The illusion of sharp-wave sequence replay

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Abstract

Alternate title The anisotropic structure of hippocampal SPW sequences

One-sentence summary Sharp wave sequences correlate only positively with each other despite replaying running sequences forward and backward.

Evidence against bidirectional sharp-wave replay.

Abstract Hippocampal sharp-wave (SPW) sequences are believed to contribute to the encoding of episodic memories by "replaying" experience on a faster timescale. This belief stems from the observation that some SPW sequences correlate significantly with templates generated from an animal's running experience. As these correlations are both positive and negative, it is believed that SPW sequences replay experience bidirectionally. We compared SPW sequences directly without the use of running templates. Surprisingly, correlations between SPW sequences were significantly positive, with negative correlations occurring at chance level. This suggests that SPW sequences are not activated bidirectionally. Further, this observation held regardless of how SPW sequences correlated with running sequences, suggesting that SPW sequences do not replay experience as previously believed.

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1 Introduction

The hippocampus is a brain region necessary for episodic memory (Scoville 1996; Morris et al. 1982). Sequential firing patterns of hippocampal neurons are believed to serve as the physiological substrate of episodic memory (Eichenbaum 2014; Buzsáki 2015). Specifically, when an animal moves through space, position-selective neurons called *place cells* (O'Keefe and Nadel 1978) are activated sequentially, forming so-called *place-cell firing sequences* (Fig. 1A). Similarly, when an animal runs on a running wheel during a memory task, neurons called *episode cells* (Pastalkova et al. 2008) are activated sequentially, forming so-called *episode-cell firing sequences*. Both of these types of running sequences evolve over the timescale of seconds.

Another type of sequential firing is observed during brief bursts (Fig. 1B, C) of hippocampal network activity called *sharp waves* (SPWs), which occur throughout stationary behaviors such as eating, grooming, and drinking (Buzsáki et al. 1983; Buzsaki et al. 1992). SPWs are characterized by a distinct change of the

local-field potential (LFP) across the pyramidal layer of CA1 in the hippocampus induced by synchronized CA3 input (Fig. 1B, C top; (Buzsáki et al. 1983; Buzsáki 1986; Sullivan et al. 2011)). The accompanying *SPW sequences* are usually brief (50–150 ms; (Nguyen 2009)) but often consist of spikes from a large number of neurons (Buzsáki 1986). Interestingly, during some SPWs, place/episode cells fire in an order similar to that in which they fired while the animal was running in a maze or wheel (Fig. 1B, C bottom). This phenomenon is referred to as *replay* of running sequences during SPWs (Foster and Wilson 2006; Jackson et al. 2006; O'Neill et al. 2006). It has been suggested that the role of SPW sequences is to aid in the storage of running experiences in memory (Pavlides and Winson 1989; Eschenko et al. 2008; Girardeau et al. 2009; Karlsson and Frank 2009; Singer and Frank 2009; Dupret et al. 2010; Ego-Stengel and Wilson 2009; Jadhav et al. 2012; Girardeau et al. 2014) by reactivating the running experience of an animal on a faster time scale and, thus, inducing experience-dependent changes in synaptic plasticity within the local and downstream networks (Buzsáki 1989; O'Neill et al. 2008; O'Neill et al. 2010; Carr et al. 2011; Atherton et al. 2015; Buzsáki 2015). Interestingly, replay during SPWs has been observed (Foster and Wilson 2006; Diba and Buzsáki 2007) in both the forward and backward directions relative to the original running sequence (Fig. 1D, red and blue arrow). This observation led to belief that SPW sequences can be activated bidirectionally (i.e. forward and backward). However, the bidirectionally of SPW sequence activation was never confirmed directly (Fig. 1D, black arrow).

