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Encoding and Retrieval in the CA3 Region of the Hippocampus: A Model of Theta-Phase Separation

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Kunec, Steve, Michael E. Hasselmo, and Nancy Kopell. Encoding and retrieval in the CA3 region of the hippocampus: a model of theta-phase separation. *J Neurophysiol* 94: 000–000, 2005. First published February 23, 2005; doi:10.1152/jn.00731.2004. Past research conducted by Hasselmo et al. in 2002 suggests that some fundamental tasks are better accomplished if memories are encoded and recovered during different parts of the theta cycle. A model of the CA3 subfield of the hippocampus is presented, using biophysical representations of the major cell types including pyramidal cells and two types of interneurons. Inputs to the network come from the septum and the entorhinal cortex (directly and by the dentate gyrus). A mechanism for parsing the theta rhythm into two epochs is proposed and simulated: in the first half, the strong, proximal input from the dentate to a subset of CA3 pyramidal cells and coincident, direct input from the entorhinal cortex to other pyramidal cells creates an environment for strengthening synapses between cells, thus encoding information. During the second half of theta, cueing signals from the entorhinal cortex, by the dentate, activate previously strengthened synapses, retrieving memories. Slow inhibitory neurons (O-LM cells) play a role in the disambiguation during retrieval. We compare and contrast our computational results with existing experimental data and other contemporary models.

INTRODUCTION

Extensive research indicates a role for the hippocampal formation in the initial encoding and retrieval of episodic memories (Eichenbaum and Cohen 2003). Lesions of the hippocampus impair retrieval, after a delay, of recent episodic events such as memories for word pairs, without impairing immediate recall of information, and without impairing semantic memory or retrieval of remote episodic memories. However, the mechanisms by which the hippocampus encodes and retrieves episodic memories are not fully understood. Previous models have proposed basic mechanisms for encoding of associations through changes in synaptic strength within the hippocampus (Hasselmo and Schnell 1994; Hasselmo et al. 2002; Jensen and Lisman 1996; Lisman 1999; Treves and Rolls 1992; Tsodyks et al. 1996; Wallenstein and Hasselmo 1997). The model presented here extends this previous modeling work by explicitly simulating the timing of firing of different hippocampal cell types relative to the theta rhythm (Csicsvari et al. 1999; Fox et al. 1986; Skaggs et al. 1996) and proposing functional roles for different classes of inhibitory interneurons (Csicsvari et al. 1999).

A recent model (Hasselmo et al. 2002) proposes that the hippocampal theta rhythm could contribute to encoding and

retrieval of memories, by separating encoding and retrieval of memories into different functional cycles. This hypothesis is related to earlier work on cholinergic presynaptic inhibition of excitatory synaptic transmission in the hippocampus (Hasselmo and Fehrlau 2001), but focuses on the faster time course of theta rhythm cycles, in contrast to the cholinergic effects that last for many seconds.

The separation of encoding and retrieval would occur continually, but would be particularly important for separating memories that might interfere, such as in reversal of learned tasks when episodic memories of recent nonreward aid shifting from one response to another response. This theory is based on extensive physiological data indicating specific changes within each cycle of the theta rhythm (Buzsaki 2002; Buzsaki et al. 1983; Stewart and Fox 1990). These data include evidence for cyclical changes in the relative strength of synaptic input from entorhinal cortex versus synapses arising from region CA3 (Brankack et al. 1993), as well as cyclical changes in the induction of long-term potentiation during theta rhythm (Hyman et al. 2003; Pavlides et al. 1988). The basic theory is summarized in Fig. 1. During encoding, the hippocampal region receives stronger input from the entorhinal cortex, whereas recurrent connections between CA3 pyramidal cells, efferents from CA3 to CA1, and hippocampal output are relatively weak. During the retrieval cycle, the converse is true; input into the hippocampus is at a minimum, but intraregional, hippocampal transmission and hippocampal output are stronger. Both cycles are defined relative to the theta rhythm measured at the hippocampal fissure.

To support this hypothesis, this article describes a biophysical model of the CA3 region that simulates 2 separate functional cycles within each cycle of the theta rhythm, allowing transitions between encoding and retrieval. Furthermore, the model aims to reproduce experimental results of Fox et al. (1986), Skaggs et al. (1996), and Csicsvari et al. (1999), all showing that the various cell types within the hippocampus fire at a preferred phase relationship with respect to the underlying theta rhythm and to each other. Simulating this data requires replication of the phasic firing of interneurons relative to theta rhythm, which provides an important functional perspective on the role of these interneurons in transitions within each theta cycle.

We focus on the CA3 region for various reasons. Chief among them is the anatomical data (Amaral and Witter 1989) showing that the CA3 region contains an extensive, recurrent

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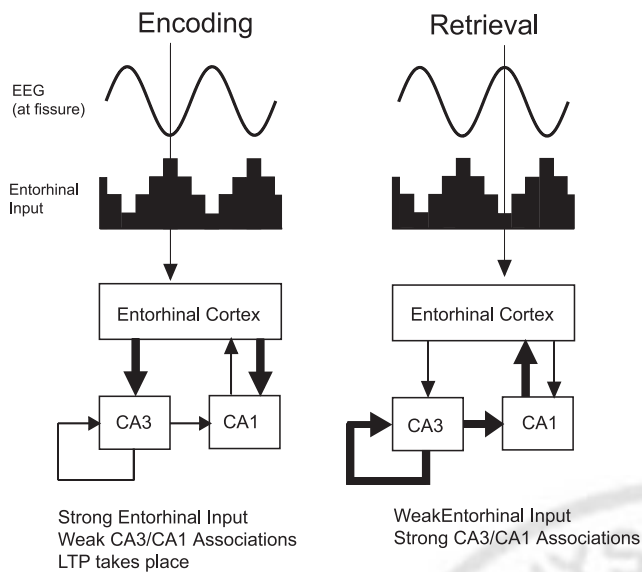


FIG. 1. Theory of encoding and retrieval on separate theta phases. During reversal of learned tasks, different functional cycles occur during different portions of theta. During encoding, at the trough of the theta oscillation recorded from the hippocampal fissure, relatively strong input from the entorhinal cortex enters the hippocampal region but there is weak excitation within CA3. During this time, long-term potentiation takes place within the hippocampus, strengthening connections among the principal cells. During retrieval, at the maximum of the theta oscillation recorded at the hippocampal fissure, the entorhinal input is reduced, but intrahippocampal excitation and hippocampal output is stronger, as previously encoded memories are recalled and passed out of the hippocampus.

collateral system that is well equipped to perform autoassociative functions. Also, the CA3 subfield receives input directly from Layer II of the entorhinal cortex and indirectly from Layer II by the dentate gyrus. We propose that the separate perforant path inputs are needed to facilitate the encoding of information within the CA3 recurrent collateral network. The indirect dentate input selects novel components of Layer II activity for transmission (Kitchigina et al. 1997), whereas the direct entorhinal input contains more broad-based contextual information, possibly derived from the perirhinal cortex (Barnes et al. 1990). The CA3 region can either encode the new data or append the novel data to previously stored memories.

METHODS

Network model of CA3 subfield

Figure 2 illustrates the simulated CA3 region. Its neuronal components consist of 5 pyramidal cells, one O-LM (oriens-lacunosum-moleculare) cell and a population of inhibitory basket cells. The modeled subregion also receives several inputs: direct entorhinal cortex input, indirect entorhinal input (by the dentate gyrus), and input from the septum. Each constituent will be discussed further in the following subsections. Their mathematical implementation appears in APPENDIX 1, A–F.

PYRAMIDAL CELLS. The pyramidal cell population consists of 5 modified Traub–Pinsky–Rinzel cells (Pinsky and Rinzel 1994). They are all-to-all coupled, mimicking (for this small system) the extensive recurrent collateral system of CA3. Each cell consists of 4 compartments: one somatic and 3 dendritic.

As suggested by anatomical studies, each pyramidal cell receives somatic inhibition from the population of basket cells (Freund and Buzsaki 1996), proximal excitation from the dentate gyrus (Witter

1993), mid-dendritic excitation from other pyramidal cells (recurrent collaterals) (Amaral and Witter 1989), distal inhibition from O-LM cells (Freund and Buzsaki 1996; Klausberger et al. 2003), and distal excitation from direct entorhinal cortex input (Witter and Amaral 1991).

O-LM CELLS. The cell bodies and dendrites of the interneurons designated as oriens-lacunosum-moleculare (O-LM) generally reside within stratum oriens, with the dendrites extending horizontally through the layer. However, their axons mainly project to the stratum lacunosum-moleculare. O-LM cells can intrinsically oscillate at a theta rhythm, and they receive excitatory input from pyramidal cells and inhibitory input from the basket cell population (Freund and Buzsaki 1996; Gloveli et al. 2002; Klausberger et al. 2003).

In the model, we studied the effects of one O-LM cell on the small network of 5 pyramidal cells. This single O-LM cell can also represent a synchronized population of these cells.

BASKET CELLS. Basket cells are ubiquitous within the CA3 and the greater hippocampal region (Freund and Buzsaki 1996). Their cell bodies and axons rest primarily in the stratum pyramidale, while their dendrites may extend across the strata to stratum radiatum and stratum lacunosum-moleculare. In addition, the basket cell population receives excitatory input from active pyramidal cells and is regulated by an inhibitory, septal input (Freund and Antal 1998).

To gauge the effect of a large number of basket cells on individual pyramidal cells, the basket cells were modeled by a single population equation. Within the population, each cell is considered to be simply in an active or inactive state (i.e., above or below threshold, respectively). Excitatory input from individual, active pyramidal cells “turns on” a proportion of inactive basket cells. The modeled inhibitory septal input “turns off” a proportion of the basket cells equal to the active septal population.

