Space, Time and Learning in the Hippocampus: How Fine Spatial and Temporal Scales Are Expanded into Population Codes for Behavioral Control

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Space, Time, and Learning in the Hippocampus: How Fine Spatial and Temporal Scales Are Expanded into Population Codes for Behavioral Control

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Abstract
The hippocampus participates in multiple functions, including spatial navigation, adaptive timing, and declarative (notably, episodic) memory. How does it carry out these particular functions? The present article proposes that hippocampal spatial and temporal processing are carried out by parallel circuits within entorhinal cortex, dentate gyrus, and CA3 that are variations of the same circuit design. In particular, interactions between these brain regions transform fine spatial and temporal scales into population codes that are capable of representing the much larger spatial and temporal scales that are needed to control adaptive behaviors. Previous models of adaptively timed learning propose how a spectrum of cells tuned to brief but different delays are combined and modulated by learning to create a population code for controlling goal-oriented behaviors that span hundreds of milliseconds or even seconds. Here it is proposed how projections from entorhinal grid cells can undergo a similar learning process to create hippocampal place cells that can cover a space of many meters that are needed to control navigational behaviors. The suggested homology between spatial and temporal processing may clarify how spatial and temporal information may be integrated into an episodic memory.
Introduction
The multitude of seemingly independent behavioral functions carried out by the hippocampal system has attracted intense interest from researchers. Several of the most studied functions are the following: (1) The role of the hippocampal system in spatial navigation has been of special interest since O’Keefe and Dostrowsky (1971) showed the spatial correlates of pyramidal cell firing in the hippocampus. These cells tend to fire in a specific portion of the environment (place) independently of the head direction and movement speed, hence the term place cells. How place cells are formed has attracted even more interest since the recent discovery of grid cells (Hafting et al., 2005) within entorhinal cortical circuits that project to the hippocampus. (2) The role of the hippocampus in classical conditioning is limited to certain experimental paradigms that require temporal integration over a delay period; e.g., trace conditioning and sufficiently delayed non-matching to sample, and is crucial for adaptive timing of the conditioned response (Berger and Thompson, 1978; Eichenbaum et al., 1994). (3) Another function that was first highlighted by studies of patient HM (Scoville and Milner, 1957) is the role of the hippocampal system in declarative memory, especially in episodic memory. Eichenbaum et al. (1999) suggested that each episode consists of a specific combination of stimuli and behavior and discussed the evidence supporting this claim.

While these functions are often studied independently and in different species, there is no reason to believe that they are, in fact, independent. Spatial information and temporal information are crucial parts of an episode, and may be used to form an episodic memory. This paper focuses on hippocampal spatial and temporal processing and proposes that these are parallel computations performed within the same system by circuits that are sufficiently homologues to be considered variations of the same design.

The adaptive timing model of Grossberg and colleagues (Grossberg and Merrill, 1992, 1996; Grossberg and Schmajuk, 1989) proposed how the dentate gyrus (DG) and hippocampal field CA3 may interact to learn adaptively timed behavioral responses (e.g., Gibbon, 1991; Roberts et al., 1989; Smith, 1968) and neurophysiological cell activations (Berger et al., 1980; Berger et al., 1986; Hoehler and Thompson, 1980) during classical and instrumental conditioning. Here we describe a model of spatial processing that describes how the same DG-CA3 circuits may also learn place fields for spatial localization. Grossberg et al. proposed a circuit to bridge a temporal interval that can span up to several seconds, and showed how this circuit could learn to adaptively time responses within this interval. A homologous spatial circuit is described herein that can similarly expand the range of positions and distances that can be represented, up to many meters, but instead of providing the information in the form of “now is the time…,” it signals that “here is the place…”