Prior methods for the analysis of SPW sequences have relied on averaging spiking information from entire recordings to obtain a place/episode-cell sequence template/model (Wilson and McNaughton 1994; Nádasdy et al. 1999; Foster and Wilson 2006; Jackson et al. 2006; Diba and Buzsáki 2007; Davidson et al. 2009; Pfeiffer and Foster 2013; Dragoi and Tonegawa 2010; Grosmark and Buzsaki 2016). We developed a novel method that enabled us to compare pairs of raw spiking sequences without the use of averaging across sets of sequences. Using this method, we tested the hypothesis that SPW sequences are bidirectional by inspecting correlation values between SPW sequences. Surprisingly, we found that negative correlations occurred only at the chance level and that positive correlations occurred well-above the chance level regardless of whether the SPW sequences were significantly correlated to the running sequences. Further inspection of the lack of negative correlations among SPW sequences suggests that SPW sequences may not be bidirectional as previously thought (Diba and Buzsáki 2007; Buzsáki 2015). This raises a question of the validity of the inference of backward replay from the observation of negative correlations between running sequences and SPW sequences. If SPW sequences are indeed not bidirectional, then the observation and interpretation of backward replay must be reevaluated. Similarly, if this anisotropic characteristic of SPW sequences holds true, evaluation of SPW sequences relative to an external template may lead to misleading results. Moreover, the prevalence of positive correlations between pairs of SPW sequences regardless of how the SPW sequences were correlated with running sequences suggests that the characterization of SPW sequences as "forward replay" or "backward replay" may not be the most useful. This may suggest that behavioral experience does not have so direct of a causal effect on SPW sequence generation as was previously proposed.

2 Results

It is widely believed that SPW sequences replay running sequences in both forward and backward directions (Foster and Wilson 2006; Diba and Buzsáki 2007). If this bidirectional replay indeed exists, then the forward-replay sequences should be anticorrelated with the backward-replay sequences. To search for evidence of such bidirectionality we used data that were previously described in (Wang et al. 2015). Specifically, we used spike-sorted LFP data recorded from rat CA1 during a delayed alternation task. In addition to using the previously described analysis of place and episode cells, we detected hippocampal sharp-waves (SFig. 1.) and neuronal firing sequences associated with sharp waves (see Methods).

