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A Theory of Hippocampal Theta Correlations: Extrinsic and Intrinsic Sequences

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Abstract

Hippocampal place cell sequences have been hypothesized to serve as diverse purposes as the induction of synaptic plasticity, formation and consolidation of long-term memories, or navigation and planning. During spatial behaviors of rodents, sequential firing of place cells at the theta timescale (known as theta sequences) encodes running trajectories, which can be considered as 1-dimensional behavioral sequences of traversed locations. In a 2-dimensional space, however, each single location can be visited along arbitrary 1-dimensional running trajectories. Thus, a place cell will generally take part in multiple different theta sequences, raising questions about how this 2-dimensional topology can be reconciled with the idea of hippocampal sequences underlying memory of (1-dimensional) episodes. Here, we propose a computational model of cornu ammonis 3 (CA3) and dentate gyrus (DG), where sensorimotor input drives the direction-dependent (extrinsic) theta sequences within CA3 reflecting the 2-dimensional spatial topology, whereas the in-trahippocampal CA3-DG projections concurrently produce intrinsic sequences that are independent of the specific running trajectory. Consistent with experimental data, these intrinsic theta sequences are less prominent in the theta state, but we show that they can nevertheless be detected during theta activity, thereby serving as running-direction independent landmark cues. We hypothesize that the intrinsic sequences largely reflect replay and preplay activity during non-theta states.

eLife assessment

This **important** work presents an interesting perspective for the generation and interpretation of phase precession in the hippocampal formation. Through numerical simulations and comparison to experiments, the study provides a **convincing** theoretical framework explaining the segregation of sequences reflecting navigation and sequences reflecting internal dynamics in the DG-CA3 loop. This study will be of interest for researchers in the spatial navigation and computational neuroscience fields.

1 Introduction

As a rat navigates in an environment, place cells fire sequentially during one theta cycle (~100 ms) and form time-compressed representations of behavioral experiences (Skaggs et al., 1996), called theta sequences. Theta sequences were proposed to be driven by extrinsic (extrahippocampal) sensorimotor input (Foster and Wilson, 2007; Huxter et al., 2008; Romani and Tsodyks, 2015; Yiu et al., 2022), since they are played out in the direction of travel during locomotion and, hence, represent current behavioral trajectories. In contrast, various types of hippocampal sequences have also been proposed to arise from intrinsic hippocampal connectivity. Non-local activation of place sequences during immobile periods was observed in replay of past locations after the space has been explored (Skaggs and McNaughton, 1996; Lee and Wilson, 2002) as well as in preplay (Dragoi and Tonegawa, 2011) of prospective locations before the animal explores a novel environment. In addition, some CA3 place cells exhibit out-of-field firing at reward locations (Sasaki et al., 2018). These remote activations of place cells reflect the underlying circuit connectivity rather than the actual locomotive state of animal. Furthermore, a subset of CA3 cell pairs shows rigid theta correlations with peak lags that are independent of the traversal order of their place fields (Yiu et al., 2022), suggesting the existence of hard-wired sequences even when sensorimotor drive is present. Such intrinsic sequences that are driven by intrahippocampal connectivity (Tsodyks et al., 1996), although less predom-inantly observed during theta (Yiu et al., 2022), are generally interpreted as reflecting spatial memories or planning (Kay et al., 2020).

Existing models for theta sequences are, however, either fully extrinsic or intrinsic. The former often employ short-term plasticity (Romani and Tsodyks, 2015; Thurley et al., 2008), which creates synaptic couplings that are temporally stronger along the instanta-neous forward direction. In contrast, intrinsic models such as the Tsodyks et al. (1996) model use a fixed asymmetrical weight matrix pre-designed to align with one movement trajectory (for review see Maurer and McNaughton, 2007; Jaramillo and Kempter, 2017). Neither of these models alone can explain the simultaneous presence of rigid and flexible correlations in theta sequences. Here we present a network model that accounts for both types of correlations by separating their generation into two anatomically distinct layers: CA3 and dentate gyrus (DG). Extrinsic sequences are generated in the CA3 layer by short-term synaptic plasticity mechanisms, while the intrinsic sequences are played out by the CA3-DG feedback loop with fixed asymmetrical weights, as inspired by the experimental evidence that lesions of DG abolish non-local activation of CA3 place cells (Sasaki et al., 2018) and CA3 theta correlations (Ahmadi et al., 2022).

In this paper, we present a model for theta correlations that unifies both extrinsic and intrinsic mechanisms. Extrinsic and intrinsic sequences can propagate simultaneously in separate directions, along the movement trajectory and the pre-designed CA3-DG feedback loops, respectively. As a result, spike correlations display directionality as the two sequences cross each other at various angles: The more parallel they are, the stronger the correlation. Our simulations are in quantitative agreement with directionality properties found in experimental data (Yiu et al., 2022) and propose that rigid correlation structure can serve as a stable temporal pattern, which is recognizable across multiple movement directions. This temporal “landmark” pattern allows spatial encoding even if sensory-motor experience is lacking and may reflect the mechanistic basis for replay in non-theta states.

2 Methods

Neuronal model

Generation of neuronal action potentials is modelled according to Izhikevich (2003). The soma potential v and the adaptation variable u of unit i at time t (in ms) follows the equations:

$$\dot{v}_i(t) = 0.04v_i^2(t) + 5v_i(t) + 140 - u_i(t) + I_i(t)$$
$$\dot{u}_i(t) = a\,[b\,v_i(t) - u_i(t)]$$
$$I_i(t) = I_i^R(t) + I_i^S(t) - I^\theta(t)$$

Any time $v(t)$ crosses the threshold 30 mV from below, we register a spike for the neuron and reset the soma potential by $v(t) \leftarrow c$ and the adaptation variable by $u \leftarrow u(t)+d$. For the excitatory pyramidal place cells, we use parameters a = 0.035, b = 0.2, c = −60 mV, d = 8, which provides the neuron with burst firing characteristics. For the inhibitory interneurons, the parameters were a = 0.02, b = 0.25, c = −65 mV, and d = 2, which corresponds to fast spiking patterns. $I(t)$ is the total sum of recurrent $I^R(t)$, sensory $I^S(t)$ and oscillatory theta input

$$I^\theta(t) = 7\left[1 + \cos\left(\frac{2\pi t}{100\text{ms}}\right)\right]/2$$

We chose to use the phenomenological spike generation model of Ichikevich (2003), since it allows to adjust burst firing properties with only very few parameters that efficiently emulate the bifurcation dynamics of spike generation in biophysically more realistic neuron models with many little constrained parameters. Synaptic integration below threshold is not affected by the spike generation model and will thus be treated by conventional synaptic models.

Spatial input

The place field centers $\mathbf{p}_i^{CA3} = \left[x_i^{CA3}(t), y_i^{CA3}(t)\right]$ of 80 × 80 = 6400 excitatory CA3 cells equally tile the 80 by 80 cm square arena. Place cell firing rates are modelled direction-sensitive, with preferred heading directions ψ_i^{CA3} semi-randomized among each 2×2 tile of place cells by randomly rotating a set of 4 equally spaced direction angles by a uniformly distributed angle ξ, i.e.

$$\left[\psi_i^{CA3}, \psi_{i+1}^{CA3}, \psi_{i+2}^{CA3}, \psi_{i+3}^{CA3}\right] = \left[0°, 90°, 180°, 270°\right] + \xi \mod 360° .$$

The sensory input $J_i^S(t)$ into the i-th neuron depends on the instantaneous position, p(t) = [$x(t)$, $y(t)$], and heading direction $\psi(t)$ of the animal as

$$J_i^S(t) = \begin{cases} A_i^S(t)\, I^{MEC}(t) & \text{if } d\left(\mathbf{p}(t), \mathbf{p}_i^{CA3}\right) \leqq 5\text{cm} \\ 0 & \text{if } d\left(\mathbf{p}(t), \mathbf{p}_i^{CA3}\right) > 5\text{cm} \end{cases}$$
$$A_i^S(t) = \mathrm{A}^{\mathrm{pos}} + \mathrm{A}^{\mathrm{dir}} \exp\left(\cos\left(\psi(t) - \psi_i^{\mathrm{CA3}}\right) - 1\right)$$
$$I^{\mathrm{MEC}}(t) = \frac{1}{2}\left[1 + \cos\left(\frac{2\pi t}{100\text{ms}} + 70°\frac{\pi}{180°}\right)\right] ,$$

where $\mathrm{A}^{\mathrm{pos}}$ is the amplitude of positional tuning and $d(\cdot)$ computes the Euclidean distance between two positions. The positional tuning curve is implemented as a rectangular box function, where the place cell only receives sensory input if the animal is within 5cm from the field center. Directional tuning is implemented as an additional amplitude gain $\mathrm{A}^{\mathrm{dir}}$ to the positional current depending on the circular difference between the animal's heading and the neuron's preferred heading direction ψ_i^{CA3}. The sensory input is assumed to be modulated by theta oscillations from medial entorhinal cortex (MEC) $I^{\mathrm{MEC}}(t)$ with a phase shift of 70° (Mizuseki et al., 2009).

The sensory input J^S is subsequently transformed to the input current I^S via short-term facilitation (STF)

$$\dot{s}_i^F(t) = \frac{(S_0^F - s_i^F(t))}{\tau^F} + (S_1^F - s_i^F(t))\Phi^F J_i^S(t)$$
$$I_i^S = J_i^S(t)\left[s_i^F(t)\right]^2 ,$$

,where the facilitation variable s_i^F decays to S_0^F with a time constant τ^F = 500ms and increases to S_1^F when the sensory input J_i^S is present. The time constant τ^F of facilitation of neocortical synapses was in the range suggested by Tsodyks et al. (1998) following previous experimental reports (Mejías and Torres, 2008; Zucker and Regehr, 2002). Φ^F controls the strength of the STF. The facilitation variable is squared to include non-linear interactions in presynaptic calcium dynamics. As a result, facilitated sensory input I_i^S increases over time and becomes stronger in the later part of the field.

Note that only the CA3 place cells receive the sensory input. $I_i^S(t)$ is not applied to the place cells in DG and all of the inhibitory interneurons.

CA3 recurrent connections

Place cells in CA3 connect with each other by excitatory synapses. The excitatory synaptic current $I_i^E(t)$ is conductance-based, and follows the equations:

$$\dot{g}_i^E(t) = \frac{-g_i^E(t)}{\tau^E} + \frac{1}{N_J}\sum_{j,f} W_{ij}\, s_j^D(t)\, \delta(t - t_j^{(f)} - \tau_0) \qquad (1)$$

$$I_i^E(t) = \left[V^E - v_i(t)\right] g_i^E(t) \qquad (2)$$

The conductance g_i^E of a post-synaptic cell *i* is increased by the spike arrivals at times $t_j^{(f)}$ from the pre-synaptic cell *j*, and decay with a time constant τ^E = 12ms. N_J = 6, 400 is the number of presynaptic place cells, V^E = 0mV is the reversal potential of the excitatory synapses and τ_0 = 2ms is the synaptic transmission delay.

The synaptic weights W_{ij} from cell *j* to cell *i* depend on the distance between place cell centers and on the similarity of their preferred heading angles, i.e.,

$$W_{ij}^{\mathrm{CA3}} = J_{ij}\left\{B^{\mathrm{pos}} + B^{\mathrm{dir}} \exp\left[K^{\mathrm{CA3}}\left(\cos(\psi_i^L - \psi_j^L) - 1\right)\right]\right\} \exp\left(\frac{-d(\mathbf{p}_i^{CA3}, \mathbf{p}_j^{CA3})^2}{2\sigma^2}\right) ,$$

where B^{pos} and σ = 2cm correspond to the maximum strength and width of the location-specific interaction, respectively. B^{dir} and K^{CA3} control the maximum strength and the concentration of the directional dependence, respectively. J_{ij} models the rightward asymmetry of the cell connections, which was only turned on when we simulated the 2-d variant of Tsodyks et al. (1996) model in **Figure 1C-F** and otherwise turned off in the rest of our analysis.

$$\begin{aligned} &\text{If rightward asymmetry is ON,} && J_{ij} = 1 \quad \text{if } x_j^{CA3} < x_i^{CA3}, \text{ else } 0 \\ &\text{If rightward asymmetry is OFF,} && J_{ij} = 1 \end{aligned}$$

Furthermore, the recurrent synaptic conductances underwent short-term synaptic depression (STD), as was proposed in Romani and Tsodyks (2015) to serve as sequence generator in 2-d space. The mechanism penalizes the recurrent input into the place cells behind the animal. As a

result, the differential recurrence strengths translate to a gradient of spike phases and produces extrinsic sequences in the direction of travel. We model the STD by the variable $s_i^D(t)$ which represents the available synaptic resource and follows the dynamics:

$$\dot{s}_i^D(t) = \frac{1 - s_i^D(t)}{\tau^D} - U^D \delta(t - t_i^{(f)}) \ ,$$

Where s_i^D recovers to 1 with a time constant τ^D = 500 ms and is depleted by a fraction U^D every time a spike occurs. The recovery time constant is comparable to experimentally obtained values of cortical neurons (200ms-800ms in Tsodyks and Markram (1997); Markram et al. (1998); Abbott et al. (1997); Zucker and Regehr (2002)) and previous modelling work (450-800ms in Romani and Tsodyks (2015); Haga and Fukai (2018); Tsodyks and Markram (1997); Tsodyks et al. (1998)). The STD only applies to synaptic connections when presynaptic cells are CA3 place cells. $s_i^D(t)$ is fixed at 1 when the pre-synaptic cells are inhibitory interneurons or DG place cells.

DG layer

We simulated N_{DG} = 40 × 40 = 1600 place cells in the DG layer, with place field centers equally tiling the environment. The DG cells do not receive sensory input. Their positional $(x_i^{\mathrm{DG}}, y_i^{\mathrm{DG}})$ and directional (ψ_i^{DG}) tunings are determining synaptic strengths to and from the CA3 layer. The directional tuning is semi-randomized as described for CA3. The synaptic current dynamics follow equations (1) and (2). Excitatory synaptic weights from CA3 place cells to DG place cells are defined as

$$W_{ij}^{\mathrm{CA3-DG}} = C_j^{CA3}\, B^{\mathrm{DG}} \exp\left[K^{\mathrm{DG}}\left(\cos(\psi_i^{\mathrm{DG}} - \psi_j^{\mathrm{CA3}}) - 1\right)\right] \exp\left(\frac{-d(\mathbf{p}_i^{DG}, \mathbf{p}_j^{CA3})^2}{2\sigma^2}\right) \ ,$$

,which are dependent on the differences in the place field centers and preferred heading angles between the CA3 and DG populations. The variable C_j^{CA3} strengthens outgoing connections from CA3 place cells on the path corresponding to the intrinsic sequence by choosing

$$C_j^{\mathrm{CA3}} = \max_{k\in[-10,10]} \left\{ \exp\left(\frac{-d(\mathbf{p}_k^C, \mathbf{p}_j^{CA3})^2}{2\sigma^2}\right) \right\} \ ,$$

Where $\mathbf{p}_k^C$ varies with the intrinsic path direction θ_{DG} as $\mathbf{p}_k^C = [2k\ \cos(\theta_{\mathrm{DG}}), 2k\ \sin(\theta_{\mathrm{DG}})]$.

The excitatory synaptic strengths from DG to CA3 are chosen such that DG cells project back to CA3 cells with place field centers shifted by a vector $\mathbf{r}$ = [4 cos(θ_{DG}), 4 sin(θ_{DG})] of fixed length of 4 cm along the intrinsic path, i.e.,

$$W_{ij}^{\mathrm{DG-CA3}} = B^{\mathrm{DG}} \exp\left[K^{\mathrm{DG}}\left(\cos(\psi_i^{\mathrm{CA3}} - \psi_j^{\mathrm{DG}}) - 1\right)\right] \exp\left(\frac{-d(\mathbf{p}_i^{\mathrm{CA3}} - \mathbf{r}, \mathbf{p}_j^{\mathrm{DG}})^2}{2\sigma^2}\right) \ . \quad (3)$$

The model has no synaptic connections between DG excitatory neurons.

