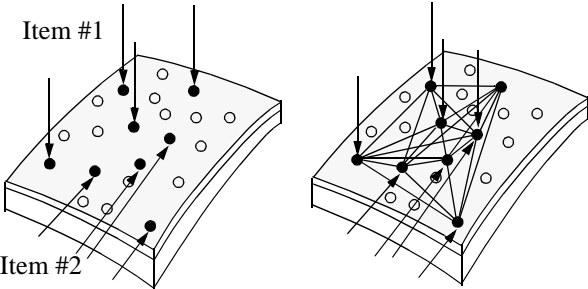


Figure 2

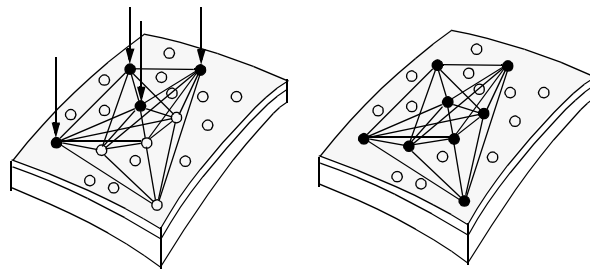


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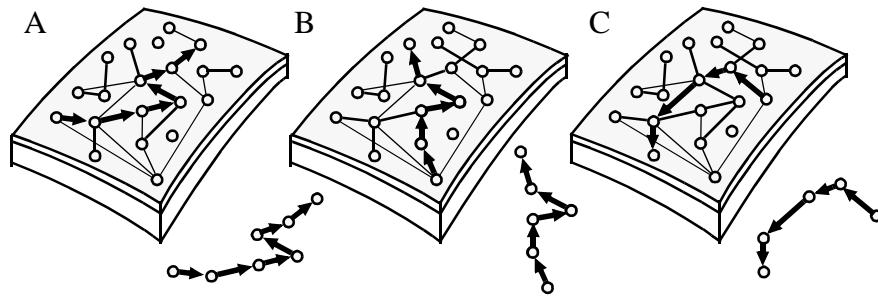


Figure 4

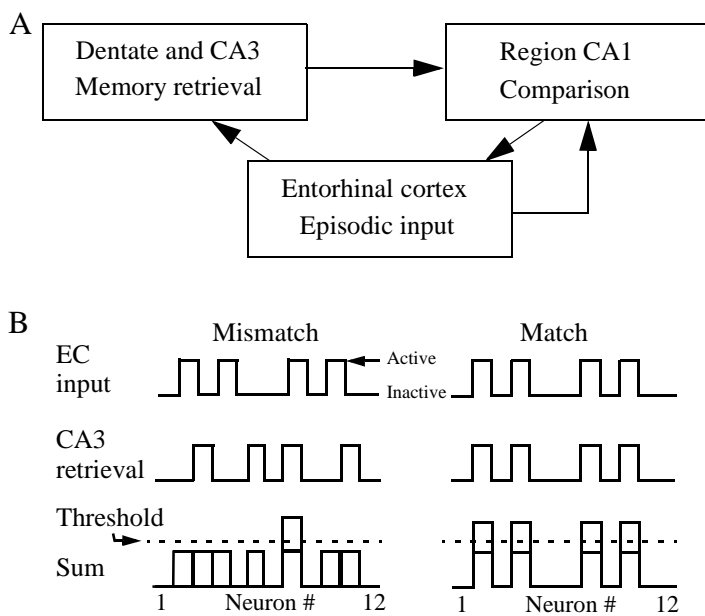


Figure 5

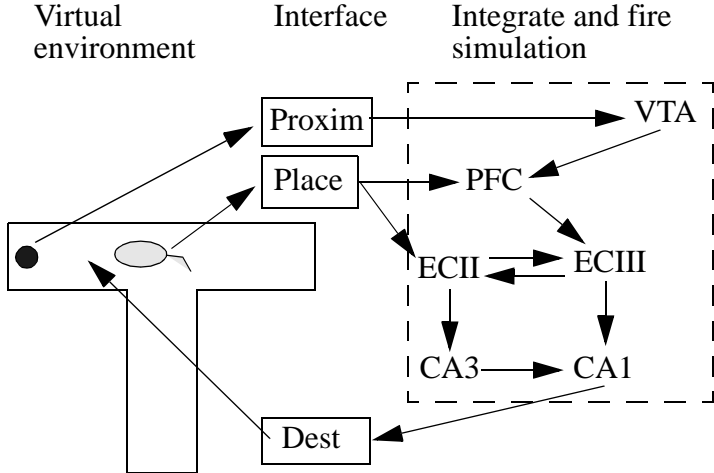
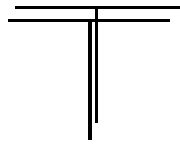
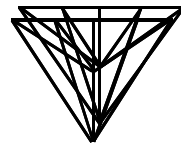


Figure 6

Connectivity pattern



Encoding and retrieval
on separate phases



Encoding and retrieval
simultaneous

Figure 7

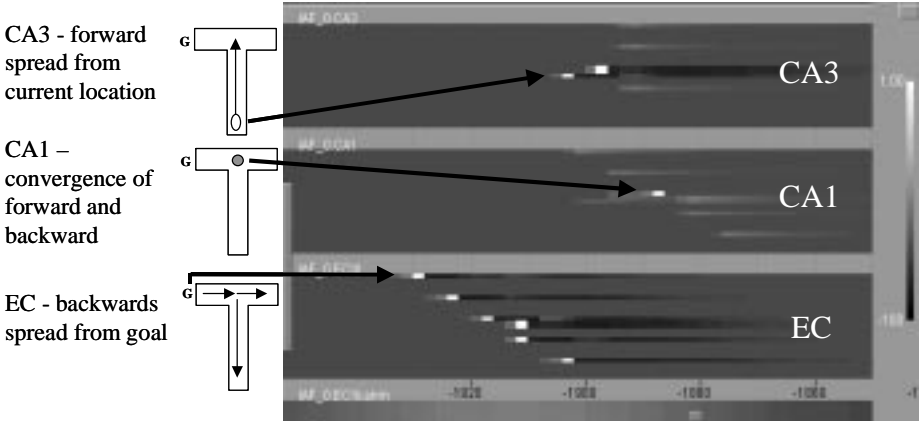


Figure 8