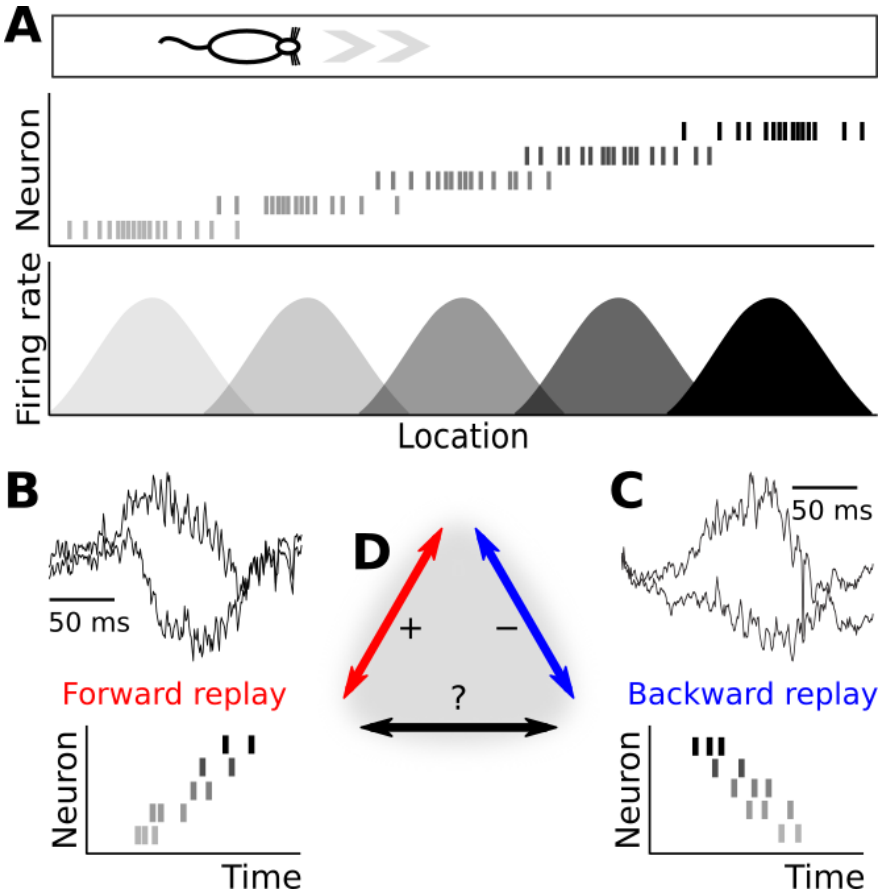

Figure 1: Illustration of the main question. **A.** Top: A cartoon of an animal traversing a linear track. Middle: A cartoon of spike trains emitted during the run by five place cells. Bottom: A cartoon of a place cell sequence template: firing rate profile of each neuron was estimated by averaging spike trains over repeated runs. **B,C.** A SPW event (top) and a cartoon of a spiking sequence (bottom). **D.** Red/blue arrows: Previously, positive and negative correlations between SPW sequences and a template sequence were observed. Black arrow: Here we inspect the correlations between SPW sequence pairs.

2.1 Sequence representation and correlation

Direction can be assigned to of a (group of) running sequence(s) by correlating spike times with an animal's motion. This direction is captured by the ordering of neurons in the template sequence generated using these running sequences. Replay was initially observed in SPW sequences using such templates. Correspondingly, directions of replay (forward and backward) were attached to replay sequences. But this conception of direction in SPW sequences relies on the observation of an animal's motion. Since SPW sequences occur primarily during periods of immobility, this associated motion cannot be inherent to the SPW sequence itself. We define a novel sequence representation—the *bias vector*—to describe the "direction" of neuronal firing that is inherent to each sequence.

When considering distinct active neurons i and j in a sequence $\mathbf{s}$, only two directions of neuronal firing are possible: i tends to precede j, or j tends to precede i. The /firing bias/ $b_{ij}(\mathbf{s})$ captures this direction and how strongly $\mathbf{s}$ points in that direction:

$$b_{ij}(\mathbf{s}) = \frac{c_{ij}(\mathbf{s}) - c_{ji}(\mathbf{s})}{c_{ij}(\mathbf{s}) + c_{ji}(\mathbf{s})},$$

where $c_{ij}(\mathbf{s})$ is the number of times neuron i fires before neuron j in $\mathbf{s}$ (Fig. 2A). More specifically, the sign of $b_{ij}(\mathbf{s})$ is the direction of firing between neurons i and j in sequence $\mathbf{s}$; the magnitude of $b_{ij}(\mathbf{s})$ is the strength of this tendency.

The overall direction of neuronal firing in $\mathbf{s}$ is given by the vector of all its firing biases: $B(\mathbf{s}) = [b_{ij}(\mathbf{s})]_{i<j}$. We call $B(\mathbf{s})$ the /bias vector/ of $\mathbf{s}$. Much information about a sequence $\mathbf{s}$ is contained in its bias vector $B(\mathbf{s})$. For instance, if spikes from distinct neurons are not interlaced in $\mathbf{s}$, then there is an evident neuronal ordering represented by $\mathbf{s}$. This ordering is recoverable from the bias vector $B(\mathbf{s})$: Since no spikes are interlaced, each firing bias $b_{ij}(\mathbf{s})$ is binary (± 1), indicating whether neuron i always precedes ($+1$) or always follows (-1) neuron j in sequence $\mathbf{s}$. In this way, the bias vector generalizes the concept of a neuronal ordering despite considering only pairwise neuronal firing preferences.

