Left-right-alternating theta sweeps in entorhinal-hippocampal maps of space. Vollan AZ, Gardner RJ, Moser MB, Moser EI. Nature. 2025 Mar; 639(8056):995-1005. Article

Re-interpretation based on the IPL mechanism

It is well-established that place cells—CA1 pyramidal neurons activated when an animal occupies specific spatial locations—generate somatic spike sequences at progressively earlier phases of the theta cycle, a 4–12 Hz extracellular potential rhythm, as the animal moves through their place fields. This results in a temporally compressed sequence of place cell activity thought to encode the animal's trajectory (Skaggs et al., 1996; Dragoi & Buzsáki, 2006; Foster & Wilson, 2007). The present study (Vollan et al., 2025) shows that ensembles of place cells generate a positional signal that extends linearly outward from the animal's location into the surrounding space—a phenomenon referred to as theta sweeps.

Research on place cells predominantly emphasizes motor actions, despite the brain generating a first-person perspective that informs the animal of its spatial location. Therefore, the underlying mechanism must account for both motor behavior and the emergence of first-person spatial experience. Current approaches to studying the nervous system rely exclusively on the animal's movement, limiting interpretations to observable behavior and leaving the first-person dimension unexamined. Additionally, although only a small subset of possible input signals can elicit neuronal firing—input degeneracy—existing analyses are restricted to the resolution of neuronal firing itself. This raises the question: "If we investigate the level of input terminals (dendritic spines or postsynaptic terminals), can we uncover the operational mechanism that generate both motor actions and first-person properties?"

The semblance hypothesis (Vadakkan, 2007, Vadakkan, 2013) posits that inter-postsynaptic functional LINKs (IPLs) formed between dendritic spines of CA1 pyramidal neurons generate an inner sensation (semblance) of space, thereby contributing to first-person positional awareness as well as the additional potentials necessary for motor activity. This framework raises critical questions: What mechanisms drive an animal's progression along a trajectory? And how do ensembles of place cells generate the positional signal known as theta sweeps, which extend linearly from the animal's current location into the surrounding environment?

Based on the semblance hypothesis, dynamic semblances at inter-LINKed spines give rise to the subjective experience of movement. Firing of a place cell is a threshold event: a CA1 neuron activates when it receives sufficient input signals from (a) direct synaptic signals from CA3 neurons, and (b) IPL-mediated inputs from interconnected spines. Theta oscillations emerge as a vector sum of two components: (a) vertical (synaptic) inputs from CA3→CA1 transmissions, enhanced by recurrent collaterals in CA3, and (b) horizontal (IPL-mediated) inputs that laterally propagate across spines. The phase and amplitude of the theta rhythm reflect the interplay between these two input streams, shaping the sequences of place cell activity.

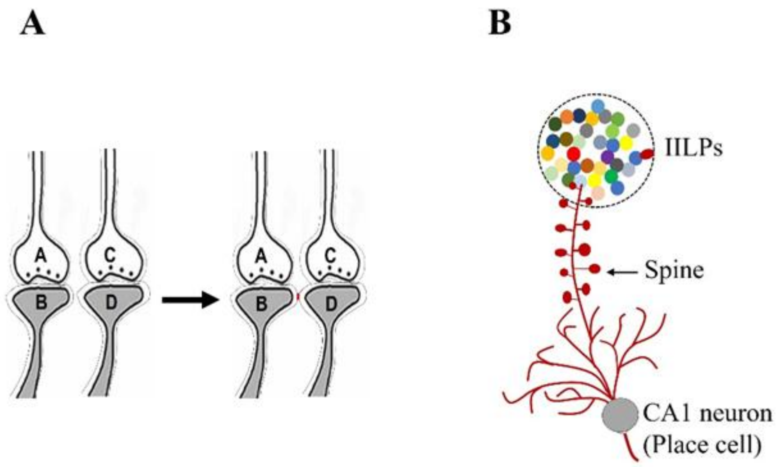

Figure 1. Illustrations of inter-postsynaptic functional LINK (IPL) and a group of interconnected IPLs. A) During associative learning, an IPL (highlighted in red) forms between spines (postsynaptic terminals) B and D, which are located on different dendritic branches—typically from different neurons, and only rarely from the same neuron. **B**) A single CA1 pyramidal neuron (place cell) is drawn, showing a dendrite with spines along its length. Note that the average distance between spines exceeds the average spine diameter (Konur et al., 2003), allowing interactions between spines on separate dendritic branches—most