The spatial case is in general more complex than the temporal, but it can be reduced to the latter by the following assumptions. First, assume that the spatial environment is one-dimensional. Second, assume that the movement always proceeds in one direction. Finally, assume that the movement speed is constant. Under these assumptions, the spatial position of the animal is linearly dependent on time from the trial onset. The last two assumptions can be relaxed by using an appropriate path integration system. This system by definition should accommodate for changes in an animal's velocity and direction, and provide some measure of distance between the place where the trial started and the current location of the animal. Such a spatial output is similar to the output of a time integration system that records the time between the trial onset and current moment.
Figure 1. Homologous entorhinal-dentate-CA3 circuits for spatial and temporal processing. See text for details.
Both spatial and temporal representational systems need to solve the following problem. The brain builds representations and guides the behavior over spatial scales of many meters and temporal scales of many seconds, while many individual neurons operate on much smaller spatial and temporal scales. One approach to solving this problem is to use a population code for space and time that combines a limited number of integrators with fixed but different spatial or temporal periods. These fixed periods can span a spectrum of spatial or temporal scales, and indeed the Grossberg et al model of adaptively timed learning is called the spectral timing model. This paper investigates how a representation of space that is much larger than any individual scale of the spectrum can be built by combining several spatial scales in a manner that strikingly resembles the circuitry that has been proposed for spectral timing; see Figure 1.

In the spatial domain, the recent exciting discovery of grid cells in the entorhinal cortex (EC) by Hafting et al. (2005) casts a new light on the input signal that can lead to adaptive formation of the large behavioral scales that are needed for navigation. This paper shows how a proper combination of multiple scales of grid cells leads to formation of hippocampal place cells through two stages of converging inputs as shown in Figure 1.

In the first stage of a spectral timing model, multiple cue cell outputs from the entorhinal cortex converge on cells in the dentate gyrus. Different DG cells are tuned to respond to different temporal delays along a spatial gradient in a septal-temporal direction (Nowak and Berger, 1992). Such a gradient of temporal delays may be implemented within EC-DG projections by using a gradient of different Ca$^{++}$ concentrations that influence metabotropic glutamate receptors (mGluR) across the cells in the gradient (Fiala et al., 1996; Grossberg and Merrill, 1992, 1996).

A gradient of spatial coordinates can be based on entorhinal grid cells. Hafting et al. (2005) reported that there exists a gradient of spatial periods, or scales, of grid cells in EC that is aligned with the dorso-ventral EC axis. Spatial scale increases from 40cm at the most dorsal recording sites to 70cm in the most ventral sites (Hafting et al., 2005). The dorso-ventral gradient of grid cells periods instantiates the spectrum of spatial scales that was discussed above. Within each spatial scale, grid cells have various orientations of the grid and shifted grid positions. According to these results, for a specific orientation, about five evenly shifted grid cells are sufficient to cover the space without gaps. The model presented here thus uses five cells per spatial scale. This is represented in the sketch of the first stage of the spatial model in Figure 2. When the animal moves through the environment, different grid cells from each spatial scale are periodically active. Multiple grid cell outputs from the entorhinal cortex converge on cells in the dentate gyrus.

The spatial model outlined in Figures 1 and 2 can be called a spectral spacing model by comparison with its homologous spectral timing model. We show here how a spectral spacing model can, through a two stage entorhinal-dentate-CA3 network, expand the spatial scale of grid cells in a manner analogous to how the spectral timing model expands the temporal scale through its parallel entorhinal-dentate-CA3 network. In particular, the spectral spacing model provides an explanation of how the combination of several spatial scales leads to a unique spatial representation over an expanded spatial interval much larger than the period of any of the individual spatial scales of entorhinal grid cells.
Figure 2. Model for place cell learning. 3 populations of entorhinal grid cells of 5 cells each are aligned along the dorso-ventral gradient in entorhinal cortex and have respective spatial scales. Their firing profiles are represented as peaks of corresponding activity trace and aligned with the track. The current location of the animal causes the corresponding grid cells to fire (filled circles). The dentate gyrus granule cell that receives strong projections from all three of the active grid cells fires in response to this input (filled circle) and activates the interneuron to suppress other granule cells. The back-propagating action potential in this granule cell (dotted arrow) triggers learning of projections from active entorhinal grid cells; cf. Grossberg (1975). For clarity, only currently active projections are shown.