The direction of neuronal firing in sequence $\mathbf{s}$ is the direction of the bias vector $B(\mathbf{s})$; the magnitude of $B(\mathbf{s})$ is the strength of the tendency for $\mathbf{s}$ to point in that direction. Because of this, sequence similarity can be estimated by use of the cosine similarity on bias vectors (Fig. 2B). More specifically, the correlation $\mathrm{corr}(\mathbf{s}_1, \mathbf{s}_2)$ of sequences $\mathbf{s}_1$ and $\mathbf{s}_2$ is the cosine similarity of their bias vectors when only neurons active in both sequences are considered. The *significance of correlation* of sequence $\mathbf{s}_2$ to sequence $\mathbf{s}_1$ is the proportion of shuffled versions of $\mathbf{s}_2$ that are at least as strongly correlated to $\mathbf{s}_1$ as $\mathbf{s}_2$ is to $\mathbf{s}_1$ (Fig. 2C). In our analysis, we considered only significant correlation values. See Methods for more details.

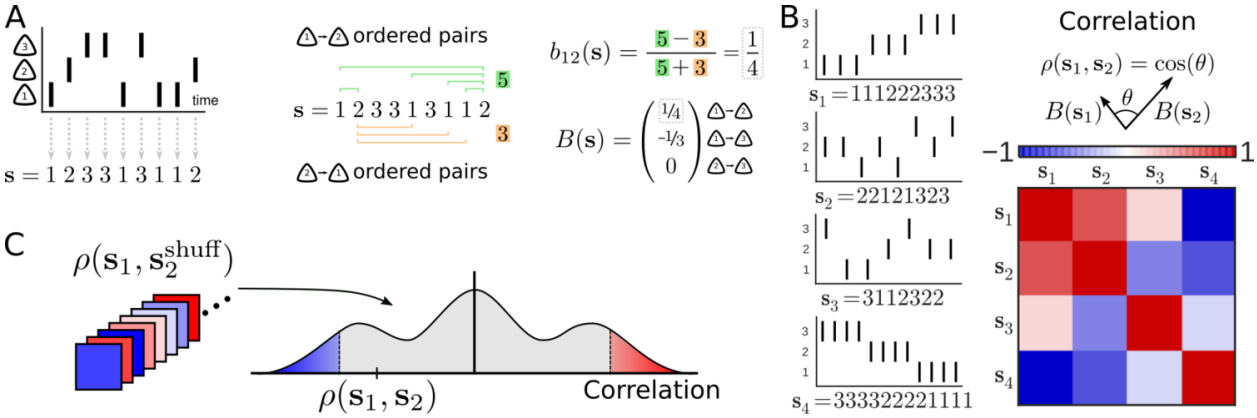

Figure 2: Steps of the Bias Vector Correlation method. **A.** An example spiking sequence $\mathbf{s}$ is transformed into ordered spikes (left), the spike ordering bias is determined for each pair of neurons (middle), and the bias vector is constructed based on the biases of all cell pairs (right). **B.** Four example sequences (left) are compared by calculating the correlation coefficients between bias vectors of each sequence (right). **C.** Repeated shuffling of spike order in one of the sequences in a pair gives rise to a distribution of correlation values that is used to determine the significance of the correlation value of the original sequences. Blue/red areas under the graph indicate correlation that are significantly negative/positive; gray area indicates insignificant correlation values.

2.2 Analysis of running sequences

Because of the presence of place cells and episode cells, we expected that running sequences generated during a common behavioral condition—for example, during an outbound run in the left arm—should be highly positively correlated with each other (Fig. 3B, C). We tested our method on spiking sequences generated while animals ran through the arms of the track or on the track's running wheel (Fig. 3A). As expected, these running sequences were overwhelmingly positively correlated within each group of running sequences (Fig. 3D, SFig. 2., red blocks along the diagonal). Such systematic positive correlations among running sequences were observed through all of our data (4 animals, 18 recordings) at well-above the chance

level (Fig. 3E). Negative correlations were also found between some pairs of running sequences that were generated while running in opposite directions through the same maze arm (Fig. 3C–E). This agrees with the previous observation that some place cells are activated independent of running direction on a linear track (McNaughton et al. 1984).