EXTRAHIPPOCAMPAL INPUTS. An important hippocampal input comes from the septum. It is known that lesioning the septal area eliminates the hippocampal theta rhythm and septal cells can oscillate in a theta rhythm without hippocampal theta (Green and Arduini 1954; Petsche et al. 1965). The septum provides inhibition to the

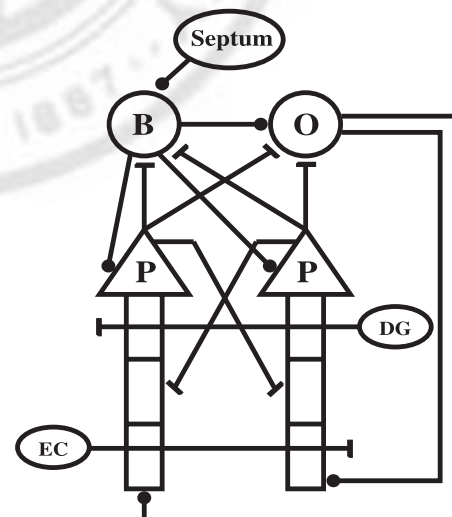


FIG. 2. Simulated CA3 network. Septal input exclusively inhibits the basket cell population (B). Basket cells inhibit both the oriens-lacunosum-moleculare (O-LM) cell (O) and the pyramidal cells (P). O-LM cell inhibits the distal dendrites of the pyramidal cells. Pyramidal cells excite each other, by their recurrent collaterals, and they also excite both interneuron types. Dentate gyrus input (DG) proximally excites a small subset of pyramidal cells. Direct entorhinal input (EC) diffusely excites the distal dendrites of the pyramidal cells, impinging on all of them. In this diagram, filled circles represent inhibitory synapses, whereas flat rectangles represent excitation.

hippocampus, exclusively inhibiting local basket cells within CA3 (Freund and Buzsaki 1996).

In addition to the septal input, the CA3 region receives 2 other extrahippocampal inputs. Both originate in Layer II of the entorhinal cortex and both synapse onto the dendrites of the CA3 pyramidal cells. One projects directly from Layer II, whereas the other contacts dentate gyrus granule cells, which then synapse on the proximal dendrites of CA3 pyramidal cells in stratum lucidum. This pathway is thus gated by the relative activity of dentate neurons. Each input has different properties and targets. The dentate input projects proximally within the stratum lucidum, whereas the entorhinal input projects distally to the stratum lacunosum-moleculare (Witter 1993; Witter and Amaral 1991). According to experimental evidence (Brazhnik and Fox 1997; King et al. 1998), septal, inhibitory neurons fire 180° out-of-phase with the entorhinal and dentate thetas.

Within the simulation, the dentate input is chosen to be relatively strong and selective, exciting only a subset of the pyramidal cells. However, the entorhinal input is relatively weak and diffuse, projecting to all of the pyramidal cells. It simulates the broad-based contextual information as discussed in the INTRODUCTION.

RESULTS

Mechanisms for encoding and retrieval

We now discuss how the model encodes and retrieves during each theta period. Figure 3, *A* and *B* summarizes each functional cycle and how the components of the network interact.

ENCODING CYCLE. Past studies have suggested that the septum paces the theta rhythm within the hippocampus (Stewart and Fox 1990); thus we treat the septal rhythm as the initiator of the encoding/retrieval process within the simulation. The entire cycle begins with increased activity within the septum. The septum contains GABAergic and cholinergic neurons that have been shown to oscillate in a theta rhythm (Brazhnik and Fox 1997; King et al. 1998) and whose GABAergic cells have been shown to project exclusively to inhibitory cells of the hippocampus (Freund and Antal 1998). We focus on the GABAergic effects of the septum because the cholinergic timescale was found to work too slowly to affect dynamics during a theta period (Hasselmo and Fehla 2001).

During the simulated encoding cycle of theta, we propose the following: the GABAergic cell population of the septum is at an activity minimum, and therefore transmits the least amount of inhibition to the basket cells of the CA3. Having the least amount of inhibition impinging on them, the CA3 basket cell population is free to do several things: Primarily, the basket cells exert tight control over the firing properties of their associated pyramidal cells. While released from septal inhibition, the basket cells produce gamma oscillations. During the lulls in the inhibition from basket cells, which occur with gamma rhythmicity, pyramidal cells receiving sufficient excitation can fire. The secondary influence of these interneurons is more subtle; they silence the O-LM cells present in the system. This inhibition also activates the intrinsic, hyperpolarization-activated *h*-current of the O-LM cell (Maccaferri and McBain 1996), and primes the O-LM cell to fire during the retrieval cycle.

The model CA3 receives 2 excitatory inputs: indirect entorhinal input by the dentate and a direct entorhinal input. Only the dentate input is strong enough to cause pyramidal cells to fire during encoding. We suggest that this selected activity is analogous to novel sensory information being transmitted from the dentate gyrus, where intrinsic properties of that region may naturally orthogonalize combined data (McNaughton 1991; Treves and Rolls 1994). The direct entorhinal input within this model represents contextual information. During encoding, the rate of its input increases (Hasselmo et al. 2002).

Within our model, long-term potentiation (LTP) may occur between presynaptic neurons and postsynaptic targets if 2 things occur: 1) a presynaptic cell fires an action potential and 2) the mid/distal dendrites of the postsynaptic cell are depolarized (Golding et al. 2002). This is the theorized mechanism for encoding novel information by creating cell ensembles or adding to existing cell ensembles by this process; that is, if the novel data from the dentate gyrus cause certain pyramidal cells to fire and the “familiar” signal from the entorhinal cortex simultaneously depolarizes the dendrites of postsynaptic targets, the novel information is appended to the old. APPENDIX 1F

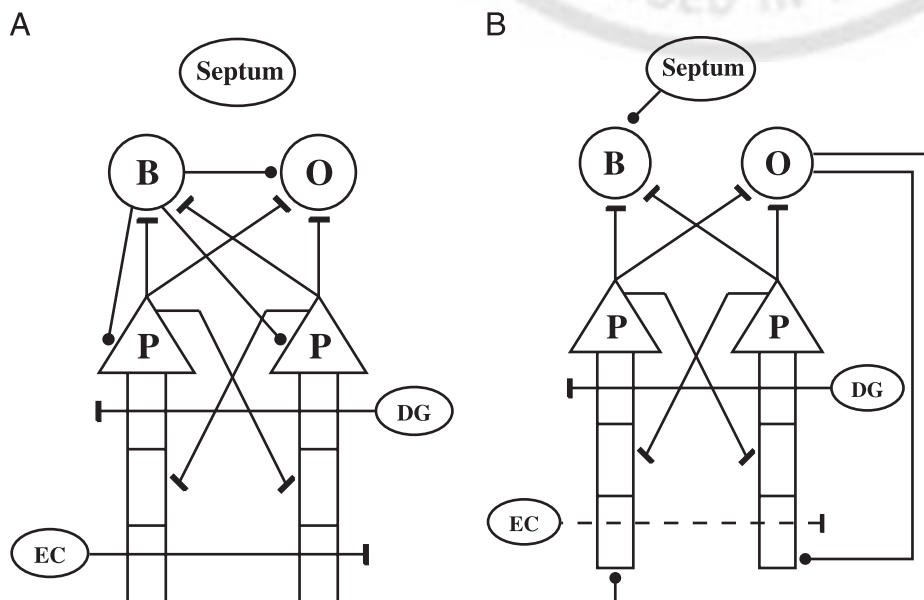


FIG. 3. Modulatory changes in network interactions during encoding and retrieval. *A*: encoding: at a minimum, the septal inhibition allows the basket cell population (*B*) to inhibit both the O-LM cell (*O*) and the pyramidal cell population (*P*). O-LM cells are prevented from firing during encoding, whereas only pyramidal cells receiving strong enough input proximally from the dentate gyrus (*DG*) can fire during encoding. If a presynaptic cell firing from dentate input coincides with dendritic depolarization resulting from distal entorhinal input (*EC*), strengthening of synaptic connections between these 2 cells can occur. *B*: retrieval: at a maximum, the septal activity inhibits the basket cell population, thus allowing both O-LM and pyramidal cells to fire. O-LM cells can inhibit the distal dendrites of the pyramidal cells, preventing retrieval errors. Dentate input acts as a cueing mechanism to initiate retrieval by the previously strengthened recurrent collaterals between pyramidal cells. Entorhinal input is weaker (dotted line), but still aids in retrieval by depolarizing the cells (i.e., priming them to fire).

discusses the computational implementation of this strengthening mechanism.

The use of the Golding et al. mechanism differs from other strengthening paradigms, such as Hebbian modification (Hebb 1949) and spike-time-dependent plasticity (STDP) (Bi and Poo 2001), which require both the pre- and postsynaptic cell to produce somatic spikes. For STDP, axonal delays could play a crucial role in determining the relative timing of action potentials, and therefore whether potentiation or depression would occur. Our model assumes the axonal delays are small compared with the decay time of the *N*-methyl-D-aspartate (NMDA) synapse, creating an adequate window during which the presynaptic cell can fire and form a stronger connection.

RETRIEVAL CYCLE. The retrieval cycle begins as the GABAergic cells of the septum approach maximum activity. Because of this septal input, the basket cells of the CA3 region are inhibited, releasing both the pyramidal cells and the O-LM cell from inhibition. Pyramidal cells may now fire more easily, which is crucial for retrieving information, i.e., allowing previously formed cell ensembles to fire together.

The nonseptal, dentate input now serves as a cueing mechanism: If the dentate input excites a pyramidal cell during this time, any synapses that were strengthened during encoding (from the cued cell to other cells) will activate, recalling the memory by firing the rest of the cell ensemble.