In the second stage of a spectral timing model, output of DG cells with a fixed preferred delay, or temporal phase, converge on hippocampal CA3 cells to form a full temporal spectrum that can span a behavioral time scale of hundreds of milliseconds or seconds; see Figure 1. In the second stage of a spectral spacing model, DG cells with a fixed preferred spatial phase, as explained below, provide signals that converge on hippocampal CA3 cells to form a full spatial spectrum that can span a behavioral spatial scale of many meters.

Here we propose a mechanism for how dentate gyrus granule cells receive inputs from several nearby spatial scales in the entorhinal cortex and learn to combine these inputs to generate place cells that operate on a much larger spatial scale than individual grid cells. Fuhs and Touretzky (2006) showed to some extent that combining input from multiple spatial scales does lead to unique place fields. However, they did not analyze how the synaptic connectivity
between grid cells and place cells can learn to combine spatial scales, what is the maximal spatial expansion that can be achieved by combining certain scales, or what is the theoretical foundation for this expansion.

In both spectral timing and spectral spacing systems, transient Now Print learning signals act at the dentate gyrus to selectively tune a subset of temporal or spatial phases. In the spatial model, the modulatory Now Print signal that enhances the synaptic modification is theta-bound and likely to be induced by cholinergic and GABAergic inputs from medial septum. Hasselmo et al. (2001) suggested, based on experimental data, how septal modulation can enhance spatial learning on certain phase of the theta rhythm. In the temporal model, Now Print can also be theta-bound, especially in the light of the data on stimulus-evoked theta reset (Givens, 1996). The spectral timing model predicts that the temporal window during which a Now Print signal is effective is provided by metabotropic glutamate receptor (mGluR) dynamics (Fiala et al., 1996; Grossberg and Merrill, 1992; Ichise et al., 2000). Each of the fixed delays in the spectral timing model is proposed to be due to an mGluR burst that occurs at a different delay. These different delays are predicted to be determined by different calcium concentrations that are organized on a spatial gradient across the cells with different delays. If the homolog between temporal and spatial learning persists down to the biochemical level, then one would expect the temporal window during which a Now Print signal is effective in the spectral spacing model to also be determined by mGluR, but without different delays across cells. Indeed, the spatial learning is disrupted by blocking mGluR (Balshun et al., 1999). The remainder of this paper analyzes the spectral spacing model, because the spectral timing model has previously been presented.

Materials and Methods

As in the data of Hafting et al. (2005), EC grid cell activity for each spatial scale is a periodic process (Figure 2). The only difference between the scales is the period of this activity, and therefore, of the inputs to DG. Thus DG cells add several periodic processes $a_1 x_1(t) + a_2 x_2(t) + \ldots + a_n x_n(t)$ through synaptic integration. EC inputs could, in principle, be set up as a gradient of influences from different spatial scales, or as a set of equal influences for all scales (in the latter case $a_1 = a_2 = \ldots = a_n$). The period of the resulting process does not depend on these coefficients as long as they are non-zero; it only depends on periods of components and is equal to their least common multiple (e.g., see p.143 in Hartmann, 1997). As a result, the total space that can be covered by unique input combinations, and therefore unique representations, within a transversal DG slice is predicted to have the size of the least common multiple of the incoming grid periods. It will not depend on whether a gradient of influences or equal influences were used (the supporting simulation results with Gaussian profiles of influences normalized to match total input signal are not shown). For simplicity, this paper illustrates how an equal influence of spatial scales to determine the resulting DG activity.

In the model simulations, different DG slices receive different combinations of nearby spatial scales. Suppose, for example, there are scales of 40, 50, 60, and 70cm along a dorso-ventral gradient in EC. Assume that the slice closer to the septal end of DG receives the three finest scales, while a slice of DG that is closer to the temporal end receives the three coarsest scales. Then the first DG population will expand space up to 6m (least common multiple of 40, 50, and 60cm), and the second population will expand it to 21m (least common multiple of 50, 60, and 70cm). Note that both of these numbers are still less than the maximal possible expansion for combining all four inputs (42m). On the other hand, there are now two spatial
scales in two transverse slices of DG, which can be further used downstream in the hippocampus to support the gradient of place field sizes observed by Kjelstrup et al. (2006). There can also be some interaction between these scales in DG based on mossy cells that mainly project between different transverse slices (Patton and McNaughton, 1995).