2.3 Analysis of running vs. SPW sequences

Replay of running sequences during SPWs was originally discovered by comparing SPW sequences to a template generated by pooling spike locations across running trials (Wilson and McNaughton 1994; Nádasdy et al. 1999; Foster and Wilson 2006; Jackson et al. 2006; Csicsvari et al. 2007; Diba and Buzsáki 2007; Davidson et al. 2009). We inspected correlations between running sequences and SPW sequences to see if signs of replay of place-cell and episode-cell sequences (Foster and Wilson 2006; Jackson et al. 2006; O'Neill et al. 2006) could be observed using our method. We defined a replay sequence to be any SPW sequence that was significantly correlated (see Methods) with at least three running sequences from a specific behavioral condition such that at least 75% of these correlations were of the same polarity. A replay sequence correlating primarily positively (resp., negative) with a group of running sequences was referred to as forward (resp., backward) replay.

We observed replay of place-cell sequences in about 0.0–29.8% of SPW sequences (SFig. 3.), which agrees with previous reports (Dragoi and Tonegawa 2011). Further, the direction of the replay was about equally distributed between forward and backward (Fig. 3F, top, (Davidson et al. 2009)). Similarly, we observed replay of episode-cell sequences in about 2.3–36.3% of SPW sequences. Again, the direction of the replay was about equally distributed between forward and backward (Fig. 3F, bottom). Importantly, since episode fields are only experienced in one direction during behavior, this result shows that the direction of replay during SPWs is independent of an animal's running experience. These results confirmed that our method can reliably identify forward and backward replay of place-cell and episode-cell sequences during SPWs.

2.4 Analysis of SPW sequences

If SPW sequence replay of running sequences is bidirectional in the sense that the same group of neurons is activated in both forward and backward directions during SPWs, then correlations between forward and backward replay sequences should be overwhelmingly negative (Fig. 4A, left). We found that positive and negative correlations occurred almost equally frequently when comparing forward and backward replay sequences (Fig. 4B). Further, negative correlations occurred only at the chance level and positive correlations occurred well above the chance level (Fig. 4B, inset). These results held true in every recording ($n = 18$) and in every animal ($n = 4$) that we analyzed. This finding also held true for wheel-run sequences, eliminating any potential effect that might be introduced by traversing the maze arms in multiple directions. This suggested that replay sequences tend to be positively correlated with each other regardless of how they correlate with any running sequence. This observation implies that a randomly chosen positive replay sequence and a randomly chosen negative replay sequence are likely to be positively correlated despite exhibiting different directions of replay. While this is unintuitive, it does not present a mathematical problem: Two sequences that are oppositely correlated with the same reference sequence can be positively correlated with each other (Fig. 4C, SFig. 4.).

Although we did not find negative correlations between forward-replay and reverse-replay sequences to occur above the chance level, negative correlations might still exist within the global population of SPW sequences. We expanded our search for negative correlations to include all SPW sequences, including those that demonstrated no replay behavior. In all recordings, we found that SPW sequence pairs were overwhelmingly positively correlated and that negative correlations occurred only at the chance level (Fig. 4D, SFig. 5-6.). This suggests that there may be some intrinsic properties of SPW sequences and/or the underlying network that cause these sequences to be predominantly positively correlated with each other. If so, this could suggest that the structure of SPW sequences may not be influenced by running experiences as previously conjectured