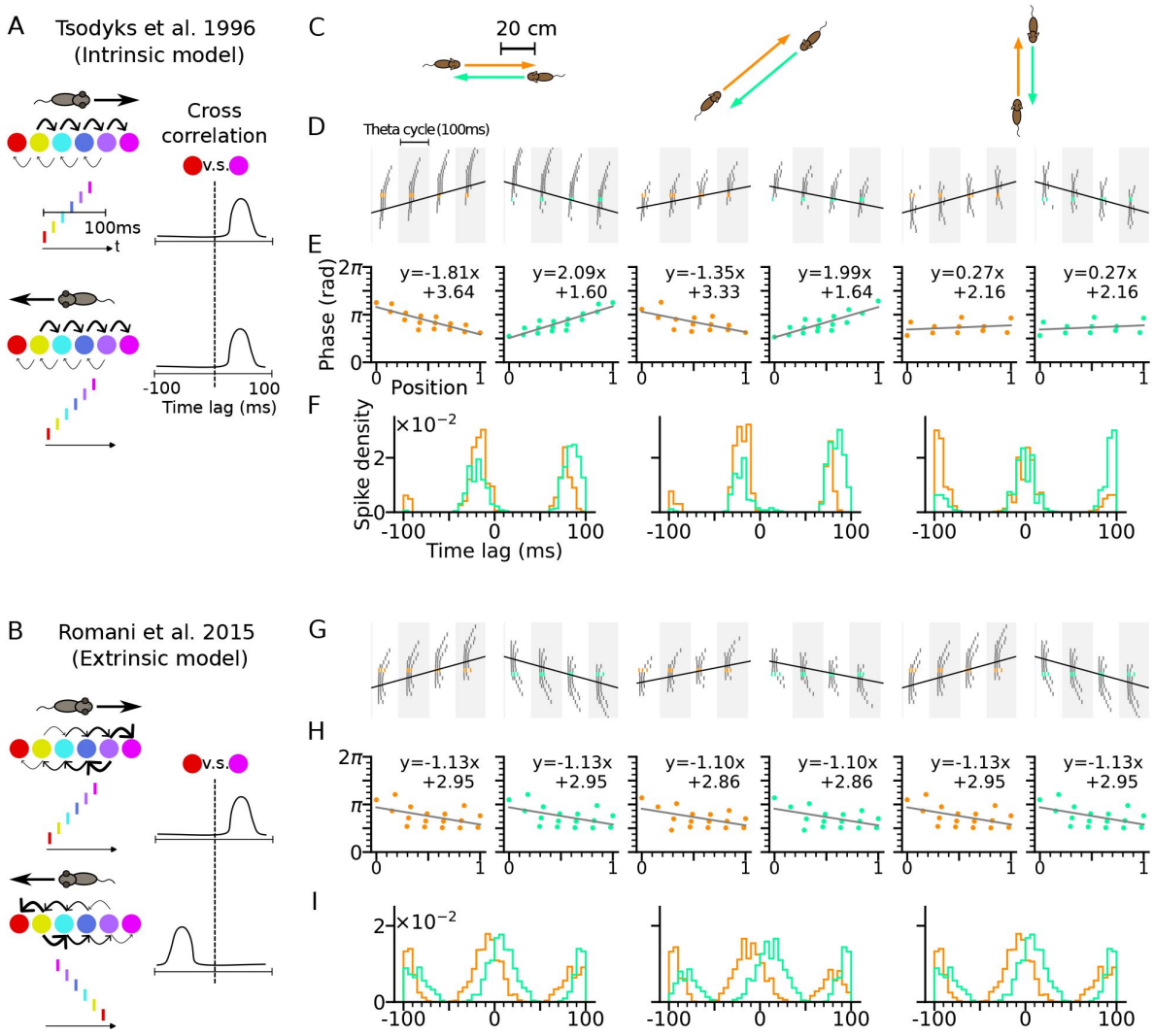

Figure 1.

Phase precession depends on running direction in intrinsic models but not extrinsic models. (A) Left: Schematic illustration of the intrinsic Tsodyks et al. (1996) model. When the animal runs through a series of place fields (solid circles) in 1-D, the place cells fire action potentials in sequence at the theta timescale (spike raster with corresponding colors). Recurrent connectivity is pre-configured and asymmetrical (connection strengths indicated by arrow sizes). Right: Cross-correlation function between the red and magenta cell, which remains the same for both running directions. (B) Left: Schematic illustration of the extrinsic Romani and Tsodyks (2015) model. Recurrent connections behind the animal are temporarily depressed by short-term plasticity, and thereby, become movement-dependent. Right: Cross-correlation flips sign in the opposite running direction. (C) Simulated trajectories (duration 2 s) in a 2-d environment (80 × 80 cm) with speed 20 cm/s in left and right (left column), diagonal (middle), and up and down (right) directions. (D-F) Simulation results from the intrinsic model (with fixed asymmetrical connectivity inspired by the Tsodyks et al. (1996) model). Place cells only project synapses to their right neighbors. (D) Spike raster plots of place cells along the orange (left panel) and light green (right panel) trajectories (colors defined in C). Theta sequence order remains the same in the reversed running direction. Black line indicates animal position. (E) Phase-position relation for the spikes colored in C. Linear-circular regression (gray line) parameters are indicated on top. Positions of the animal at the first and last spike are normalized to 0 and 1, respectively. (F) Averaged cross-correlation of all cell pairs separated by 4cm along the trajectory. Reversal of running direction does not flip the sign of the peak lags. (G-I) Same as D-F, but for the extrinsic model (spike-based variant of Romani and Tsodyks (2015) model). Correlation peaks flip after reversal of running direction.

Inhibitory synapses

The model additionally contains N_I = 250 inhibitory interneurons (denoted as Inh) each for the CA3 and the DG layer. They provide inhibitory feedback separately to the excitatory cells within each layer (CA3-Inh-CA3 and DG-Inh-DG). The dynamics of their synaptic currents mirrors the excitatory synapses, i.e.,

$$\dot{g}_i^I(t) = \frac{-g_i^I(t)}{\tau^I} + \frac{1}{N_I}\sum_j^{N_I} W_{ij}^{X-Y}\delta(t - t_j^{(f)} - \tau_0)$$

$$I_i^I(t) = \left[V^I - v_i(t)\right] g_i^I(t) \ ,$$

with τ^I = 10ms, V^I = −80mV. CA3 and DG have all-to-all connections to their inhibitory populations with uniformly randomized strengths, i.e. $W_{ij}^{X-Y} = W_0^{X-Y}\xi$, with $\xi \sim U(0, 1)$. W_0^{X-Y}. is the maximum synaptic strength, and the notation X-Y corresponds to Inh-CA3 and Inh-DG connections. There is no synaptic connection between inter-neurons, i.e. $W^{\text{Inh–Inh}}$ = 0, neglecting gamma oscillatory activity in the model.

The total recurrent current entering each excitatory neuron is thus the sum of the excitatory and inhibitory current:

$$I_i^R(t) = I_i^I(t) + I_i^E(t)$$

Excitatory synapses to interneurons

Interneurons only receive all-to-all excitatory currents from their respective layer. Those currents are modelled according to eqs.(1-2). The synaptic weights are constant and denoted by $W_0^{\text{CA3–Inh}}$ and $W_0^{\text{DG–Inh}}$.

Parameters of the models

Model parameters that are adjusted in different analyses are listed in **table 1**. The values of the synaptic weights and spatial input were chosen to allow for a large range of phase precession and stability of the network activity. For the analyses including the DG layer, weights are adjusted to allow coexistence of extrinsic and intrinsic sequences.

Cross-correlation analysis

Cross-correlation represents the probability that a spike of one place cell would occur following a certain time lag from the spike of the another cell. Cross-correlation is always empirically computed as a histogram of time lags between spike pairs with a resolution of 5ms in a window of 200ms. Throughout the present study, the direction of a time lag is designated as the lag of the first encountered cell relative to the next cell along the trajectory, except in **Figure 1**, where the direction of time lag follows the cell order along the 0°, 45° and 90° trajectory in each comparison group, and in **Figure 2**, where the time lag direction is from left to right cells.

Correlation lag is derived by band-pass (4-12 Hz) filtering the cross-correlation his-togram and applying a Hilbert transform on the filtered signal. The phase of the analytic signal at time lag 0 is the correlation lag.

Extrinsicity and intrinsicity

We apply quantitative measures for the extrinsic or intrinsic nature of cross-correlations in a pair of place fields following Yiu et al. (2022). We compare the cross-correlation histograms of a field pair for a running direction along the DG loop (θ_{DG}) and opposite to the loop (θ_{DG} + 180°).

Name \Figure	1 (In)	1 (Ex)	2	3	4 (C.)	4 (L.)	5	6A	6B (C.)	6B (L.)	7
A^{pos}	7.5	9.0	6.5					9.5	7.5		6.5
A^{dir}	0		6					9	8		6
S_0^F	1		0			1.25	0	0.25	0	1.25	0
S_1^F	1		2			1.25	2	1.5	2	1.25	2
Φ^F	0		0.001			0	0.001			0	0.001
B^{pos}	1100		0								
B^{dir}	0		2000	1500			2000	0			1500
K^{CA3}	0		1								
J_{ij}	ON	OFF									
U^D	0	0.9	0.7								
N_{DG}	0		$40 \times 40 = 1600$								
B^{DG}	0		3000	0	4000		4000	0			4000
K^{DG}	0		1								
N_I	0		250								
$W_0^{\mathrm{CA3-Inh}}$	0		50								
$W_0^{\mathrm{Inh-CA3}}$	0		5								
$W_0^{\mathrm{DG-Inh}}$	0		350								
$W_0^{\mathrm{Inh-DG}}$	0		35								

Table 1

Model parameters used in simulations according to Figure panels. In, Ex, C. and L. refer to intrinsic, extrinsic, control and lesion respectively.

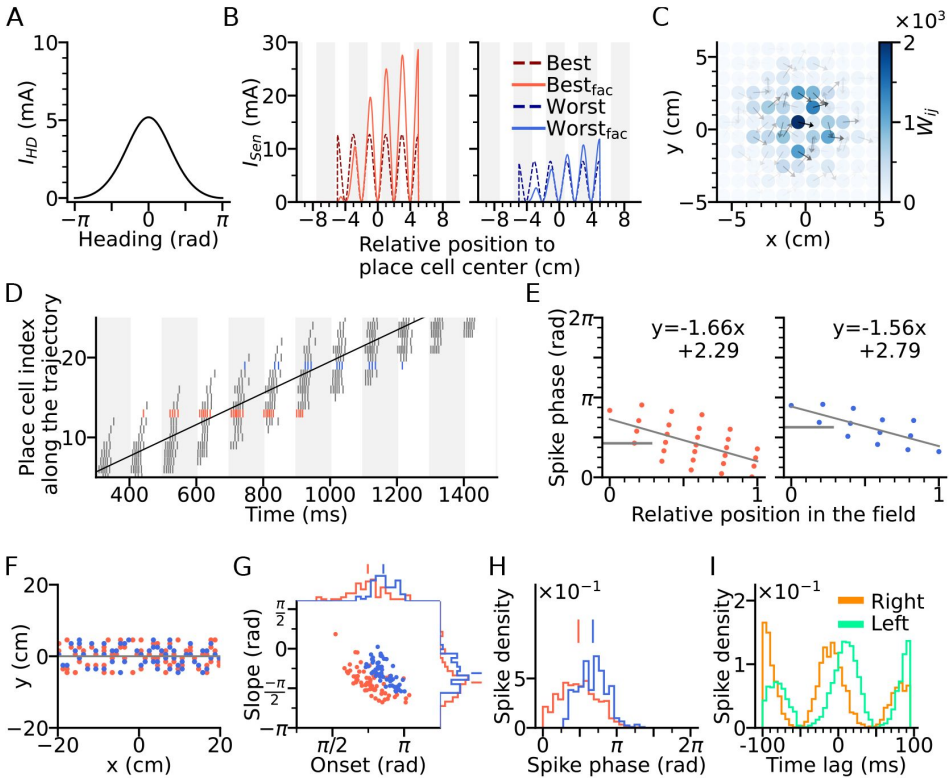

Figure 2.

Directional input gives rise to spikes at lower theta phase. (A) Directional input component of an example place cell. (B) Total sensory input as the sum of directional and positional drive of an example place cell for the animal running along (red dashed line, left) and opposite (blue dashed line, right) the preferred heading direction of the cell, respectively named as *best* and *worst* direction. The sensory input is modelled by oscillatory currents arriving with +70° phase shift relative to theta peaks (gray vertical lines). Place fields are defined by a 5cm rectangular envelope. Solid lines depict the input current including short-term synaptic facilitation. (C) Synaptic weights (W_{ij}, color) from the place cell at the center (the darkest dot) to its neighbors in the 2-d environment. Each dot is a place field center in 2-d space. Arrows depict their preferred heading directions. (D) Spike raster plot sorted by visiting order of the place fields along the trajectory. Spikes of the cells with best and worst direction are colored in red and blue, respectively. (E) Phase position plots for the cells with best and worst direction from D (labels as in **Figure 1E**). The mean phase is marked as horizontal gray bar. (F) Example place cell centers with best (< 30° different from the trajectory; red) and worst (> 150°; blue) directions relative to the rightward trajectory (gray line). Only centers of cells that fire more than 5 spikes are shown. (G) Slopes and onsets of phase precession of the population from (F). Marginal slope and onset distributions are plotted on top and right, respectively. Note higher phase onset in the worst-direction case. (H) Spike phase distributions. Higher directional inputs generate lower spike phases. (I) Average spike correlation between all pairs with 4cm of horizontal distance difference when the animal runs rightwards and leftwards. Peak lags are flipped as expected from an extrinsic model.

Extrinsicity (Ex) is computed as the Pearson's correlation (r) between two cross-correlation histograms, and intrinsicity

(In) between the histogram of θ_{DG} and the horizontally flipped histogram of θ_{DG} + 180°. The Pearson's correlation is then transformed ($r' = (r + 1)/2$) to be in the range of 0 and 1. An extrinsic correlation would give an extrinsicity near 1, since the effect of DG loop is minimal and correlation histograms are similar in both θ_{DG} and θ_{DG} + 180° directions. A pair of place fields with intrinsic correlation would see cross-correlation horizontally flipped in the θ_{DG} + 180° condition due to the large effect of DG loop, and hence, give an intrinsicity near 1. We classify a pair as extrinsic if its extrinsicity exceeds intrinsicity, and vice versa.

Tempotron

A tempotron is a neuronally inspired classifier (readout neuron) whose dendritic synaptic weights can be adapted to recognize temporal patterns of spikes arriving at the afferents (for details, see Gütig and Sompolinsky (2006)). Briefly, the soma potential of the tempotron follows the equations

$$V(t) = \sum_i w_i \sum_{i,f} K(t - t_i^{(f)})$$

$$K(t - t_i^{(f)}) = V_0(\exp[-(t - t_i^{(f)})/\tau] - \exp[-(t - t_i^{(f)})/\tau_r]) \ ,$$

,where w_i is the adaptable weight of the afferent fiber conveying spikes from place cell i to the tempotron. $K(t-t_i^{(f)})$ is a post-synaptic potential (PSP) kernel with decay and rising time constants of τ = 5ms and τ_r = 1.25ms respectively. V_0 is a factor which normalizes the PSP kernel to 1. A spike is said to occur if $V(t)$ crosses the firing threshold V_Θ = 2 from below. After threshold crossing, the afferents will be shunted and spike arrivals will not evoke more PSPs for the rest of the pattern. A pattern is defined as the set of spike times of all the pre-synaptic place cells in a theta cycle (100ms).

The weight w_i follows the update rule

$$\Delta w_i = 0.01 \sum_{t_i^{(f)} < t_{\max}} K(t_{\max} - t_i^{(f)})$$

$$w_i \leftarrow w_i + \Delta w_i \qquad \text{If a } (+) \text{ pattern does not elicit a spike,}$$

$$w_i \leftarrow w_i - \Delta w_i \qquad \text{If a } (-) \text{ pattern does elicit a spike,}$$

where $t_{\max}$ is the time at the peak of the soma potential $V(t)$. The learning rule assigns credit to the afferents based on spike timing. Spike times closer to the peak are considered to have higher contribution to the tempotron firing, hence their afferents are incremented by a larger step. After training, spike times with similar temporal correlations as the (+) patterns would be able to evoke enough PSP in the tempotron's soma and elicit a spike as a positive response of binary classification, while those similar to (−) patterns would not elicit a spike from the tempotron.

We trained the tempotrons to identify the spike patterns of place cells at locations with and without intrinsic connectivity separately. To this end, we modified our network such that DG loops are present at the upper half of the arena, spanning the space from x=-20cm to x=+20cm at y=+20cm in direction θ_{DG} = 0°, while the loop is absent in the lower half of the arena.