From a mathematical point of view, the best spatial scales to combine in order to achieve the maximal space expansion would have periods equal to prime numbers. For example, the scales of 40, 50, and 60cm suggested above have a total space coverage of 6m, while the nearby scales of 41, 53, and 59cm can cover up to 1.282km. On the other hand, if one uses five grid cells per spatial scale and three spatial scales, combining inputs from them will lead to only $5^3=125$ place fields across this space. It is just as unlikely that the brain uses prime numbers or multiples of 10 as scale periods, so the grid cell periods are likely to attain intermediate values. The simulations below show that these intermediate values are capable of providing both space expansion and dense place field coverage over the expanded space.

The first two simulations compare DG activity resulting from inputs from two spatial scales of 40 and 50cm that can expand the spatial representation up to 2m, and inputs from two spatial scales of 44 and 52cm that can expand the space up to 5.72 m. The simulations used a 6m track so that both results can be accomplished within the same setup. An interneuron (basket cell) driven by the combined activity of all granule cells inhibits the granule cells (Patton and McNaughton, 1995). The general structure of the network is shown in Figure 2. Only two spatial scales (two populations of EC grid cells) were used in the simulations. An ideal result would be a unique DG firing pattern for every combination of entorhinal inputs. Such a result would achieve precise spatial localization on the expanded spatial interval.

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<tr>
<td>50(52)</td>
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<th>Grid cell index</th>
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<tr>
<td>52</td>
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<tr>
<th>Spatial Scale</th>
<th>Grid cell index</th>
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<tbody>
<tr>
<td>44</td>
<td>0.050 0.050 <strong>0.950</strong> 0.111 0.050</td>
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<tr>
<td>52</td>
<td>0.082 <strong>0.986</strong> 0.114 0.050 0.050</td>
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</table>

**Table 1.** (a) Pre-wired ideal synaptic weights for EC-DG projections for a single granule cell. (b) Random synaptic weights for EC-DG projections for a single granule cell. (c) Synaptic weights for EC-DG projections after fourth run for the same granule cell as in panel (b). Boldface highlights the two inputs that drive place field activity in this cell (double peak field 12 in Figures 3d and 3e).
The first two simulations used prewired EC-DG connection weights. In the ideal case, each DG cell will have weights so that only one of the EC cells per spatial scale has a strong influence on DG cell activity. That can be represented as a weight set shown in Table 1a. In this example, the DG cell responds when the second cell fires in the 40cm scale (44cm for the second simulation) and the fourth cell fires in the 50cm scale (52cm for second simulation). There are 25 possible combinations of EC inputs, so 25 custom weight sets were crafted and preloaded into the EC-DG projections to 25 granule cells. The simulation was run for 30 simulated seconds over 6m linear track simulating motion from the leftmost end to the rightmost end at a constant speed of 20cm/s. This allows direct correspondence between spatial coordinates and time.

The third simulation tested whether the ideal weights used in the first two simulations can result from a competitive learning process (Grossberg, 1976, 1978; Kohonen, 1984; Rumelhart and Zipser, 1988). For this simulation, a DG slice consisted of 125 granule cells to allow some redundancy. The synaptic weights of EC-DG projections were generated randomly. An example of a set of random weights is shown in Table 1b. These weights were updated during the simulation according to the spike-timing dependent plasticity rule with postsynaptically gated decay (Gorchetchnikov et al., 2005; Grossberg, et al., 2002). Several runs through the track were completed until the weight change during a single run fell below 5% for all weights.

Cellular dynamics were modeled with the KInNeSS software package (available for download at http://www.kinness.net) using conventional compartmental membrane equations described elsewhere (Gorchetchnikov and Hasselmo, 2005). The precise sets of currents and parameters for each population are provided in the addendum.