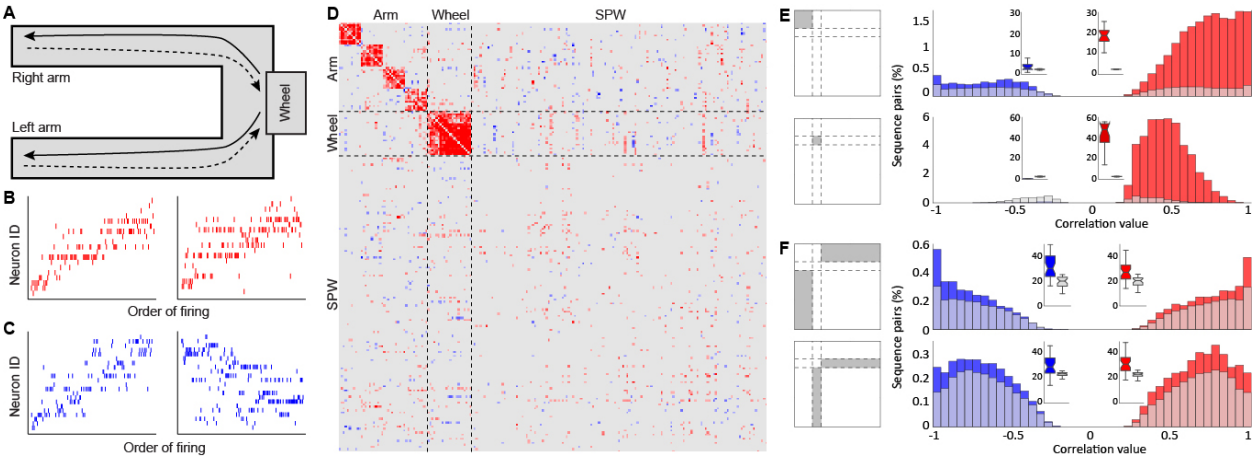

Figure 3: Analysis of running and SPW sequences with Bias Vector Method. **A.** Schematic of a two-arm maze. **B.** Two positively correlated example place-cell spiking sequences recorded during two outbound runs through the left arm of the maze. **C.** Two negatively correlated example place-cell spiking sequences recorded during an outbound and an inbound run through the right arm of the maze. **D.** Correlation matrix of spiking sequences recorded during arm runs, wheel runs, and SPWs. The red diagonal blocks in the section comparing arm runs to arm runs represent the four possible directions of running through the maze, as depicted in panel A. Shades of red / blue: significant positive / negative correlation values, respectively. Gray: non-significant correlations. **E.** Correlations between running sequences. Left: Section of the correlation matrix summarized in the histogram on the right. Right: Distributions of significant correlation values pooled across all data. Gray bars show shuffled data. Insets: The average percentage of sequence pairs that were significantly correlated (4 animals, 18 recordings). **F.** Same as panel E but for correlations between a running sequence and a SPW sequence.

based on the observation "replay" sequences.

3 Discussion

In summary, we used a novel vector representation of neuronal firing sequences to investigate the relationships between individual firing sequences. In particular, this method eliminated the need to pool/average data across trials (Foster and Wilson 2006; Jackson et al. 2006; Diba and Buzsáki 2007) or an entire recording (Davidson et al. 2009; Dragoi and Tonegawa 2010; Pfeiffer and Foster 2013; Grosmark and Buzsaki 2016) in order to generate a "template" for comparison. This enabled us to investigate relationships between spiking sequences generated under various behavioral conditions and at different timescales.

Most surprisingly, we found that SPW sequences are not negatively correlated with each other more frequently than by chance. In contrast, we found that SPW sequences are positively correlated with each other regardless of whether sequence "replay" is observed in either sequence. Counterintuitively, these results held even when selecting one forward-replay sequence and one backward-replay sequence. Further, these relationships among SPW sequences were not due to insufficient neuronal overlap between specific groups of SPW sequences. However, the lack of negative correlations between SPW sequences is not compatible with the belief that SPW sequences are bidirectional in the sense that the same group of neurons is activated in both forward and backward directions during SPWs. Instead, our data indicate that SPW sequences are unidirectional. This result strongly suggests that SPW sequence structure is not determined by the activation of episode-cell and place-cell sequences during running. If correct, this conclusion contradicts the prevalent view that SPW sequences replay the running experience of animals.