As suggested by Hasselmo and colleagues (2002), the entorhinal input may be less active during retrieval, but may still provide a weaker, background excitation to the CA3 region to aid in the retrieval process, causing depolarized cells to fire. However, this excitation must be prevented from activating unwanted or similar memories (see following text). The newly uninhibited O-LM cell has this responsibility in our model. After being released by the basket cell population, which previously activated its intrinsic *h*-current, the O-LM cell fires. In doing so, it strongly inhibits the CA3 network, targeting the distal dendrites of pyramidal cells (Freund and Buzsaki 1996), where direct entorhinal input arrives.

Parameter constraints for encoding and retrieval

Figure 4 depicts output from our model, showing successful encoding and retrieval. Successful encoding for the simulation

F4

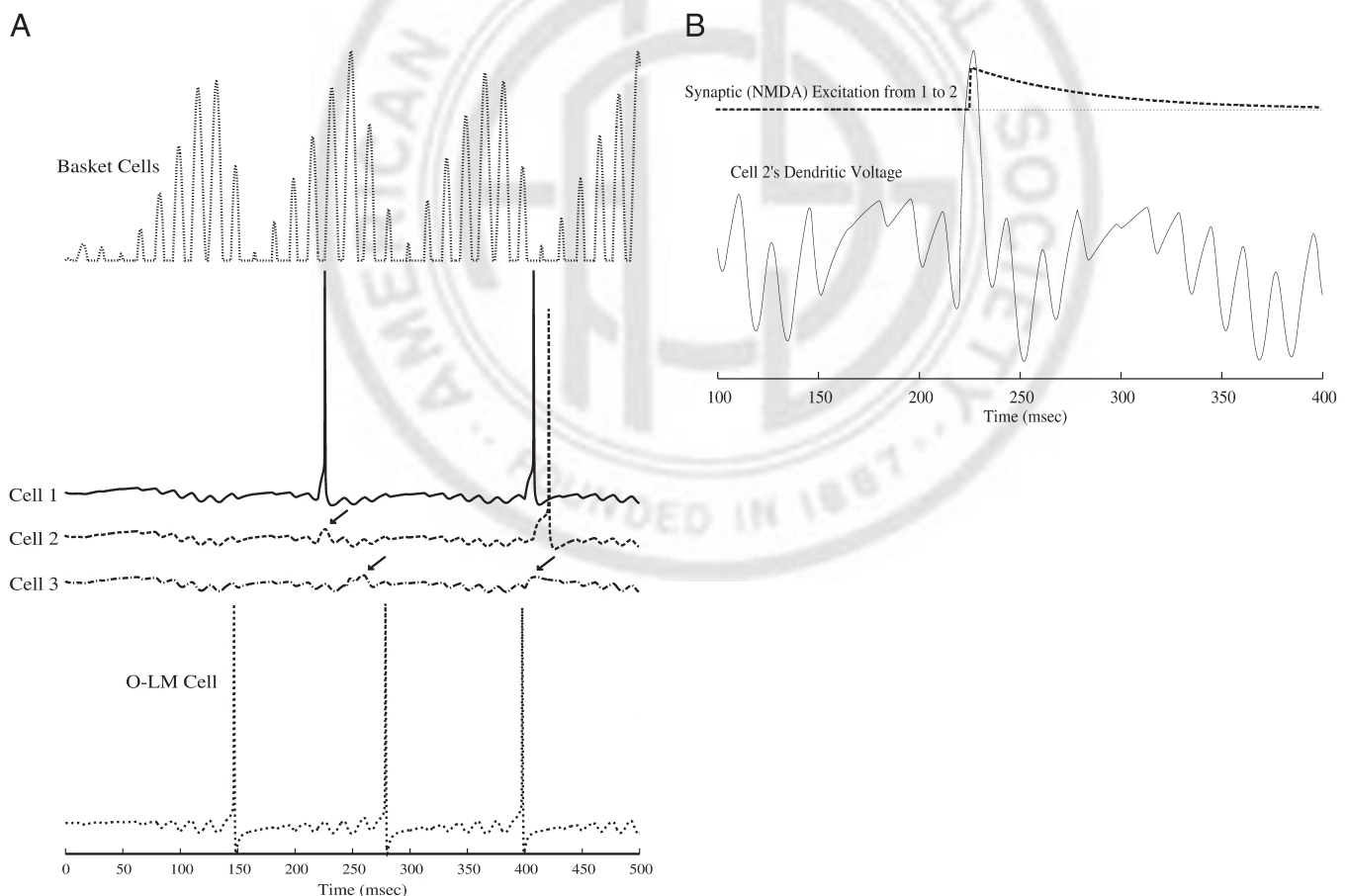


FIG. 4. Example of simulated encoding and retrieval. *A*: at time 220 ms, dentate input causes the voltage of Cell 1 to fire a spike. At the same time, Cell 2 receives entorhinal input (arrow on Cell 2). As depicted in the *right* figure, if the presynaptic cell fires an action potential and the postsynaptic cell's dendrites are depolarized, the synaptic connection is strengthened, creating a 2-cell assembly. At time 245 ms, Cell 3 receives dentate input, but basket cell inhibition prevents the cell from firing during encoding (first arrow on Cell 3). At time 400 ms, a cueing input from the dentate causes Cell 1 to fire and contextual input from the entorhinal input impinges on both Cell 2 and Cell 3. When Cell 1 fires, Cell 2 fires as a result of the stronger connection; Cell 3 does not fire because of input from the O-LM cell (second arrow on Cell 3). Basket cell population regulates overall cell firing during the simulation, restricting cells to gamma cycles. *B*: because of dentate input at 220 ms, Cell 1 fires, causing an *N*-methyl-D-aspartate (NMDA)-mediated current with time course shown at *top*. At the same time, the distal dendrites of Cell 2 receive input from the entorhinal cortex, depolarizing the dendrites (but not causing a dendritic spike). Both of these conditions serve to strengthen the connection from Cell 1 to Cell 2 for use during retrieval.

is defined by the development of LTP during the encoding cycle (i.e., Cell 1 fires an action potential as a result of dentate input and the dendrites of Cell 2 are depolarized by entorhinal input). Successful retrieval occurs if Cell 1 spikes from dentate cueing input and Cell 2 fires as a result of the strengthened connection, thus completing the pattern.

Cell 3 is a nonassembly cell. During the course of the simulation, Cell 3 receives input at 2 separate times. It receives dentate input during the encoding cycle, representing novel information that is not supposed to be added to the current cell assembly. During retrieval, Cell 3 receives entorhinal input, representing contextual information not associated with the current cell assembly. Cell 3 does not fire because it is being inhibited. In the former case, it fails to fire because it receives input during a peak in gamma inhibition. In the latter, the inhibition of the O-LM cell prevents it from firing. If Cell 3 fires during either encoding or retrieval, this is considered an error.

We varied 4 different model parameters and studied how changes in their values affected simulated encoding and retrieval. We concentrated our efforts on 1) basket to pyramidal cell synaptic conductance, 2) basket to O-LM cell synaptic conductance, 3) pyramidal to pyramidal cell synaptic conductance (after LTP), and 4) O-LM to pyramidal cell synaptic conductance.

BASKET TO PYRAMIDAL INHIBITION. Through inhibition, the basket cell population controls when the other cell types can fire. We varied the inhibitory synaptic conductance to both the pyramidal cells and the O-LM cell. For encoding and retrieval, the basket to pyramidal cell connection is especially important. When that strength was varied, several functional regimes were observed, as summarized in Table 1.

If there is little or no inhibition, retrieval is possible, but encoding is problematic. During encoding, if there is no inhibitory control, dentate input can cause nonassembly pyramidal cells to fire at times other than during lulls in inhibition, as Cell 3 does in Fig. 5. LTP, and ultimately retrieval, can still occur. As the inhibitory strength from basket to pyramidal cells is increased, the ability to encode successfully is achieved. If the inhibition reaches a certain strength, retrieval is halted. The cueing spike for pattern retrieval can fire, but the basket cell inhibition, combined with the O-LM inhibition, prevents the rest of the pattern from being retrieved. Finally, if the inhibition is sufficiently strong, the model loses its ability to encode. This occurs when the inhibition suppresses dendritic potentials such that the dendrite is not sufficiently depolarized to cause LTP.

BASKET TO O-LM INHIBITION. The basket cell inhibition activates the *h*-current within the O-LM cell model. The parameter

TABLE 1. *Effects of B to P inhibition strength on model output*

Conductance Value Range, mS/cm ²	Effect
0–0.096	During encoding, dentate-induced spikes any time (LTP can occur), unregulated encoding Retrieval occurs correctly
0.097–0.270	Encoding and retrieval occur correctly
0.271–0.496	Encoding and retrieval cueing, but no pattern completion
≥0.497	No LTP during encoding