Results

The results of the first and second simulations are presented in Figures 3a-d. They show that the periodicity of the model dentate granule cell activities follow the theoretically calculated period. Only 10 out of 25 cells show place fields for entorhinal input with periods 40 and 50 cm (Figure 3b). All 25 cells show place fields when fed with entorhinal input with periods of 44 and 52cm (Figure 3d). One fifth of these place fields (fields 3, 10, 12, 19, and 21) show two peaks in different parts of the track. In both simulations, place fields cover about half of the space; the other half is filled with single spikes of various granule cells. The average firing rate for cells in the first simulation is 0.43Hz for cells that have place fields, 0.2Hz for cells that do not show place fields, and 0.3Hz overall. The firing rate within a place field is 10Hz, driven by the 10Hz theta rhythm-bound entorhinal input. The average firing rate for cells in the second simulation is 0.335Hz, and the average firing rate within a place field is 10Hz.

The results of the third simulation are presented in Figure 3e. The simulation was stopped after the fourth run because the change in synaptic weights fell below the criterion. Here, 20 out of 25 place fields that were shown during the prewired simulation were replicated after learning. However, five place fields shown during the second simulation were not learned and are marked in Figure 3e by black crosses. Out of those five place fields, four were single-peaked and one was double-peaked, and seven of the place fields that had single peaks during a prewired run developed second peaks during learning (fields 7, 8, 16, 18, 23 and 24). Due to a redundant number of granule cells, often different cells developed the same place fields (for example 10 cells developed place field 1). Table 1c shows the synaptic weights that evolved through learning, starting from the initial random weights shown in Table 1b after 4 runs.
Figure 3. Simulation results: panels (a) and (b) refer to the first simulation; panels (c) and (d) refer to the second simulation, panels (c) and (e) refer to the third simulation. (a) activity for EC input with periods of 40cm and 50cm used in the first simulation. (c) activity for EC input with periods of 44cm and 52cm used in the second and third simulations. (b), (d), and (e): spiking activity of dentate granule cells in the first, second, and third simulations, respectively. Red
vertical bars show the theoretical limit of space expansion. Light green vertical bars show single peak place fields. Light orange vertical bars show double peak place fields. Numbering of place fields in (b) and (d) correspond to the cell number in the population. Red triangles in (e) point to learned place fields that correspond to prewired place fields in (d). Black crosses mark prewired place fields in the second simulation that did not develop through learning. Orange bars with numbers in (e) show additional second peaks that developed through learning for place fields that had single peak in prewired case. The number next to the bar corresponds to the number of the original place field.

**Discussion**

The results of the first two simulations show that the spatial expansion was performed according to theoretical predictions. In the case of 40 and 50cm spatial scales, only 10 cells have reliable place fields, while with scales 44 and 52cm, all 25 cells had reliable place fields. In both cases, only about one-half of the expanded spatial interval was covered by place fields, while the other half was only marked by individual spikes that can be considered spontaneous firing. Since the size of place fields in the model approximately corresponds to the size of the entorhinal grid cell field with the smallest scale (about 10cm), this space coverage can be used to calculate the number of grid cells and spatial scales that are needed to cover a specific space. For example, combining three spatial scales leads to 125 possible input combinations, which can result in 125 place fields of about 10cm each. Therefore, these fields can cover 12.5m of space, which will be half of the expanded interval. Thus, the three spatial scales to be combined should have a least common multiple around 25m for the maximal efficiency of the model.

How can the model cover the other half of the expanded interval? The simulations presented here only used one transverse slice of DG that combines information from just two spatial scales. In reality, there are many more similar slices and more spatial scales to combine per slice. An addition of a second DG slice that combines the information from the same two spatial scales so that these scales are shifted by about 30cm from the original scales will produce the pattern of activity in this second slice that is the exact replica of the pattern in Figure 3d except for 30cm shift. This second pattern will fill the gaps in place fields of the first pattern. Combining the activity from these two slices through convergence of DG-CA3 projections will lead to complete coverage of the space by DG input to CA3 cells. In other words, two DG slices will provide two phases of the spatial code and CA3 will combine these phases in a population code for an expanded spatial interval. For the case of the first 2 simulations, addition of another EC-DG slice would mean adding 15 more grid cells and 25 more granule cells, a minor change comparing to the number of respective cells in entorhinal cortex and DG.

