Supplemental Data

Computational Influence of Adult Neurogenesis on Memory Encoding

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Supplemental Material (Part I)

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Figure S1. Sample spatial responses of model neurons
(A) Spatial response of IEC neurons to different environments. Each column is a separate neuron. The spatial response was measured in the equivalent of a 1m x 1m square.
(B) Spatial "grid cell" response of mEC neurons. Note how the size of the grid is constant between environments, but the rotation and offset changes.
(C) Spatial response of a set of GC neurons.

Red - High firing; Blue - Low firing; Grey - Not firing
**A**

Survival Fraction

- Neuron age (days)

- Survival Fraction

- Neuron age (days)

**B**

Neuron Voltage (mV)

- Time (seconds)

- Activation Threshold

- Resting Potential

**C**

Proportion of ideal # synapses

- Neuron age (weeks)

**D**

Proportion Competitive Synapses

- Neuron age (weeks)

**E**

- mEC spike train

- Filter EC spike train with STDP profile

- Comparison of GC spiking to filtered EC spike train

- Covariance of GC spiking and filtered EC over time

- Synapse will experience LTD by 3.8%
Figure S2. Description of model behavior
(A) Fraction of new neurons surviving to different ages. Most neuron death occurs in the first two to three weeks.
(B) How neuron activity is calculated in the model using a digitized firing rate model. The voltage (blue) is calculated for each 25 ms time step. If the voltage surpasses an activation threshold, the firing rate of the neuron is calculated which may lead to a spike at that time.
(C) Timeline of afferent synapse formation onto immature granule cells.
(D) Timeline of synaptic competition in the model. New neurons initially have a higher percentage of “competitive” synapses, though many of these competitions are completed by the time the neuron is mature.
(E) How learning is computed in the model. For each synapse, the spiking of the pre-synaptic neuron is filtered with a STDP curve and compared to the spike-train of the post-synaptic neuron. The temporal covariance of the pre- and post-synaptic neurons is used to determine the amount the synapse learns.
Figure S3. Network architecture
Probability that two neurons are connected given as a function of relative distance. The x-axis of each panel refers to the difference between two neuron’s location along septo-temporal axis. The y-axis of each panel represents to the ratio of existing synapses to potential synapse sites. The increase of connection densities for long distances in some of the panels is due to the ringed layer structure - neurons on the edges of the network layers were permitted to project to the opposite edge.
Figure S4. Physiological maturation of granule cells in model
(A) Resting potential decreases as volume increases (Supplemental Methods Equation. IV. 24).
(B) Relative effect of GABA on immature neurons is age dependent (Supp. Eqn. IV.23)
(C) Maximum firing rate of neuron increases with age. Neurons must receive glutametergic synapses to fire. (Supp. Eqn. IV.25-26)
(D) Membrane capacitance is proportional to the volume of the neuron. The size of the neuron (and the volume) increases with age and the growth of connections (Supp. Eqn. IV. 2-4; IV.20)
(E) Membrane resistance decreases as number of connections increases (Supp. Eqn. IV. 21)
(F) The membrane time constant $\tau$ is a function of resistance, volume, and the mature time constant (Supp. Eqn. IV.22). The maximum $\tau$ is set at 4 times the time constant of mature neurons.
Figure S5. Pattern separation
(A) Pattern separation in the NG networks. The full population of GC shows the pattern integration effect at low levels of input similarity (red), whereas the mature neurons (>6 weeks of age) remain very effective at pattern separation.
(B) The degree of pattern integration depends on the number of immature neurons that are present in network. The y-axis shows the ratio of GC output similarity to the No NG network for different levels of input similarity.
Figure S6. Temporal associations
(A) The time elapsed between two events as well as the input similarity of the two events both affect the similarity of their encoding by the GC layer.
(B) Time between events affects pattern separation in NG networks regardless of whether the inputs vary contextually (IEC inputs) or spatially (mEC inputs).
(C) Time between events does not affect pattern separation in No NG networks regardless of whether inputs vary in mEC or IEC.
Figure S7. Ages of neurons that respond to familiar and novel environments

(A-B) Average firing rate of GCs born at different times in response to the four FEs and the NE in the NG network on day 160 (A) and day 200 (B). The asterisk indicates the group of highly active neurons that responded indiscriminately to all environments.

(C-D) Average firing rate of GCs born at different times in response to the four FEs and the NE in the No NG network at day 160 (C) and day 200 (D). Note how the No NG network lacks GCs born after day 120 because neurogenesis was stopped at that time.
Aging

(A) Pattern separation in aging networks with decreasing neurogenesis (day 120 – red; day 520 – green).

(B) Pattern separation in aging networks with constant neurogenesis.

(C) Effect of time on pattern integration for aging networks with constant neurogenesis (Day 120 – solid line; Day 520 – dashed line).

Stress

(D) Pattern separation in stressed networks before (day 120 – red), during (day 180 – blue), and after (day 280 – green) stress.

(E) Pattern separation in non-stressed networks at same times (Day 120- red; day 180 - blue; day 280 – green).

(F) Effect of time on pattern integration for aging networks with constant neurogenesis (Day 120 – solid line; Day 180 – dashed line; Day 280 – dotted line).

Figure S8: Aging and stress
Figure S9: Response of networks with full neurogenesis to familiar environments
(A) Aging of GCs in aged network with constant neurogenesis to familiar environments (FEs) after full growth (gray:>2Hz; green:>4Hz; blue:>6Hz; firing 2Hz or below not shown). Note that sizes of dedicated GC populations do not decrease in size with constant neurogenesis.
(B) Control for stress network, aged through 280 days without any reduction of neurogenesis.
Supplemental Material (Part II)

1. Expanded Description of Model

Overview

We developed a six-layer neural network model to investigate the role of adult neurogenesis in the pattern separation ability of the DG. The following pages describe the underlying architecture and functions of the model.

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I. General Model Structure and Timeline

Scales of simulation

Simulations were performed on a 6-layer neural network model of the dentate gyrus (referred to here as “the model” or “the network”). Each layer contained many individually simulated neurons. Two of these layers (IEC and mEC) served as input layers. There were 11 different sets of connections between different layers.

Timeline of model simulation

Building the model

Prior to simulation, the model is initially generated with a population of immature GC neurons and full populations of all other cell layers. All connections that are independent of the GC layer were initialized at onset, while all connections involving the GC layer are formed during simulation.

1> Load basic model parameters
2> Initialize all neuron layers (section II)
3> Initialize non-GC connections (section II)

“Growing” the model

The model was then simulated with a specific input structure for many events to permit the original neurons GC layer to mature and further GC neurons to be born (neurogenesis). This is referred to as “growing” the model. Section VII describes the nature of the input structure.

A full run through the model during training takes the following form:

1> Load model
2> Determine how inputs will look in experiment (Section VII)
3> Advance through time – each full loop through model considered an “event”
   1. Update all neurons’ physiology properties based on age and connectivity (section IV)
   2. Calculate inputs for event (or time-vector of inputs) (section VII)
   3. Compute neuronal activity (see section III)
      1. Neuronal activity was calculated for a series discrete time “steps”
   4. Synaptic Learning (see section V)
   5. Mature immature neurons (section IV)
   6. Add new neurons (section IV)
   7. Cell death (section VI)
4> Export grown model & activity history

Experiments

The model was tested within different environments at many different locations. During testing, there was no neurogenesis, maturation, learning or cell death (a “static” model) so there is no interaction between different test trials. Section VII describes the nature of the input structure.