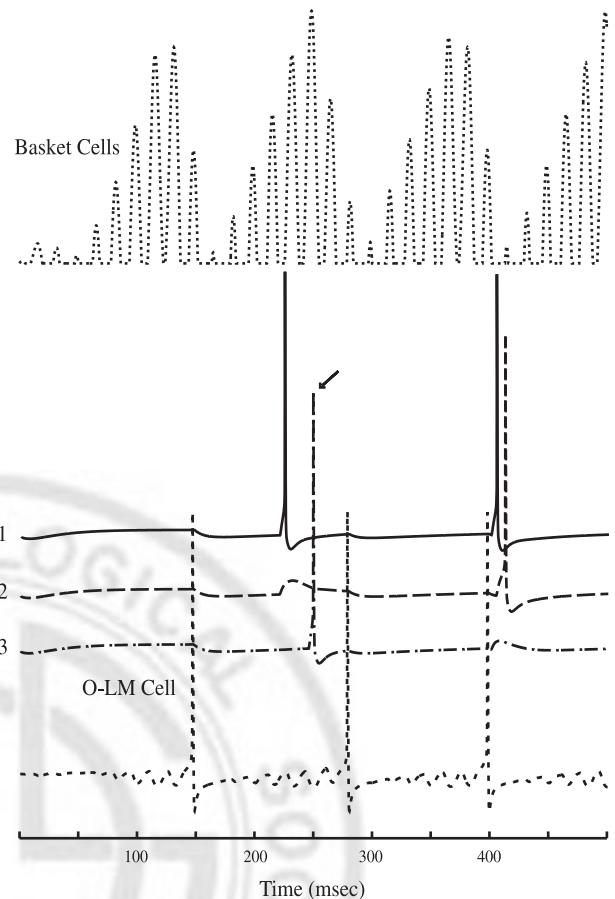


FIG. 5. Weak inhibition from basket cells allows nonassembly cells to fire during encoding. Without sufficient basket cell inhibition, dentate-receiving pyramidal cells can fire at any time during encoding. Cell 3 fires at about 250 ms (arrow), possibly encoding that cell with the wrong input. In Fig. 4A, Cell 3 is suppressed by basket cell inhibition.

study results are summarized in Table 2. In all cases, encoding is preserved. If there is no inhibition to the O-LM cell, then the cell does not fire unless excited sufficiently by pyramidal cell activity. Thus the O-LM cell does not fire before the pyramidal cells and cannot provide inhibition initially during retrieval. This scenario allows nonassembly cells that receive entorhinal input to fire during retrieval.

As basket to O-LM inhibition increases from zero, the inhibition applied to the O-LM cell causes it to fire, but not

TABLE 2. *Effects of B to O-LM inhibition strength on model output*

Conductance Value Range, mS/cm ²	Effect
0–0.224	Encoding occurs correctly O-LM cell fires inconsistently (not on every theta cycle) Nonassembly pyramidal cell may fire due to EC input if no O-LM inhibition, creating erroneous retrieval
0.225–0.485	Encoding occurs correctly O-LM cell fires consistently (on every theta cycle), but too late on some or all cycles Nonassembly pyramidal cells fire due to EC input, creating erroneous retrieval
≥0.486	O-LM cell fires consistently on every theta cycle Encoding and retrieval occur correctly

consistently on every theta cycle until the inhibition strength is increased further. However, in these conditions, retrieval still has problems: The O-LM cell fires too late in some cases, allowing nonassembly cells to fire.

In the regime of consistent but late firing, the O-LM cell fires at the same angular phase of the theta oscillation. For still larger values, the inhibition causes the *h*-current to activate faster and, as a result, the O-LM cell fires earlier. Because the basket cell inhibition occurs with a gamma rhythmicity, the O-LM cell fires during an earlier gamma cycle, when the inhibition is at a minimum, as seen in Fig. 6. Now, the pyramidal cells receive the needed O-LM inhibition to prevent errors, and both encoding and retrieval occur correctly.

PYRAMIDAL TO PYRAMIDAL EXCITATION. Changes in the recurrent collateral strengths of pyramidal cells can affect the encoding/retrieval process. We varied the post-LTP connection strength to investigate its importance. The results are shown in Table 3.

Retrieval occurs only if the post-LTP connection strength is strong enough to overcome the inhibition of the O-LM cell. The timing of the retrieval depends on the connection strength. Higher excitation causes the postsynaptic cell to reach threshold more rapidly and fire earlier. For lower strengths in this regime, the postsynaptic pyramidal cell fires later in the retrieval cycle.

TABLE 3. *Effects of P to P LTP strength on model output*

Conductance Value Range, mS/cm ²	Effect
0	No encoding or retrieval
0.001–0.057	Encoding occurs correctly No retrieval
0.058–0.346	Encoding and retrieval occur correctly
≥0.347	Encoding occurs correctly Erroneous postsynaptic action potentials after retrieval

Eventually, if the recurrent strength is too strong, the over-excitation causes the postsynaptic cell to fire multiple times, which may lead to an explosive increase in network activity.

O-LM TO PYRAMIDAL INHIBITION. The O-LM to pyramidal cell inhibition strength influences the retrieval cycle. The results are summarized in Table 4. If there is no O-LM inhibition, encoding still occurs, but retrieval cannot be performed correctly because both the assembly cells and any nonassembly cells (those that fire as a result of direct entorhinal input but are not a part of the desired pattern) are allowed to fire. As the strength of O-LM to pyramidal cell connection is increased, eventually the nonassembly cells are suppressed.

If the inhibition from the O-LM cell becomes too strong, it prevents pattern completion, even though a retrieval cueing

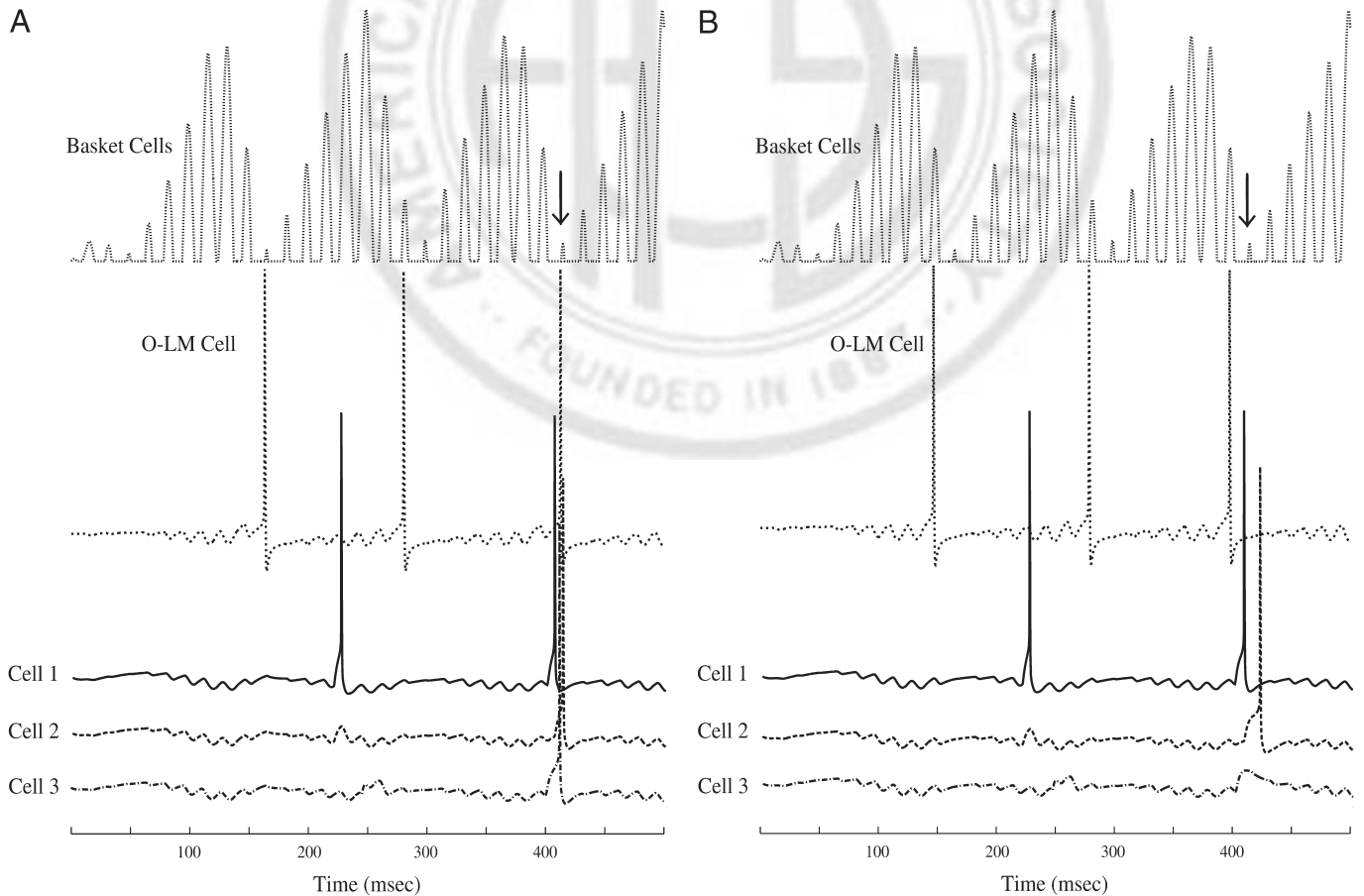


FIG. 6. Increasing basket cell inhibition causes O-LM cell to fire on earlier gamma cycle. *A*: conductance of the basket cell to O-LM inhibition is not strong enough and the O-LM cell fires late in the retrieval cycle. It does not prevent nonassembly Cell 3 from firing. Conductance is g_{io} 0.4 mS/cm². *B*: if the conductance is increased to g_{io} 0.5 mS/cm², the O-LM fires earlier, skipping to an earlier gamma cycle, and is now in a position to prevent errors; Cell 3 does not fire. To illustrate the change in firing time when the inhibition is increased, the arrows represent approximate time that the O-LM cell fired while being weakly inhibited.

TABLE 4. *Effects of O-LM to P inhibition strength on model output*

Conductance Value Range, mS/cm ²	Effect
0–0.004	Encoding occurs correctly
0.005–0.057	Nonassembly cell spikes during retrieval
0.058–0.092	Encoding and retrieval occur correctly
0.093–0.116	Encoding occurs correctly
≥0.117	Retrieval cueing spike but no pattern completion
	Encoding occurs, but no retrieval cueing spike
	No encoding (no LTP), no retrieval

spike is fired. For even larger inhibition, the cueing spike produced by the dentate-receiving cell is suppressed. No retrieval is possible at this point. A last parameter threshold is crossed when the O-LM inhibition is so strong that the pyramidal cells cannot recover from inhibition fast enough to encode properly. The dendrites cannot be sufficiently depolarized to cause LTP. In this regime and beyond, both encoding and retrieval are impossible.