The double-peak place fields in simulations 2 and 3 correspond to data recorded by Jung and McNaughton (1993) showing a significant fraction of multi-peaked dentate gyrus place fields. While these multiple peaks seem to be at odds with the idea of unique spatial representation that this paper proposes, this is not really the case. Again, addition of another DG slice to the network can resolve the ambiguity of multiple peaks. If a second slice combines two other spatial scales, both of the slices would probably have multi-peaked place fields. On the other hand, due to the difference in input spatial scales to these slices, it is highly unlikely that both peaks of the same place field in one slice will coincide with both peaks of some multi-peaked place field in another slice. As a result, through the convergence of inputs from these two slices in CA3, different CA3 cells will be active for different peaks of the same DG place field.
The more slices one adds to the model, the higher the chances that the total population activity of DG cells is able to provide unique spatial coding over an arbitrary length of the track. Moreover, additional input to granule cells from lateral entorhinal cortex can provide contextual information and lead to remapping of DG representations even when grid cell input does not change.

The firing rate of the model DG cells outside of the main place field is low and comparable with the spontaneous firing rate of these cells recorded experimentally (Jung and McNaughton, 1993). The model predicts that this rate is not truly spontaneous: a positive correlation should exist between firing of cells outside of their place fields and the activity of grid cells that are active when the animal is in the place field. This prediction follows from the size of overlap between firing of grid cells in different spatial scales. For example, in Figure 3c, yellow cells in both spatial scales have a long overlap of their activities at about 5.6-5.7m that results in a place field 25 in Figure 3d, but these cells also have much shorter overlaps of activity at about 0.45, 2.6, and 3.1m, which result in individual spikes in Figure 3d that can be considered as spontaneous by an outside observer.

Simulation 3 illustrates that the mechanism suggested here can be achieved through a self-organization process in EC-DG projections. Moreover, this process does not have to be limited to EC-DG projections; a similar process can take place in direct EC-CA1 projections. CA1 has much smaller number of cells than DG, which will lead to a larger number of entorhinal inputs per CA1 cell and a less precise spatial representation in CA1 than the one shown here. This property corresponds to data showing that place fields exist in CA1 after DG-CA3 lesion, but these fields are less precise than their normal counterparts (Brun et al., 2002).

Previous work on spectral timing has shown how correct timing of a response can be learned using DG-CA3 interactions, such that the DG provides a spectrum of timings over a range of delays, thereby enabling task-appropriate behavioral timing to be learned by the network using a cue-driven process that is modulated by reinforcement (Grossberg and Merrill, 1992, 1996; Grossberg and Schmajuk, 1989). In the case of spectral spacing, the DG provides a spectrum of grid-based spatial coordinates that can be used to learn place codes capable of spanning a large behaviorally-appropriate space. This space can, in turn, be organized with respect to landmarks and reward locations by a cue-driven process, much as in the case of spectral timing. Future studies will attempt to characterize this spatial cue-driven process using a unified framework in which two widely studied functions of the hippocampus, namely spatial and temporal processing, are combined and shown to benefit from homologous circuitry.

Addendum

Entorhinal cell description

At this point of model development, EC grid cells are just input generators that provide bursts of spikes to DG granule cells. These bursts are tuned to represent grid cell activity.

DG granule cell description

DG granule cells in the model consist of two compartments: soma and dendrite. The reasons for a two-compartmental structure is firstly to increase the integration time for synaptic inputs from EC coming to dendrites, and secondly to make the inhibition (coming to the soma) relatively
faster and more effective than the excitation (coming to the dendrites). This improves the competitive interactions between DG cells.