A full run through the model during training takes the following form:
1> Load model
2> Determine how inputs will look in experiment (Section VII)
3> Simulate model at different locations
   a. Update all neurons’ physiology properties based on age and connectivity (section IV)
   b. Calculate inputs for event at current position (section VII)
   c. Compute neuronal activity (see section III)
      i. Neuronal activity was calculated for a series discrete time “steps”
4> Export grown model & activity history

**Table I: General Model Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{vt_{day}}$</td>
<td>10 events</td>
</tr>
<tr>
<td>$E_{vt_{week}}$</td>
<td>70 events</td>
</tr>
<tr>
<td>$t_{step}$</td>
<td>25 ms</td>
</tr>
<tr>
<td>$t_{event}$ (training)</td>
<td>10 s</td>
</tr>
<tr>
<td>$t_{event}$ (testing)</td>
<td>500 ms</td>
</tr>
<tr>
<td>Range</td>
<td>40%</td>
</tr>
</tbody>
</table>

$E_{vt_{day}}$ is the number of simulated events in each day
$E_{vt_{week}}$ is the number of simulated events in each week
$t_{step}$ is the length of each discrete time-interval for which activity is calculated
$t_{event}$ (training) is the length of time that each event is simulated during training
$t_{event}$ (testing) is the number of time that each event is simulated during testing
Range is the septotemporal extent of the model used in these experiments

**Simulation details**

Simulations and all subsequent analysis was performed using MATLAB 7.4 running on a Linux platform
and were performed on a cluster of four Dell Precision 490n machines (2 x Dual Core Xeon 5130 2Ghz;
16GB RAM), for a total of 16 independent processors using the MATLAB Distributed Computing
Engine.

The model contains involves considerable usage of random variables. Random numbers were either
generated from a uniform distribution, using the $\text{rand}$ ( ) function in MATLAB, or from a Gaussian
distribution, using the $\text{randn}$ ( ) function in MATLAB, which returns a random value from a normal
distribution with mean 0 and standard deviation of 1. To attain a random value, $\eta$, from a different
Gaussian distribution (mean = $\mu$, standard deviation = $\sigma$), we used the following equation

$$\eta(\mu, \sigma) = \mu + \sigma \times \text{randn}()$$  \hspace{1cm} (I.1)

The random seed was initialized to a unique value (current date/time) prior to all simulations.
Statistics

For each of the simulation runs described below, eight different model networks were generated and simulated independently. While the initialization parameters were the same for each network, the environments used and their growth differed across runs, resulting in considerably different networks at the point at which they were examined.

Error bars plotted in the data represent the standard deviation across the different model networks.
II. Overview of model structure

The computational dentate gyrus was set up as a six layer neural network model in MATLAB, with each layer representing a cell-group within the DG-Hilus circuit or one of its inputs(see Figure 1A). Each layer consisted of many individual nodes, or neurons, the number of which was scaled down appropriately from actual rat cell counts (see supp Table II).

*Note on neuron and connection parameters:* Several groups have previously modeled the dentate gyrus computationally and each of these studies has settled on different levels of criteria in determining which neurons to use and how to interpret the limited anatomy and physiology data. Because it is difficult to ascertain the completeness of much of this data, we tend to err on the side of not include those neurons and connections that we have severely limited knowledge. For instance, there are many interneuron types in the DG that, being relatively rare, have only been characterized by a handful of anatomical studies without any known examination of physiology or function. While these neurons undoubtedly have functional consequences in the network, not enough is known to incorporate into the model. Likewise, there are descriptions of synaptic connectivity that are thus not sufficient to incorporate into the model. For example, sometimes the existence of a connection is anecdotal or qualitative with functional relevance unclear (e.g., mossy cell dendrites entering molecular layer), and other times the extent to which a physiology finding can be generalized is vague (e.g., CA3 input back onto mossy cells). As the functional consequences of this information becomes clear, we will be able to incorporate it into this work.

**Neuron initialization and parameters:**

Each neuron in the model was defined by a set of physical and physiology parameters and has a set of dynamic variables used to calculate activity within events. For non-neurogenic cell layers, many of the physiology parameters were uniform across like neurons, but because neurogenesis introduces heterogeneity, the physiology parameters were tracked separately for each neuron within the GC layer.

**Physical parameters**

The following physical parameters were determined for each individual neuron and were stable within events, but may be dynamic over longer periods of time due to maturation.

- $\chi_s$ is the relative dorsal-ventral axis position (0 $\leq \chi_s \leq$ 1)
- $\chi_t$ is the relative transverse axis position (0 $\leq \chi_t \leq$ 1)
- $\chi_v$ is the within layer depth (0 $\leq \chi_v \leq$ 1)
- $\delta_s$ is the spatial radius (dorsal-ventral axis) of the dendritic arborization (0 $\leq \delta_s \leq$ 0.2)
- $\delta_t$ is the spatial radius (transverse axis) of the dendritic arborization (0 $\leq \delta_t \leq$ 0.2)
- $\delta_v$ is the dendritic length (0.1 $\leq \delta_v \leq$ 3)

For non-neurogenic neuron layers, the neurons were uniformly distributed along the dorsal-ventral axis ($\chi_s$), and have randomly distributed in the $\chi_t$ and $\chi_v$ axes. All non-neurogenic neurons have fully developed dendritic arborizations: $\delta = \delta_{\text{MAX}}$.

For the neurogenic layer (the GC layer), when the model is initialized a bulk population of immature neurons were provided. As with other cell layers, the neurons were uniformly distributed along the dorsal-ventral axis ($\chi_s$), and have randomly distributed in the $\chi_t$ and $\chi_v$ axes. However, the immature GC neurons have no dendritic arborization: $\delta = \delta_{\text{MIN}}$. The maturation process used to grow the dendrites is
described below. Subsequent neurons added to the layer were provided with random \( \chi_R \) and \( \chi_S \) locations, though they were biased to the inner GC layer (\( \chi_R = \text{mean}(\chi_R) \)) and also have minimum dendrites.

The neurogenic layer also tracks several other physical parameters over time:

- \( \text{Age} \) is the age of the neuron (weeks)
- \( R_{\text{mem}} \) is the membrane resistance (G-Ohms; estimated from number of synapses)
- \( \text{Vol} \) is the approximate volume of the neuron (estimated from size of neuron)

These parameters were not directly used in calculating activity, but were important for calculating maturation-dependent physiology parameters (see below).

### Table II: Neuron Numbers

<table>
<thead>
<tr>
<th>Cell Layer</th>
<th>Cell Number ( (N_{\text{layer}}) )</th>
<th>Actual Cell Number (approximate)</th>
<th>Neurogenesis rate (cells/day)</th>
<th>Death rate ( (k_{\text{death}}) ) (for inactive neurons only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IEC</td>
<td>200</td>
<td>100,000</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>mEC</td>
<td>200</td>
<td>100,000</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BC</td>
<td>120</td>
<td>10,000</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>MC</td>
<td>220</td>
<td>30,000</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>HI</td>
<td>220</td>
<td>30,000</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>GC</td>
<td>800 (start)</td>
<td>1,000,000</td>
<td>10/day</td>
<td>.0015</td>
</tr>
<tr>
<td></td>
<td>~1600 (test)</td>
<td>~1600 (test)</td>
<td>~15%/month</td>
<td>~1.5%/day</td>
</tr>
</tbody>
</table>

### Physiology parameters

The following physiology parameters are user-defined values for individual neurons in the model. These parameters were static within an event, but may be dynamic over longer periods of time due to maturation. Their use will be described in subsequent sections:

- \( V_{\text{Threshold}} \) is the voltage (relative to rest) above which the neuron fires
- \( dF/dV \) is the change in firing rate for each mV above threshold
- \( F_{\text{max}} \) is the maximum firing rate for the neuron
- \( F_{\text{min}} \) is the minimum firing rate for the neuron (neurons that burst)
- \( E_{\text{GABA}} \) is a maturation dependent parameter that represent the neuron’s relative sensitivity to GABA, relative to glutamate
- \( E_{\text{Glutamate}} \) is the parameter that represent the neuron’s relative sensitivity to glutamate and is set to be equal to 1.
- \( \tau \) is the membrane time constant of the neuron
- \( \text{Age}_{\text{fire}} \) is the age at which the immature firing rate is estimated

For all non-neurogenic cell layers, these neurons were initialized to values in Table II, and they remain constant throughout the study. For the neurogenic cell layer (GC only), most of these parameters were initialized at immature values and slowly approach their mature levels (see section IV)
### Table III: Neuron Parameters