Model produces desired phase relationship

Consistent with prior data (Bragin et al. 1995; Brankack et al. 1993; Csicsvari et al. 1999, 2003; Dickson and de Curtis 2002; Dickson et al. 2000a), input waxes and wanes according to the theta rhythm with each theta cycle being divided into gamma cycles.

There are several cell types known to participate in the theta rhythm. Fox and colleagues recorded from CA3 interneurons, known as “theta cells” and CA3 pyramidal cells, called “complex spiking cells,” in freely moving, awake rats (Fox et al. 1986). Both types of recorded cells fired during the peak of dentate theta. Csicsvari and collaborators recorded from CA1 pyramidal cells and 2 types of interneurons (one had cell bodies in stratum pyramidale; the other had cell bodies in the

alveus/oriens layer) from an awake rat conditioned to run on a wheel (Csicsvari et al. 1999). On average, the 3 groups of cells fired in a specific order: The pyramidal-layer interneurons fired first, just before the trough of the CA1-pyramidal theta. The alveus/oriens interneurons fired approximately 40° later. Finally, the pyramidal cells fired about 20° later than that.

Note that the 2 groups used different recording methods. Fox et al. (1986) recorded theta from the hippocampal fissure and Csicsvari et al. (1999) recorded from the pyramidal cell layer of CA1. As shown by Bragin et al. (1995), the dentate (fissure) theta and the CA1 theta are 180° out-of-phase with each other. Thus the activity shown by Fox at the peak of dentate theta corresponds to the trough of the CA1 pyramidal theta.

To investigate whether the model could reproduce the observed experimental phase relationships, random spiking excitation was given to the pyramidal cells through both the dentate and entorhinal pathways. The spikes were Poisson distributed with determined rates (see APPENDIX 1D). The dentate input had a steady spike rate of 5 Hz, whereas the entorhinal input varied from 5 Hz, during the middle of the encoding cycle, to 2.5 Hz during the middle of retrieval.

Figure 7 displays the firing histograms of the 3 cell groups within the simulation. Note that the simulated pyramidal cells do have a phase preference corresponding to the lull in entorhinal/dentate input. Also, the O-LM cells do fire at the minimum of input corresponding to peaks of fissure theta, as shown in the Fox data (theta cells fire at 0° relative to fissure theta). The phase order has been reproduced by the simulations. Initially, as seen in the Csicsvari data, the basket cells fire. The O-LM cell follows and then the pyramidal cells.

If one considers the peak of the simulated data, as plotted in Fig. 8, A–C, the phase peaks disagree by 30° with the experimental results of Csicsvari, but it is more consistent with the work of Skaggs and collaborators (1996), who show a 60°-phase difference between the basket cells and the pyramidal cells.

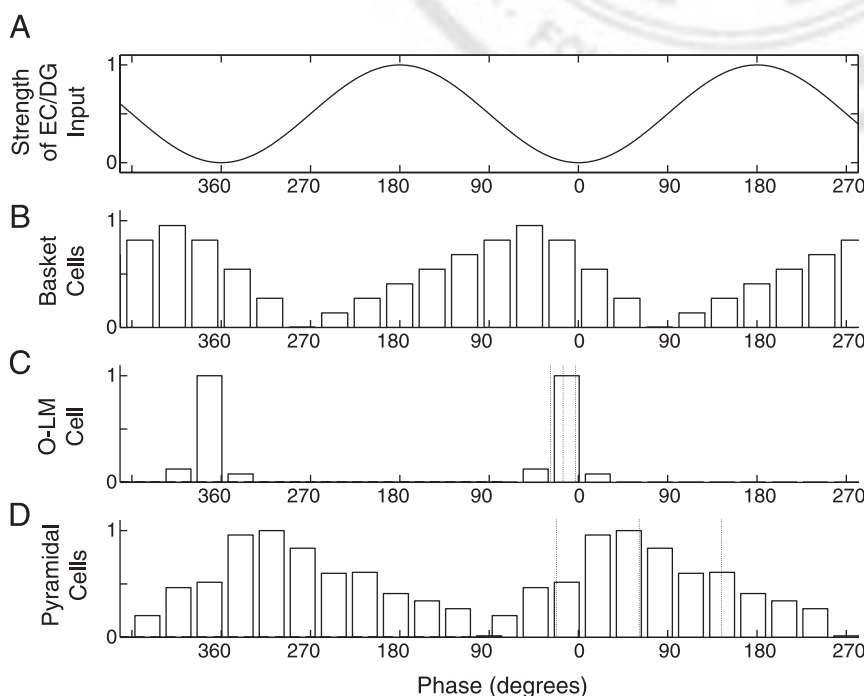


FIG. 7. Simulated firing histograms. *A*: simulated effective strength of the theta-modulated input as measured from the pyramidal layer of CA3, which is 180° out of phase with the theta measure at the hippocampal fissure. *B*: basket cell population oscillates in response to inhibitory input from the septum. Shape of this population is chosen to mimic the shape of the local field theta seen in the hippocampus. (Note that because we are concerned with the phase relationships as compared with the local theta oscillation, the gamma oscillation inherent within the basket cell population is not reflected in this histogram.) *C*: O-LM activity ($n = 1421$) has a mean phase (middle dotted line) of $-15.525 \pm 0.004^\circ$ (95% confidence) and has SD of 12.7° (outer dotted lines). *D*: pyramidal cell ($n = 1349$) mean phase (middle dotted line) is $61.275 \pm 0.3376^\circ$ (95% confidence) and has SD of 83.3° (outer dotted lines). *Bottom 3 histograms*: y-axis represents the number of cells firing, where each plot is normalized by the maximum number among the bins for that cell type. Simulation was run for 200 trials, each 1,000 ms long.

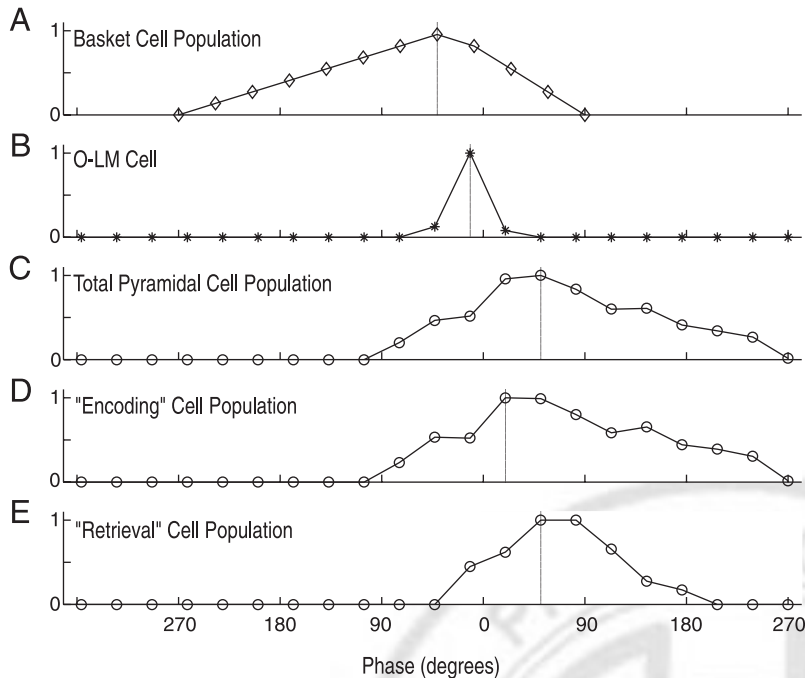


FIG. 8. Comparing cell population peak firing activity. *A*: peak of the basket cell population occurs at about -41° . *B*: peak of the O-LM cell is about $+51^\circ$. *C*: peak of the total pyramidal cell population occurs at about $+20^\circ$. *D*: peak of the “encoding” cells ($n = 1228$), i.e., those that dentate input, occurs at about 20° . *E*: peak of the “retrieval” cells ($n = 121$), i.e., those that do not receive dentate input, occurs at about 51° . In these plots the y-axis represents the number of cells firing, where each plot is normalized by the maximum number for that cell type. Simulation was run for 200 trials, each 1,000 ms long.

If the simulated pyramidal cell data are divided by dentate-receiving cells (“encoding” cells) and nondentate-receiving cells (“retrieval” cells), the results change. The “retrieval” cells have the same peak as the model’s total cell population, as in Fig. 8*E*. The peak of the “encoding” cells occurs approximately 30° earlier, making their peak consistent with the experimental data of Csicsvari, as seen in Fig. 8*D*.

DISCUSSION

This detailed biophysical model of hippocampal region CA3 demonstrates the biological feasibility of the separation of encoding and retrieval processes into separate theta cycles. The simulation can replicate the spike-timing relationships observed with single-unit recording during theta rhythm (Csicsvari et al. 1999; Fox et al. 1986; Skaggs et al. 1996). The simulation of specific classes of interneurons suggests their potential role in encoding and retrieval, that is, spike-timing control and error prevention. Our model emphasizes the cooperation of extrahippocampal inputs for proper memory formation and recall. Several factors may disrupt network stability, such as extrahippocampal input frequency and potentiated NMDA synapses.

Firing phases of major cell types

An intriguing result seen within the CA1 region of the hippocampus during theta is that the peak of basket cell activity occurs 60° before the pyramidal cell peak and 40° before the interneurons recorded within the alveus/oriens region (Csicsvari et al. 1999). For an 8-Hz theta rhythm, that is a time difference of nearly 20–21 ms between the basket cells and the pyramidal cells. However, the inhibitory process from basket cells to pyramidal cells typically involves γ -aminobutyric acid-A ($GABA_A$), whose decay time constant is relatively fast, on the order of 10 ms, half the time between the basket cell and pyramidal cell peak.