During training, we applied "non-moving" spatial inputs to the CA3 place cells at the with-loop (0 cm, 20 cm) and no-loop (0 cm, -20 cm) locations for 1 second, as if the animal were standing still at the locations, evoking the activities representing the two location cues. For computational efficiency, we restricted our analysis to the populations of CA3 place cells within the 20cm squared boxes centered at the two locations. Each population contains 400 pre-synaptic cells, forming the input space for the tempotron. The spikes from the with-loop population will train the first

tempotron and those from the no-loop population will train the second tempotron. Prior to training, the input spikes are sub-divided to 10 patterns based on their theta cycles. Each pattern has a window of 100ms. We added noise to the patterns by jittering the spikes with Gaussian noise $N \sim (0, (2\text{ms})^2)$ for 100 times. As a result, each tempotron receives 10 × 100 = 1000 training patterns from the activity evoked by the location. All training patterns are (+) patterns and there is no (−) pattern.

After training, trajectories (20cm long, 1s duration) with running directions from 0° to 360° with 15° increment were simulated to cross each of the locations. The trajectories produce a mix of extrinsic and intrinsic sequences in the with-loop population and only extrinsic sequences in the no-loop population. The patterns evoked by the running trajec-tories were separately applied to the tempotrons. The input spikes for testing were also subdivided into theta cycles and jittered in the same manner as during training, forming 1000 testing patterns for each running direction. A sequence is said to be correctly identified if the tempotron fires at at least 1 out of 10 theta cycles along the trajectory. The accuracy rate for each running direction of trajectory is computed across the 100 jittered realizations.

Code availability

We used Python 3 for simulations and visualization. The codes are available from a github repository (*https://github.com/yyhhoi/directionalnet*).

3 Results

Dependence of theta sequences on heading directions

Extrinsic and intrinsic sequences

Theta-scale correlations of place cells have been explained by previous models using two different types of network mechanisms, intrinsic and extrinsic ones. For *intrinsic* models spike correlations are explained by only the recurrent connectivity of the neuronal network (**Figure 1A**). For *extrinsic* models, the spike correlation is defined by sensory-motor parameters such as movements (**Figure 1B**). We first illustrate how these mechanisms work for two exemplary representatives of these two major model classes.

For intrinsic models, we refer to the Tsodyks et al. (1996) model where phase precession is generated by the fixed asymmetrical connectivity between place cells. Spike phases of the place cells ahead of the animal decrease as the excitatory drive is gradually increasing, but only along the direction in which the connection strength is asymmetrically stronger (for example, rightward in **Figure 1A**), called the *asymmetry direction*. Here we simulate a network of CA3 place cells with fixed asymmetrical connectivity as suggested in the Tsodyks et al. (1996) model (see Methods for the implementation) and applied our model to behavioral running trajectories in a 2-d open space (**Figure 1C**). Phase precession and spike correlations (**Figure 1D-E**) are compared for opposite running directions. In our simulations, all place cells project excitatory synapses to their counterparts with rightward neighboring place fields (see CA3 recurrent connections in Methods). Phase precession therefore is determined by how closely the running direction matches the asymmetry direction imposed by the intrinsic connections. The closer the trajectory angle aligns with this asymmetry direction, the more negative is the slope of phase precession (**Figure 1E**). Since in this case, the theta sequence only propagates rightwards as place cells are sequentially activated from left to right, the signs of spike correlations between cell pairs remain invariant to the movement direction (**Figure 1F**, see Cross-correlation analysis in

Methods). Intrinsic models thus cannot explain experimentally observed directional independence of phase precession and directional dependence of theta spike correlations (Huxter et al., 2008).

Our example of an extrinsic model is based on our spiking simulations of the originally rate-based model by Romani and Tsodyks (2015), where phase precession was explained by symmetric recurrent connections that undergo running direction-dependent attenuation by short-term synaptic depression (STD): place fields with centers behind the current animal position on the trajectory thereby received largely reduced recurrent input resulting in recurrently driven theta sequences to play out only in forward direction. We simulated our spiking variant of the Romani and Tsodyks (2015) model with the same trajectories as the intrinsic model (**Figure 1G-I**), and recovered direction-independent phase precession (**Figure 1H**). Since now, the theta sequences are played out in the same direction as the movement, theta spike correlations are symmetrically reversed (**Figure 1I**) as shown experimentally in CA1 neurons (Huxter et al., 2008; Yiu et al., 2022).

In area CA3, however, theta spike correlations are neither solely extrinsic (Yiu et al., 2022; Kay et al., 2020), since phase precession properties change in relation to running directions, nor are they solely intrinsic since reversal of correlation is still observed in most of the sequences (Huxter et al., 2008; Yiu et al., 2022). We therefore propose a new theory of phase precession for CA3 incorporating both intrinsic and extrinsic factors.

Directional sensory input

To, however, fully explain directional properties of theta phase precession and theta spike correlations by a model, also directional modulations of firing rates (Yiu et al., 2022) need to be taken into account.

We therefore included both directional and positional modulation of the sensory input to the model place cells (**Figure 2A-B**) with randomized preferred heading directions (See Spatial input in Methods). The sensory input is assumed to arise from MEC, and hence, it is also theta-modulated and phase-shifted by 70° with respected to the peak of theta cycle (Mizuseki et al., 2009). Furthermore, since the precession slope observed in the Romani and Tsodyks (2015) model is limited (−1.13 radians per field size, see **Figure 1H**) as compared to the experimental reports (−4.44 radians (Yiu et al., 2022) and about −2.0 radians (Harris et al., 2002) per field size), we introduced short-term synaptic facilitation (STF) to the sensory input (Berretta and Jones, 1996; Thurley et al., 2008) generating temporally asymmetric depolarization as suggested by intracellular recordings in vivo (Harvey et al., 2009) (**Figure 2B**). STF amplifies the sensory current at the later part of the field, thus creating phase precession with steeper slopes thereby extending the phase range. Finally, we designated the synaptic weights to be stronger between place cells with similar preferred heading directions (**Figure 2C**) as has been proposed (Brunel and Trullier, 1998) as a result of Hebbian plasticity applied to directional firing fields.

A simulation of the place cell network was performed for a rightward trajectory through the arena based on our variant of the extrinsic Romani and Tsodyks (2015) model (**Figure 2D**). We focus on two sets of place cells, one for which the trajectory aligns with the preferred heading direction of the field (red, denoted as *best* direction) and one for which the trajectory runs opposite the preferred heading direction (denoted as *worst* direction) (**Figure 2F**). Phase precession has a lower onset and marginal spike phase along best direction than along the worst (**Figure 2G-H**), which is consistent with experimental data (Yiu et al. (2022) report mean spike phases ± SEM for best and worst direction of 1.61±0.02 and 2.22 ±0.03 in radians respectively), reflects that larger depolarizations generally yield shorter latencies. Directionality of the input, although it yields lower spike phases through higher depolarization, does not affect spike pair correlations, which

remains solely extrinsic (**Figure 2I**). Thus, even though rate directionality and directional bias in recurrent connectivity can render phase precession directionally dependent, they are not sufficient to account for intrinsic sequences.

Generation of intrinsic sequences by the DG-CA3 recurrent network

To explain the expression of intrinsic sequences in CA3, we propose them to be generated by the interaction of two networks, CA3 and DG (**Figure 3A**). DG is a good candidate region to be involved in phase precession, since lesions of it were shown to reduce prospective spiking (Sasaki et al., 2018) and to lower the onset phase of phase precession (Ahmadi et al., 2022). In our model, the neurons in DG receive excitatory synaptic inputs from CA3 place cells (putatively via hilar mossy cells) and project back to the CA3 cells with place field centers at a different location (Equation 3) to induce propagation of intrinsic sequences along a specific spatial direction. The CA3 cells at the target location of DG input are then activated and evoke higher depolarization in cells with place fields at the next DG target locations through the feedback. This scheme produces a rigid sequence whose activation order is independent of the movement direction. The connection pattern of DG-CA3 projections (for brevity, we also refer to it as "DG loop" in the subsequent text) could be determined by pre-existing network structure or past experience through associative learning, or both.

Figure 3, provides schematic illustrations, for a DG layer that either only projects CA3 activity to their rightward neighbours (θ_{DG} = 0°, **Figure 3A**) or only to their left-ward neighbors (θ_{DG} = 180°, **Figure 3E**). Simulations for both cases (θ_{DG} = 0° and θ_{DG} = 180°) assume a rightward trajectory. Apart from the addition of the DG layer, the model architecture and parameters of CA3 layer are the same as in **Figure 2** (including best and worst direction in place field firing rate), which only generates extrinsic sequences through STD in the CA3 recurrent synaptic connections. DG-loop connectivity is additionally modulated by firing rate directionality of the CA3 place fields. Fields with similar preferred heading directions are more strongly connected via the loop than those with opposite preferred heading directions (see DG layer in Methods).

We found that, when the simulated animal is running in the same direction as the DG-CA3 projection, phase precession starts from a higher phase (**Figure 3C-D**) due to the forward activation of place cells through DG layer (recovering the effect of asymmetric connectivity in the original Tsodyks et al. (1996) model), as compared to the model with-out DG layer (**Figure 2G-H**). Spike phases in best direction remain lower than along the worst direction (**Figure 3D**). When, however, the animal is running against the DG-CA3 projection (**Figure 3E**), extrinsic sequences are still present in forward direction, evoked by the movement of the animal, but the intrinsic sequences are played out backward as determined by the direction of fixed recurrence (see cyan and yellow shaded regions in **Figure 3F**). The latter is reflected by the higher phase at the end of the phase position plots (**Figure 3G**) which leads to flatter precession slopes and decreases the fraction of phase precession (slope < 0) of all traversal trials (**Figure 3H**). A closer look into pair correlation reveals that for trajectories opposite to the DG-loop projection (θ_{DG} = 180°), spike probability is added to positive time lags (**Figure 3I**). Therefore, introducing fixed recurrence through DG loops elicits both extrinsic and intrinsic sequences and qualitatively changes theta sequences.

To quantify the degrees of extrinsic and intrinsic sequence firing in a way allowing comparison to experimental reports, we use the measures *extrinsicity* and *intrinsicity* (Yiu et al., 2022) that are based on pairs of place cells with overlapping place fields (see Methods for details and Discussion). In our simulation, extrinsically and intrinsically driven cell pairs are both present in the population (**Figure 3J**), indicating a coexistence of extrinsic and intrinsic sequences.. Our model reproduces a greater extrinsicity for cell pair activity when running direction aligns with both best place field directions as compared to when it aligns to both worst field directions, since along the best direction, cells receive more sensory depolarization, and thus, the movement-dependent

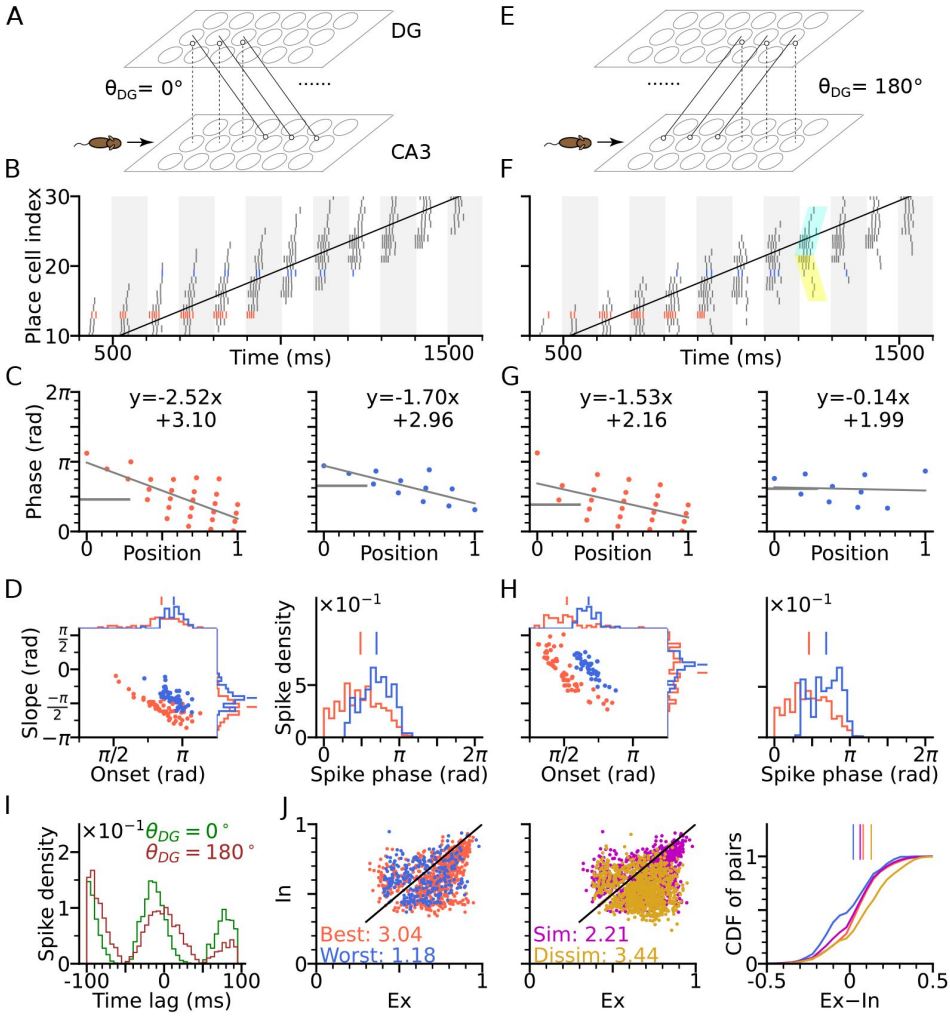

Figure 3.

DG-CA3 loop introduces directionality of theta sequences. (A) Illustration of synaptic connections from CA3 place cells to DG and vice versa. DG layer mirrors the place cell population in CA3 and redirects the CA3 inputs back to different locations. Here, DG cells project into CA3 place cells with fields 4 cm displaced to the right of the pre-synaptic CA3 cells. θ_{DG} denotes the angular difference between the DG projection direction and the animal's movement direction. (B) Spike raster plots sorted by cell indices along the trajectory (2 s duration) from x=-20cm to x=20cm. Cells with best and worst angles are marked by red and blue colors, respectively. (C) Phase-position plots as is **Figure 2E**. (D) Distributions of precession slopes, onsets and spike phases as in **Figure 2G-H**. (E-H) Same as A-D, but with DG cells projecting opposite to the animal's movement direction (θ_{DG} = 180°). In F, cyan and yellow shaded regions indicate the examples of forward sequence induced by the movement (extrinsic), and backward sequence induced by the DG recurrence (intrinsic), respectively. (I) Average spike correlations for θ_{DG} = 0° and θ_{DG} = 180° for pairs separated by 4cm along the trajectory. Note that for θ_{DG} = 180°, there is a relative excess of spike-pairs with positive lags. (J) Left: Intrinsicity and extrinsicity (see Methods) for all pairs from the populations with best (red) and worst (blue) direction. Pair correlations above and below the identity line are classified as intrinsic and extrinsic, respectively. Numbers are the ratios of extrinsically to intrinsically correlated field pairs. Note that the red best direction pairs are more extrinsic than the blue worst direction pairs due to higher sensory input. Middle: Ex/Intrinsicity of pairs with similar (< 30°) and dissimilar (> 150°) preferred heading angles. Pairs with similar preferred heading angles are more intrinsic due to stronger DG-CA3 recurrence. Right: Cumulative distribution of the differences between extrinsicity and intrinsicity. Dissimilar and best direction pairs have higher bias to extrinsicity than similar and worst direction pairs, respectively.

extrinsic sequences are more activated. The model also explains, why pairs with similar preferred heading directions may be less extrinsic than pairs with approximately opposite preferred heading direction (dissimilar pairs), since the DG loop preferentially connects CA3 place cells with similar preferred heading directions. Both of the results follow the same trend as found in experimental data (Yiu et al. (2022) report ratios of extrinsically to intrinsically correlated CA3 field pairs of 1.57 for both-best directions, 0.41 for both-worst directions, 0.87 for similar pairs and 2.43 for dissimilar pairs).

Thus, by introducing feedback excitation via the DG layer, intrinsic sequences are able to propagate in fixed directions on top of the movement-dependent extrinsic sequences. Theta sequence directionality is reflected through the change in spike correlation, which varies as a function of the difference between the direction of DG feedback and movement direction.