<table>
<thead>
<tr>
<th>Cell Layer</th>
<th>(V_{\text{Threshold}}) (mV)</th>
<th>(dF/dV) (Hz/mV)</th>
<th>(F_{\text{max}}) (Hz)</th>
<th>(F_{\text{min}}) (Hz)</th>
<th>(E_{\text{GABA}}^*)</th>
<th>(\tau) (ms)</th>
<th>(Age_{fire}) (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IEC</td>
<td>25</td>
<td>.008</td>
<td>20</td>
<td>0</td>
<td>-1</td>
<td>20</td>
<td>--</td>
</tr>
<tr>
<td>mEC</td>
<td>25</td>
<td>.008</td>
<td>20</td>
<td>0</td>
<td>-1</td>
<td>20</td>
<td>--</td>
</tr>
<tr>
<td>BC</td>
<td>12</td>
<td>.043</td>
<td>230</td>
<td>0</td>
<td>-1</td>
<td>10</td>
<td>--</td>
</tr>
<tr>
<td>MC</td>
<td>20</td>
<td>.048</td>
<td>50</td>
<td>0</td>
<td>-1</td>
<td>30</td>
<td>--</td>
</tr>
<tr>
<td>HI</td>
<td>15</td>
<td>.088</td>
<td>69</td>
<td>0</td>
<td>-1</td>
<td>30</td>
<td>--</td>
</tr>
<tr>
<td>GC – immature</td>
<td>20</td>
<td></td>
<td>30</td>
<td>0</td>
<td>2</td>
<td>~160</td>
<td>4</td>
</tr>
<tr>
<td>GC – mature</td>
<td>35</td>
<td>.083</td>
<td>72</td>
<td>20</td>
<td>-1</td>
<td>40</td>
<td>--</td>
</tr>
</tbody>
</table>

### Activity variables

The following variables for individual neurons were dynamic within an event and were used to determine the activity of the neurons:

- \(V\) is the voltage (relative to rest) of neuron \(i\)
- \(f\) is the firing of neuron in the previous time step
- \(P_{\text{Fire}}\) is the potential for that neuron to fire in that time step
- \(\kappa\) is a tracking variable that distributes spiking according to the firing rate.

### Connection initialization and parameters:

Connections in the model were described by a set of static parameters and a set of experience-dependent variables.

#### General parameters

First, each synapse type has general parameters describing the structure of the connection within the network. Connections were made using a normal distribution around a target zone.

- \(\mu_{\text{syn}}\) (Target) – The average dorsal-ventral location of the synapse relative to source neuron’s soma
- \(\sigma_{\text{syn}}\) (Range) – The spatial variance of the dorsal-ventral synapse location
- \(\rho_{\text{syn,local}}\) (Density) – The density of synapses at the center of synapse distribution
- \(\rho_{\text{syn,ideal}}\) (Ideal Density) – The relative density of synapses in the whole network
- \(w_{\text{max}}\) – The maximum synaptic strength for the connection
- \(w_{\text{max,immature}}\) – The maximum synaptic strength for the connection onto an immature neuron
- \(k_{\text{synapse}}\) – The rate at which synapses mature (independent from neuron maturation rates)
- \(k_{\text{comp}}\) is the rate that synaptic competition winners are determined
- \(\delta_{z,\text{syn}}\) – The size of an immature neuron’s dendrite required for that synapse to be formed
- \(\delta_{x,\text{max}}\) is the spatial width (dorsal-ventral axis) of the dendritic arborization of a fully mature neuron
- \(\delta_{y,\text{max}}\) is the spatial width (transverse axis) of the dendritic arborization of a fully mature neuron
- \(age_{\text{ref}}\) is the reference age (weeks) approximating when non-spiny synapses are first present
- \(k_{\text{conn}}\) is the approximate number of weeks required for connection to fully develop (weeks)

At runtime, the parameters \(\mu_{\text{syn}}\) and \(\sigma_{\text{syn}}\) are adjusted for the Range over which the model is simulated. As the model is only simulating a thick slice of the dentate gyrus, rather than the whole structure, the parameters must be rescaled accordingly. The scaling is as follows:
\[
\mu_{\text{syn}} = \frac{\mu^0_{\text{syn}}}{\text{Range}} \tag{II.1}
\]

\[
\sigma_{\text{syn}} = \frac{\sigma^0_{\text{syn}}}{\text{Range}} \tag{II.2}
\]

Range is a number between 0 and 1, and set to equal 0.4 in these simulations. This serves to

In the case of the long-range MC to GC projection, the scaling of \(\mu_{\text{syn}}\) and \(\sigma_{\text{syn}}\) is also constrained by the additional equalities \((-0.50 \leq \mu_{\text{syn}} \leq 0.50)\) and \((\sigma_{\text{syn}} \leq 0.30)\) to ensure that the source neuron
Table IV: Connection Parameters (Independent of Model Range)

<table>
<thead>
<tr>
<th>Connection</th>
<th>$\mu^\text{syn}$</th>
<th>$\sigma^\text{syn}$</th>
<th>$\rho^\text{syn,local}$</th>
<th>$\rho^\text{syn,ideal}$</th>
<th>$w^\text{max}$ (mV)</th>
<th>$w^\text{max}$ immature (mV)</th>
<th>$k^\text{synapse}$</th>
<th>$k^\text{comp}$</th>
<th>$\delta_z$</th>
<th>$\text{age}_{\text{ref}}$</th>
<th>$k^\text{conn}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Granule Cell Afferents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IEC to GC</td>
<td>0</td>
<td>0.14</td>
<td>75%</td>
<td>0.105</td>
<td>1.7</td>
<td>0.05</td>
<td>0.1</td>
<td>3</td>
<td>3</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>mEC to GC</td>
<td>0</td>
<td>0.14</td>
<td>75%</td>
<td>0.105</td>
<td>2.2</td>
<td>2.2</td>
<td>0.05</td>
<td>0.1</td>
<td>2.5</td>
<td>3</td>
<td>2.25</td>
</tr>
<tr>
<td>MC to GC</td>
<td>+/-0.3</td>
<td>0.15</td>
<td>50%</td>
<td>0.15</td>
<td>2.8</td>
<td>2.8</td>
<td>0.05</td>
<td>0.1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>BC to GC</td>
<td>0</td>
<td>0.2</td>
<td>50%</td>
<td>0.1</td>
<td>2.2</td>
<td>-1.0</td>
<td>--</td>
<td>--</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>HI to GC</td>
<td>0</td>
<td>0.1</td>
<td>100%</td>
<td>0.1</td>
<td>3.0</td>
<td>-3.0</td>
<td>--</td>
<td>--</td>
<td>3</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Basket Cell Afferents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IEC to BC</td>
<td>0</td>
<td>0.14</td>
<td>75%</td>
<td>0.105</td>
<td>2.4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>mEC to BC</td>
<td>0</td>
<td>0.14</td>
<td>75%</td>
<td>0.105</td>
<td>3.2</td>
<td>--</td>
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<td>--</td>
<td>--</td>
</tr>
<tr>
<td>MC to BC</td>
<td>+/-0.3</td>
<td>0.15</td>
<td>50%</td>
<td>0.15</td>
<td>1.7</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td>GC to BC</td>
<td>0</td>
<td>0.05</td>
<td>100%</td>
<td>0.05</td>
<td>32.7</td>
<td>2.2</td>
<td>--</td>
<td>--</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Hilar Neuron Afferents</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>GC to MC</td>
<td>0</td>
<td>0.05</td>
<td>100%</td>
<td>0.05</td>
<td>5.6</td>
<td>2.2</td>
<td>--</td>
<td>--</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>GC to HI</td>
<td>0</td>
<td>0.05</td>
<td>100%</td>
<td>0.05</td>
<td>5.6</td>
<td>2.2</td>
<td>--</td>
<td>--</td>
<td>1.5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Synapse Generation

Synapses were created according to the following equations. Note: because the network is initialized with only immature granule cells, synapses to and from the GC layer were created during the maturation process and not during initialization (see section IV). The following equations describe how synapses were chosen at both times.

For each neuron in the source layer, the number of synapses that the neuron connects to, $N^\text{synapses}$, is determined by:

$$N^\text{synapses} = N^\text{target} \times \rho^\text{syn,ideal}$$  \hspace{1cm} (II.3)

where:

$N^\text{target}$ is the number of neurons in the target cell layer

$\rho^\text{syn,ideal}$ is the ideal density of that projection

Once the number of synapses required for the source neuron was determined, a set of non-repeating target (or source) neurons were selected by the following equation which was repeated until $N^\text{synapses}$ were found for each neuron

$$tar = N^\text{target} \times \eta(\mu^\text{syn}, \sigma^\text{syn})$$  \hspace{1cm} (II.4)

where:

$\eta(\mu^\text{syn}, \sigma^\text{syn})$ represents a random number from a Gaussian distribution of standard deviation $\sigma^\text{syn}$ around the target zone $\mu^\text{syn}$.