This discrepancy is eliminated by considering not just one basket cell inhibiting the entire population of pyramidal cells, but an entire population of basket cells that fire with a particular population shape. Notice in Fig. 8 the basket cell population reaches a peak at about -41° , but continues to inhibit the pyramidal cells as the total number of active basket cells decline. Because fewer of the basket cells suppress the pyramidal cells, the pyramidal cells can overcome the inhibition. As a result, the pyramidal cells fire at the appropriate phase, about 20° .

In Fig. 8, we see a shift in the phase peak during retrieval between the “retrieval” (nondentate-receiving) and the “encoding” (dentate-receiving) cells. One might expect the “retrieval” cells to peak at the experimentally measured phase. However, the dentate-receiving cells also fire during recall when they receive cueing input from the dentate. They fire first to initiate the pattern completion. The “retrieval” cells follow, making their peak later in phase. This result may imply that the majority of cells recorded in the Csicsvari experiment correspond to the dentate-receiving cells of our simulation.

Relevance of gamma during encoding

We explained in RESULTS (and summarized in Table 1) that if there is no basket cell inhibition, and therefore no gamma frequency oscillation in the inhibition, then nonassembly pyramidal cells may fire at any time during the simulation, as in Fig. 5. During minima in the gamma inhibition, the pyramidal cells have windows during which LTP can occur. If a pyramidal cell receives input during maxima in the gamma inhibition, the presynaptic cell will not fire (as shown in the left Fig. 4, left arrow for Cell 3) or the dendrites of the postsynaptic cell will not be depolarized.

It is known that more than one frequency of gamma is observed during sensory binding (Brecht et al. 2004). These various gammas may be associated with different cell assemblies. Gamma oscillation at one particular frequency, as de-

scribed above, can prevent unwanted firing during inhibition minima of another gamma frequency. This would prevent cells from binding to incorrect input, which would lead to improper encoding.

O-LM cell prevents errors

In the simulated CA3 subnetwork, the O-LM cell provides a mechanism whereby cell assemblies may be disambiguated and a way to prevent error during retrieval. This hypothesis arose by considering the unique architecture of the O-LM cell. Its axons project mainly to the lacunosum-moleculare layer of CA3 (Freund and Buzsaki 1996). The direct entorhinal input arrives in the same region (Witter and Amaral 1991). We propose that if, during the retrieval process, the context signal from the entorhinal cortex aids in recalling cell assemblies by weakly depolarizing the region, then inadvertent convergence of these excitatory inputs may cause nonassembly cells to fire during retrieval. In a slightly different scenario, when cueing information arrives by the dentate gyrus, nonstrengthened recurrent synapses may still cause other cell assemblies to fire at the same time, causing ambiguities within recall. In both cases, sufficient inhibition provided by the O-LM cell in the same area as the entorhinal excitation during retrieval can prevent these problems. The slow decay of the O-LM inhibition within the model (a rate of 0.01/ms) allows these error-prevention effects to remain until retrieval has ended.

It should be mentioned that the O-LM inhibition arrives in the stratum lacunosum-moleculare, whereas retrieval using the recurrent collaterals occurs by the stratum radiatum. In the simulation, inhibition of the distal compartment also inhibits the middle compartment, and thus O-LM cells can help with disambiguation. This may occur within the actual hippocampus, but it is also possible that other interneurons, such as bistratified or trilaminar interneurons may assume this role (Freund and Buzsaki 1996) because their axons terminate in stratum radiatum. If included in our simulation, either could receive pyramidal cell input during retrieval and suppress unwanted activity among the recurrent collaterals.

An essential characteristic of the O-LM model is the *h*-current. This current is hyperpolarization-activated and controls the timing of the O-LM cell spikes. The former quality makes O-LM cells ideal targets for inhibitory cells, including other O-LM cells. The O-LM cell is primed to fire by the inhibition during the encoding cycle, so that it can participate during the retrieval cycle.

Timing of extrahippocampal inputs

The current model tests the hypothesis that the hippocampal region can perform both encoding and retrieval of memories during behavioral tasks. Hasselmo et al. (2002) used the theta oscillation recorded from the hippocampal fissure as the pacing rhythm. We constructed a simulated theta rhythm containing input from 3 extrahippocampal rhythms: from the dentate gyrus, direct from the entorhinal cortex, and from the septum. However, the model contains 2 other extrahippocampal rhythms: direct entorhinal and septal. The relative timing of these inputs may be crucial to separation of encoding and retrieval processes.

Because the direct entorhinal input and the dentate input in the simulation originated from the same source, we assumed

they arrive at the same time and phase. Experimental data show that the GABAergic cells within the septum prefer to fire at a 180°-phase difference with theta recorded from the dentate gyrus (Brazhnik and Fox 1997; King et al. 1998). We propose that, as the GABAergic cells within the simulated septum reach peak activity, they exclusively inhibit the basket cells of the CA3 region, which allows retrieval of cell assemblies. When the septal cells are at a firing minimum, the basket cells quiet all but the strongest activity within the CA3 region, allowing only cueing input from the dentate to cause pyramidal cell spiking.

Network stability

The simulated network loses stability if the connections among all of the pyramidal cells become strengthened. Under these conditions, the pyramidal cells begin to fire repeatedly until the end of the simulation.

To prevent this “blowup,” the frequency of dentate and entorhinal input needs to be sufficiently low. If high-frequency excitation is given to the pyramidal cell network, then eventually every cell-to-cell connection will be strengthened. We found in our small network that keeping the Poisson spike rate about ≤ 5 Hz suffices. We surmise that if the network were scaled-up, this maximum rate may also be increased, as the likelihood of coinciding input spikes decreases, causing less LTP.

Preventing instability also requires constraints on α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA synapses in the LTP process. In our simulation, LTP depends on the increase in NMDA conductance occurring when the dendrite of the postsynaptic cell is depolarized. However, it is the conductance of the AMPA synapse that actually increases in the model when the excitatory connection is strengthened. This is consistent with experimental data (Lisman and Zhabotinsky 2001).

Problems occur if the NMDA conductance is also increased after LTP. In this case, when a postsynaptic cell spikes during retrieval, the slowly decaying NMDA excitation diffuses down the dendrites and allows encoding to occur during retrieval if other cueing spikes or retrieval spike are produced. This ultimately leads to network instability.

LTP ACTIVATION TIME CONSTANT. Changes in the rate at which LTP is activated by a single presynaptic action potential does not affect the encoding or retrieval processes. However, it does affect when the stored pattern will be available for retrieval. If LTP activates too slowly, then the stored pattern will not be available during the immediate next retrieval cycle.

For our simulation, the threshold for the time constant is 27 ms. If this time constant is increased (the rate of LTP activation is decreased), the pattern cannot be recalled on immediately after the retrieval cycle. The network must wait for later retrieval cycles to access the memory. By tuning this time constant, retrieval can be delayed for any number of cycles.

The ability to control when a pattern can be retrieved could have implications for temporal coding and may possibly suggest “speed limits” of recall within the brain. If more than a single spike is needed for sufficient LTP to occur, then high-frequency bursts by the presynaptic cell will make the LTP occur much faster and make retrieval more immediate than single spikes.

Phase reset

The effects shown in these simulations are consistent with experimental data on theta-phase reset. Rizzuto and colleagues (2003) demonstrate that this phenomenon appears in intracranial EEG recordings of hippocampal theta from humans during short-term recognition-memory tasks. In our modeling framework, this reset of the theta cycle could be mediated by a reset of septal input. Reset of the theta cycle can enhance performance by ensuring that the onset of a new sample stimulus coincides with the onset of the encoding phase, so that new encoding is not delayed by the retrieval phase. Additional data from Rizzuto et al. indicate that the phase reset during test stimuli presented for recognition is about 180° different from the phase reset during sample stimuli being encoded. This difference in phase reset could ensure that test stimuli coincide with dynamics of retrieval, allowing a more rapid response.

Comparison with other models

We compare and contrast our current study to previous models, individually at first, but as a whole at the end.

In their model of region CA3, Treves and Rolls (1992) propose specific functional roles for different synaptic inputs to region CA3. Our model agrees with the fundamental philosophy of this theory, although there are some differences. Treves and Rolls suggest that the dentate alone is responsible for encoding of new episodic memories, whereas a separate system—the direct entorhinal input—is primarily responsible for retrieval. In our model, these 2 inputs collaborate. During encoding, the dentate initiates presynaptic activity in region CA3, whereas the entorhinal input depolarizes the postsynaptic dendrites, creating an environment to strengthen these synapses. During retrieval, the dentate provides cues to initiate ensemble activity, whereas the entorhinal cortex provides limited background excitation to aid retrieval. These models are not inconsistent, but the greater biophysical detail of our model will allow more detailed analysis of the dynamical interaction of these different synaptic inputs.

A related hypothesis for region CA3 was presented by Hasselmo, Schnell, and Barkai, who proposed that increases in cholinergic modulation could suppress synaptic transmission at recurrent collaterals, allowing a dominant influence of entorhinal and dentate gyrus input during encoding (Hasselmo et al. 1995). Reductions in cholinergic modulation would allow stronger recurrent excitation to dominate the dynamics. However, the cholinergic effects occur on a slower timescale than the theta frequency (Hasselmo and Fehrlau 2001).

Levy (1996) focused specifically on the CA3 region, using McCulloch–Pitts neurons as the principal unit of the model. Levy's CA3 network can solve a variety of problems that an actual hippocampus may accomplish, including simple sequence completion (heteroassociation), spontaneous rebroadcast, one-trial learning, assembling correct subsequences, and sequence completion with ambiguous subsequences. However, Levy's model does not address other important issues, notably the potentially different roles of the entorhinal and dentate gyrus inputs, which are combined into a single excitatory input within Levy's model. In addition, Levy's CA3 model does not include theta-rhythm oscillations.