Lesion of DG reduces theta compression and phase precession range

One prediction of the DG-loop model, consistent with findings from DG lesion experiments (Ahmadi et al., 2022), is that DG would contribute to the temporal organization of spike sequences in CA3. To verify this hypothesis also in the model, we implemented a lesion of DG by disabling activity in the DG layer. To compensate for reduced excitatory drive caused by the lesion, we then increased probability of release of the sensory inputs thereby increasing the initial input amplitudes but removing short-term synaptic facilitation (**Figure 4A**).

We found that a DG lesion would reduce theta compression in sequence activity. Theta compression (Dragoi and Buzsáki, 2006) refers to the compression of seconds-long behavioural experience of place-field crossing into a neural representation of spike sequences at a shorter (theta) timescale. To quantify the strength of theta compression, we plotted the pair correlation lags versus the distance between the centers of two fields (abbreviated as “lags” and “pair distance” respectively), after simulating a rightward tra-jectory (**Figure 4B-C**). The magnitude of the linear-circular regression slope a measures how much theta phase encodes a certain interval in space, and therefore, the strength of theta compression. As a result, theta compression is reduced for the DG-lesioned case (a = 0.053 radians/cm for both θ_{DG} = 0° and θ_{DG} = 180°), as compared to the control case (a = 0.183 radians/cm for θ_{DG} = 0° and a = −0.059 radians/cm for θ_{DG} = 180°) reproducing the finding (Ahmadi et al., 2022) that spatial encoding via theta sequences crucially depends on intact DG and suggesting that the loss of DG inputs could be compensated for by the increase of release probability in the spared afferent synapses from the MEC. The DG lesion also reduces the spike phase and phase range of phase precession (**Figure 4D**), which indicates the participation of DG loops in high-phase spiking. Both weaker phase precession and theta compression stress the important role of DG in temporal organization of CA3 sequences.

Theta sequences in 2-d and out-of-field firing

So far, the model was only evaluated on bidirectional linear tracks, where running directions completely overlapped with the orientation of the DG loop connectivity. Now, we extend our analysis to 2-d space by examining oblique trajectories which cross the orientation of DG-loop projection at certain angles.

We first arrange the DG-loop connections such that the DG-loop orientation crosses a rightward trajectory at 45° and 225° (**Figure 5A-F**). Similar to the cases of θ_{DG} = 0° and θ_{DG} = 180° (**Figure 3D** and **3H**), precession slopes are steeper and onsets higher when the trajectory direction aligns more with the orientation of the DG-loop, but with a smaller effect size for oblique crossings (**Figure 5A** and **5C**) since DG-loop connectivity area only overlaps with part of the trajectory near the intersection. We further resolve the precession slope, onset and marginal phase for each place cell into 2-d maps (**Figure 5B** and **5D**). Intrinsic sequences with a higher marginal spike phase can be clearly seen along the belt of DG-loop projections and are even extended to the outside of trajectory predicting “off-track” spikes at high phases. Depending on the alignment

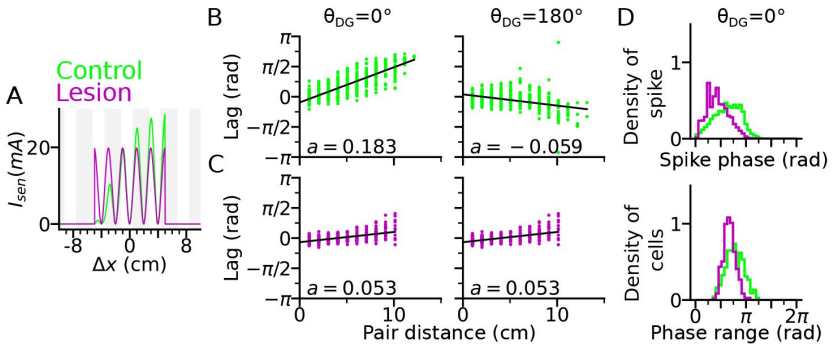

Figure 4.

DG lesion reduces theta compression and phase precession range. DG recurrence is turned off to simulate the lesion condition. (A) Positional sensory inputs into a place cell in lesion (purple) and control (green) cases. The control case is identical to **Fig 3**. In the lesion case, DG input is compensated by increased sensory input with increased probability of synaptic release, hence reduced short-term synaptic facilitation. (B) Theta compression, i.e., correlation between peak correlation lag and distance of field centers in the control case. Each dot represents a field pair. Linear-circular regression line is indicated in black. Note that the sign of regression slope (a in radians/cm) is determined by the directions of DG loop (negative in θ_{DG} = 180°). (C) same as B, but for the lesion case. Theta compression is reduced as compared to the control condition. (D) Top: Distribution of spike phase during phase precession in all active (spike count > 5) cells in control and lesion case. Bottom: Distribution of phase precession range for all active cells.

between movement direction and DG-loop orientation, the slope becomes either more negative (θ_{DG} = 45°) or more positive (θ_{DG} = 225°). Analysis of extrinsicity and intrinsicity was conducted for all field pairs and confirmed the same trend as in **Figure 3** that best and dissimilar pairs are more extrinsic than worst and similar pairs, respectively (**Figure 5E**). As a quantitative prediction, we computed the angle differences between field centers of cell pairs for the extrinsic and intrinsic populations, and observe that place field center differences in extrinsically correlated field pairs are mostly oriented horizontally (along the running direction) while place field center differences from intrinsically correlated field pairs are oriented along the DG-loop orientation θ_{DG} = 45°, as by design (**Fig 5F**).

The analysis above is repeated for the geometric configurations that DG-loop connectivity is minimally interacting with the place cell activity induced by movement, i.e., when DG-loop orientation and the movement direction are perpendicular to each other (θ_{DG} = 90° and θ_{DG} = 270°, **Figure 5G**). Similar effects as in **Figure 5B** and **5D** on precession slope, onset and marginal phases are also observed in the 2-d map, except that the effects are further restricted to the intersection area in the middle. Also, the whole population has become more extrinsic as compared to the 45° and 225° cases (**Figure 5H**, see the numbers for extrinsic-intrinsic ratios) due to the smaller overlapping area between DG-loop projection and the trajectory. Lastly, the pair center difference orientation confirms that field pairs with extrinsic correlations follow the trajectory direction while those with intrinsic correlation are biased towards the DG-loop orientations (90°).

The results demonstrate the distinct roles of extrinsic and intrinsic sequences in 2-d spatial encoding. The former represents trajectory direction while the latter the associative memory towards specific locations. They can be played out at the same time separately in different directions and only interact with each other when they overlap. The interaction is reflected in directional dependence of phase precession properties, most notably the higher spike phases from the DG-CA3 recurrent input, as well as increased intrinsicity of pair correlation and extended firing fields along the orientation of the DG-loop projections. Intrinsic sequences also triggered out-of-field firing (**Figure 5B, D, G**) at late theta phases. In this case, the DG-loop connects to cells with remote place fields. These cells could even display multiple separated place fields, with high spike phases indicating the target location of the intrinsic sequence.

Topology-free mechanisms of extrinsic phase precession

A well-known problem of phase precession models based on recurrent connectivity that applies to both, the original intrinsic Tsodyks et al. (1996) and Romani and Tsodyks (2015) model, is that they do not explain how the topological connectivity matrix (in our case W^{CA3}) is generated (Lisman and Redish, 2009; Jaramillo and Kempter, 2017). Extrinsic theta sequences in a first exposure to a novel environment should therefore be missing. Although Feng et al. (2015) find that theta sequences on a first exposure of a novel linear track are indeed much weaker (maybe only reflecting intrinsic sequences), their results nevertheless indicate a very fast learning time scale that is hard to reconcile with recurrent learning of a full spatial topology (particularly the generalization to 2-d). Also their result might be hampered by place field plasticity that dominates the decoder towards backward-shifted place maps of later trials (Parra-Barrero and Cheng, 2023). We there-fore explored, whether extrinsic 2-d sequences could also be generated by a model that is not relying on 2-d topology in the recurrent weights. To this end, we disabled the CA3 recurrence and compensated the missing level of excitation by an increased strength of the spatial input and the DG loops (see Methods for changes in model parameters). Our simulations show that extrinsic sequences can still be generated by spatial input alone (**Figure 6A**), relying only on the short-term facilitation mechanism. Simulating CA3 activity with lesioned DG similarly abolishes the temporal organization of theta sequence and reduces the phase range (**Figure 6B**). The results demonstrate that the temporal order of extrinsic sequences could be coordinated solely by sensorimotor drive and does not necessarily require CA3 recurrence.

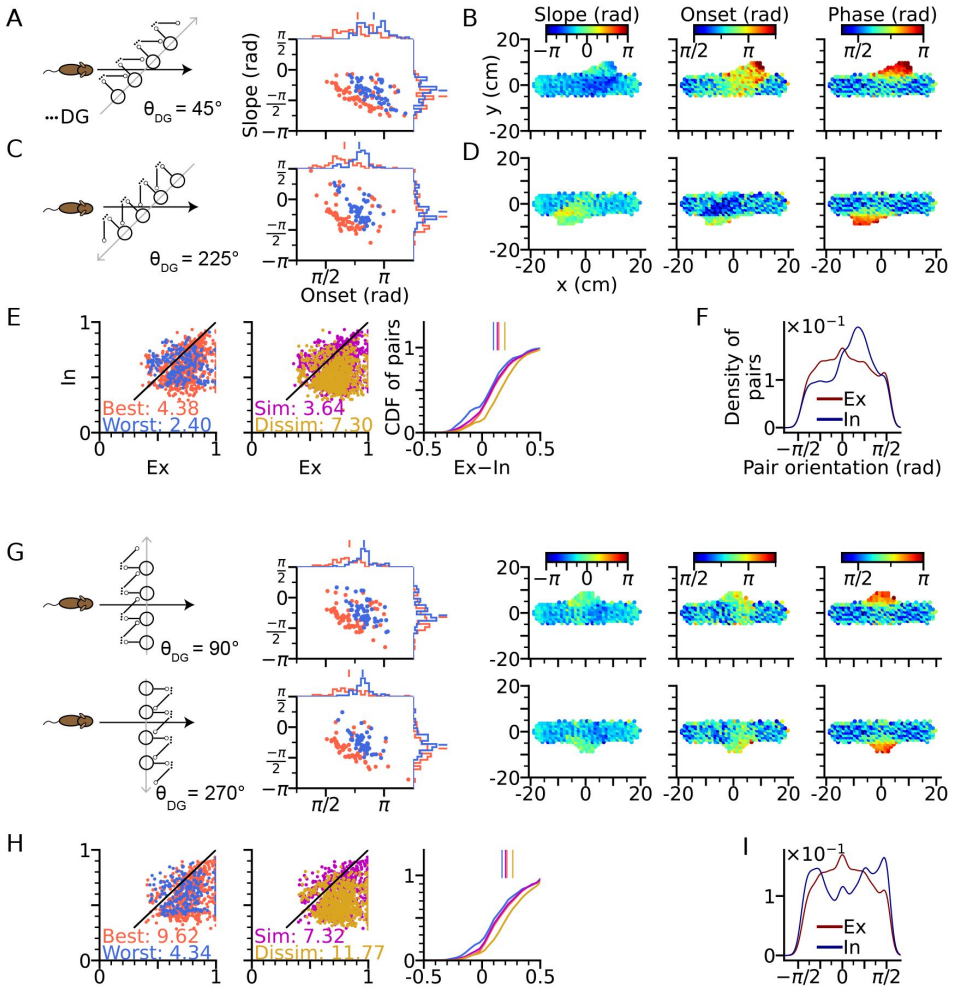

Figure 5.

Intrinsic sequences lead to direction dependent 2-d phase precession and out-of-field firing (A) Left: Schematic illustration of DG-loop projection being tilted by 45° relative to the trajectory. Right: Distributions of phase precession onsets and slopes from the place cells along the trajectory as in **Figure 2G**. (B) Slopes (left), onsets (middle) and mean spike phases (right) of phase precession from the place cells as a function of field center. High spike phases and onsets occur along the DG-loop orientation where intrinsic spiking dominates and yield out-of-field firing (see the extrusions from horizontal dot clouds) with late onsets and phases. (C-D) Same as A-B, but DG-loop projection is at 225° relative to trajectory direction. (D) For DG loops pointing opposite to the sensorimotor drive, prospective firing along the DG loop yields less steep precession slopes and lower onset. (E) Extrinsicity and intrinsicity of all place field pairs along the trajectory as in **Figure 3J**. Some pairs are totally extrinsic (Ex=1) because DG projection is absent at those parts of the trajectory. (F) Density of field pairs with extrinsic/intrinsic correlation as a function of the orientation of field center difference vector relative to the x axis. Intrinsic fields peak at 45°. (G) Same as A-D, but DG-loop orientations are perpendicular to the trajectory direction at 90° (top) and 270°. Prospective spikes from intrinsic sequences are initiated in the perpendicular directions. (H) Same as E, but with higher Ex-In ratios. (I) Field pairs with intrinsic correlations are at ±90°.

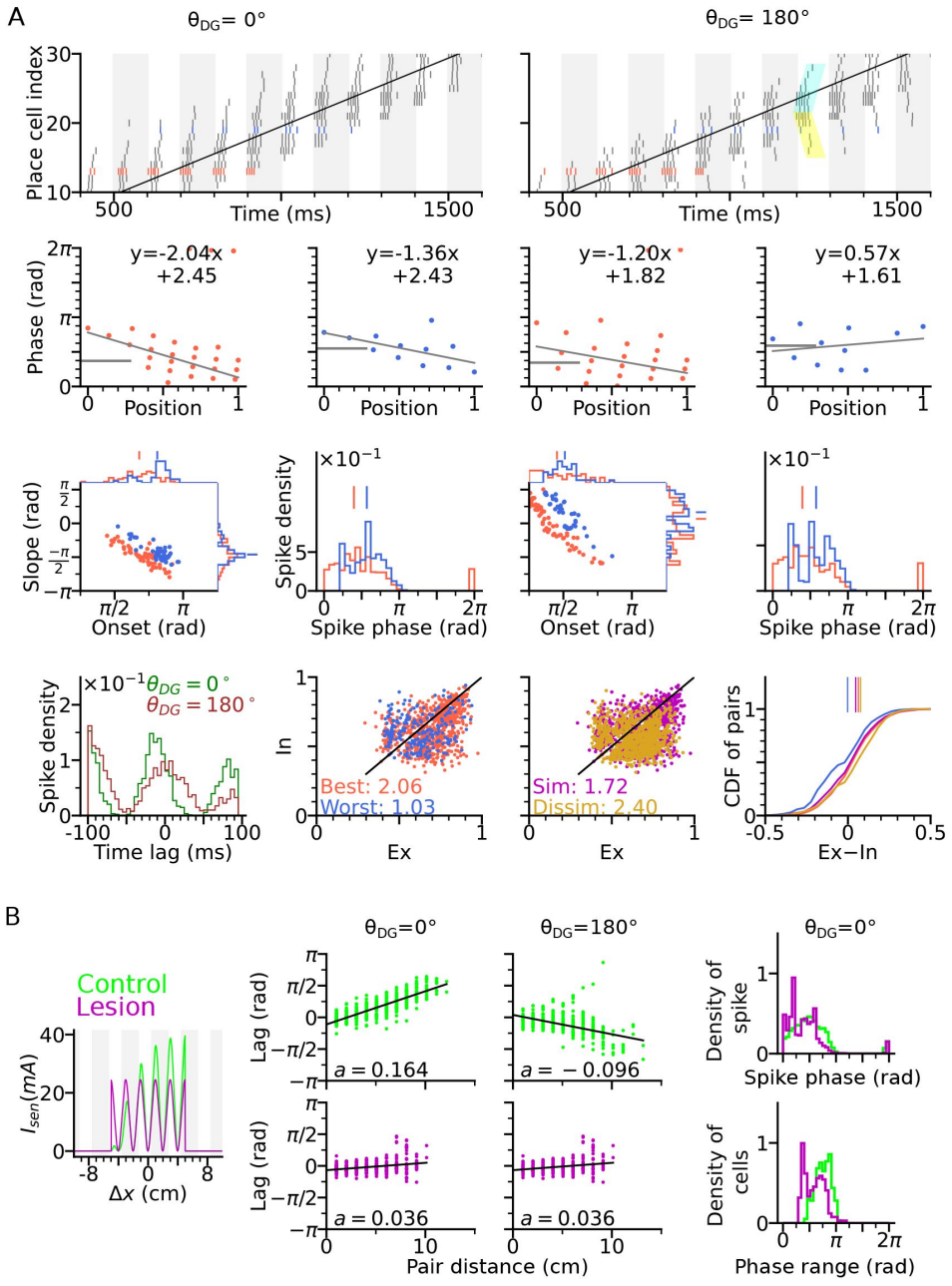

Figure 6.