Importantly, only one synapse was permitted between two neurons, if a synapse already existed with the selected neuron equation II.4 was repeated.
Each cell layer was treated as a “circle” in order to eliminate boundary effects in the number of synapses each neuron receives. That is, if a projection field of a neuron extended beyond the edge of the cell layer, the target (or source) neuron was selected from the opposite end of the network, as follows:

$$\begin{align*}
if (\text{tar} > N_{\text{target}}) & \rightarrow \text{tar} = \text{tar} - N_{\text{target}} \\
if (\text{tar} < 1) & \rightarrow \text{tar} = N_{\text{target}} + \text{tar}
\end{align*}$$

\text{(II.5)}

\text{(II.6)}

This simplification reduces errors associated with simulating only a “slice” of hippocampus, but precludes the ability to make any conclusions about trans-laminar behavior that may emerge. This approximation will not be needed in larger scale models that extend the full septotemporal length of the hippocampus.

The initial synaptic strength, $w_{i,\text{tar}}$, of each synapse from the source neuron $i$ onto its target neuron, $\text{tar}$, was calculated by the following equations:

$$\begin{align*}
if \left\{ \begin{array}{ll}
\text{spine} & w_{i,\text{tar}} = 0.1 \leq \eta(0.5, 0.25) \leq 0.9 \\
\text{non-spine} & w_{i,\text{tar}} = 1
\end{array} \right.
\end{align*}$$

\text{(II.7)}

where

- \text{spine} indicates that the synapse type utilizes dendritic spines (IEC to GC, mEC to GC, MC to GC)
- \text{non-spine} indicates that the synapses is not spiny

\(\eta(0.5, 0.25)\) represents a random number from a Gaussian distribution of standard deviation 0.25 around a mean of 0.5. This value is constrained by an upper limit of 0.9 and a lower limit of 0.1.

\textbf{Variable parameters}

For spiny synapses (those that are capable of learning), the strength of the synapse, $w_{ij}$, was determined by both a fixed and a variable component that were specific to each synapse and change over time. These parameters were initialized for each synapse between neurons $i$ and $j$ as follows:

$$\begin{align*}
\tilde{w}_{ij}^{\text{fixed}} & = 0.5 \times w_{ij} \\
\tilde{w}_{ij}^{\text{variable}} & = 0.5 \times w_{ij} \\
\tilde{w}_{ij}^{\text{lost}} & = 0.5 \times (1 - w_{ij})
\end{align*}$$

\text{(II.8)}

\text{(II.9)}

\text{(II.10)}

- $w_{ij}$ is the strength of the connection from neuron $i$ to neuron $j$
- $\tilde{w}_{ij}^{\text{variable}}$ is the plastic component of existing synaptic strength
- $\tilde{w}_{ij}^{\text{fixed}}$ sets the lower limit of strength below which the synapses may not shrink
- $\tilde{w}_{ij}^{\text{lost}}$ sets the upper limit of strength above which the synapse cannot grow

We also ran the network in a local region of the DG, rather than over the full longitudinal axis, in order to better view the orthogonalization by the DG. The pattern separation ability of the DG is thought to be effective even in local areas where most neurons have similar connections, and only the subtle differences lead to activity. To adjust the network for wider/narrower ranges of the hippocampus, the ‘range’
parameter was scaled accordingly. In addition, connection strengths were modified to account for the
different number of resulting synapses (broader network = sparser projections).

*Selection of Neuron and Connection Physiology Parameters:*

The physiology and cell counts of the modeled neurons in the network are given in supp Table II, III, and
connection parameters are given in supp Table IV. These physiology properties were estimated from both
physiology studies(Soltesz et al., 1995; Lubke et al., 1998; Jinno et al., 2003) and modeling studies
(Patton and McNaughton, 1995; Santhakumar et al., 2005). Connectivity was determined by review
literature of the dentate gyrus circuit and interneurons (Patton and McNaughton, 1995; Freund and
Buzsaki, 1996; Anderson et al., 2007). Finally, synaptic weights were estimated to accurately represent
the relative impact of different connections and maintain the network at observed activity levels (Jung and
McNaughton, 1993; Leutgeb et al., 2007).

The maturation process of new neurons was also taken from the literature. Generally, the new neurons
morphology and physiology was made to closely replicate (Zhao et al., 2006) and (Esposito et al., 2005),
respectively.

There are certain caveats to extracting physiology data from the literature. Most physiology studies of
dentate gyrus interneurons are from studies using slice recordings from either postnatal or very young
adult rats (typically less than 35 days old in the studies cited above). In contrast, studies investigating
adult-born neurons use older animals by necessity. Furthermore, there is considerable variation across
different studies, and results are not necessarily comparable across different methodologies.
Nevertheless, we believe that so long as the relative values of these parameters are consistent with
biological system, the specific values of many of these properties are less consequential.
III. Computing Activity – Digitized Firing Rate Model

Overview:

We used a model that we refer to as a digitized firing rate model (DFR). In the DFR model, the network was updated at a time scale considerably longer than a normal spiking model, but at shorter intervals than a firing rate model would typically have. We chose to model at this resolution because the physiology of new neurons and many dentate gyrus interneurons are not well understood at the high resolution necessary for a conductance based model. However, parameters that would affect firing rate, such as time constants, maximum firing rates, and activation thresholds, are better understood, allowing us to model at a slightly longer time scale.

Basic function:

The DFR model sums over synaptic inputs over a broad time scale \( t_{\text{step}} = 25 \text{ms} \), calculates the resulting membrane depolarization and estimates a firing rate for that neuron. Then, this firing rate is used to calculate the number of spikes that neuron would have over that 25ms time. For most neurons in this system, maximum firing rates are sufficiently low as to not result in more than one spike per time step.

Synaptic inputs:

For each 25ms time step, the membrane voltage of each neuron \( V_i(t) \), relative to rest, was calculated by the following equation for each neuron \( i \):

\[
V_i(t) = e^{-t_{\text{step}}/\tau_i} \times V_i(t-1) + \sum_{j=1}^{J} E_{\text{Glutamate},i}^* \times f_j(t-1) \times w_{\text{max}} \times w_{ji} + \sum_{k=1}^{K} E_{\text{GABA},i}^* \times f_k(t-1) \times w_{\text{max}} \times w_{ki}
\]

(III.1)

where for each neuron \( i \):

- \( j=1 \ldots J \) are Glutamatergic neurons
- \( k=1 \ldots K \) are GABAergic neurons.
- \( \tau_i \) is the membrane time constant of neuron \( i \)
- \( E_{\text{Glutamate},i}^* \) and \( E_{\text{GABA},i}^* \) are maturation dependent parameters that represent the neuron’s sensitivity to glutamate and GABA, respectively.
- \( f_j(t-1)/f_k(t-1) \) is the firing of neuron \( j/k \) in the previous time step
- \( w_{\text{max}} \) is the maximum strength for that synapse type
- \( w_{ji} \) and \( w_{ki} \) is the relative strength of the connection from neuron \( j(k) \) to neuron \( i \)

The first term in equation (III.1) is the neuron’s settling to its resting potential, and the second and third terms sum over all excitatory \( (j: 1 \text{ to } J) \) and inhibitory \( (k: 1 \text{ to } K) \) neurons that project onto neuron \( i \), weighted by the strength of each synapse \( (w_{ji} \text{ & } w_{ki}) \) and the response of neuron \( i \) to the neurotransmitter \( (E_{\text{Glutamate}}^* \text{ & } E_{\text{GABA}}^*) \).