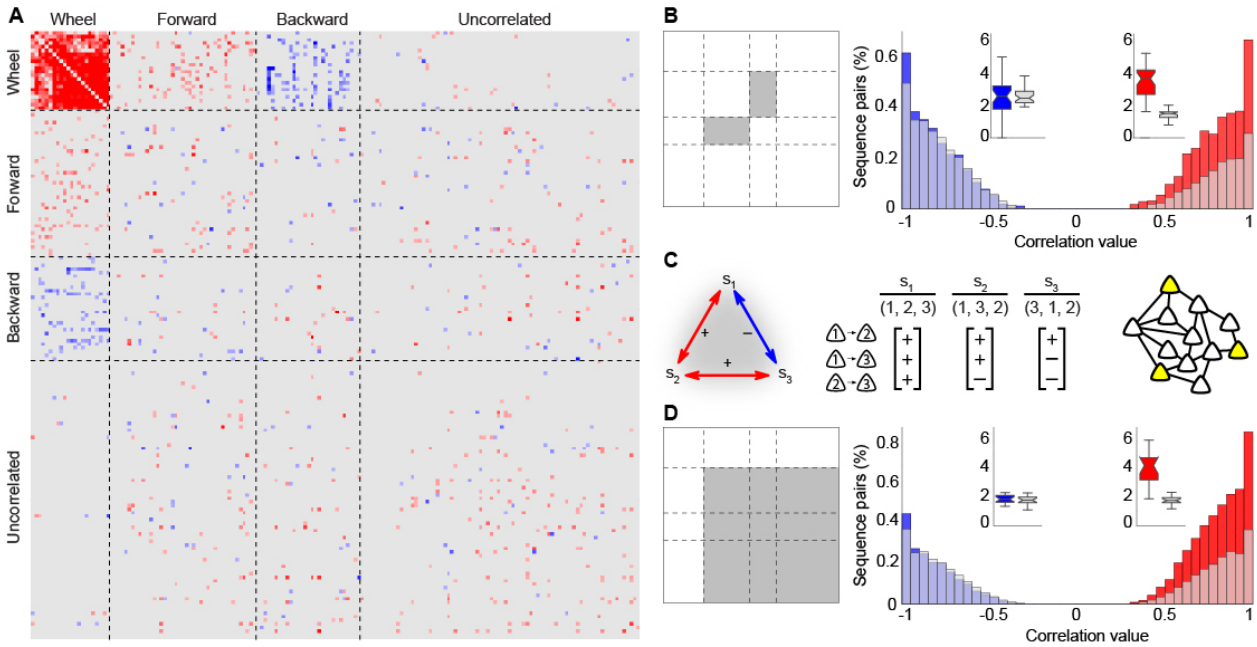

Figure 4: Correlation values among SPW sequence pairs. **A.** An example correlation matrix with SPW sequences that were either positively (Forward), negatively (Backward), or uncorrelated with wheel-run sequences. Shades of red / blue: significant positive / negative correlation values, respectively. Gray: non-significant correlations. **B.** Left: section of the correlation matrix summarized in the histogram on the right. Right: Distribution of correlation values among SPW sequences with opposite relationship to episode-cell sequences. **C.** Left: A minimal example of three sequences $\mathbf{s}_1$, $\mathbf{s}_2$ and $\mathbf{s}_3$ that mimic our results. Sequence $\mathbf{s}_2$ and $\mathbf{s}_3$ have an opposite relationship with a reference sequence $\mathbf{s}_1$ but are mutually positively correlated. Middle: each sequence consists of three spikes generated by neurons 1 through 3. Bias vectors are under each respective sequence ('+' corresponds to +1, '-' corresponds to -1). Right: Indirect connections between neurons 1 - 3 (yellow) likely support these unintuitive relationships. **D.** Distribution of correlation values between SPW sequence pairs of all types.

If SPWs are unidirectional as our data suggests, then we must reconcile this finding with the fact that running sequences are significantly positively and negatively correlated with SPW sequences (Fig. 3F; (Foster and Wilson 2006; Diba and Buzsáki 2007)). We propose a simple solution to this issue, which is that running sequences should not be considered as forward-moving templates for the purpose of SPW analysis. Instead, we propose that place-cell and episode-cell sequences travel relatively complex trajectories through the network, sometime along, sometime against, and sometime independently of the preferred direction of SPW sequences (SFig. 7). This complex trajectory might arise from the fact that these long-lasting sequences are built up gradually from theta sequences (Skaggs et al. 1996; Dragoi and Buzsáki 2006).

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