Extrinsically driven theta correlations can be temporally organized by sensorimotor drive alone without CA3-CA3 recurrence. Simulations were performed without CA3-CA3 recurrence but with stronger spatial input. (A) Same as **Figure 3**. Extrinsically driven theta correlations and phase precession are still present. (B) Same as **Figure 4**. DG is still integral to the theta compression in a network model without CA3-CA3 recurrence.

Functional role of intrinsic sequences

While the function of extrinsic theta sequences in encoding the actual trajectory of an animal (connecting the recent past, present and near future locations) is obvious, the potential role of the less readily apparent intrinsic sequences is not straight forward. Simulations of trajectories in 2-d (**Figure 5**) suggest intrinsic activity may serve a role to identify certain location-direction pairs independent of the current trajectory. Here we follow this idea by evaluating the hypothesis that the intrinsic sequences signal a stable "landmark" (location/direction pair) cue by a temporal code that is invariant to different directions of approach.

To test our hypothesis, we constructed a downstream readout neuron that would reliably identify the presence of the intrinsic sequence independently of the animal's running direction, whereas it would not be able to do so for only extrinsic sequences. To this end, we trained the synaptic weights using the tempotron learning rule (Gütig and Sompolin-sky, 2006), which is able to implement binary classification based on temporal relations of input spike patterns (see Tempotron section in Methods). Two tempotrons were trained to recognize the spike patterns from the place cells, one taking input from a model with DG-loop connectivity at $\theta_{DG} = 0°$, and one without DG-loop connectivity to serve as a control only having access to extrinsic sequences (**Figure 7A**). Non-moving spatial inputs were applied to the CA3 place cells at the centers of with-loop and no-loop populations and their spike patterns in subsequent theta cycle were used as training patterns, mimicking a situation in which network activity is evoked without sensory-motor input as, e.g., in a offline situation before the animal walks or maybe even has seen the environment. The training patterns have only (+) labels, which the tempotrons are trained to recognize by firing a spike (**Figure 7B**). We then test the tempotrons with spike patterns induced by the animal running on different trajectories through the trained location with running directions varying between 0° to 360° (**Figure 7C**). All spikes in each training and testing pattern are individually jittered by adding a noise term $\sigma \sim N(0, 2ms^2)$ for 100 times, producing 100 samples for each pattern. The tempotron is said to successfully recognize the sequence of a trajectory direction if any of the theta cycles throughout the trajectory elicits a spike, i.e., while running, the readout cell would evaluate the place cell sequence in every theta cycle for information on the trained landmark.

We found that the tempotron trained on the intrinsic sequence from the DG loop is able to recognize the sequence patterns produced for all running directions, while the tempotron trained without a DG-loop fails to identify the extrinsic sequences most of the time (see accuracies in **Figure 7D**). The reason is that the spike patterns induced by intrinsic sequences remain similar to the training pattern despite being approached in other directions (see sequential contributions in **Figure 7E**), while spike patterns for the no-loop condition are different between training and testing (**Figure 7F**). The distinction is further illustrated in **Figure 8**, where 2-d maps of spike time gradients in one theta cycle are plotted with respect to running direction/training condition. Sequences always contain components that propagate along the projection direction of DG loop, while, without such a loop, they only propagate along the running direction. Moreover, during training, the no-loop condition evokes concentric waves, reflecting the 2-d topology of the recurrent weights. Similar results were also achieved without CA3-CA3 recurrence (Figure S1 and **Figure 8C**).

Our results show that intrinsic sequences can provide a stable correlation signal which allows reliable decoding of locations through temporal correlations. The intrinsic temporal code remains detectable even when mixed with extrinsic sequences.

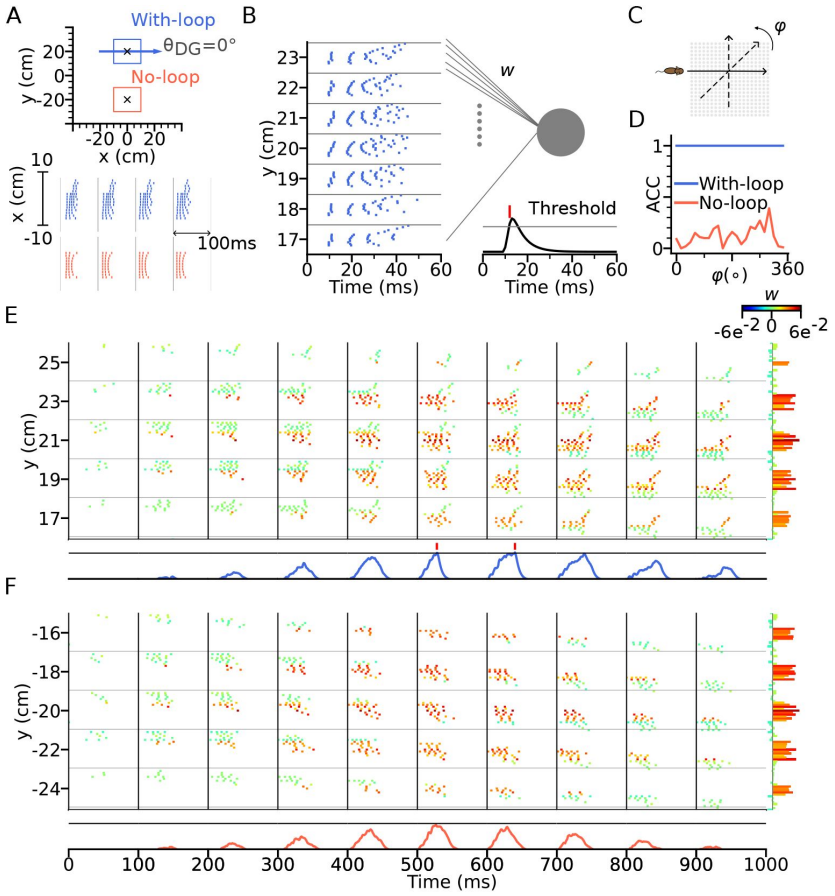

Figure 7.

Intrinsic sequences provide a stable landmark for positional decoding using a tempotron. (A) Top: Two tempotrons are trained for place cell populations within the top (with DG loop; blue) and bottom (no DG loop; red) squares, to recognize the presence of the corresponding sequence activities. DG-loop rightward projection is indicated by blue arrow and only exists in the blue square. Non-moving spatial inputs are applied to the CA3 network centered at the two locations (marked by black crosses) to evoke spike sequences for training. Bottom: Resulting spikes of the place cell network zoomed in to the subset of field centers from x=-10 to x=10 for y=+20 (with-loop, top raster plot) and y=-20 (no-loop, bottom). Each theta cycle is one (+) training pattern, which the tempotron is trained to detect by eliciting a spike. (B) Example training pattern with spikes of place cells from x=-10 to x=10 (in each rectangular row) fixed at different values of y. Only one theta cycle is shown. Each place cell delivers spikes to the dendrite of the tempotron, producing post-synaptic potentials (PSPs) at the soma (line plot at the bottom). Synaptic weights are adapted by the tempotron learning rule such that PSPs can cross the threshold (gray line) and fire for the detection of the sequence. After the tempotron has fired, the PSPs will be shunted. (C) Sequence detection is tested while the simulated animal ran on a trajectory with varying direction (φ) from 0° to 360° with a 15° increment to detect the presence of the sequence. (D) Detection accuracies (ACC) for with-loop (red line) and no-loop (blue) input populations. Note that the tempotron cannot detect the no-loop sequences when tested on trajectories at various angles. (E) Detection of the intrinsic sequence for a trajectory φ = 180° for the DG-loop condition. Spike raster is shown for every two horizontal rows of place cells in the arena and color-coded by the synaptic weights (see color bar on the right). Tempotron soma potential is shown at the bottom for each pattern. (F) Same as E, but for no-loop inputs. The tempotron remains silent.

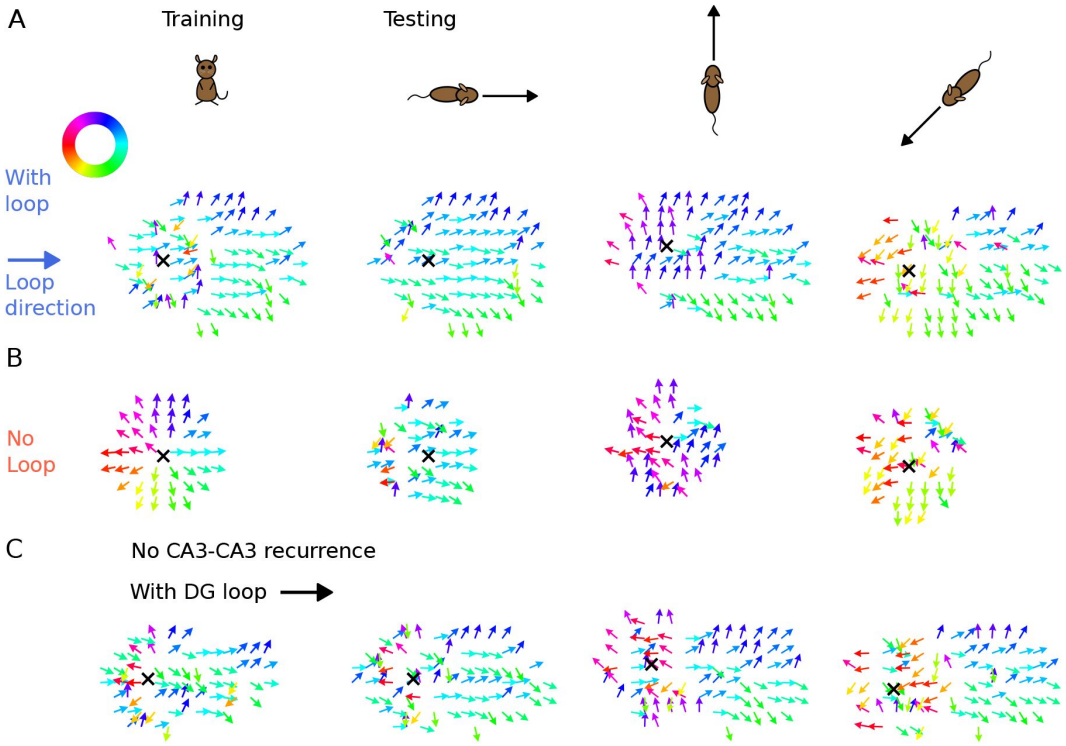

Figure 8.

Illustration of spike time gradients in one theta cycle (500-600ms) with and without DG loop. (A) Time gradients with a DG loop projecting to the rightward direction (θ_{DG} = 0°). Each arrow is located at a CA3 place field center. The arrow direction indicates the spike time gradient, equivalently the "travelling direction" of sequence activity, which is calculated as the sum of the directions to the 8 neighbouring field centers, weighted by the difference between their mean spike times in one theta cycle. Arrow direction is color-coded according to the color wheel. Black cross marks the instantaneous position of the animal. The first column shows the training condition when a non-moving spatial stimulus is applied. The three columns on the right show the testing condition when the rat is running in various directions. The sequence mostly propagates rightwards, following the DG-loop direction even when the animal runs in different directions. (B) Same as A without a DG loop. Sequences propagate outward from the animal position as a concentric travelling wave during training. During testing, spike time gradients follow the running direction. (C) Same as A, using the network model without CA3 recurrence. As in **Figure 6**, the extrinsic sequence is driven solely by the STF mechanism of the spatial input. Intrinsic sequences in this model still remain invariant to running directions and function as spatial landmarks.

4 Discussion

We presented a model of hippocampal theta sequences in 2-d environments, suggesting that both extrinsic and intrinsic mechanisms are required to explain experimental reports that phase precession and spike timing correlations are non-homogeneous across running directions. Although phase precession already becomes directional by including direction-dependent sensory input into a purely extrinsic model, directionality of spike timing correlations cannot be explained by such a model. We, however, demonstrated that the correlation preference could be implemented by fixed recurrent loops via a model DG layer. We further supported the model assumptions by showing that DG lesions plus compensatory sensory drive can abolish the theta compression effect in CA3 spiking activity (Ahmadi et al., 2022). By employing a spike-based temporal pattern decoder (tempotron), we showed that the intrinsic sequences could function as stable signatures that act as anchors of the spatial code.

Early intrinsic models (Tsodyks et al., 1996) were challenged owing to their inability to generate phase precession in backward travel (**Figure 1E**, also see Cei et al. (2014)), as well as the predominantly extrinsic correlations observed in CA1 (Huxter et al., 2008). In our hybrid model, phase precession still occurs during backward travel (θ_{DG} = 180°) but at a lower probability as indicated by the larger fraction of positive phase-position slopes (**Figure 3H**). Also, extrinsic sequences still dominate over intrinsic sequences as indicated by the majority of field pairs being extrinsic (**Figure 3J**). Both the reduced expression of phase precession in reverse runs and the dominance of extrinsic sequences are in accordance with the experimental data (Yiu et al., 2022).

The mixture of extrinsic and intrinsic mechanisms in our theory, naturally gives rise to the directionality of spike correlations and phase distributions. As the trajectory aligns itself with the DG loops, the ratio of intrinsic to extrinsic sequences increases. As a result, spike correlations become more rigid and the phase distribution is shifted upward due to the accumulated synaptic transmission delay from the reverberating activity between CA3 and DG populations. Adding directional sensory input activates extrinsic sequences in the best direction more strongly, and hence, leads to an association between best-angle (worst-angle) pairs and extrinsicity (intrinsicity). These predictions of our model are corroborated by past reports of higher spike phases in the non-preferred arm of a T-maze (Kay et al., 2020) as well as the association of rigid correlations with upward shifts in spike phases and an increase in worst-angle pairs (Yiu et al., 2022). The experimental distinction between extrinsic and intrinsic components in theta sequences has so far only been achieved in pairs of place cells, owing to the limited number of simultaneously recorded place cells with overlapping fields. Our model predicts that similar distinctions should also be observable in higher-order statistics, obtained from overlapping fields of a larger number of cells. Instead of correlation lags, we suggest to use temporal pattern detection methods (e.g. Chenani et al. (2019)) to unveil the respective sequence contributions.

Since intrinsic sequences can also propagate outside the trajectory (out-of-field firing in **Figure 5**) and activate place cells non-locally, our model predicts direction-dependent expansion of place fields, or even multiple place fields, with the intrinsic sequence's target location exhibiting late spike phases and higher phase precession onsets. Remote activation during locomotion has already been observed in a previous study (Sasaki et al., 2018) where CA3 place cells preferentially firing at one arm of the maze were also activated at reward locations at other arms. In our model, only short-range intrinsic connectivity was considered, thus, place field boundaries expand locally but in a skewed manner matching the sequence direction. Skewness of place fields has been reported by a number of studies (Mehta et al., 1997; Shen et al., 1997; Mehta et al., 2000; Ekstrom et al., 2001; Lee et al., 2004; Burke et al., 2008; Cei et al., 2014; Roth et al., 2012; Dong et al., 2021) showing place fields to be asymmetrically expanded opposite to the direction of travel. This effect was connected to plasticity as it develops after repeated traversal, and due to its dependence on NMDA receptor activation (Ekstrom et al., 2001; Burke et

al., 2008; Shen et al., 1997). These plasticity studies show that the hippocampal place code is shaped by intrinsic synaptic computations including temporal activation patterns in theta sequences (Feng et al., 2015). Apart from being conducted on linear tracks and not 2-d environments, most of this work focused on CA1 and associated Schaffer collateral plasticity. Yet some prior studies (Lee et al., 2004; Roth et al., 2012) did show that place fields in CA3 were more skewed than in CA1, which our model would explain by CA3 expressing more intrinsic sequences than CA1 consistent with prior experimental observations (Yiu et al. (2022) reported ratios of extrinsically to intrinsically driven cell pairs of 1.44 in CA1 and 1.23 in CA3).

A further prediction of hard-wired DG loops is that the resulting activity patterns (intrinsic sequences) should not remap under conditions of global or partial remapping (Leutgeb et al., 2004). Instead the same intrinsic sequence components should be observable in multiple environments, however, they might only be seen in a small fraction and thus this prediction is potentially hard to test.