Recently, Lisman (1999, 2003) proposed that the dentate gyrus and CA3 collaborate to encode and recall specific epi-

sodic memories, through feedforward and feedback connections. CA3 is considered an autoassociative network, whereas a feedback loop including mossy cells in the hilus and dentate gyrus granule cells mediates the heteroassociative task. The role of direct perforant path input is assigned to provide contextual information from the environment, producing a “depolarizing bias” that would assist the dentate in causing pyramidal cells to fire during retrieval. Our model uses the dentate gyrus in a similar manner. However, Lisman's model differs from our model on the subject of error prevention, suggesting that presynaptic depression prevents contextual entorhinal input from causing erroneous pyramidal cell spiking. We use O-LM cells as our error-preventing mechanism.

A number of models of theta-phase precession (O'Keefe and Recce 1993) have been developed that relate to the encoding and retrieval of sequences (Jensen and Lisman 1996; Tsodyks et al. 1996; Wallenstein and Hasselmo 1997). In models of theta-phase precession (Jensen and Lisman 1996), Lisman specifically describes a role for gamma-rhythm oscillations in the retrieval of sequences. In that model, the CA3 interneuron population precisely segregates pyramidal cell spiking into separate pattern groupings by oscillating at gamma frequency, arising from excitation. Our model includes the gamma separation, but has not been designed to incorporate the heteroassociative spread of activity that could model theta-phase precession.

Our research differs from all these previous models in several ways. First, if it is assumed the CA3 region encodes episodic memories and holds these data for later retrieval within its autoassociative network, none of the previous works addresses how the system can do both of these functions during the same learning task, as suggested by previous work (Hasselmo et al. 2002), or how the system can switch between modes of operation. We adopted the Hasselmo et al. hypothesis that the theta rhythm naturally parses the CA3 function into encoding and retrieval cycles. We added an explicit simulation of the pacing for this mechanism by theta-rhythmic inhibition from the septal region.

Second, none of these models focuses on the detailed biophysics underlying how neurons operate. For example, certain intrinsic currents within pyramidal cell dendrites may affect action potential timing, which is crucial for synaptic plasticity. Our model uses biophysical representation of 2 different cell types. Each model cell type involves nontrivial currents, such as the *h*-current, that affect timing in surprising ways.

Third, the biophysical representations include another type of inhibitory cell present within the hippocampus: the O-LM cell. Both basket cells and O-LM cells control pyramidal cell activity during the encoding and retrieval process. We propose that the basket cells generally prevent pyramidal cells from firing during the encoding process unless the latter receives strong excitation from the dentate gyrus, whereas O-LM cells help prevent errors and facilitate disambiguation during retrieval.

Finally, all previous articles rely on Hebbian plasticity. For our plasticity to occur, the postsynaptic neuron need not produce an action potential, but simply needs a depolarized dendritic membrane potential to elicit the strengthening process (Golding et al. 2002). This may allow faster encoding that could be crucial to CA3's autoassociative role of episodic “photographer.” Also, this dendritic synaptic plasticity may

prevent interference during encoding that might occur if there were extra spiking activity that activated the recurrent collaterals.

APPENDIX 1: MODEL EQUATIONS AND PARAMETERS

This APPENDIX contains the mathematical formulations of the major cell types and the computational implementation of the model. Simulations use the program XPP, created by Ermentrout (2002). Data analysis was performed by MATLAB. Both codes are available by E-mail request. Parameter units are measured in mV for potentials, $\mu\text{A}/\text{cm}^2$ for applied currents, mS/cm^2 for maximal conductances, and $\mu\text{F}/\text{cm}^2$ for capacitances.

A: Pyramidal cells

The CA3 pyramidal cells are 4-compartment neurons, based on the reduced Traub–Pinsky–Rinzel model (Pinsky and Rinzel 1994). The compartments include one soma and 3 dendritic regions (corresponding to stratum lucidum, radiatum, and lacunosum-moleculare, respectively).

The soma compartment has the following equations and parameters

$$v'_s = I_0 + g_c(v_{d,1} - v_s) - g_{Na}m_\infty^2(v_s)h_s(v_s - E_{Na}) - g_Kn_s(v_s - E_K) - g_Aa_s(v_s - E_A) - g_L(v_s - E_L) - g_{ie}s_{ie}(v_s - E_{isyn})$$

$$h'_s = \alpha_h(v_s)(1 - h_s) - \beta_h(v_s)h_s$$

$$n'_s = \alpha_n(v_s)(1 - n_s) - \beta_n(v_s)n_s$$

$$a'_s = \alpha_a(v_s)(1 - a_s) - \beta_a(v_s)a_s \quad (A1)$$

where $m_\infty(v_s) = \alpha_m(v_s)/[\alpha_m(v_s) + \beta_m(v_s)]$, $\alpha_m(v_s) = 0.32(13.1 - v_s)/[e^{(13.1-v_s)/4} - 1]$, $\beta_m(v_s) = 0.28(v_s - 40.1)/[e^{(v_s-40.1)/5} - 1]$, $\alpha_h(v_s) = 0.128e^{(17-v_s)/18}$, $\beta_h(v_s) = 4/[1 + e^{(40-v_s)/5}]$, $\alpha_n(v_s) = 0.016(35.1 - v_s)/[e^{(35.1-v_s)/5} - 1]$, $\beta_n(v_s) = 0.25e^{0.5-0.025v_s}$, $\alpha_a(v_s) = H(v_s - 5)$, and $\beta_a(v_s) = 0.05H(5 - v_s)$. The parameters $I_0 = -0.3$, $g_c = 2$, $g_{Na} = 30$, $E_{Na} = 120$, $g_K = 20$, $E_K = -15$, $g_A = 0.01$, $E_A = -90$, $g_L = 0.1$, $E_L = 0$, $g_{ie} = 0.25$, and $E_{isyn} = -5$.

The parameters and equation for the dendritic compartments ($i = 1, 2, 3$) are

$$v'_{d,i} = I_{0,i} + DG_{input}(v_{d,1}) + EC_{input}(v_{d,3}) + g_c(v_{d,i-1} - 2v_{d,i} + v_{d,i+1}) - g_{Ca}S_{d,i}^2(v_{d,i} - E_{Ca}) - g_{AHP}q_{d,i}(v_{d,i} - E_K) - g_{KCa}c_{d,i}\chi([Ca]_{d,i})(v_{d,i} - E_K) - g_L(v_{d,i} - E_L)$$

$$s'_{d,i} = \alpha_s(v_{d,i})(1 - s_{d,i}) - \beta_s(v_{d,i})s_{d,i}$$

$$q'_{d,i} = \alpha_q([Ca]_{d,i})(1 - q_{d,i}) - \beta_q([Ca]_{d,i})q_{d,i}$$

$$c'_{d,i} = \alpha_c(v_{d,i})(1 - c_{d,i}) - \beta_c(v_{d,i})c_{d,i}$$

$$[Ca]_{d,i}' = \alpha_{[Ca]}(v_{d,i})(1 - [Ca]_{d,i}) - \beta_{[Ca]}(v_{d,i})[Ca]_{d,i} \quad (A2)$$

where $\alpha_s(v_{d,i}) = 1.6/[1 + e^{-0.072(v_{d,i}-65)}]$, $\beta_s(v_{d,i}) = 0.02(v_{d,i} - 51.1)/[e^{(v_{d,i}-51.1)/5} - 1]$, $\alpha_q([Ca]_{d,i}) = \min(0.00002[Ca], 0.01)$, $\beta_q([Ca]_{d,i}) = 0.001$, $\alpha_c(v_{d,i}) = H(50 - v_{d,i})e^{(v_{d,i}-10)/11-(v_{d,i}-6.5)/27}/18.975 + H(v_{d,i}-50)2e^{(6.5-v_{d,i})/27}$, $\beta_c(v_{d,i}) = H(50 - v_{d,i})2e^{(6.5-v_{d,i})/27} - \alpha_c(v_{d,i})$, and $\chi([Ca]_{d,i}) = 250/[1 + e^{250([Ca]_{d,i}-1)}]$. The parameters $I_{0,i} = 0$, $g_c = 1$, $g_{Ca} = 5$, $E_{Ca} = 140$, $g_{AHP} = 0.8$, $E_K = -15$, $g_{KCa} = 15$, $E_A = -90$, $g_L = 0.1$, and $E_L = 0$.

For compartment $i = 2$, the radiatum compartment, each pyramidal cell receives synaptic input from each of the 4 other cells, but not from itself. And each cell has both AMPA and NMDA receptors. Therefore the dendritic voltage equation for the second compartment has this additional term

$$- \sum_{k=1}^4 (g_{AMPA}S_{k,AMPA} + g_{NMDA}S_{k,NMDA})(v_{d,2} - E_{esyn})$$

where $g_{AMPA} = 0.001$, $g_{NMDA} = 0.001/[1 + 0.13632e^{-(v_{d,2}-12.5)}]$, and $E_{esyn} = 60$. Note that the NMDA conductance is voltage dependent, as described in de Schutter (2001).

For compartment $i = 3$, the lacunosum-moleculare compartment, each pyramidal cell receives synaptic input from the O-LM cell. Therefore the dendritic voltage equation for the third compartment has this additional term

$$-g_{oe}s_{oe}(v_{d,3} - E_{isyn})$$

where $g_{oe} = 0.5$ and $E_{isyn} = -15$.