The somatic potential is calculated according to

\[
C_M \frac{dV_i^S}{dt} = -g_L(V_i^S) + g_A(E_A - V_i^S) + g_D^S(V_i^D - V_i^S) + I_i^O + w_{inh}g_q^i(E_i^I - V_i^S),
\]

(1)

where \( C_M \) is the membrane capacitance, \( V_i^S \) is the somatic potential of the cell \( i \), \( g_L \) is the leakage conductance, \( g_A \) and \( E_A \) are the AHP conductance and reverse potential, respectively, \( g_D^S \) is the diffusion coefficient from dendrite to soma, \( V_i^D \) is the potential in the dendrite of the cell \( i \), \( I_i^O \) is the quadratic integrate-and-fire representation of currents producing a spike, and the last term is the synaptic inhibition from an inhibitory interneuron so that \( E_i^I \) is a reverse potential of the inhibitory GABA channel, \( g_q^i \) is a channel conductance controlled by presynaptic action potential of the interneuron (cell \( q \)), and the synaptic weight \( w_{inh} \), which roughly corresponds to billions of channels per cm² of the membrane.

The dendritic potential is calculated according to

\[
C_M \frac{dV_i^D}{dt} = -g_L(V_i^D) + g_D^D(V_i^S - V_i^D) + (E_E^E - V_i^D) \sum_j g_{j,i}^{E} \omega_{j,i},
\]

(2)

where \( C_M \) is the membrane capacitance, \( V_i^D \) is the dendritic potential of the cell \( i \), \( g_D^D \) is the diffusion coefficient from soma to dendrite, \( V_i^S \) is the potential in the soma of the cell \( i \), \( g_L \) is the leakage conductance, and the last term is the synaptic excitation from EC cells so that \( E_E^E \) is a reverse potential of the excitatory AMPA channel, \( g_{j,i}^{E} \) is a channel conductance controlled by presynaptic action potentials of the EC cell \( j \), and \( \omega_{j,i} \) is the synaptic weight of the projection from entorhinal cell \( j \) to DG cell \( i \).

Both diffuse coefficients \( g_D^S \) and \( g_D^D \) are calculated as shown for a generic coefficient \( g_D^z \) from \( z \)-th compartment’s diameter \( d_z \) and length \( l_z \), and axial resistance \( R_{SD}^z \) between soma and dendrite, which is identical for both compartments:

\[
g_D^z = \frac{d_z}{4l_z^2R_{SD}^z}.
\]

(3)

Both \( g_q^j \) and \( g_j^{E} \) are controlled by the presynaptic action potential as summarized below for a generalized synaptic conductance \( g_z \). Note, that \( g_z \) only provides the shape of synaptic conductance, while its magnitude is determined by the maximal conductance of the channel \( \mathcal{g} \), and its timing is determined by a time \( t_z \) that is reset to zero by the arrival of the presynaptic action potential to this particular synapse. Note also, that this time reset includes axonal delay on the way to this synapse, so a same presynaptic spike in the soma will arrive at different axonal
terminals made by the same cell at different times, and as a result will cause a shift in time for the respective postsynaptic potentials.

\[
g_z = \begin{cases} \frac{\bar{g}p}{\tau_f - \tau_r} \left( e^{\frac{t_z}{\tau_r}} - e^{\frac{t_z}{\tau_f}} \right) & \text{if } \tau_r \neq \tau_f \\ \frac{g}{\tau_f} e^{\frac{t_z}{\tau_f}} & \text{otherwise} \end{cases}
\]  

(4)

where \( \bar{g} \) is the maximal conductance of the channel, \( \tau_r \) and \( \tau_f \) are raise and fall synaptic time constants, respectively, and \( t_z \) is the time since an action potential in the \( z \)-th axonal terminal between presynaptic and postsynaptic cells; \( p \) is a scaling coefficient that enforces

\[
\max \left( \frac{p}{\tau_f - \tau_r} \left( e^{\frac{t_z}{\tau_r}} - e^{\frac{t_z}{\tau_f}} \right) \right) = 1.
\]  

(5)

The conductance for the AHP current \( g_{AHP} \) is also calculated according to equations (4) and (5), except that the triggering spike in this case is produced by the same cell and there is no transmission delay.