Neuronal activity:

Whether a neuron fires or not \( (f(t)) \) was computed by the following equations:
if \(V(t) > \Delta V_{\text{threshold}}\) \[ P_{\text{Fire}} = \text{minimum} \left( F_{\text{Max}} \times t_{\text{step}}, F_{\text{Min}} \times t_{\text{step}} + \kappa(t - 1) + (V(t) - \Delta V_{\text{threshold}}) \times \left( \frac{dF}{dV} \right) \right) \] (III.2)

if \(V(t) \leq \Delta V_{\text{threshold}}\) \[ P_{\text{Fire}} = \kappa(t - 1) \] (III.3)

\[ f(t) = \text{round}(P_{\text{Fire}}) \] (III.4)

\[ \kappa(t) = P_{\text{Fire}} - f(t) \] (III.5)

if \(V(t) < -10mV\) \[ V(t) = -10mV \] (III.6)

if \(V(t) > \Delta V_{\text{threshold}}\) \[ V(t) = \Delta V_{\text{threshold}} \] (III.7)

where for each neuron \(i\):
- \(P_{\text{Fire}}\) is the potential for that neuron to fire in that time step
- \(\Delta V_{\text{Threshold}}\) is the voltage (relative to rest) above which the neuron fires
- \(F_{\text{Max}}\) is the maximum firing rate for the neuron
- \(F_{\text{Min}}\) is the minimum firing rate for the neuron
- \(\kappa\) is a tracking variable that distributes spiking according to the firing rate.
- \(dF/dV\) is the change in firing rate for each mV above threshold

When \(P_{\text{Fire}} > 0.50\), the neuron spikes \((f(t) = 1;\) III.4\), and the tracking variable \(\kappa\) is lowered (III.5), thereby reducing the likelihood of a spike in the next timestep. In the event that \(0 < P_{\text{Fire}} < 0.5\), then neuron does not spike \((f(t) = 0)\), but the \(\kappa\) of the neuron persists until the next time step, making a spike then more probable.

In the model, the \(\kappa\) term was randomized within a very narrow range \((\eta(0.025, 0.05))\) at the beginning of each event to account for variations in the initial state of the neurons.

**Theta:**

We assume that the activity in the model is occurring during periods known to exhibit theta rhythm. Theta is believed to be an oscillating inhibitory influence on the network, though the actual mechanism by which it occurs is unclear. We implemented theta by including an 8Hz oscillating dampening effect on the voltage neurons carry over from one time step to another. This has the effect of gradually “resetting” the network every 125ms.

\[ V_i(t) = V_i(t) \times (1 - \text{maximum} (\text{cosine}(\theta_0 + (t \times t_{\text{step}})/125ms), 0)) \] (III.8)

The phase of theta \((\theta_0)\) is uniformly random at the beginning of each event.
IV. Neurogenesis and Maturation

Overview:

The addition of new neurons to the network is the focus of this study, so we designed this aspect of the model to best reflect what is known about the maturation process.

New neurons were born into the network randomly and in a raw form. Initially, they have no synapses and very unique physiological properties. Over time, the neurons matured by gradually increasing in size, which in turn permitted the gradual addition of new synapses.

Addition of new neurons:
The model ran at a user-defined neurogenesis rate (New neurons / day). After each activity event, there was a random chance that a new neuron will be added. The new neuron was simply added to the existing layer in a random location, and the sizes of the connection matrices were adjusted accordingly, however with no initial connections. The physiology of the new cells was initialized at levels observed in new neurons (see supp Table III).

General maturation of immature neurons

After each activity event, neurons which are less than 10 weeks of age were considered immature neurons and part of the maturation process. Furthermore, there was an activity dependent aspect to the maturation, as new neurons can only mature if they were effectively being integrated into the network.

During maturation, the following happens to immature neurons:

1. Age of neuron increases – the age of each neuron, Age, is measured in weeks and is updated after each experienced event:

   \[ Age_i = Age_i + \frac{1}{Evt_{week}} \]  
   (IV.1)

   where \( i \) are all neurons that are less than ten weeks old.

2. Neurons grow in size (activity dependent) – the relative size of granule cells was tracked in the model, and used during synapse formation. One parameter tracked how far into the molecular layer the primary dendrite reaches (\( \delta_z \)), and the other two parameters determined the transverse (\( \delta_x \)) and longitudinal breadth (\( \delta_y \)) of the dendritic arborization.

   For all neurons \( i \) that were depolarized during the previous event, the size of the neuron’s apical dendrite grew at a fractional rate:

   \[ \delta_{z,i} = \delta_{z,i} + 1.5 \frac{1}{Evt_{week}} \]  
   (IV.2)

   The dendrite’s arborization (x,y spread) only grew after the apical dendrite reached the molecular layer (\( \delta_{z,i} > 2 \))

   \[ \delta_{x,i} = \delta_{x,i} + 0.2 \frac{1}{Evt_{week}} \]  
   (IV.3)
\[ \delta_{y,i} = \delta_{y,i} + \frac{0.2}{Evt_{\text{week}}} \]  

(in the model, the full z-extent is arbitrarily 3, and the full x/y radii are 0.2: 20% of the longitudinal axis)

**Maturation of synaptic connectivity**

3. *Addition of synapses (size dependent)* – Immature neurons become capable of forming synapses at different times in their development. The probability of forming a new synapse was related to both the length \( \delta_z \) and width \( \delta_x \) of the dendritic arborization. The probability that a particular type of synapse will be generated onto or from an immature neuron, \( i \), is given by the following equations:

\[ N_{\text{syn,ideal}} = \rho_{\text{syn,ideal}} \times N_{\text{target/source}} \]  

\[ \text{if (spine)} \rightarrow N_{\text{syn,i}}^* = N_{\text{syn,ideal}} \times \frac{\delta_{z,i}}{\delta_{z,\text{max}}} \]  

\[ \text{if (non-spine)} \rightarrow N_{\text{syn,i}}^* = N_{\text{syn,ideal}} \]  

\[ \text{if (} \delta_z > \delta_{z,\text{syn}} \text{)} \rightarrow P_{\text{syn}} = \frac{\left( N_{\text{syn,i}} - N_{\text{syn,i}}^* \right)}{\left( 0.5 \times Evt_{\text{week}} \times k_{\text{conn}} \right)} \]

where:

- \( N_{\text{target/source}} \) is the total number of source / target neurons for the connection
- \( \rho_{\text{syn,ideal}} \) is the ideal density for that connection
- *spine* indicates that the post-synaptic structure of the synapse is a spine. Only IEC, mEC and MC inputs onto GC are classified as spiny.
- *non-spine* indicates that the synapse does not use normal spines. All GC outputs and HI and BC synapses onto GCs are non-spiny
- \( \delta_z \) is the spatial width of the dendritic arborization of neuron \( i \)
- \( \delta_{z,\text{max}} \) is the spatial width of the dendritic arborization of a fully mature neuron
- \( N_{\text{syn,i}} \) is the current number of synapses for the neuron
- \( N_{\text{syn,ideal}} \) is the ideal number of synapses for the neuron
- \( N_{\text{syn,ideal}}^* \) is the ideal number of synapses for a fully mature neuron
- \( \delta_z \) is the dendritic length of neuron \( i \)
- \( \delta_{z,\text{syn}} \) is the minimum dendritic length requirement for each synapses type
- \( k_{\text{conn}} \) is the rate of synapse formation
- \( Evt_{\text{week}} \) is the number of simulated events in each week

For instance basket cells, which target the soma, could synapse early in maturation, whereas EC inputs, which are at the distal ends of dendrites, required the neuron to be fully grown. For spine-based synapses, the extent of the dendritic arborization determines how many synapses are desired. For instance, if a fully mature neuron has 50 synapses, then one with 50% of the “volume” will have a target number of 25 synapses. If the neuron has less than the target number of synapses, it
may gain a new synapse, the probability of which scales with the drive. For example, if the neuron has 20 synapses with an ideal of 25, then it will have a strong probability of gaining a new synapse.

When a new synapse is to be formed, an appropriate neuron in the target/source layer is selected. This selection of the partner neuron is dependent on two factors: the topography of the projection is taken into account (would an axon/dendrite of the partner neuron be nearby the new neuron?) and that there is not already a connection between those two neurons. Once selected, a new synapse is formed between the two neurons and is initialized at a random strength. The equations used were the same as discussed in the connection setup description (Equations II.4-II.10)

4. Addition of Competitive Synapses:
For spiny synapses, once a source neuron is selected, there is a possibility that the synapse formed will “compete” with an existing synapse. The probability that this occurs is related to the relative density of the projection and the number of possible competitors. The set of possible competitors for a synapse from projecting neuron \( j \) is determined by:

\[
S_{\text{PossComp}} = \left\{ \text{Syn}_j \neq \text{Comp} \cup |x_j - x_j, i| \leq 0.4 \right\}
\]

where:
- \( \text{Syn}_j \) represents all neurons that receive a synapse from neuron \( j \),
- \( \text{Comp} \) represents those synapses that are already competing (not allowed for second competition)
- \(|x_j - x_j, i|\) is the transverse distance (within slice) between the possible competitor and the immature neuron \( i \)

Essentially, possible competitors were restricted to those neurons already receiving a non-competitive input from the source neuron, and the immature neuron and possible competitor must be close enough to have overlapping dendritic arborizations.