often from different neurons—which facilitates the formation of IPLs. When one spine involved in an IPL forms an additional IPL with another spine, and this process continues across multiple related associative learning events, a cluster of inter-LINKed spines emerges. This cluster is referred to as an *islet of inter-LINKed spines* (IILPs). Note that the differently coloured circles within the IILPs represent spines belonging to different neurons.

How the semblance framework explains outward-sweeping position signals

Movement triggers sequential reactivations of inter-postsynaptic functional LINKs (IPLs). As the animal moves, sensory inputs activate CA3→CA1 synapses, leading to IPL reactivations between the spines of different CA1 neurons. These reactivations contribute vector components to theta oscillations. Since the dendritic arbours of CA1 neurons overlap extensively, IPLs can form between non-adjacent CA1 neurons spaced up to nearly the twice the width of dendritic arbour of a CA1 neuron. Depolarization is expected to propagate across different IPLs within an IILPs providing potentials to different inter-LINKed spines. Due to input degeneracy (Vadakkan, 2019), a neuron's firing is not constrained by the exact location of the spine on which final input required to reach threshold. Depolarization from distant inter-LINKed spines can bring remote CA1 neurons to threshold. As a result, IPL reactivations pre-activate specific CA1 neurons ahead or lateral to the exact location where the animal is. If CA1 neurons ahead of the present location fires, then we interpret it as "representing future positions, producing a predictive "sweep" of place cell activity ahead of the animal".

The above dendritic arbour-determined, IILPs-mediated, semblance-augmented operation thus provides: (a) the first-person spatial experience of a location, (b) an explanation for theta sweeps, (c) a reason why IPLs between spines of distant CA1 neurons pre-activate those neurons, generating predictive firing sequences beyond immediate sensory input, and (d) an account of how place cell ensembles produce a position signal that sweeps linearly outward—i.e., theta sweeps—from the animal’s current location into the surrounding space.