B: O-LM cell

The O-LM cell is modeled as a single compartment. The biophysical equations and parameters for the O-LM cell were assembled from various sources (Dickson et al. 2000b; Fransen et al. 2002, 2004; White et al. 1998)

$$v'_o = I_0 - [g_{Na}m_o^3(v_o)h_o + g_{Nap}m_{po}](v_o - E_{Na}) - g_Kn_o^4(v_o - E_K) - g_H(0.65\lambda_{fo} + 0.35\lambda_{so})(v_o - E_H) - g_L(v_o - E_L) + E_{syn} + I_{syn}$$

where

$$E_{syn} = - \sum_i g_{eo}S_{eo,i}(v_o - E_{esyn})$$

and

$$\begin{aligned} I_{syn} &= -g_{io}S_{io}(v_o - E_{isyn}) \\ m'_o &= \alpha_m(v_o)(1 - m_o) - \beta_m(v_o)m_o \\ h'_o &= \alpha_h(v_o)(1 - h_o) - \beta_h(v_o)h_o \\ m'_{po} &= \alpha_{mpo}(v_o)(1 - m_{po}) - \beta_{mpo}(v_o)m_{po} \\ n'_o &= \alpha_n(v_o)(1 - n_o) - \beta_n(v_o)n_o \\ \lambda'_{fo} &= \frac{\lambda_{fsc}(v_o) - \lambda_{fo}}{\tau_{\lambda}(v_o)} \\ \lambda'_{so} &= \frac{\lambda_{sac}(v_o) - \lambda_{so}}{\tau_{\lambda}(v_o)} \end{aligned} \quad (B1)$$

where $\alpha_m(v_o) = 0.32(v_o + 54)/[1 - e^{-(v_o+54)/4}]$, $\beta_m(v_o) = 0.28(v_o + 27)/[e^{(v_o+27)/5} - 1]$, $\alpha_h(v_o) = 0.128e^{-(v_o+27)/18}$, $\beta_h(v_o) = 4/[1 + e^{-(v_o+27)/5}]$, $\alpha_{mpo}(v_o) = 1/[0.15[1 + e^{-(v_o+38)/6.5}]]$, $\beta_{mpo}(v_o) = e^{-(v_o+38)/6.5}/[0.15[1 + e^{-(v_o+38)/6.5}]]$, $\alpha_n(v_o) = 0.032(v_o + 52)/[1 - e^{-(v_o+52)/5}]$, $\beta_n(v_o) = 0.5e^{-(v_o+57)/40}$, $\lambda_{fsc}(v_o) = 1/[1 + e^{(v_o+79.2)/9.78}]$, $\tau_{\lambda}(v_o) = 0.51/[e^{(v_o-1.7)/10} + e^{-(v_o+340)/52}] + 1$, $\lambda_{sac}(v_o) = 1/[1 + e^{(v_o+2.83)/15.9}]^{58}$, and $\tau_{\lambda}(v_o) = 5.6/[e^{(v_o-1.7)/14} + e^{-(v_o+260)/43}] + 1$. The parameters $I_0 = -9.5$, $g_{Na} = 52$, $g_{Nap} = 0.5$, $E_{Na} = 55$, $g_K = 11$, $E_K = -90$, $g_H = 1.45$, $E_H = -20$, $g_L = 0.5$, $E_L = -65$, $g_{eo} = 0.001$, $g_{io} = 0.5$, $E_{isyn} = -75$ mV, and $E_{esyn} = 60$.

C: Basket cell population

The basket cells are modeled as a population of “ON-or-OFF” elements, using the following equation

$$B_{pop} = B_{pop} + R(t)[\Gamma(t) - \Theta(\tau)] + \sum_{i=1}^5 p_i \quad (C1)$$

The variable B_{pop} , which varies between 0 and 1, represents the proportion of the basket cell population in an active state (i.e., above

threshold). The population receives excitatory input and inhibitory, septal input. When the i th pyramidal cell spikes, the constant ρ_i determines the fraction of the basket cell population ($\rho_i \leq 1$) made active by excitatory input from that pyramidal cell. For this model, $\rho_i = 0.1$. The septal input, $\Theta(\tau)$, is also represented by a fraction between 0 and 1. This input changes with time and drives the basket cell population in a theta frequency

$$\Theta(\tau) = \begin{cases} 3\tau \frac{\nu_{\theta}}{1,000} & \text{if } \tau \leq \frac{1}{3} \frac{1,000}{\nu_{\theta}} \\ \frac{3}{2} \left(1 - \tau \frac{\nu_{\theta}}{1,000}\right) & \text{if } \tau > \frac{1}{3} \frac{1,000}{\nu_{\theta}} \end{cases} \quad (C2)$$

where $\tau = \text{mod}(t, 1,000/\nu_{\theta})$ and $\nu_{\theta} = 8$ Hz, the frequency of the theta rhythm in the simulation. (Note: The function mod sets the “theta” time τ equal to 0 whenever simulation time t is a multiple of $1,000/\nu_{\theta}$.) The function $\Gamma(t) = 1/2 \langle 1 + \sin \{ \nu_{\gamma} [t + (\pi/2)] \} \rangle$ represents the gamma component of the basket cell oscillation. Here $\nu_{\gamma} = 60$ Hz.

The function $R(t)$, which represents the onset of septal inhibition and gamma oscillation, is expressed as

$$R(t) = \begin{cases} \frac{\nu_{\theta}}{1,000} t & \text{if } 0 \leq t < \frac{1,000}{\nu_{\theta}} \\ 1 & \text{if } t \geq \frac{1,000}{\nu_{\theta}} \end{cases} \quad (C3)$$

D: Entorhinal cortex and dentate gyrus inputs to CA3

Dentate gyrus and entorhinal cortex inputs are modeled by Eq. D1 and can be scaled by a synaptic conductance, $g_{dg} = 0.05$ and $g_{ec} = 0.025$.

$$f(t) = H(t - t_{\text{spike}})H(t_{\text{spike}} + 1 - t) \quad (D1)$$

where t_{spike} is the spike time.

When using simulated, random input, the spike arrival times are chosen from a Poisson distribution with predetermined rates. We assume that each spike is independent, so the Poisson distribution reduces to an exponential distribution.

The choice of spike time ψ is made by first choosing a random number δ from a uniform distribution of (0, 1). This number is substituted into the inverse of the exponential cumulative density function

$$\psi = \frac{1,000}{\nu} \ln \delta$$

where ν is the desired frequency of input. For the dentate input, $\nu = 5$ Hz. For the varying, entorhinal input $\nu = 5/2[1 - \Theta(t)]$.

E: Synapses

All synapses in the simulation follow the same general dynamic. If the voltage of the presynaptic cell crosses a predetermined threshold, the synapse activates and the postsynaptic cell receives excitation or inhibition, respectively. The corresponding differential equation is

$$s' = H(v_{\text{pre}} - \theta)\alpha(1 - s) - H(\theta - v_{\text{pre}})\beta s \quad (E1)$$

where α and β are the rise and decay constants, respectively. For pyramidal cell to basket cells or O-LM cells, $\alpha_e = 20/\text{ms}$ and $\beta_e = 0.19/\text{ms}$. For O-LM cells to pyramidal cells, $\alpha_o = 5/\text{ms}$ and $\beta_o = 0.01/\text{ms}$. The synaptic threshold for both types of cells is $\theta = 35$ mV.

The entorhinal cortex and dentate gyrus inputs operate in the same way. Their inputs vary between 0 and 1, and the chosen threshold is 0.1. The rise constant for both the entorhinal and dentate inputs is $\alpha_{\text{ecldg}} = 20/\text{ms}$. The decay constant for both input is $\beta_{\text{ec}} = 0.19/\text{ms}$.

The synaptic connection for the basket cell population is very similar, but with a few changes

$$s'_{Bpop} = \alpha H(B_{pop})(B_{pop} - s_{Bpop}) - \beta s_{Bpop}$$

where B_{pop} is the active basket cell population and H is the Heaviside function. This equation limits the effective strength of the basket cell synapses s_{Bpop} because $s_{Bpop} = \alpha B_{pop}/(\alpha + \beta)$ is the steady state. The rise constant $\alpha = 3.333/\text{ms}$ and the decay constant is $\beta = 0.179/\text{ms}$.

The pyramidal to pyramidal connections consist of both AMPA and NMDA synapses. The AMPA synapses have rates $\alpha_{\text{AMPA}} = 20/\text{ms}$ and $\beta_{\text{AMPA}} = 0.19/\text{ms}$. The NMDA synapses have $\alpha_{\text{NMDA}} = 0.667/\text{ms}$ and $\beta_{\text{NMDA}} = 0.017/\text{ms}$.

F: Synaptic strengthening

Synaptic strengthening occurs from the dentate-receiving cell to the entorhinal-receiving cell if the following 2 events occur simultaneously (Golding et al. 2002):

- 1) A pyramidal cell that receives dentate gyrus input fires.
- 2) Depolarization (arising from entorhinal cortex excitation) occurs at the mid/distal dendrites of the targeted pyramidal cell.

This rule is similar to the synaptic equations. The model first checks to see whether on any time step

$$H(V_j - V_{th})H(s_i - s_{th}) = 1$$

where H is the Heaviside function, V_j is the postsynaptic cell's dendritic voltage, $V_{th} = -3$ mV is the LTP voltage threshold, s_i is the presynaptic cell's NMDA synaptic effective strength, and $s_{th} = 0.3$ the LTP synaptic threshold.

If this is true, the following equation is used for the LTP from cell i to cell j

$$\frac{dL_{ij}}{dt} = (1 - L_{ij})/\tau_{\text{LTP}}$$

where $\tau_{\text{LTP}} = 100$ ms. The LTP does not decay in the simulation because the actual decay time constant is on the order of days, and therefore beyond the timescale of the simulation (Barnes and McNaughton 1980).

After strengthening, the AMPA synaptic conductance is raised by $g_{\text{LTP}} = 0.06$.

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AQ: 1

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