

Simulation of single unit recording data in a neural simulation guiding movement of a virtual rat in a virtual environment.

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100 word abstract:

The Catacomb software package was used to develop a hippocampal simulation with interacting populations of spiking neurons, which guides the movements of a virtual rat in a virtual environment. This helps define specific functional problems and find specific solutions constrained by the physiological data. The network spiking activity can be observed in the same format as unit data obtained when a rat performs a spatial navigation task, including representation of the location of the rat when a cell fires (to create place field maps), and the timing of spikes relative to the local field potential (to analyze theta phase precession).

1000 word description:

Many neural simulations do not explicitly address the movements of an agent in an environment, making it difficult to relate the activity of the simulation to electrophysiological data from awake behaving animals. The hippocampal simulation described here uses interacting populations of spiking neurons, which guide the movements of a virtual rat in a virtual environment. This proves useful in defining specific functional problems and in finding specific solutions constrained by the physiologically realistic structure of the model. Simulations demonstrate specific dynamical requirements necessary to obtain these functions in a biologically realistic representation of the hippocampal formation, allowing explicit simulation of previous theoretical work from this laboratory. 1.) Encoding of new information without interference from previously encoded information requires transitions between encoding and retrieval states (Hasselmo et al., 2002a), 2.) Selection of the shortest pathway to the closest goal location or the best match to a retrieval cue requires mechanisms for timing and synchronization of retrieval activity (Hasselmo et al., 2002b), and 3.) Encoding of a pathway or an episodic memory requires buffering of information to allow strengthening of synapses between sequentially activated place cells (Fransen et al., 2002). The activity of the network can be observed in exactly the same format as the unit data obtained when a rat performs a spatial navigation task, including representation of the location of the rat when a cell fires (to create place field maps), and the timing of spikes relative to theta rhythm in the local field potential (to analyze theta phase precession).

We focused on modeling the behavior of a rat in a T-maze reversal task (M'Harzi et al., 1987). The Catacomb system describes the environment of this T-maze in terms of solid walls and reward locations.

FIG 3. Interaction of neural simulation with virtual rat in virtual T-maze. The location of the virtual rat causes "place" input which activates entorhinal cortex layer II. Layer II has intrinsic

properties for 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. Subthreshold place input also enters prefrontal cortex region (PFC). Sensory input for proximity to objects ("proxim") activates a unit which represents the ventral tegmental area (VTA) response to food reward. Input from VTA enters the PFC along with place input and causes spiking and activation of intrinsic cellular mechanisms which maintain 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 next desired location. This spiking output guides the movements of the virtual rat toward the desired goal.

In the simulation, as the virtual rat moved through the maze, information about its location (place) and its proximity to food reward (proxim) were sent from the virtual rat to the neural simulation, as shown in Figure 3. Multiple stages of sensory processing mediating this function can be added in future development. The place signal represents information encoded by "place cells" (see section B.2.). A virtual food-reward is placed at the end of one arm of the T-maze (e.g. left arm). The virtual rat encodes the environment and the location of the food during initial exploration. Subsequently, when placed in the stem of the virtual T-maze, the output of the simulation can guide the virtual rat to go up the stem, make the correct turning choice and go to the food reward (Hasselmo et al., in press, 2002b). This output took the form of neural firing from region CA1 of the model representing the next desired location of the rat. This simplifies many stages of motor output which can be modeled in future work. The virtual rat can also encode new food locations and find these new food locations.

Entorhinal cortex buffer. The first problem arises from the discrepancy between the slow transition between different places (on the order of hundreds of msec) and the evidence that induction of long-term potentiation (LTP) occurs with relatively brief delays <40 msec between the pre-synaptic spike and the post-synaptic spike (Levy and Steward, 1983; Holmes and Levy, 1992; Bi and Poo, 1998; Markram et al., 1997). In our neural simulations, the window for LTP was 35 msec. Self-sustained spiking activity of entorhinal cortical neurons provides a buffer (Fransen et al., 2002; Hasselmo et al., 2000; 2002b) that repeats prior place cell spiking so that it can occur in the short time window just prior to the next cell firing.

FIG 4. Membrane potentials of two entorhinal neurons performing buffer function. Synaptic activation of the first neuron (black line) causes it to spike on one phase of subthreshold theta frequency oscillations. Intrinsic calcium-sensitive cation currents (Fransen et al., 2002) are modeled with dual exponential functions causing the cell to continue firing while another cell (gray line) is activated, allowing them to fire in close temporal proximity.

2. Separate phases of encoding and retrieval during theta rhythm. During the rat's initial exploration of the maze, the buffering of activity allows sequential spiking of adjacent place cell representations in entorhinal cortex layer III and region CA3 of the hippocampus. These regions contain initially weak all-to-all excitatory connections which are strengthened whenever a presynaptic spike occurs less than 35 msec before a postsynaptic spike. This allows formation of a representation of the environment in both layer III and region CA3 in the form of strengthened connections between place cells representing adjacent locations.

To obtain effective encoding, it was necessary to suppress the spread of retrieval activity during encoding. This was obtained by modeling phasic changes in synaptic currents and LTP induction during theta rhythm (Hasselmo et al., 2002a) which are consistent with experimental data. These phasic changes provide a separation of encoding and retrieval dynamics which are essential to the function of the model, and

provide an important basis for hypotheses about theta phase dependencies in the projects described in this application.

IG 5. Separation of encoding and retrieval during theta rhythm (from Hasselmo et al., 2002a).