Once the possible list of competitors is chosen, the probability that a competitive synapse is formed, \( P_{\text{comp}} \), is given by:

\[
\rho_{\text{syn}} = \frac{N_{\text{Syn,Total}}}{N_{\text{Source}} \times N_{\text{Target}}}
\]

\[
\rho_{\text{syn,ratio}} = \frac{\rho_{\text{syn}}}{\rho_{\text{syn,ideal}}}
\]

\[
P_{\text{comp}} = \frac{N_{\text{PossComp}}}{(\rho_{\text{syn,ratio}})^2}
\]

where:
- \( N_{\text{Syn,Total}} \) is the total number of synapses of that connection type
- \( N_{\text{Source}} \) is the total number of source neurons for that connection
- \( N_{\text{Target}} \) is the total number of target neurons for that connection
- \( \rho_{\text{syn,ideal}} \) is the ideal density for that connection
- \( N_{\text{PossComp}} \) is the number of neurons in the set available for competition \( (S_{\text{PossComp}}) \)
- \( P_{\text{comp}} \) is then compared to a random number to determine if the new synapse is either competitive with an existing synapse or formed de novo.
\[ \text{Syn} = \begin{cases} \text{Comp} & \text{if } P_{\text{comp}} > \text{rand} \\ \text{deNovo} & \text{if } P_{\text{comp}} < \text{rand} \end{cases} \]  

(IV.13)

If the synapses is selected to be competitive, a random neuron from \( S_{\text{PostComp}} \) is selected to be its competitor.

5. Determining Winner of Competitive Synapses

The ultimate ‘winner’ of the competition is decided by comparing the relative activities of the two competing neurons, the overall activity level of the cell layer, and the strengths of the synapses. At any given time, only neurons whose activity is below a certain activity threshold are susceptible to losing a connection:

\[ f_{\text{thresh}} = \mu_f - \sigma_f \]  

(IV.14)

where:

- \( f_{\text{thresh}} \) is the firing rate below which neurons may lose synapses
- \( \mu_f \) is the average firing rate for the cell layer
- \( \sigma_f \) is the standard deviation of the cell layer’s firing rate

If one neuron is below threshold, and the other is above this threshold, then the probability that it loses the synapse is given by:

\[ P_{\text{lose},1} = \left( \frac{1 - w_1}{k_{\text{comp}}} \right) e^{-\frac{5\times\left( \frac{\tilde{f}_1 - \tilde{f}_2}{\sigma_f} \right)^2}{2}} \]  

(IV.15)

where:

- \( w_1 \) is the synaptic weight of the source neuron onto the low-firing neuron
- \( k_{\text{comp}} \) is the rate that synaptic competition winners are determined
- \( \tilde{f}_1 \) is the time-weighted average firing rate of the low-firing neuron
- \( \tilde{f}_2 \) is the time-weighted average firing rate of the high-firing neuron

If both neurons are firing below \( f_{\text{thresh}} \), then the probability for each to lose is calculated by the following equation (same for both neurons):

\[ P_{\text{lose},1} = \left( \frac{1 - w_1}{k_{\text{comp}}} \right) e^{-\frac{5\times\left( \frac{\tilde{f}_1 - \mu_f}{\sigma_f} \right)^2}{2}} \]  

(IV.16)

It is possible for both neurons to lose at the same time, though this is rare. Finally, it is also possible that both synapses ‘win’ – in essence the synapse splits into two separate synapses. This can only occur if both synapses are very strong:

\[ \text{if } (\min(w_1, w_2) > 0.5) \rightarrow P_{\text{win},1,2} = \frac{w_1 \times w_2}{0.25 \times k_{\text{comp}}} \]  

(IV.17)
where \( w_1 \) and \( w_2 \) are the synaptic weights onto both neurons.

When two synapses cease to be competitive, the ‘winning’ synapses are simply reassigned to being non-competitive, whereas the losing synapses are removed from the network entirely.

6. Maturation of non-plastic synapses

Non-synaptic synapses, including all inhibitory synapses and GC outputs, are all initialized with a fixed synaptic weight that does not change over time. The age of the immature neuron does impose a bias on the synaptic strength that gradually disappears as the neuron matures. The realized strength of non-synaptic synapses, \( w \), is calculated by:

\[
\text{bias} = \min\left(\frac{\text{Age} - \text{Age}_{\text{ref}} - 0.5 \times k_{\text{conn}}}{k_{\text{conn}}}, 1\right) \quad (\text{IV.18})
\]

\[
w = w_{\text{immature}} + (1 - \text{bias}) \times (w_{\text{mature}} - w_{\text{immature}}) \quad (\text{IV.19})
\]

where

- \( \text{bias} \) is the degree that the synapse weight is adjusted due to the neuron’s age
- \( \text{Age} \) is the age of the GC
- \( \text{Age}_{\text{ref}} \) is the age of the neuron when it begins to receive connections of that type
- \( k_{\text{conn}} \) is the number of weeks that the synapse requires for maturation
- \( w_{\text{mature}} \) is the strength of the fully mature synapse
- \( w_{\text{immature}} \) is the strength of the synapse when those synapses first appear on the newborn neurons.

Maturation of physiology parameters

Prior to any event being processed by the network, the physiology of each individual neuron is calculated from its age and physical parameters (i.e., size, # of synapses).

Mature granule cells have a standard physiology which is shown in Table III. New neurons, however, have distinct properties during their early maturation (van Praag et al., 2002; Ambrogini et al., 2004; Esposito et al., 2005; Ge et al., 2006; Overstreet-Wadiche and Westbrook, 2006). The properties that have been well described include membrane resistance (\( R_{\text{mem}} \)), capacitance (\( C_{\text{mem}} \)), resting potential (\( V_{\text{rest}} \)), firing rate (\( f_{\text{max}} \)), and response to GABA. Some of these electrical properties can be attributed in part to the physical dimensions of the neuron – for example, capacitance scales with neuron volume and resistance is inversely related to number of synapses. From studies looking at this maturation process, the development of the other key properties to the model can be estimated as well for each neuron:

\[
V_{\text{ol}} = 0.12 + \max(5, \delta_x) \times \max(5, \delta_y) \times \delta_z \times \frac{N_{\text{Connections}}}{N_{\text{Connections,Max}}} \quad (\text{IV.20})
\]

\[
R_{\text{mem}} = 4 - 3.8 \times \tanh\left(\frac{N_{\text{Connections,Max}}}{2 \times (\max(0,N_{\text{Connections,Max}} - N_{\text{Connections}}) - 0.5)}\right) \quad (\text{IV.21})
\]

\[
\tau = \frac{V_{\text{ol}} \times R_{\text{mem}}}{0.12} \times \tau_{\text{mature}} \quad (\text{IV.22})
\]

\[
\text{if} (\tau > 4 \times \tau_{\text{mature}}) \rightarrow \tau = 4 \times \tau_{\text{mature}} \quad (\text{IV.23})
\]

\[
E^{*}_{\text{GABA}} = E^{*}_{\text{Glutamate}} \times \min(1, \text{Age} - 2) \quad (\text{IV.24})
\]
\[ \Delta V_{\text{threshold}} = \Delta V_{\text{threshold,mature}} - \left(1 - \frac{Vol_{\text{mature}}}{Vol_{\text{immature}}} \right) \times (\Delta V_{\text{threshold,mature}} - \Delta V_{\text{threshold,immature}}) \]  

\[ F_{\text{Max}} = t_{\text{step}} \times (F_{\text{Max,mature}} - \left(\frac{10 - \text{Age}_{\text{mature}}}{10 - \text{Age}_{\text{fire}}} \right) * (F_{\text{Max,mature}} - F_{\text{Max,immature}})) \]  

\[ \text{if} \ (N_{\text{Spines}} = 0) \rightarrow F_{\text{Max}} = 0 \]  

\[ F_{\text{Min}} = t_{\text{step}} \times (F_{\text{Min,mature}} - \min(1, \left(\frac{10 - \text{Age}_{\text{mature}}}{10 - \text{Age}_{\text{fire}}} \right) * (F_{\text{Min,mature}} - F_{\text{Min,immature}}))) \]  

\[ \frac{dF}{dV} = \frac{F_{\text{Max}}}{(e^{t_{\text{step}}/\tau} - 1) \times \Delta V_{\text{threshold}}} \]  

where:

- \( N_{\text{Connections}} \) is the total number of synapses that the neuron makes
- \( N_{\text{Connections, max}} \) is the total number of synapses that a fully connected neuron would make
- \( N_{\text{Spines}} \) is the total number of spiny synapses that the neuron makes (IEC, mEC, and MC afferents onto GCs)
- \( Vol \) is the estimated volume (arbitrary units). Proportional to capacitance
- \( R_{\text{mem}} \) is the estimated membrane resistance (GΩ)
- \( \tau \) is the estimated membrane time constant (ms)
- \( E_{\text{GABA}}^* \) is the relative response to GABA
- \( \Delta V_{\text{threshold}} \) is the voltage (relative to rest) required for the neuron to reach threshold (mV)
- \( F_{\text{Max}} \) is the maximum firing rate of the neuron
- \( F_{\text{Min}} \) is the minimum firing rate of the neuron (i.e., any firing is bursting)
- \( \text{Age}_{\text{fire}} \) is the age at which the immature neuron firing rate is estimated
- \( dF/dV \) is the change in firing rate for each mV above threshold

Because the properties such as synapse number and volume are scaled arbitrarily, the values are computed in without units and then compared to the corresponding values for mature neurons with their known physiology correlates. The physiological maturation of neurons in the model is shown in Figure S4.
V. Network Learning

The dentate gyrus is the site of significant synaptic plasticity, with substantial amounts of LTP having been shown in the perforant path input. In the model, we assume that the synapse classes which are excitatory and on spines experience learning (EC to GC, MC to GC), whereas aspiny neurons and GABAergic synapses do not learn.

Learning rule:
We used a simple spike-timing covariance learning algorithm to train the network. This STDP learning was implemented after each event by filtering the input layer spike train with a STDP profile, making time before each spike positive and time after each spike negative. This filtered input signal was then compared to spike train of the downstream neuron, and the covariance of the two neurons was used to determine the direction of learning. (Lin et al., 2006)

\[
\text{stdp} = \{-0.1, -0.3, 0.0, 0.5, 0.15\} \tag{V.1}
\]

\[
\hat{f}_i(t) = \text{stdp}(1) \times f_i(t - 2) + \text{stdp}(2) \times f_i(t - 1) + \text{stdp}(3) \times f_i(t) + \text{stdp}(4) \times f_i(t + 1) + \text{stdp}(5) \times f_i(t + 2) \tag{V.2}
\]

\[
\text{Cov}_{ij} = \left(\frac{\hat{f}_i - \mu_{f_i}}{\sum f_j}\right) \cdot f_j \tag{V.3}
\]

\[
\tilde{w}_{ij}^{\text{variable}} = w_{ij} - \tilde{w}_{ij}^{\text{fixed}} \tag{V.4}
\]

\[
\tilde{w}_{ij}^{\text{free}} = 1 - w_{ij} - \tilde{w}_{ij}^{\text{lost}} \tag{V.5}
\]

\[
\tilde{w}_{ij}^{\text{possible}} = \tilde{w}_{ij}^{\text{free}} + \tilde{w}_{ij}^{\text{variable}} \tag{V.6}
\]

\[
\tilde{w}_{ij}^{\text{variable}} = \tilde{w}_{ij}^{\text{variable}} + \text{Cov}_{ij} \times \left(\tilde{w}_{ij}^{\text{possible}} - \tilde{w}_{ij}^{\text{variable}}\right) \tag{V.7}
\]

\[
w_{ij} = \tilde{w}_{ij}^{\text{variable}} + \tilde{w}_{ij}^{\text{fixed}} \tag{V.8}
\]

where:

- \(f_i\) is the spike train of the source neuron
- \(f_j\) is the spike train of the target neuron
- \(\hat{f}_i\) is the STDP filtered signal from the source neuron
- \(\text{stdp}\) is the spike-timing dependent plasticity filter used

\(\text{Cov}_{ij}\) is the covariance between the filtered source neuron trace and the spike train of the target neuron

- \(\tilde{w}_{ij}^{\text{variable}}\) is the plastic component of existing synaptic strength
- \(\tilde{w}_{ij}^{\text{free}}\) represents the potential range into which the synapse can grow
- \(\tilde{w}_{ij}^{\text{possible}}\) is the total potential of the synapse for plasticity
- \(\tilde{w}_{ij}^{\text{fixed}}\) sets the lower limit of strength below which the synapses may not shrink
- \(\tilde{w}_{ij}^{\text{lost}}\) sets the upper limit of strength above which the synapse cannot grow
As dendritic spines mature in the model, their relative level of plasticity decreases. This is accomplished by transferring a portion of the variable strength to fixed strength, and a portion of free strength to lost strength.

\[
\begin{align*}
\tilde{w}^{\text{fixed}}_{ij} &= \tilde{w}^{\text{fixed}}_{ij} + k_{\text{synapse}} \times \tilde{w}^{\text{variable}}_{ij} \\
\tilde{w}^{\text{variable}}_{ij} &= (1 - k_{\text{synapse}}) \times \tilde{w}^{\text{variable}}_{ij} \\
\tilde{w}^{\text{lost}}_{ij} &= \tilde{w}^{\text{lost}}_{ij} + 0.4 \times k_{\text{synapse}} \times \tilde{w}^{\text{free}}_{ij} \\
\tilde{w}^{\text{free}}_{ij} &= (1 - 0.4 \times k_{\text{synapse}}) \times \tilde{w}^{\text{free}}_{ij}
\end{align*}
\] (V.9-12)

Immature neurons:
Immature neurons have been shown to have a significantly different response to LTP. In particular, the potentiation seen in 4 to 6 week old neurons is considerably higher than that seen before and afterwards (Schmidt-Hieber et al., 2004; Ge et al., 2007). This increased ability for learning is not simulated directly in the model, rather the increased number of younger, more plastic synapses in immature neurons leads to a profile of potential LTP that heavily biases younger neurons.

VI. Cell Death

Cell death in the model is limited to the GC layer. This cell death is activity dependent – if a cell fires substantially less than the average activity in the network, there is a small probability that the neuron may die. There is no enforced rate of death, if no cells qualify for dying, then no cells will die. Mature cells can die, but do so rarely.

\[
f_{\text{thresh}} = \max(\mu_j - 2 \times \sigma_j, 0.25 \times \mu_j)
\] if \(Age < 10\) or \(N_{\text{Spines}} < \left( \mu_{\text{Spines}} - \sigma_{\text{Spines}} \right)\) \(\Rightarrow P_{\text{Die}} = k_{\text{death}}\) (VI.2)

where:
\(\mu_j\) is the average firing rate of the neuron layer
\(\sigma_j\) is the standard deviation of the firing rates of the neuron layer
\(f_{\text{thresh}}\) is the firing rate threshold below which a neuron may die
\(Age\) is the age of the neuron (in weeks)
\(N_{\text{Spines}}\) is the total number of spiny synapses onto the neuron (IEC, mEC, MC afferents onto GC)
\(\mu_{\text{Spines}}\) is the average number of spiny synapses onto that type of neuron
\(\sigma_{\text{Spines}}\) is the standard deviation of the number of spiny synapses onto that type of neuron
\(f\) is the filtered firing rate of the neuron
\(P_{\text{Die}}\) is the probability that the neuron may die
\(k_{\text{death}}\) is the rate at which neurons susceptible to death may die

When a cell dies, its connections are eliminated and the neuron is noted as dead in the network, which precludes the possibility of future growth and activity in the network.
VII. Experimental Design

**Entorhinal Cortex Inputs**

Lateral entorhinal cortex (lEC) neurons were chosen to depolarize at different levels for each environment.

\[ V_{lEC} = \left( \frac{\text{abs}(\eta(0,1)) \times \text{abs}(\eta(0,1))}{2} \right) \times \frac{df}{dV} + V_{\text{thresh}} \]  

(VII.1)

where:
- \( V_{lEC} \) is the depolarization of a lEC neuron for that environment
- \( V_{\text{thresh}} \) is the depolarization required to fire
- \( \frac{df}{dV} \) is the increase in firing rate per unit of increased depolarization
- \( \eta(0,1) \) is a random number selected from a Gaussian distribution with a mean of zero and a standard deviation of one. In this equation we force this to be positive.