The back-projection from CA3 to DG is a crucial anatomical prerequisite of our model, but was rarely explored compared to the feed-forward inputs via the perforant pathway. The proposed CA3-DG recurrent structure of this model, albeit simplified, is consistent with the anatomical evidence. Pyramidal cells in CA3 innervate the mossy cells at the DG hilus (Scharfman, 1994, 2016), which then project to granule cells through both excitatory and inhibitory pathways (Hsu et al., 2016; Scharfman, 1995; Larimer and Strowbridge, 2008; Soriano and Frotscher, 1994), and subsequently back to CA3 pyramidal cells. An optogenetic study (Hsu et al., 2016) showed that the net effect of mossy cells on granule cells was predominantly inhibitory, suggesting that the DG ensembles excited by mossy cell synaptic drive are sparsified by suppressing unwanted out-of-ensemble activity. Indeed, past studies showed that reliable excitatory effect could be observed when granule cells were depolarized (Scharfman, 1995) and when they received back-propagation of sharp wave bursts from CA3 population (Penttonen et al., 1998). This indicates that the excitatory recurrent pathway from CA3 via DG exists and might allow activity reverberation between two layers. While our model, owing to its simplicity and generality does not require any DG specific pathways and would work equally well with any other anatomical interpretation of the CA3 feedback, we hypothesize the intrinsic feedback connectivity to arise via the DG, particularly because DG lesions were shown to eliminate the coordinated temporal structure of CA3 activity and to be instrumental to sequence organization (**Figure 4** and Ahmadi et al. (2022)).

Our model assumed a connectivity pattern in the DG loops, in which neurons activate the neighbours along a specific direction, as inspired by Hebb's phase sequences (Hebb, 1949) and, hence, replay of the loop would activate a spatially plausible virtual trajectory. The loop connectivity could either arise from previous learning, or might be present already beforehand (Dragoi and Tonegawa, 2013), with spatial topology inherited by associating 2-d sensory features to cell ensembles in the loop (Leibold, 2020). The resulting topology can exhibit discontinuous long-range jumps to other locations (Sasaki et al., 2018) or consist of a discrete set of (behaviorally relevant) locations (Pfeiffer, 2022).

Different from other phase precession models, we also included heading direction as part of the sensory input, as inspired by past literature that CA1 (Markus et al., 1995; Acharya et al., 2016; Stefanini et al., 2020), CA3 (Mankin et al., 2019) and DG place cells (Stefanini et al., 2020) exhibit directional selectivity in firing rates, potentially inherited from the upstream head-direction cells in the medial entorhinal cortex (Giocomo et al., 2014) and postsubiculum (Taube et al., 1990). As a result, the directional drive immediately translates to phase directionality in theta sequences, partly contributing to the upward shift of the phase distribution in the worst angles. Such phase directionality arises naturally from the intracellular dynamics of a spike-based model, where stronger depolarization causes earlier spiking. This phase-rate dependence has already been used in previous models (Harris et al., 2002; Mehta et al., 2002; Thurley et al.,

2008), where the increasing depolarization within place fields directly relates to decreasing spike phases. The causal effect of firing rate on spike phases, however, was disputed by Huxter et al. (2003) as they showed that precession slopes and spike phases remained the same between high- and low-spiking runs, suggesting that the phase is not single-handedly determined by firing rate. In our model, firing rate is determined by both low-phase spiking from sensory input and high-phase spike arrivals of DG-CA3 loops, both producing opposing effects on the phase distribution. Thus, depending on the strength and geometry of the DG-CA3 connectivity, spike phases are not fully determined by firing rate.

By using a tempotron to decode the spike patterns, we show that the spike patterns of intrinsic sequences can serve as a stable landmark which remains decodable across multiple running directions. The invariant temporal patterns could serve as anchors of spatial memories in a novel environment, since place fields only stabilize after the animal becomes familiar with the environment (Wilson and McNaughton, 1993). The pre-existing sequence motifs, even at times when the spikes of the neurons are not spatially tuned to a location, can still encode the position based on their temporal relations alone. The idea has previously been spelled out (Cheng, 2013) and numerically verified (Leibold, 2020; Parra-Barrero and Cheng, 2023) with multiple fixed sequences that form a decodable spatial representation.

Intrinsic sequences may thus act as a scaffold around which a new spatial code can be built for new but similar behavioral contexts, where similarity could e.g. be identified by a salient feature. Once the behavioral context of a situation changes, new intrinsic sequences would be observable. These intrinsic landmarks need to be stable across time, as shown for some dentate gyrus representations (Hainmueller and Bartos, 2018). We speculate that offline sequences observed during replay and preplay (for review see Buhry et al., 2011; Dragoi and Tonegawa, 2014), would correspond to the intrinsic activity patterns and indicate the context expectation of an animal (which can be detected by a tempotron). The functional roles of intrinsic sequences may thus not be limited to spatial memories. While, in the spatial domain, intrinsic sequences could be interpreted as spatial trajectories (Kay et al., 2020; Sasaki et al., 2018), virtual non-spatial trajectories could represent working memories contents (Jensen et al., 1996) available for general decision making processes.

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References

Abbott L. F., Varela J. A., Sen K., Nelson S. B. (1997) **Synaptic Depression and Cortical Gain Control** *Science* **275**:221–224

Acharya L., Aghajan Z., Vuong C., Moore J., Mehta M. (2016) **Causal Influence of Visual Cues on Hippocampal Directional Selectivity** *Cell* **164**:197–207

Ahmadi S., Sasaki T., Sabariego M., Leibold C., Leutgeb S., Leutgeb J. K. (2022) **Distinct roles of dentate gyrus and medial entorhinal cortex inputs for phase precession and temporal correlations in the hippocampal ca3 area** *bioRxiv*

Berretta N., Jones R. (1996) **Tonic facilitation of glutamate release by presynaptic N-methyl-d-aspartate autoreceptors in the entorhinal cortex** *Neuroscience* **75**:339–344

Brunel N., Trullier O. (1998) **Plasticity of directional place fields in a model of rodent CA3** *Hippocampus* **8**:651–665

Buhry L., Azizi A. H., Cheng S. (2011) **Reactivation, replay, and preplay: how it might all fit together** *Neural Plast*

Burke S. N., Maurer A. P., Yang Z., Navratilova Z., Barnes C. A. (2008) **Glutamate receptor-mediated restoration of experience-dependent place field expansion plasticity in aged rats** *Behavioral Neuroscience* **122**:535–548

Cei A., Girardeau G., Drieu C., Kanbi K. E., Zugaro M. (2014) **Reversed theta sequences of hippocampal cell assemblies during backward travel** *Nature Neuroscience* **17**:719–724

Chenani A., Sabariego M., Schlesiger M. I., Leutgeb J. K., Leutgeb S., Leibold C. (2019) **Hippocampal CA1 replay becomes less prominent but more rigid without inputs from medial entorhinal cortex** *Nat Commun* **10**

Cheng S. (2013) **The CRISP theory of hippocampal function in episodic memory** *Front Neural Circuits* **7**

Dong C., Madar A. D., Sheffield M. E. J. (2021) **Distinct place cell dynamics in CA1 and CA3 encode experience in new environments** *Nature Communications* **12**

Dragoi G., Buzsáki G. (2006) **Temporal Encoding of Place Sequences by Hippocampal Cell Assemblies** *Neuron* **50**:145–157

Dragoi G., Tonegawa S. (2011) **Preplay of future place cell sequences by hippocampal cellular assemblies** *Nature* **469**:397–401

Dragoi G., Tonegawa S. (2013) **Distinct preplay of multiple novel spatial experiences in the rat** *Proceedings of the National Academy of Sciences* **110**:9100–9105

Dragoi G., Tonegawa S. (2014) **Selection of preconfigured cell assemblies for representation of novel spatial experiences** *Philos Trans R Soc Lond B Biol Sci* **369**

Ekstrom A., Meltzer J., McNaughton B., Barnes C. (2001) **NMDA Receptor Antagonism Blocks Experience-Dependent Expansion of Hippocampal "Place Fields"** *Neuron* **31**:631–638

Feng T., Silva D., Foster D. J. (2015) **Dissociation between the Experience-Dependent Development of Hippocampal Theta Sequences and Single-Trial Phase Precession** *Journal of Neuroscience* **35**:4890–4902

Foster D. J., Wilson M. A. (2007) **Hippocampal theta sequences** *Hippocampus* **17**:1093–1099

Giocomo L., Stensola T., Bonnevie T., Van Cauter T., Moser M.-B., Moser E. (2014) **Topography of Head Direction Cells in Medial Entorhinal Cortex** *Current Biology* **24**:252–262

Gütig R., Sompolinsky H. (2006) **The tempotron: a neuron that learns spike timing–based decisions** *Nature Neuroscience* **9**:420–428

Haga T., Fukai T. (2018) **Recurrent network model for learning goal-directed sequences through reverse replay** *eLife* **7**

Hainmueller T., Bartos M. (2018) **Parallel emergence of stable and dynamic memory engrams in the hippocampus** *Nature* **558**:292–296

Harris K. D., Henze D. A., Hirase H., Leinekugel X., Dragoi G., Czurkó A., Buzsaki G. (2002) **Spike train dynamics predicts theta-related phase precession in hippocampal pyramidal cells** *Nature* **417**:738–741

Harvey C. D., Collman F., Dombeck D. A., Tank D. W. (2009) **Intracellular dynamics of hippocampal place cells during virtual navigation** *Nature* **461**:941–946

Hebb D. O. (1949) **The organization of behavior: A neuropsychological theory**

Hsu T.-T., Lee C.-T., Tai M.-H., Lien C.-C. (2016) **Differential Recruitment of Dentate Gyrus Interneuron Types by Commissural Versus Perforant Pathways** *Cerebral Cortex* **26**:2715–2727

Huxter J., Burgess N., O'Keefe J. (2003) **Independent rate and temporal coding in hippocampal pyramidal cells** *Nature* **425**:828–832

Huxter J. R., Senior T. J., Allen K., Csicsvari J. (2008) **Theta phase–specific codes for two-dimensional position, trajectory and heading in the hippocampus** *Nature Neuroscience* **11**:587–594

Izhikevich E. (2003) **Simple model of spiking neurons** *IEEE Transactions on Neural Networks* **14**:1569–1572

Jaramillo J., Kempter R. (2017) **Phase precession: a neural code underlying episodic memory?** *Curr Opin Neurobiol* **43**:130–138

Jensen O., Idiart M. A., Lisman J. E. (1996) **Physiologically realistic formation of autoassociative memory in networks with theta/gamma oscillations: role of fast NMDA channels** *Learning & Memory* **3**:243–256

Kay K., Chung J. E., Sosa M., Schor J. S., Karlsson M. P., Larkin M. C., Liu D. F., Frank L. M. (2020) **Constant Sub-second Cycling between Representations of Possible Futures in the Hippocampus** *Cell* **180**:552–567

Larimer P., Strowbridge B. W. (2008) **Nonrandom Local Circuits in the Dentate Gyrus** *Journal of Neuroscience* **28**:12212–12223

Lee A. K., Wilson M. A. (2002) **Memory of sequential experience in the hippocampus during slow wave sleep** *Neuron* **36**:1183–1194

Lee I., Rao G., Knierim J. J. (2004) **A Double Dissociation between Hippocampal Subfields: Differential Time Course of CA3 and CA1 Place Cells for Processing Changed Environments** *Neuron* **42**:803–15

Leibold C. (2020) **A model for navigation in unknown environments based on a reservoir of hippocampal sequences** *Neural Networks* **124**:328–342

Leutgeb S., Leutgeb J. K., Treves A., Moser M. B., Moser E. I. (2004) **Distinct ensemble codes in hippocampal areas CA3 and CA1** *Science* **305**:1295–1298

Lisman J., Redish A. D. (2009) **Prediction, sequences and the hippocampus** *Philos Trans R Soc Lond B Biol Sci* **364**:1193–1201

Mankin E. A., Thurley K., Chenani A., Haas O. V., Debs L., Henke J., Galinato M., Leutgeb J. K., Leutgeb S., Leibold C. (2019) **The hippocampal code for space in Mongolian gerbils** *Hippocampus* **29**:787–801

Markram H., Wang Y., Tsodyks M. (1998) **Differential signaling via the same axon of neocortical pyramidal neurons** *Proceedings of the National Academy of Sciences* **95**:5323–5328

Markus E., Qin Y., Leonard B., Skaggs W., McNaughton B., Barnes C. (1995) **Interactions between location and task affect the spatial and directional firing of hippocampal neurons** *The Journal of Neuroscience* **15**:7079–7094

Maurer A. P., McNaughton B. L. (2007) **Network and intrinsic cellular mechanisms underlying theta phase precession of hippocampal neurons** *Trends Neurosci* **30**:325–333

Mehta M. R., Barnes C. A., McNaughton B. L. (1997) **Experience-dependent, asymmetric expansion of hippocampal place fields** *Proceedings of the National Academy of Sciences* **94**:8918–8921

Mehta M. R., Lee A. K., Wilson M. A. (2002) **Role of experience and oscillations in transforming a rate code into a temporal code** *Nature* **417**:741–746

Mehta M. R., Quirk M. C., Wilson M. A. (2000) **Experience-Dependent Asymmetric Shape of Hippocampal Receptive Fields** *Neuron* **25**:707–715

Mejías J. F., Torres J. J. (2008) **The role of synaptic facilitation in spike coincidence detection** *Journal of Computational Neuroscience* **24**:222–234

Mizuseki K., Sirota A., Pastalkova E., Buzsáki G. (2009) **Theta Oscillations Provide Temporal Windows for Local Circuit Computation in the Entorhinal-Hippocampal Loop** *Neuron* **64**:267–280

Parra-Barrero E., Cheng S. (2023) **Learning to predict future locations with internally generated theta sequences** *PLoS Comput Biol* **19**

Penttonen M., Kamondi A., Sik A., Acsády L., Buzsáki G. (1998) **Feed-forward and feed-back activation of the dentate gyrus in vivo during dentate spikes and sharp wave bursts** *Hippocampus* **7**:437–450

Pfeiffer B. E. (2022) **Spatial learning drives rapid goal representation in hippocampal ripples without place field accumulation or goal-oriented theta sequences** *The Journal of Neuroscience* **42**:3975–3988

Romani S., Tsodyks M. (2015) **Short-term plasticity based network model of place cells dynamics** *Hippocampus* **25**:94–105

Roth E. D., Yu X., Rao G., Knierim J. J. (2012) **Functional Differences in the Backward Shifts of CA1 and CA3 Place Fields in Novel and Familiar Environments** *PLoS ONE* **7**:1–10

Sasaki T., Piatti V. C., Hwaun E., Ahmadi S., Lisman J. E., Leutgeb S., Leutgeb J. K. (2018) **Dentate network activity is necessary for spatial working memory by supporting CA3 sharp-wave ripple generation and prospective firing of CA3 neurons** *Nature Neuroscience* **21**:258–269

Scharfman H. E. (1994) **Evidence from simultaneous intracellular recordings in rat hippocampal slices that area CA3 pyramidal cells innervate dentate hilar mossy cells** *Journal of Neurophysiology* **72**:2167–2180

Scharfman H. E. (1995) **Electrophysiological evidence that dentate hilar mossy cells are excitatory and innervate both granule cells and interneurons** *Journal of Neurophysiology* **74**:179–194

Scharfman H. E. (2016) **The enigmatic mossy cell of the dentate gyrus** *Nature Reviews Neuroscience* **17**:562–575

Shen J., Barnes C. A., McNaughton B. L., Skaggs W. E., Weaver K. L. (1997) **The Effect of Aging on Experience-Dependent Plasticity of Hippocampal Place Cells** *The Journal of Neuroscience* **17**:6769–6782

Skaggs W. E., McNaughton B. L. (1996) **Replay of Neuronal Firing Sequences in Rat Hippocampus During Sleep Following Spatial Experience** *Science* **271**:1870–1873

Skaggs W. E., McNaughton B. L., Wilson M. A., Barnes C. A. (1996) **Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences** *Hippocampus* **6**:149–172

Soriano E., Frotscher M. (1994) **Mossy cells of the rat fascia dentata are glutamateimmunoreactive** *Hippocampus* **4**:65–69

Stefanini F., Kushnir L., Jimenez J. C., Jennings J. H., Woods N. I., Stuber G. D., Kheirbek M. A., Hen R., Fusi S. (2020) **A Distributed Neural Code in the Dentate Gyrus and in CA1** *Neuron* **107**:703–716

Taube J., Muller R., Ranck J. (1990) **Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis** *The Journal of Neuroscience* **10**:420–435

Thurley K., Leibold C., Gundlfinger A., Schmitz D., Kempter R. (2008) **Phase Precession Through Synaptic Facilitation** *Neural Computation* **20**:1285–1324

Tsodyks M., Pawelzik K., Markram H. (1998) **Neural Networks with Dynamic Synapses** *Neural Computation* **10**:821–835

Tsodyks M. V., Markram H. (1997) **The Neural Code between Neocortical Pyramidal Neurons Depends on Neurotransmitter Release Probability** *Proceedings of the National Academy of Sciences of the United States of America* **94**:719–723

Tsodyks M. V., Skaggs W. E., Sejnowski T. J., McNaughton B. L. (1996) **Population dynamics and theta rhythm phase precession of hippocampal place cell firing: A spiking neuron model** *Hippocampus* **6**:271–280

Wilson M. A., McNaughton B. L. (1993) **Dynamics of the Hippocampal Ensemble Code for Space** *Science* **261**:1055–1058

Yiu Y.-H., Leutgeb J. K., Leibold C. (2022) **Directional Tuning of Phase Precession Properties in the Hippocampus** *The Journal of Neuroscience* **42**:2282–2297

Zucker R. S., Regehr W. G. (2002) **Short-Term Synaptic Plasticity** *Annual Review of Physiology* **64**:355–405

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Reviewer #1 (Public Review):

In the manuscript entitled "A theory of hippocampal theta correlations", the authors propose a new mechanism for phase precession and theta-time scale generation, as well as their interpretation in terms of navigation and neural coding. The authors propose the existence of extrinsic and intrinsic sequences during exploration, which may have complementary

functions. These two types of sequences depend on external input and network interactions, but differ on the extent to which they depend on movement direction. Moreover, the authors propose a novel interpretation for intrinsic sequences, namely to signal a landmark cue that is independent of direction of traversal. Finally, a readout neuron can be trained to distinguish extrinsic from intrinsic sequences.