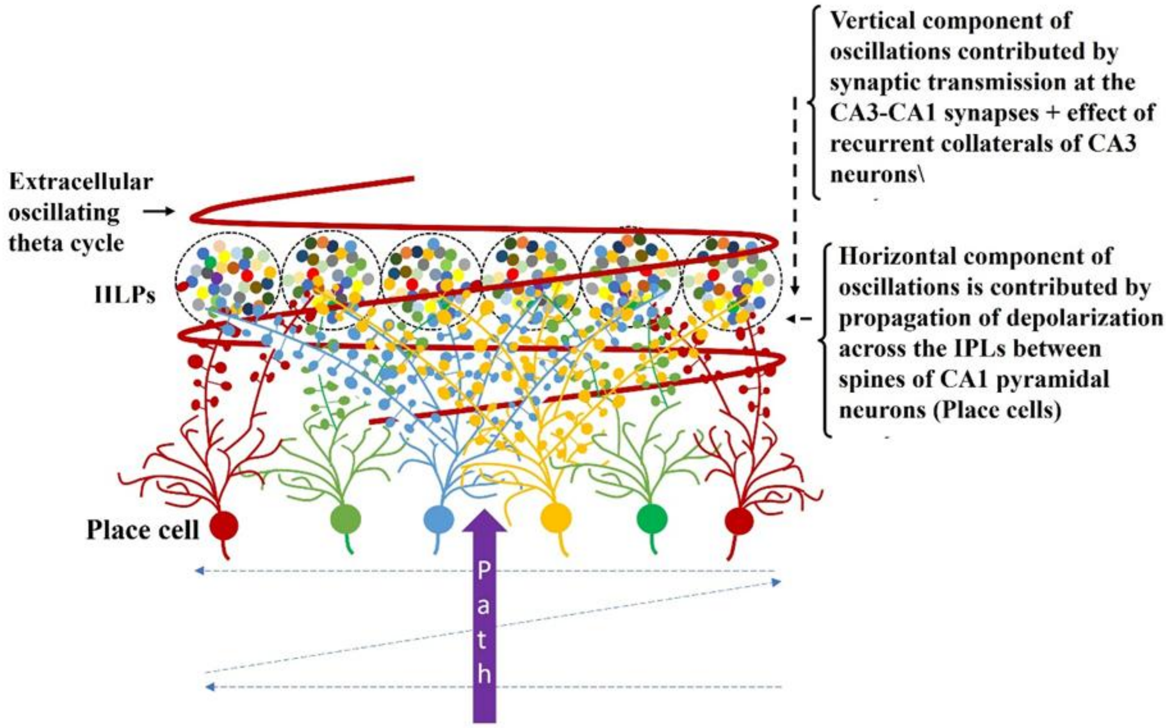

Figure 2. Relations between animal’s path, pyramidal neurons, IILPs, and theta cycle. Note that the 3-D relations between them is drawn in 2-D. For simplicity, to include more information into the figure (see **Fig.3**), instead of drawing in x-y plane from left to right, theta cycle is drawn into the z axis. The theta cycle (red waveform) occurs along with a temporally compressed sequence of CA1 pyramidal neuron firing, believed to encode the animal’s trajectory. At a specific point along the path, place cell ensembles generate a position signal that sweeps linearly outward—referred to as theta sweeps (indicated by zig-zagged dotted arrows perpendicular to the animal’s path)—from the animal’s current location into the surrounding environment. The dendritic arbour of each CA1 pyramidal neuron extends laterally and overlaps with the arbours of even distant CA1 neurons, allowing for the formation of IPLs. Consequently, although the animal progresses forward along a path, CA1 neurons representing off-path locations are also activated, as reported in the present study (Vollan et al., 2025). For clarity, horizontal and vertical components are illustrated in the x and y

directions. This diagram should be interpreted by considering the angle between the animal's forward movement and the direction of recording of the extracellular potential oscillations using differential electrodes. Regardless of this angulation, the horizontal and vertical components of the oscillations will be contributed by IPLs located in the 3D space, since CA1 dendritic arbours extend in all directions.