Medial entorhinal cortex (mEC) inputs were generated using a previously described method (Solstad et al., 2006).

Each mEC neuron was assigned three parameters: grid size/frequency (\( \lambda \)), grid orientation (\( \theta \)), and spatial offset (\( \phi \)). Grid size varied with the dorsal-ventral location of the neuron (\( \chi \)), while orientation and offset were random. As with biological observations, the orientation and offset varied between environments, and the inter-neuronal relationships (\( \phi_1 - \phi_2 \) & \( \theta_1 - \theta_2 \)) remained constant. Therefore, the generation of a new environment involved the random selection of an environmental orientation (\( \theta_{\text{env}} \)) and offset (\( \phi_{\text{env}} \)).

The calculation of an mEC neuron’s relative response, \( G \) for a spatial location \((x,y)\) is given by:

\[ k_1 = \frac{4\pi \lambda}{\sqrt{6}} \times \left[ \begin{array}{c} \cos(\theta + \frac{\pi}{12}) + \sin(\theta + \frac{\pi}{12}) \times (x - \phi_x) + \\ \cos(\theta + \frac{\pi}{12}) - \sin(\theta + \frac{\pi}{12}) \times (y - \phi_y) \end{array} \right] \]  

(VII.2)

\[ k_2 = \frac{4\pi \lambda}{\sqrt{6}} \times \left[ \begin{array}{c} \cos(\theta + \frac{5\pi}{12}) + \sin(\theta + \frac{5\pi}{12}) \times (x - \phi_x) + \\ \cos(\theta + \frac{5\pi}{12}) - \sin(\theta + \frac{5\pi}{12}) \times (y - \phi_y) \end{array} \right] \]  

(VII.3)

\[ k_3 = \frac{4\pi \lambda}{\sqrt{6}} \times \left[ \begin{array}{c} \cos(\theta + \frac{3\pi}{4}) + \sin(\theta + \frac{3\pi}{4}) \times (x - \phi_x) + \\ \cos(\theta + \frac{3\pi}{4}) - \sin(\theta + \frac{3\pi}{4}) \times (y - \phi_y) \end{array} \right] \]  

(VII.4)

\[ G = \frac{2}{3} \left( \frac{k_1 + k_2 + k_3}{3} + .5 \right) \]  

(VII.5)
As with IEC neurons, mEC neurons also have an space-independent environmental bias that this spatial gain is added to.

\[ V_{mEC} = G \times \text{abs} \left( 0.75 + \frac{\text{abs}(\eta(0,1))}{5} \right) \times \frac{df}{dV} + V_{\text{thresh}} \]  

\hspace{1cm} (VII.6)

**Input Structure and Experimental Design**

During training and growth, each “event” experienced in the model involves the network ‘moving’ along a path within context for twenty seconds. The mEC neurons fire according to the spatial location at each instant, whereas the IEC neurons fire at rates determined by the environment’s context.

During the testing phase, the network is successively placed in static locations within that environment for either 500ms. During this time, mEC and IEC firing rates remain constant. These trials completely tile the environment and the responses of the model are recorded for each location.

**Growth phase of experiment**

After the model is initialized with , the model then “grows” in a series of environments. Each environment had a separately calculated IEC activity vector, as well as a random mEC activity vector and shifted grid loci (\( \theta_{\text{env}} \) and \( \varphi_{\text{env}} \)).

Each environment is used for a total of 40 days, which allows considerable growth of the GC layer as well as experience-dependent maturation to the environments. Each day consists of 10 separate training events that consist of the animal moving along a random path for 10 seconds.

**Pattern separation task**

Pattern separation is examined in the model by examining the similarity of the network responses across different sets of EC inputs. In the novel pattern separation task shown in Figure 2, two initial contexts (IEC patterns) were designed to be nearly orthogonal, and then ten intermediate contexts were designed using varying proportions of neuron activities from each of the environments. This allowed for the examination of several degrees of IEC overlap (contextual similarity). Within each context, the network was tested at many evenly spaced locations to vary mEC input (i.e., spatial similarity). The similarities between responses of each network at these different locations and contexts were then compared to the similarities of the input neurons.

The normalized dot product (NDP) is used to calculate similarity in the model. NDP is determined by comparing the vectors or a neuron layers responses using the following equation:

\[ \text{Sim}_{i,j} = \text{NDP}(X_i, X_j) = \frac{X_i \cdot X_j}{\|X_i\| \times \|X_j\|} \]  

\hspace{1cm} (VII.7)

where \( X \) is a 1 by N vector representing the response of the cell layer ‘X’ to the \( i^{th} \) or \( j^{th} \) event.
**Temporal separation**

The impact of maturation on pattern separation was investigated by extending the pattern separation task over time. After testing the pattern separation ability, the networks then continued to grow within a new environment for the model equivalent of one day (10 events). The networks were then tested on the same test environments. This was repeated for a total of 10 days. After this testing, the similarity of the outputs from different days were compared.

**Response to familiar and novel environments**

Networks were re-exposed to the environments that they experienced during training (familiar environments; FEs) as well as a novel environment (NE). The response of the network was measured independently for 500 ms at 400 equally spaced locations in each context (forming a 20x20 grid). The response of GCs were summed over the full 500ms to represent the response to that spatial location.

Each FE as well as the NE was examined in this manner without any learning, neurogenesis, maturation or cell death.

**Modulation of neurogenesis: Aging**

Aging was simulated in the computational model by extending the study. Networks were generated as in the earlier studies through three environments (120 days). At the onset of the fourth environment, the neurogenesis rate began to decrease gradually. Every 10 days, the rate of neurogenesis ($NG$) decreased by the prescribed amount, which in our experiment was 5%.

$$NG(d) = NG(d-10) \times 0.95$$  \hspace{1cm} (VII.8)

where $d$ is the current day of the simulation.

Environments were changed every 40 days, as in the other studies. The simulation continued for 400 days (through 10 additional environments).

Pattern separation was measured every 40 days, including the onset of the study at day 120. The two environments used to examine pattern separation were held constant throughout the study. In addition, unlike the experiments described above, the test environment was not entirely random, but biased slightly to ensure that the environment used for each network was unique from all of the familiar environments to reduce the effects of specific network learning from biasing the results. Ten potential test environments were selected, and the one with the minimal overlap (measured by NDP – eq. VII.7) with the 13 training environments was chosen to use as the first test environment. The vector representing this environment was then shuffled to create the second environment for the pattern separation experiment.

The temporal dynamics of the pattern separation was measured at both day 120 (before the age-related decrease in neurogenesis) and at the end of the experiment (day 520).

**Modulation of neurogenesis: Stress**
Stress was simulated as an acute decrease in neurogenesis rate from 10 neurons / day to 2.5 neurons / day on day 120. This decreased rate was maintained for 60 days, at which time the rate increased back to 10 neurons / day. The simulation continued through day 280, for a total of seven 40-day environments. The rate of neurogenesis (NG) was measured in new neurons/day according to the following equations:

\[
\begin{cases}
0 < d < 120 & NG = 10 \\
120 < d < 180 & NG = 2.5 \\
180 < d < 280 & NG = 10
\end{cases}
\]  

(VII.9)

where \(d\) is the day of the simulation.

Environments were changed every 40 days, and the simulation continued through day 280.

Pattern separation was measured every 5 days, starting with the onset of the study at day 120. Similar to the aging study, pattern separation was measured using the same test environments at each time-point, which were chosen to be distinct from the training environments. The temporal dynamics of pattern separation were measured at onset, just prior to neurogenesis recovery (day 180), and at the end of the study (day 240).
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