**Bimodal dendritic processing in basket cells drives distinct memory-related oscillations.**

**Tzilivaki et al., 2025**

**Methods**

**Model implementation and availability**

Simulations were conducted using NEURON (v7.6)1 on a High-Performance Computing Cluster, utilizing 111 CPU cores on a 64-bit CentOS Linux operating system.

**All codes/scripts and datasets required to reproduce the results and figures, as well as all statistical analyses, are accessible in the ModelDB database.**

Please visit:

<https://modeldb.science/2018008> Access code:: 280621Interneurons!

**They are also freely available on Github:** <https://github.com/AlexandraTzilivaki/Tzilivakietal2024>

**Neuronal populations**

1. Fast Spiking Basket Cells (FSBCs)

Two multi-compartmental biophysical models of CA3 FSBCs were employed, adopted from Tzilivaki et al. (2019)2. These FSBCs models include detailed anatomical reconstructions of somata and dendritic trees taken from Neuromorpho database (originally published in Tukker et al. 20073), (**Figures 1, S1**). Both FSBCs feature bimodal nonlinear dendritic branches, characterized by both supralinear and sublinear branches. They are equipped with fast voltage-dependent sodium channels (gnafin), delayed rectifier potassium channels (gkdrin), slow inactivation potassium channels (gslowin), slow calcium-dependent potassium channels (gkcain), A-type potassium channels in proximal and distal dendritic regions (gkadin, gkapin), h-currents (ghin), and L-, N-, and T-type voltage-activated calcium channels (gcal, gcan, and gcat, respectively). These models have been extensively validated against experimental data and accurately capture the intrinsic features and electrophysiological responses of hippocampal FSBCs (See original reference2 and Supplementary Information). The mean dendritic diameter and total dendritic length were measured for the supralinear and sublinear dendrites of the two FSBCs morphological reconstructions. Dendritic volume was calculated as per Tzilivaki et al. (2019)2 using the following formula:

To causally manipulate the dendritic morphologies of FSBCs to generate fully supralinear or sublinear trees (**Figure S2**), we performed causal manipulations according to the approach described in Tzilivaki et al. (2019)2. We fixed the diameter and length of all dendrites to create trees with average supralinear or sublinear dendritic volume (**Figure S1B**), which dictated the integration mode as shown in the original modeling publication. Dendritic Input Resistance was calculated using the following formula:

where I = −100 pA injected in each dendritic branch and DV is the generated IPSP.

For more detailed information about the FSBC models, please refer to the relevant publication2 and **Tables S1-2, 4-5**.

1. Pyramidal Cells (PCs)

Biophysically relevant hippocampal PC models with reduced morphology (n = 20) were adopted from Hadler et al. (2024)4. These models consist of somata and proximal, distal, and basal dendritic branches. PCs include a Ca2+ pump and buffering mechanism, Ca2+ activated slow AHP and medium AHP potassium (K+) currents, an HVA L-type calcium (Ca2+) current, an HVA R-type Ca2+current, an LVA T-type Ca2+ current, an h-current, a fast sodium (Na+) current, a delayed rectifier K+ current, a slowly inactivating K+ M-type current, and a fast inactivating K+ A-type current. These current mechanisms were non-uniformly distributed along the somatodendritic compartments. They were validated based on *in vitro* data to replicate the electrophysiological profile and basic dendritic architecture of hippocampal CA3 PCs4,5. The PC models do not include detailed nonlinear dendritic trees, as this was beyond the scope of this study. Incorporating realistic anatomical reconstructions for PCs would have significantly increased computational complexity and reduced simulation speed. For more information, see Hadler et al. (2024)4 and **Tables S3-5**.

**Synaptic properties**

The PC models were equipped with AMPA, NMDA, and γ-aminobutyric acid type A (GABAA) synapses, while the FSBCs included Ca2+ permeable AMPA (CP-AMPA), NMDA, GABAA, and autaptic GABAA synapses. The synaptic conductance values for every connection type were calibrated based on experimental6–9 and modelling studies2 and are listed in **Table S5**To ensure the robustness of our finding, we repeated the simulations upon increased or decreased synaptic conductance values (15% change) (see sensitivity analysis **Figure S2**)

**Hippocampal Microcircuit**

The hippocampal microcircuit configuration was adopted from Hadler et al. (2024)4. The model consists of 20 PCs and 2 FSBCs. In each random simulation trial (n = 30), each PC contacted up to seven (7) randomly chosen PCs with one AMPA and one NMDA synapse activation per contact. Each FSBC received synaptic input from fifteen (15) randomly chosen PCs in each simulation trial. Additionally, each PC received thirteen (13) feedback inhibitory GABAergic inputs from each FSBC per simulation trial. Each FSBC formed five (5) GABAergic synapses per simulation trial and was self-inhibited through autapses. For further details, see the Simulation Paradigms chapter and Hadler et al. (2024)4.