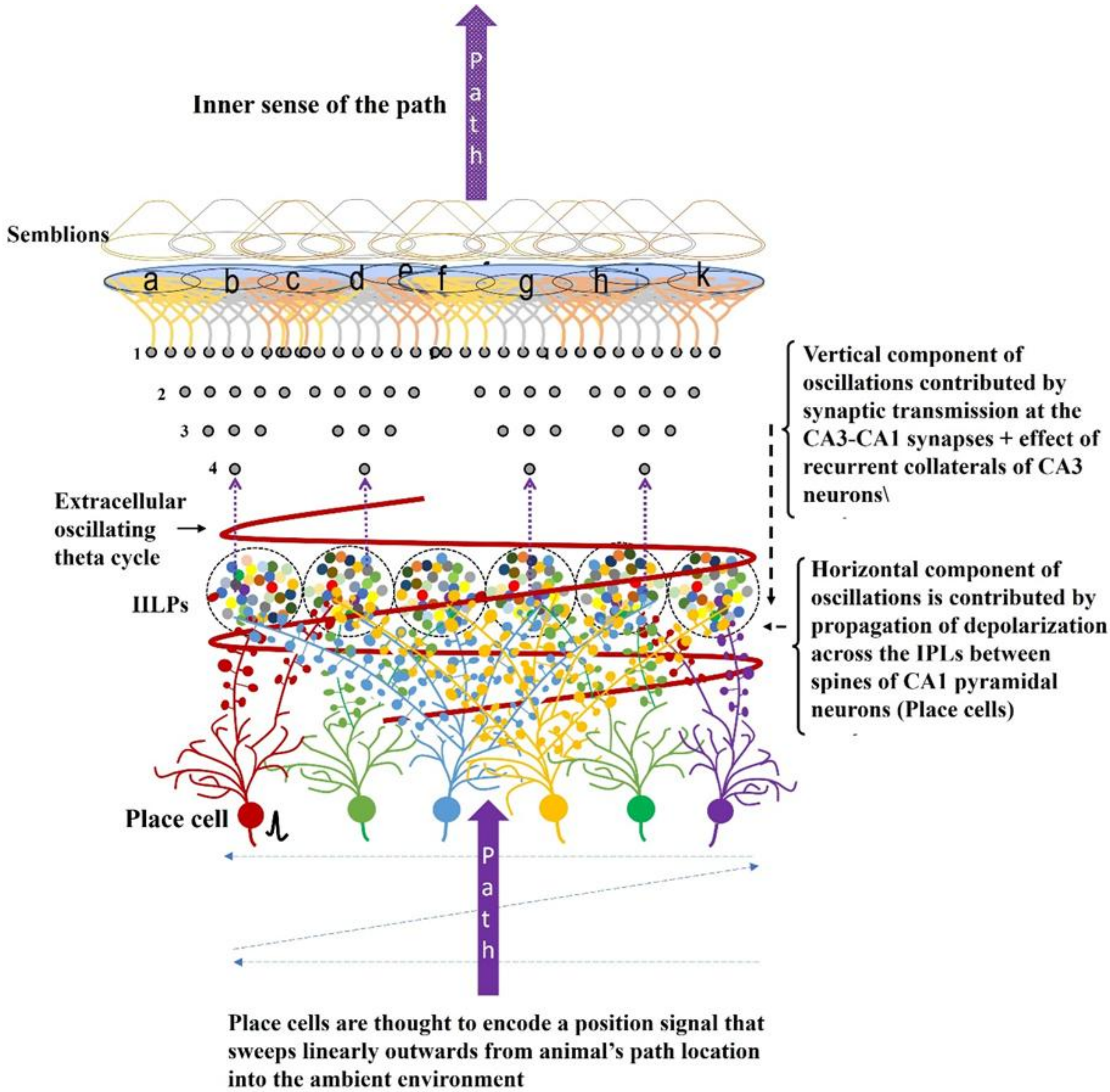

Figure 3. This figure illustrates how an animal moves along a path and generates an internal sense of its motion while left–right-alternating theta sweeps occur. This is a modification of **Fig.2** to show first-person units (semblions) (Vadakkan, 2013) generated on four inter-LINKed spines within four islets of inter-LINKed spines (IILPs). It is important to visualize the dendritic arbour as existing in 3-D space. Imagine the left-most CA1 pyramidal neuron (shown in red) fires as the animal moves

forward. This occurs because only this CA1 neuron receives sufficient potentials via IPLs to reach the firing threshold. Even when only the left-most CA1 neuron (in red) fires (this is due to the limitations of recording), multiple IPLs—whose spines are not directly connected to the dendrites of the red CA1 neuron—get reactivated and contribute vector components to generate the theta wave. The inner sense of the path is determined by the net semblance generated at the four IPLs shown in the figure. The potentials reaching the corresponding inter-LINKed spines will lead to firing of CA1 neurons (not shown in this 2-D plane) and eventually direct the animal's movement along the path. Numbers 1 to 4 represent the neuronal orders from the sensory receptor region. Letters a to k denote the minimal sensory receptor sets capable of depolarizing the inter-LINKed spines, a necessary step in retrograde extrapolation for estimating the qualia of units of inner sensations (Vadakkan, 2013). Note that the CA1 neurons in blue and yellow are shown with dendrites extending into most of the IILPs. IPL between spines of two distant CA1 neurons can occur within an IILPs and is determined by the dendritic arbour length and breadth. Hence, there will not be an exact spatial correlation between CA1 neuron that fires, locations on the phases of theta waves, and inner sense of space.

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