The study puts forward novel computational ideas related to neural coding, partly based on previous work from the authors, including published (Leibold, 2020, Yiu et al., 2022) and unpublished (Ahmedi et al., 2022. bioRxiv) work. The manuscript will contribute to the understanding of the mechanisms behind phase precession, as well as to how we interpret hippocampal temporal coding for navigation and memory.

Reviewer #2 (Public Review):

Place cells fire sequentially during hippocampal theta oscillations, forming a spatial representation of behavioral experiences in a temporally-compressed manner. The firing sequences during theta cycles are widely considered as essential assemblies for learning, memory, and planning. Many theoretical studies have investigated the mechanism of hippocampal theta firing sequences; however, they are either entirely extrinsic or intrinsic. In other words, they attribute the theta sequences to external sensorimotor drives or focus exclusively on the inherent firing patterns facilitated by the recurrent network architectures. Both types of theories are inadequate for explaining the complexity of the phenomena, particularly considering the observations in a previous paper by the authors: theta sequences independent of animal movement trajectories may occur simultaneously with sensorimotor inputs (Yiu et al., 2022).

In this manuscript, the authors concentrate on the CA3 area of the hippocampus and develop a model that accounts for both mechanisms. Specifically, the model generates extrinsic sequences through the short-term facilitation of CA3 cell activities, and intrinsic sequences via recurrent projections from the dentate gyrus. The model demonstrates how the phase precession of place cells in theta sequences is modulated by running direction and the recurrent DG-CA3 network architecture. To evaluate the extent to which firing sequences are induced by sensorimotor inputs and recurrent network architecture, the authors use the Pearson correlation coefficient to measure the "intrinsicity" and "extrinsicity" of spike pairs in their simulations.

I find this research topic to be both important and interesting, and I appreciate the clarity of the paper. The idea of combining intrinsic and extrinsic mechanisms for theta sequences is novel, and the model effectively incorporates two crucial phenomena: phase precession and directionality of theta sequences. I particularly commend the authors' efforts to integrate previous theories into their model and conduct a systematic comparison. This is exactly what our community needs: not only the development of new models, but also understanding the critical relationships between different models.

Author Response

The following is the authors' response to the original reviews.

We would like to thank the Reviewers for their careful reading and the many thoughtful suggestions to improve our manuscript, as well as both the Editors and Reviewers for the generally positive evaluations and encouraging statements.

> *Editorial assessment:*

> *This important work presents an interesting perspective for the generation and interpretation of phase precession in the hippocampal formation. Through numerical simula- tions and comparison to experiments, the study provides solid evidence for the role of the DG-CA3 loop in generating theta-time scale correlations and sequences, which would be reinforced through the clarification of the concepts introduced in the study, in particular the notion of intrinsic and extrinsic sequences. This study will be of interest for the hippocampus and neural coding fields.*

We appreciate that our work has been considered important. In our revision we made a considerable effort to improve on the presentation of our results and the justification of our model assumptions. Particularly we aimed to clarify the meaning of intrinsic and extrinsic sequences by ad- ditional figure panels as well as fleshing out their definition via spike-timing correlations being independent or dependent on the direction of the running trajectory, respectively. To address all the requests, we added 3 new Fig- ures, multiple new Figure panels and simulated a new model variant.

Reviewer #1 in their public review assessed ”The manuscript has the potential to contribute to the way we interpret hippocampal temporal coding for navigation and memory.”

They criticized

> - *The findings generally relate to network models of phase precession (re- viewed in e.g., Maurer and McNaughton, 2007, Jaramillo and Kempter, 2017). An important drawback of these models with respect to explaining specific experimentally observed features of phase precession, is that they cannot straightforwardly explain phase precession upon first exposure onto a novel track. This is because, specific connectivity in network models may re- quire experience-dependent plasticity, which would not be possible upon first exposure. This is essential, given that the manuscript addresses the possible origin of phase precession in terms of network models and at minimum, this weakness should be discussed.*

We agree with Reviewer # 1 (and also with Reviewer # 2, who brought up a similar point) that models based on recurrence struggle to ex- plain how the recurrent connectivity matrix should come about. While we feel that a full model of how the 2-d topology in the recurrent weights can be learned goes far beyond the scope of this paper (and to our knowledge has not been solved so far in any existing model), we added a new model variant (new Figure 6 and Supplementary Figure 1), which explains the ba- sic phenomenology of extrinsic and intrinsic sequences without the need of recurrent connections, only using feed-forward synaptic facilitation. Thus, assuming recurrent connection is not necessary for our main findings. How- ever, we would like to point out that this does not exclude the possibility that recurrent connections, if set up in an appropriate way, also contribute to phase precession and theta sequences.

> - *An important and perhaps essential component of the manuscript, is the distinction between extrinsic and intrinsic models. However, the main con- cepts on which this hinges, namely extrinsic and intrinsic sequences (and the related extrinsicity and intrinsicity) could be better explained and illustrated. Along these lines, the result suggested by the title, namely, hippocampal theta correlations, may be important yet incidental in light of the new concepts (e.g., extrinsicity, intrinsicity) and computational models (e.g., DG-CA3 recurrent loop) that are put forward.*

We have added substantial new explanatory material to the figures, captions and text to more didactically introduce the concepts of in- trinsicity and extrinsicity. We have also completely rewritten the abstract and added a subtitle: ”extrinsic and intrinsic sequences”

> - *The study seems to put forward novel computational ideas related to neural coding. However, assessing novelty is challenging as this manuscript builds on previous work from the authors, including published (Leibold, 2020, Yiu et al., 2022) and unpublished (Ahmadi et al., 2022. bioRxiv) work. For example, the interpretation of intrinsic sequences in terms of landmarks had been introduced in Leibold, 2020.*

We agree with the reviewer that this paper touches on many related ideas from previous papers (not only of our lab) and is supposed to tie loose ends. Thus, the novel contribution is a biologically plausible mechanistic model of how intrinsic sequences and 2-d place maps interact on the level of interconnected spiking neurons. Such a level of explanation has not yet been available in previous work. We have considerably extended the Discussion section in our revision detailing the bigger picture underlying this theory. Also our addition of the non-recurrent model variant (see above) adds considerable novelty, since it provides an account of phase precession and preplay in novel environments.

> - *The significance of the readout tempotron neuron could be expanded on. In particular, there is room for interpretation of the output signal of that neuron (e.g., what is the significance of other neurons downstream? Why is the rationale for this output to being theta-modulated?)*

We have added an additional Figure 8 to better illustrate the inner workings of the tempotron. We also extended the discussion to better explain the potential use of the tempotron output (see above). In short, we consider the tempotron to signal a unique behaviorally important context that is independent of remapping induced by changes of sensory cues, which is a new prediction of the model. Since the context signal is resulting from DG loops it requires a stable code to also exits in the DG. Evidence for such long-term stability in DG has been found in Hainmuller & Bartos (2018).

Reviewer #2 in their public review find ”this research topic to be both important and interesting” and appreciates ”the clarity of the paper.”, com- mending our ”efforts to integrate previous theories into their model and con- duct a systematic comparison”.

We are very happy about these positive remarks and sincerely would like to thank the reviewer!

Reviewer #1 made the following specific recommendations for changes:

> *The abstract is somewhat difficult to parse. I have identified some words and/or sections that could be improved.*
>
> - *’....inherently 1 dimensional’. This statement seems to be related to an a priori interpretation of the authors. On the other hand, if offline sequences are trivially 1 dimensional because they are sequences (i.e., they constitute a vector), then online sequences would be 1-dimensional as well. What is the key difference between offline and online? Is it the omnidirectional place fields in two dimensions? Perhaps more importantly, how relevant is this fact with respect to the main results of the manuscript, which concern ex- trinsic and intrinsic sequences?*

We indeed meant that the sequences are trivially 1-dimensional. The main challenge that we would like to address in this paper is how a 2-d topology of place cells (and direction dependent theta sequences) and a 1-d sequence topology of intrinsic theta correlations and during (p)replay can be reconciled. We hope this has become clearer in the rewritten abstract.

> - *The language in lines 36-38 is overly technical. I suggest modifying the language, the language was less technical and more understandable in the body of the manuscript, which should be also reflected in the Abstract.*

We would would like to apologize for making the abstract too technical. Also in response to Reviewer #2, we decided to rewrite the ab- stract entirely.

> *The authors use a mixture of conductance based models and Izhikevich neurons, presumably for the spiking generating mechanism. The conductance component can be readily interpreted in terms of the underlying biophysics. The Izhikhevich neuron model, however, is phenomenological. I suggest you address i) the rationale for using Izhikevich model, 2) its biophysical inter- pretation, 3) and its combination with conductance-based currents.*

The reviewer is correct that spike generation is modelled using Izhikevich's model whereas synaptic integration is included in a conductance- based manner. As suggested by the reviewer, we have added further expla- nation in the Methods part, explaining that the Izhikevich approach allows to adjust burst firing properties with only few parameters by efficiently em- ulating the bifurcation structure of spike generation in the full biophysical model (1&2) and otherwise has no effect on the integration of conductance- based synaptic currents in a subthreshold regime (3).

> *Line 126: when you say preferred angle, do you mean preferred (heading) direction? If so, please maintain consistency throughout.*

We thank the reviewer for pointing out the inconsistency. We have added the word "heading" throughout the manuscript whenever ap- propriate. To further improve the consistency, we have clarified the meanings of "best" (or "worst") direction and reserved the use of it solely for cases when trajectory direction is compared with the preferred heading direction, namely, "best" ("worst") direction when trajectory is along (opposite) the preferred heading direction.

> *Line 174: When discussing cross-correlation, sometimes you mean a cross-correlation function between two place fields and sometimes to the his- togram of all such correlations? Please clarify.*

We used histograms to empirically estimate the underlying cross-correlation function. For clarity, we have specified that it is a cross- correlation histogram in the revised manuscript whenever we refer to the empirical estimate.

> *Figure 3:*
>
> *Understanding the difference between extrinsic and intrinsic sequences is fundamental for the manuscript. I suggest that in the section that refers to Figure 3 (or Figure 3 itself), you kindly provide an example depicting how extrinsic and intrinsic sequences can*
>
> *1. coexist yet be distinctly identified*

1. depend on trajectory

1. depend on DG input

By coexistence, we meant the heterogeneous population of ex- trinsic and intrinsic cell pairs and, hence, the extrinsic and intrinsic theta correlations, as shown in Figure 3J. To improve the clarity, we added the following sentence in the section that refers to Figure 3: "In our simula- tion, extrinsically and intrinsically driven cell pairs are both present in the population (Figure 3J), indicating a coexistence of extrinsic and intrinsic sequences.". To illustrate how extrinsic and intrinsic sequences depend on both tra- jectory and DG recurrence, we have also added annotations in Figure 3F to mark the extrinsic and intrinsic part of the sequence.

> *Moreover, the caption of Figure 3 refers to the directionality of the theta sequences. How does this again relate to the extrinsic/intrinsic distinction?*

We hope the highlighting in panel F of Figure 3 has resolved this problem.

> *Figure 5:*
>
> - *This is a crucial figure that should illustrate the differences between extrinsic and intrinsic sequences, as the figure caption suggests. Surprisingly, it is not at all clear where (i.e., in which panel) and how (i.e., methodologi- cally) should one distinguish one type of sequence from another. I suggest that at least one such panel is dedicated to illustrating the difference and/or detection of these sequences in time and/or from phase precession plots. Moreover, there is significant visual crowding that makes the interpretation challenging (e.g., insert a space between G and E)*

We would like to apologize that in the previous version of the manuscript, we seemed to have evoked the impression that the difference between intrinsic and extrinsic sequences should be mainly illustrated in Figure 5. We hope that our revisions of Figures 1 and 3 have made it sufficiently clear to this point. The main purpose of Figure 5 was (and is) to illustrate how intrinsic sequences can lead to out-of-field firing. We have modified the figure caption (and text) accordingly. To address the visual crowding problem in Figure 5, we have inserted a space between panels and also removed repeated labels.

> *Tempotron neuron and Figure 6:*

From the reviewer's questions on Figure 6, we feel that our presentation caused considerable confusion about the motivation and inter- pretation of the tempotron simulations. We therefore rewrote parts of the associated text and Figure caption. We hope that the revised presentation clarifies the issues. We therefore only briefly respond to the reviewer's points here, because we think they largely resulted from misunderstandings.

> - *Intuitively, and as the manuscript results suggest, late phases are asso- ciated to extrinsic mechanisms while early phases are associated to intrinsic. Why not construct a simpler classifier readout based on this fact? How does it compare to a tempotron?*

Opposite to the reviewer's comment, extrinsic mechanisms are visible at early phases (late in the field), intrinsic mechanisms at late phases (early in the field). In fact, what the tempotron

does is learning to identify the intrinsic (late phase) part and to disregard the extrinsic (early phase) part.

> - *What is the significance of theta-modulated output of the tempotron (readout) neuron?*

The theta modulation of the tempotron output is a trivial re- sult of the theta-modulation of the input, i.e., the detection of the intrinsic sequence pattern is done once every cycle.

> *Suggestion for Figure 6 related to Tempotron readout: Focus on 'with DG loop condition', as the challenge and most important point here is to identify extrinsic and intrinsic sequences. The No-loop condition could be left as a supplementary figure or side panel.*

The no-loop condition is the essential control showing that the tempotron only responds to the previously learned intrinsic pattern and can- not identify spatial location based on the extrinsic pattern.

> *Further work/predictions.*
>
> *Lines 196-198. "Since intrinsic sequences can also propagate outside the trajectory (Figure 5) and activate place cells non-locally, our model predicts direction-dependent expansion of place fields." If remote activation is 'suffi- ciently' remote, wouldn't this predict two separate place fields instead of an expansion?*

The reviewer is completely correct. Out of field spiking can be also affecting remote locations, if the intrinsic sequences link to remote place fields. This would lead to double fields, however, the intrinsic part would only be active at late theta phases. For simplicity, we have not added such a case in our paper, but we would like to thank the reviewer for this comment, since it leads to a nice prediction of the model, which can be experimentally tested and therefore was included to the discussion.

> *Lines 556-558. "In our model, firing rate is determined by both low-phase spiking from sensory input and high-phase spike arrivals of DG-CA3 loops, both producing opposing effects on the phase distribution." Is it possible to make a differential prediction based on lesions here, e.g., along the lines of reduced range phase precession, for either high phases or for low phases?*

We thank the reviewer for this great suggestion. Lesion of DG in the model does indeed reduce the phase range and mean spike phase. This further corroborates the effect of DG-loop on theta compression and high-phase spiking. We have included a new panel D in Figure 4 and a corresponding mention in the result section.