**Simulation Paradigms**

Input

The microcircuit is activated by a theta entrained presynaptic population as per Turi et al., 201810. The input was modeled as an artificial presynaptic population (N=22) using NEURON’s VecStim function. The spike times of the presynaptic population were generated using a sinusoidal theta like filter that was applied so to account for theta like modulated spike times.

Thata like probability formula (as per 10):

Where:

* spike = the spike time in msec (float)
* f\_theta = theta-cycle frequency in Hz. (float)

For the simulations shown in **Figures 1-3** and **Supplementary Figures 3-5**, f\_theta=4 Hz. For the sensitivity analysis simulations as shown in **Supplementary Figure 2**, we changed the input the theta frequency to f\_theta=5Hz.

* phi\_theta= theta cycle phase in radians.

For the simulations shown in **Figures 1-3** and **Supplementary Figures 3-5**, phi\_theta=0 (equal to 0 radians). For the sensitivity analysis simulations as shown in **Supplementary Figure 2**, we shifted the input phase so phi\_theta=0.5 (equal to 180 radians).

If the probability p(t) is greater than 0.7 a spike is generated for the specific artificial neuron (n=22). Every input neuron has its own theta modulated spike train.

Each PC received input from 5 artificial presynaptic neurons, while each FSBC received input from 7 artificial presynaptic neurons. Although the input was sufficient to activate the PC population due to its reduced morphology, 7 artificial presynaptic neurons were insufficient to evoke spiking activity in the FSBC models, given their realistic complex anatomical reconstructions. This subthreshold activation was selected to ensure that FSBCs were primarily engaged in the network due to the local inputs they received from PCs.

1. **Simulations**The microcircuit model was simulated for approximately 12,000 milliseconds (ms) with a time step of 0.1 ms. The first 200 ms were excluded from the analysis to allow the model to reach an equilibrium state. For the dispersed protocols, synapses to FSBCs (both input and local PC-to-FSBC synapses) were randomly assigned to dendrites, meaning one randomly chosen dendrite received one pair of NMDA and CP-AMPA synapses. For the clustered protocol (**Supplementary Figure S4**), the same total amount of synapses was placed in 4 randomly chosen dendrites (cluster size: 5-7 synapses (per dendrite) Data represent the results (mean and standard deviation values (std)) of thirty (30) random simulation trials for each protocol. In every trial, the total number of synaptic contacts and the connectivity ratios remained identical, but different randomly chosen neurons (from both PC and FSBC populations) were connected to different random neurons. Additionally, in each trial, different dendrites from both PCs and FSBCs were randomly chosen and synapses were activated at different parts of the chosen dendrites. This approach ensured that the results reflected the diversity, especially of the FSBCs trees, in bimodal activation protocols. Furthermore, two different anatomical reconstructions were used for our FSBC models to account for FSBCs morphological variability (see relevant chapter).
2. **LFP simulation and Spectral analysis**

To record the Local Field Potential (LFP), an *in silico* electrode was simulated based on NEURON’s extracellular function, following the modelling approach of Vladimirov et al. (2013)11. The electrode was placed close to the PCs somata and remained in the exact same position throughout the execution of all protocols and simulation trials. The sampling frequency was set at 10 kHz. Despite the microcircuit model’s small size, it efficiently generated fast and slow oscillations comparable to experimental observations12–15 while maintaining low computational complexity and demands.

The *in silico* LFP datasets were band-passed at two respective bands: slow (3 – 10 Hz) and fast (30-200 Hz). Slow and fast Peak-Frequency powers and peak Fast frequency were determined using custom-made MATLAB scripts (MATLAB, The MathWorks Inc., Natick, MA; Torrence and Compo 1998) utilizing the p-welch function (0.4 Hz resolution) and visualized as Power-Frequency plots. Phase-Amplitude Coupling (PAC) analysis was conducted using Comodulogram generation and the calculation of the modulation index (MI) metric that were adopted from Tort et al. (2008)16. Wavelet phase was calculated at 15 levels from 1-15 Hz, and the amplitude at 50 levels from 30-180 Hz. The MI was obtained by measuring the divergence of the observed amplitude distribution from the uniform distribution.

**Statistical Analysis**

Statistical analyses for multigroup comparisons were performed using the Kruskal-Wallis test, followed by a post-hoc correction for multiple comparisons (multcompare function Matlab). For pairwise comparisons where data exhibited unequal variance, p-values were calculated using the Mann-Whitney U test.

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