LEFT: During encoding phase, synaptic currents arising from EC are strong (Brankack et al., 1993; Bragin et al., 1995). Transmission from CA3 is weak, preventing retrieval, but LTP at these synapses is very strong (Holscher et al., 1997; Wyble et al., 2001), allowing encoding of the associations between entorhinal inputs. RIGHT: During retrieval phase, synaptic currents arising from EC are weak, but synaptic currents arising from CA3 are strong (Rudell et al., 1980; Brankack et al., 1993; Bragin et al., 1995; Wyble et al., 2000), allowing effective retrieval of previously encoded sequences. However, during this phase these synapses do not encode the retrieval because they do not show LTP (Holscher et al., 1997; Wyble et al., 2001), instead they show LTD or depotentiation.

This hypothesis about the function of relative phases of physiological variables is supported by behavioral data showing that fornix lesions which reduce theta rhythm (Buzsaki et al., 1983) also increase the number of errors after reversal in the T-maze task (M'Harzi et al., 1987). Thus, incorporation of theta rhythm was essential for the function of the model.

3. Convergence of goal location and current location for spatial navigation.

Once the virtual rat has learned a representation of the environment and the location of the goal within that environment, it needs to use the goal location to guide its movement. The simulation is able to guide the movement of the virtual rat through the virtual T-maze, using interactions of activity from different regions as summarized in Figure 6. As shown in Figure 6, the simulation uses backward spread from goal location in layer III combined with forward spread from current location in region CA3. The convergence of this activity in region CA1 generates spiking representing next desired location, which can guide the virtual rat in the next step along the shortest pathway to the closest goal (Hasselmo et al., in press).

FIG 6. Network activity during goal directed navigation. Each rectangle shows the activity within a specific simulated region, with time plotted horizontally and individual neurons plotted vertically. Individual spikes appear as black rectangles. On the left, a schematic of the T-maze shows how the activity of cells in the simulation corresponds to mental representations of the environment. In EC layer III (top), input from prefrontal cortex induces a spike at the goal location, and spiking spreads back from goal location through neurons representing adjacent locations into neurons representing the stem and right arm of the maze. When this activity reaches the current location, it causes spiking in EC layer II (not shown) which induces a spike in the place cell representing current location in CA3 (bottom). Spiking activity in CA3 spreads forward one step from current location before feedback inhibition shuts it off. The spiking activity in CA3 and EC layer III converges on region CA1, where it causes spiking in a neuron representing the next desired location. The virtual rat then moves to this next desired location. These mechanisms allow selection of the next step along the shortest pathway to the closest goal.

The advantage of using a spiking simulation to guide a virtual rat is that simulation units can be analyzed in exactly the same manner as neurons recorded in the hippocampus in awake behaving rats. The place fields of units can be evaluated by plotting the location of the virtual rat at the time of each spike. As shown in Figure 7, the simulation shows the experimentally observed difference in place field size in EC and region CA3.

FIG 7 – Size of place fields. Each dot represents the location of the virtual rat when a spike was fired by an individual simulated neuron in region CA1 (LEFT) or entorhinal cortex (RIGHT). Note that the broader spread of activity in entorhinal cortex causes larger place fields in EC versus CA1, consistent with experimental data (Barnes et al., 1990; Quirk et al., 1992; Frank et al., 2000).

D.2.a. Generating predictions based on different theoretical mechanisms for spike timing relative to theta rhythm. The firing of units can be evaluated relative to the phase of theta rhythm. Figure 8 shows that neurons in the simulation have properties similar to theta phase precession, with predictive firing appearing at later phases of theta when the rat is first entering the place field of a region CA1 place cell. This corresponds to activity driven by the retrieval activity in region CA3. Then, as the virtual rat moves further into the place field, this predictive firing does not occur, and firing appears at earlier phases of theta dependent upon direct input from EC layer III, bearing information about the current location. These separate phases of sensory input versus predictive retrieval could underlie the biphasic nature of theta phase precession, in which a strong correlation with position only appears in late phases of theta (Mehta et al., 2000, 2001; Aota et al., 2001).

FIG 8. Partial simulation of theta phase precession. Spiking activity of place cells in the format used for analyzing theta phase precession (Skaggs et al., 1996). X-axis shows the linear position along the path from the start of the stem to the reward location in the left arm. The Y-axis shows the position of the spike relative to theta rhythm oscillations of the entorhinal input. Simulated place cells show predictive firing for next desired location in the late phases of theta (before they move to this position). The firing is driven by direct sensory input at the time the neurons enter the position (during early phases of theta).

Further modifications of the model will be necessary to match the experimentally observed effect, which shows a smooth distribution of spikes

This talk will focus on how these processes may occur during theta rhythm oscillations in the rat hippocampal formation, which have been observed in rats during active exploration and in humans during performance of a virtual maze task. These theta rhythm oscillations depend upon cholinergic and GABAergic input from the medial septum. Modeling and analysis demonstrates that the timing of excitatory and inhibitory currents during the theta rhythm (Wyble et al., 2000) could allow separate phases of encoding and retrieval (Hasselmo, Bodelon and Wyble, 2001), which would enhance the encoding of new sequences for navigation (Wallenstein and Hasselmo, 1997) as well as enhancing the retrieval of previously encoded sequences (Sohal and Hasselmo, 1998). The specific timing of activity in entorhinal cortex and hippocampus could allow the comparison of the backward spread of activity from goal representations with the forward spread of activity from current location to guide the selection of the shortest pathway to the goal (Hasselmo, Wyble and Cannon, 2001). Simulations of the entorhinal cortex illustrate how it could buffer information about slow transitions through the environment for encoding of sequences representing specific pathways (Fransen et al., 1999; Hasselmo et al., 2000). In the absence of theta oscillations, cholinergic modulation decreases and synaptic potentials increase in magnitude (Hasselmo, 1999), these changes in dynamics could contribute to generation of sharp wave events and the consolidation of information previously encoded in the hippocampus.

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