> *Line 570. "We speculate that the functional roles of intrinsic sequences may not be limited to spatial memories.". Is there any relationship to re- play and/or sleep-dependent memory consolidation? Some speculation in the Discussion section would be welcome and appropriate.*

We have added some further speculative ideas to the last section of the Discussion. We propose that replay and preplay reflects the intrinsic sequences that express the current expectation of the animal. We have not yet thought well enough about their relation to memory consolidation to phrase this in the manuscript, but would suggest that they could serve to signal multimodal context information to the neocortex where it can evoke retrieval of unimodal memory traces.

The description of the results, as stated in the public review, can be im- proved. A key component is the definition and identification of extrinsic and intrinsic sequences.

Some comments:

- *I think that the words 'extrinsic' and 'intrinsic' are problematic as both types of sequences/models rely on external (spatial) input, hence both are in some sense 'extrinsic'. On the other hand, both are network mechanisms, thus in some sense 'intrinsic', where the asymmetry is either programmed directly onto the weights or due to synaptic depression. To add to the con- fusion, 'intrinsic' mechanisms very often refer to cellular mechanisms in neurophysiology. I kindly ask you to, ideally, reconsider the terminology, or at the very least, be very thorough and precise when describing the mech- anisms. For example, sometimes extrinsic (intrinsic) 'models' are referred to, sometimes 'sequences', sometimes 'factors', sometimes 'pairs', etc.*

We understand and appreciate the reviewers argument, but would like to stick to the terminology, since it was already used in our prior publication. We have made considerable effort to improve the explanation and illustration of extrinsic vs. intrinsic pairs in the main text, Figure 1 and 3 to highlight our definition that is based on pair correlations: Extrin- sic pairs flip the correlation lag with reversal of running direction, intrinsic pairs don't. This is simply a functional definition and should not be con- fused with potential microscopic mechanisms. One of those (DG-loops) is suggested in our paper.

- *As discussed in the public review, network mechanisms may require experience-dependent plasticity and hence cannot easily explain phase pre- cession on the first pass. Please discuss why and/or how your model fits with this observation.*

We agree that the two models under consideration both require the recurrent network be set up appropriately and there is no theory so far that would explain how. The reason we chose these two models is because they are well known in the community and relatively similar. We reasoned that comparison between an intrinsic model and an extrinsic model would make most sense if the two are a similar as possible. Nevertheless, we ex- tended the manuscript by a new set of simulations in which we do not use re- current CA3 connections and obtain phase precession solely be feed-forward synaptic facilitation (new Figure 6 and supplementary Figure S1). The new simulations show that the basic phenomenology can also be obtained with- out using recurrent CA3 connections, however, as expected when removing one mechanisms of phase precession, the range of phase range is somewhat reduced as compared to the full model.

Along a similar vein, phase precession in Figure 1E only has a range of pi/2, which is about half of the typical range of phase precession for single runs. This should be characterized as a weakness of the intrinsic model.

The precession range in spiking models is highly sensitive to a large number of parameters such that it is hard to make such definite claims (see also above response). In the original Tsodyks et al. 1996 paper the phase range went up to 270 degrees with a slightly different implementation to ours in terms of current vs. conductance-based synapses, an exponen- tial instead of a Gaussian recurrent weight function, and 1-d (original) vs 2-d (ours). We chose conductance-based synapses, and a Gaussian weight profile for better comparison with the Romani and Tsodyks (2015) model. In the original non-spiking implementation by Romani and Tsodyks (2015), the phase range was hardly 70 degrees. Our model implementation of the

Romani and Tsodyks (2015) model fits the experimentally reported phase ranges of about 70 to 180 degrees in CA3 (Harris et al., 2001).

> *Lines 282-284: "...since phase precession properties change in relation to running directions, nor are they solely intrinsic since reversal of correlation is still observed in most of the sequences (Huxter et al., 2008; Yiu et al., 2022).". To which extent is this a consequence of the phase precession model (extrinsic vs intrinsic) or the fact that place fields are sometimes directional?*

The reversal of sequences with reversed running direction is how we define extrinsic correlation. We hope our changes in relation to Figure 1 has clarified this point.

> *Figure 2: Is it i) directional input or ii) short-term facilitation that gives rise to lower phase? (or perhaps both?) Please clarify.*

It's both. This is now clarified in the revised version of the Re- sults sections related to Figure 2: higher depolarization always yields earlier phases in spiking models, however, pair correlations are not affected by ei- ther of the two mechanisms.

> *Line 320. "...onset of phase precession". Do you mean in CA3/CA1/DG?*

Thank you for pointing this out. We have clarified that this statement refers to CA3.

> *Line 323. "....at a different location". Please add rationale why it has to be at a different location and a reference to the appropriate equation.*

The sequence rationale as well as the equation number have been added.

> *Line 384. " ... predicting that loss of DG inputs is compensated for by the increase of release probability in the spared afferent synapses from the MEC.". It wasn't clear whether this was a 'homeostasis prediction', or and implementation in the model. Please clarify.*

Since the model explained the experimental observations by implementing an increased probability of release, the model predicts that in animals with DG lesion the probability of release should be enhanced. We have modified the wording to avoid confusion.

> *Line 428 "...and near future locations) is obvious, the potential role of the lesser expressed intrinsic sequence contributions is not straightforward.". Similar to my comments above regarding terminology, please clarify what are both contributions and why are intrinsic sequences 'lesser expressed'.*

We have rewritten this passage to avoid unclear wording.

> *Line 474. "...we showed that the trajectory-independent sequences". Do you mean 'intrinsic sequences'?*

We thank the reviewer for careful reading! We have changed the wording "intrinsic sequences" in the revision.

> *Line 482. "...field pairs being extrinsic". Please clarify, as the usage of extrinsic now refers to field pairs.*

Thank you for pointing this out. We went through the whole manuscript and clarified the terms.

> *Line 245 (heading). Consider rewriting as 'Dependence of theta se- quences on heading directions'. Extrinsic and Intrinsic models have not yet been introduced.*

Since the main purpose of the first Results section is to explain the difference between extrinsic and intrinsic sequences we kept these terms in the heading but modified it to "Dependence of theta sequences on head- ing directions: Extrinsic and intrinsic sequences". Additionally, we have put more emphasis on introducing the terms "extrinsic" and "intrinsic" in this section.

> *Figure 1.*
>
> - *I suggest using the same font - C and D, and F and G are too close to each other, consider adding space. For example, the exponent, 10-2 makes reading cumbersome. Line 300. Phase tail means offset phase? Phase tail may be too informal. Line 325: DG loop. Do you mean CA3-DG projection?*

We thank the reviewer for the suggestions. In the revised manuscript, we have ensured that the same font is used in all of the fig- ures. To improve the readability of Figure 1, we have added space between panels as suggested, removed repeated axis label and downsized the text "10-2". Furthermore, we have rewritten the referenced line without using the word "tail", and also, clarified the meaning of DG loop as the short form of CA3-DG projection.

> *Figure 4 caption: "DG lesion reduces temporal correlations...". It is more precise to say that the lesion reduces the slope of the fitted lag vs dis- tance. And how is this related to sequence compression?*

In the paragraph referring to Figure 4, we have elaborated on the meaning of theta compression and its relation with the the lag-distance plot. However, we argue that "reduces the slope of the fitted curve" is not comprehensive enough to express our summarized conclusion in a caption title. We have modified the wording to be "DG lesion reduces theta compression".

In addition, we have changed the slope unit to be radians per cm rather than radians per maximum pair distance, in conformity to unit standards.

> *General comment about terminology with regards to tuning and connec- tivity: it is not formally correct to compare connectivity with trajectories (e.g., lines 388-395, caption of Figure 5A, etc). Perhaps compare tuning to particular directions/preference or receptive field?*

We have corrected the wording such that the direction of DG- loop projection is compared to the direction of trajectory.

> *Line 470. '...fixed recursive loop." Sentence is not clear, do you mean recurrent loops?*

The reviewer is correct. We corrected the wording

Reviewer #2 had the following recommendations.

> *M1. The abstract focuses on the differences between online and offline hippocampal replays. However, the replay topic is not touched upon in the rest of the manuscript. I*

> *found this very confusing when I first read the pa- per. I suggest the authors reconsider the best way to approach the opening or at least discuss if and how their model would incorporate replay phenomena.*

Also in response to reviewer #1 we have rewritten the abstract focusing on the problem of how to generate 2-d topology from 1-d sequences. In addition, also in response to Reviewer#1 we added a paragraph in the discussion detailing a hypothesis on how er think replay and intrinsic se- quences work together.

> *m2. On lines 89-91, the authors provide the selection of neuronal pa- rameters for excitatory pyramidal cells and inhibitory cells in the Izhikevich model. While the choice of model is reasonable, it would be helpful to clarify the source of these neuronal parameters, especially for readers who are not familiar with the model.*

Again, also in response to reviewer # 1, we have added more motivation for the Izhikevich model.

> *M3. On lines 94-98, the model considers a 2D sheet of CA3 neurons. One of the most significant assumptions is that each 2x2 tile of place cells is considered a unit with four directional angles. What is the basis for this assumption? Is there any experimental result supporting this, or is it a completely artificial design for the model? This is important since the or- ganization of CA3 cells also affects the network architecture discussed later and impacts the realism of the model.*

This comment is related to Reviewer #1's concern on experience- dependent plasticity: How is this connectivity pattern established? We fully agree that this is an open problem for the Tsodyks et al.-type networks. The main reason for choosing them (as argued in our response to reviewer #1) is to have two published models, representing one type of sequence each, that are similar enough for comparison. In addition, we added new simulations (new Figure 6 and Supplementary Figure S1), showing that the basic phe- nomenology can also be obtained in a model without recurrent connections (see also response to Reviewer # 1)

> *m4. Similarly, on lines 111 and 140, the model uses 500 ms for the timescales of short facilitation and short-term synaptic depression. The choices of these two timescales are vital for producing directionality in extrin- sic and intrinsic sequences, yet their experimental sources are not clarified.*

In the Methods section of the revised manuscript, we have in- cluded the sources of previous experimental data and modelling work to support our choice of the time constants.

> *M5. On line 126, the authors assume that the synaptic strengths be- tween CA3 cells, Wij, are given by the distances between neurons and the similarity between their directional preferences. While this assumption seems reasonable in the sensory cortex, I am unsure if this is also the case in the hippocampus, and the authors should clarify the basis for this assumption.*

The distance dependence simply reflects the original Romani and Tsodyks 2015 model (see response to M3) and we share the concern of the reviewers. The increased connectivity for neurons with the same di- rectional preference was necessary to recover the direction dependent phase precession properties (Figure 2) in the realm of the Romani and Tsodyks 2015 model. Please also see our new Figure 6 showing simulations without the recurrent matrix.

> *More importantly, the existing connections within CA3 and DG cells completely determine the "intrinsic" sequences. But wouldn't this be fragile when place cells undergo global remapping, which can take place within only a few seconds? The author should comment on this in the discussion.*

We would like to thank the reviewer for bringing up this inter- esting point. In our thinking, the DG-CA3 connectivity is fixed (multiple 1-d trajectories, not necessarily requiring 2-d topology), i.e., the same in- trinsic sequence should show up in multiple environments (and should not remap), although it may just not be active in some environments). This is a prediction of our model and we have added it to the Discussion.

> *M6. I found the setup of DG place cells unreasonable. DG place cells are found to be granule cells rather than pyramidal cells. Moreover, the model does not consider recurrent connections between DG cells (These setups are closer to CA1 place cells).*

We agree with the reviewer, DG granule cells should rather be modelled as high-input resistance EIF neurons. However, the feedback loop via the dentate is not a direct one. It involves hilar mossy cells plus multiple hierarchies of feedback inhibition (this is probably what the reviewer means with recurrent connections between DG neurons, because granule cells are not recurrently connected in the non-pathological state). To our knowledge a biologically realistic model of the hilar-DG network does not exist and it would be far beyond the scope of this paper to develop one. We therefore see our DG feedback model rather as phenomenological. The discussion paragraph on the anatomy of the dentate gyrus touches on these points.

> *Therefore, a significant concern is: Why should it be the DG feedback projection to CA3 responsible for the "intrinsic" sequences instead of pro- jections from other brain areas?*

The reviewer is generally correct, any brain structure which im- plements fixed sequences via a loop would do. The reason why we suggest the DG to be the best candidate is purely empirical referring to papers with dentate lesions: Sasaki et al. 2018 and Ahmadi et a. 2022. We have added a similar argument to the discussion.

> *m7. On line 166, the authors claim that there are no connections between inhibitory cells at all. While I understand that this is for simplification of the model, the lack of recurrent inhibition between interneurons may have limited the model's ability to produce gamma-band dynamics (referring to PING and ING mechanisms), which are robust rhythms produced in CA3. I am very curious if the model can incorporate theta-gamma coupling by in- troducing connections between CA3 inhibitory cells.*

We have omitted the gamma oscillation for simplicity, because we do not have a hypothesis for a functional role in the context of dis- tinguishing extrinsic from intrinsic sequences (Occam's razor) and, as the reviewer correctly anticipates, they unavoidably show up when inhibitory in- terneurons connect to each other (e.g. Thurley et al. 2013). Of course, one could envision situations in which gamma for intrinsic sequences my have different frequency than for extrinsic ones, by differentially manipulating the CA3 and DG basket cell networks, but, as long as there is no experimental data, it would be pure speculation and thus we have not included it in the model.

> *m8. The authors should clarify the source of parameters in Table 1, especially the synaptic strengths. These values are vital for extrinsic and intrinsic theta sequences.*

The weight values have been chosen to allow for large theta phase precession range, coexistence of extrinsic and intrinsic sequences, and stability of the network activity. A similar statement has been added to the manuscript.

> *M9. I have another concern regarding the measurements of "extrinsic- ity" and "intrinsicity" defined on lines 185-196. Are they the best measures? To distinguish the cause of spike correlations, the "extrinsicity" and "intrin- sicity" of a pair of spikes should not be high at the same time. However, this is clearly not the case in the model, according to Figs 3 and 5. Moreover, in the data analysis carried out later, spike pairs are considered extrinsic or intrinsic merely by comparing the two measurements. I suggest the authors consider counterfactual methods in causal inference. For example, would a spike pair (cell1, cell2) still exist if we change the sensorimotor inputs or the DG-CA3 projections? If this is difficult to implement, the authors should at least discuss how different choices of measurements would impact the con- clusions of the paper.*

The problem the reviewer has identified arises from the funda- mental symmetry of theta phase quantification: if spikes of a pair of place fields have a phase difference of 180◦ one cannot say which cell leads and which cell follows, hence, the phase difference is both intrinsic (because the peak doesn't flip) and extrinsic (because the peak flips and ends up at the same phase). The fact that in some cases extrinsicity as well as intrinsicity are high simply means that the field pair has a correlation peak lag close to 180◦. Since in the experimental data set in (Yiu et al. 2022) only field pairs were available, we have not been able to use a different quantification then and decided to apply the same quantification in our model for comparison. Moreover, Figure 5F nicely shows that the measures are able to retrieve the ground-truth intrinsic DG-loop structure when considered on the population level.

In our model, though, we can go beyond 2-nd order statistics and derive sequence similarity measures including multiple cells, e.g., Chenani et al. 2019. However, since, we already know the ground truth by construction, we decided to not use these methods. We added a paragraph in the discus- sion elaborating on beyond 2nd order sequence quantification.

> *m10. The authors begin discussing "intrinsic sequences" from line 316. However, it is not defined before that (and in the rest of the paper as well), causing confusion when reading the paper. The exact definitions of extrinsic and intrinsic sequences should come earlier.*

We hope that our changes to the beginning of the results section (Figure 1), also asked for by Reviewer # 1 could clarify the confusion.

> *m11. On lines 345-347, the authors claim that "the intrinsic sequences are played out backward as determined by the direction of fixed recurrence (Figure 3F)," which is vague. If such sequences are present in that panel, it should be more explicitly indicated graphically.*

Also in response to Reviewer #1, we have graphically high- lighted the two types of sequences.

> *M12. On lines 309, 356, 484, 495, 515, and possibly other instances, the authors repeatedly claim that the model simulations are in "quantitative agreement" with their previous experimental paper. However, no experimen- tal data or comparison with the simulations are presented in this paper. The authors should at least create one figure to demonstrate the degree of consistency between them, instead of merely asking the reader to refer back to their previous paper.*

We agree with the reviewer that the experimental data of our previous paper should be presented in the manuscript. However, creating more panels or figures is likely to clutter the already crowded visuals and ob- scure our main message. We therefore decided to give numerical comparisons the previous findings in the main text whenever appropriate, specifically, in the sections referring to Figures 2, 3 and in the Discussion.