The synaptic weights from entorhinal cells to granule cells were preset in simulations one and two to the values such that a single granule cell has one strong weight from each of the spatial scales. An example of these weights is shown in Table 1a. In the simulation three these weights were set initially to the random values from uniform distribution on the interval \([0, 1,1]\). An example of these random weights is presented in Table 1b. Through the course of simulation these weights were modified according to the STDP equation derived by Gorchetchnikov et al (2005):

\[
\frac{dw_{j,i}}{dt} = \lambda \left( g_{j,i} f_N \left( V^{S}_{i} \right) (\hat{w} - \bar{w}) + w_0 - w_{j,i} \right) f_G \left( V^{S}_{i} \right),
\]  

(6)

where \( \lambda \) is the learning rate; \( \hat{w} \), \( \bar{w} \), and \( w_0 \) are maximal, minimal, and baseline weights, respectively; \( f_N \left( V^{S}_{i} \right) \) and \( f_G \left( V^{S}_{i} \right) \) are normalizing and gating functions of the postsynaptic voltage, respectively, as described previously (Gorchetchnikov et al 2005).

Action potential generation was modeled with a quadratic integrate-and-fire (IAF) equation. This equation is a reduction of the classical Hodgkin-Huxley model (Hodgkin and Huxley, 1952) that includes fast sodium, delayed rectifier potassium, and leakage currents. The quadratic IAF equation was derived through Taylor expansion of the original system by Ermentrout and Kopell (1986). Izhikevich (2004) provided a detailed comparison of quadratic IAF to other methods of spike generating. The specific version used in the model presented here was described previously by Gorchetchnikov and Hasselmo (2005):

\[
i_z^Q = s_z \left( \bar{V}_z^2 - V_z^S \right),
\]  

(7)
where $V_z$ is the somatic membrane potential, $V_z^\theta$ is the spiking threshold potential, and parameter $s_z$ has the dimension of $\frac{mS}{mV \cdot cm^2}$ for consistency with other equations.

**DG interneuron description**

The DG interneuron (basket cell) in the model consists of a single compartment where the membrane potential is calculated according to

$$C_M \frac{dV_q}{dt} = -g_L V_q + I^Q_q + w_{exc} g_q^E (E^E - V_q),$$

**Table A1. Parameters of simulations that are used across all cells.**

<table>
<thead>
<tr>
<th>Parameter Used in equations</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_M$ (membrane capacitance)</td>
<td>$(1), (2), (8)$</td>
</tr>
<tr>
<td>$E^E$ (AMPA reverse potential)</td>
<td>$(2), (8)$</td>
</tr>
<tr>
<td>$E^I$ (GABA(_A) reverse potential)</td>
<td>$(1)$</td>
</tr>
<tr>
<td>$E_A$ (AHP reverse potential)</td>
<td>$(1)$</td>
</tr>
<tr>
<td>$R_A$ (axial resistance)</td>
<td>$(3)$</td>
</tr>
<tr>
<td>$\lambda$ (learning rate)</td>
<td>$(6)$</td>
</tr>
<tr>
<td>$\bar{w}$ (maximal weight)</td>
<td>$(6)$</td>
</tr>
<tr>
<td>$\bar{w}$ (minimal weight)</td>
<td>$(6)$</td>
</tr>
<tr>
<td>$w_{q}$ (baseline weight)</td>
<td>$(6)$</td>
</tr>
<tr>
<td>$w_{exc}$ (excitatory weight)</td>
<td>$(8)$</td>
</tr>
<tr>
<td>$w_{inh}$ (inhibitory weight)</td>
<td>$(1)$</td>
</tr>
</tbody>
</table>
Table A2. Population-specific parameters used in simulations. Note that somatic passive leakage conductances for are reduced to compensate for additional leakage included in quadratic integrate and fire equation.

References


Acknowledgements

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