

Intrinsic dynamics of randomly clustered networks generate place fields and preplay of novel environments

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Abstract

During both sleep and awake immobility, hippocampal place cells reactivate time-compressed versions of sequences representing recently experienced trajectories in a phenomenon known as replay. Intriguingly, spontaneous sequences can also correspond to forthcoming trajectories in novel environments experienced later, in a phenomenon known as preplay. Here, we present a model showing that sequences of spikes correlated with the place fields underlying spatial trajectories in both previously experienced and future novel environments can arise spontaneously in neural circuits with random, clustered connectivity rather than pre-configured spatial maps. Moreover, the realistic place fields themselves arise in the circuit from minimal, landmark-based inputs. We find that preplay quality depends on the network's balance of cluster isolation and overlap, with optimal preplay occurring in small-world regimes of high clustering yet short path lengths. We validate the results of our model by applying the same place field and preplay analyses to previously published rat hippocampal place cell data. Our results show that clustered recurrent connectivity can generate spontaneous preplay and immediate replay of novel environments. These findings support a framework whereby novel sensory experiences become associated with preexisting “pluripotent” internal neural activity patterns.

eLife assessment

This study presents an **important** finding on the spontaneous emergence of structured activity in artificial neural networks endowed with specific connectivity profiles. The evidence supporting the claims of the authors is **convincing**, providing direct comparison between the properties of the model and neural data although investigating more naturalistic inputs to the network would have strengthened the main claims. The work will be of interest to systems and computational neuroscientists studying the hippocampus and memory processes.

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Introduction

The hippocampus plays a critical role in spatial and episodic memory in mammals (Morris et al., 1982 [↗](#); Squire et al., 2004 [↗](#)). Place cells in the hippocampus exhibit spatial tuning, firing selectively in specific locations of a spatial environment (Moser et al., 2008 [↗](#); O'Keefe and Nadel, 1978 [↗](#)). During sleep and quiet wakefulness, place cells show a time-compressed reactivation of spike sequences corresponding to recent experiences (Wilson and McNaughton, 1994 [↗](#); Foster and Wilson, 2006 [↗](#)), known as replay. These replay events are thought to be important for memory consolidation, often referred to as memory replay (Carr et al., 2011 [↗](#)).

The CA3 region of the hippocampus is a highly recurrently connected region that is the primary site of replay generation in the hippocampus. Input from CA3 supports replay in CA1 (Csicsvari et al., 2000 [↗](#); Yamamoto and Tonegawa, 2017 [↗](#); Nakashiba et al., 2008 [↗](#); Nakashiba et al., 2009 [↗](#)), and peri-ripple spiking in CA3 precedes that of CA1 (Nitzan et al., 2022 [↗](#)). The recurrent connections support intrinsically generated bursts of activity that propagate through the network.

Most replay models rely on a recurrent network structure in which a map of the environment is encoded in the recurrent connections of CA3 cells, such that cells with nearby place fields are more strongly connected. Some models assume this structure is pre-existing (Haga and Fukai, 2018 [↗](#); Pang and Fairhall, 2019 [↗](#)), and some show how it could develop over time through synaptic plasticity (Theodoni et al., 2018 [↗](#); Jahnke et al., 2015 [↗](#)). Related to replay models based on place-field distance-dependent connectivity is the broader class of synfire-chain-like models. In these models, neurons (or clusters of neurons) are connected in a 1-dimensional feed-forward manner (Diesmann et al., 1999 [↗](#); Chenkov et al., 2017 [↗](#)). The classic idea of a synfire-chain has been extended to include recurrent connections, such as by Chenkov et al., 2017 [↗](#), however such models still rely on an underlying 1-dimensional sequence of activity propagation.

A problem with these models is that in novel environments place cells remap immediately in a seemingly random fashion (Leutgeb et al., 2005 [↗](#); Muller and Kubie, 1987). The CA3 region, in particular, undergoes pronounced remapping (Leutgeb et al., 2004 [↗](#); Leutgeb et al., 2005 [↗](#); Alme et al., 2014 [↗](#)). A random remapping of place fields in such models that rely on environment-specific recurrent connectivity between place cells would lead to recurrent connections that are random with respect to the novel environment, and thus would not support replay of the novel environment.

Rather, these models require a pre-existing structure of recurrent connections to be created for each environment. A proposed solution to account for remapping in hippocampal models is to assume the existence of multiple independent and uncorrelated spatial maps stored within the connections between cells. In this framework, the maximum number of maps is reached when the noise induced via connections needed for alternative maps becomes too great for a faithful rendering of the current map (Samsonovich and McNaughton, 1997 [↗](#); Battaglia and Treves, 1998 [↗](#); Azizi et al., 2013 [↗](#)). However, experiments have found that hippocampal representations remain uncorrelated, with no signs of representation re-use, after testing as many as 11 different environments in rats (Alme et al., 2014 [↗](#)).

Rather than re-using a previously stored map, another possibility is that a novel map for a novel environment is generated *de novo* through experience-dependent plasticity while in the environment. Given the timescales of synaptic and structural plasticity, one might expect that significant experience within each environment is needed to produce each new map. However, replay can occur after just 1-2 laps on novel tracks (Foster and Wilson, 2006 [↗](#); Berners-Lee et al., 2022 [↗](#)), which means that the synaptic connections that allow the generation of the replayed sequences must already be present. Consistent with this expectation, it has been found that

decoded sequences during sleep show significant correlations when decoded by place fields from future, novel environments. This phenomenon is known as preplay and has been observed in both rodents (Dragoi and Tonegawa, 2011 [DOI](#); Dragoi and Tonegawa, 2013 [DOI](#); Grosmark and Buzsaki, 2016 [DOI](#); Liu et al., 2018) and humans (Vaz et al., 2023 [DOI](#)).

The existence of both preplay and immediate replay in novel environments suggests that the preexisting recurrent connections in the hippocampus that generate replay are somehow correlated with the pattern of future place fields that arise in novel environments. To reconcile these experimental results, we propose a model of intrinsic sequence generation based on randomly clustered recurrent connectivity, wherein place cells are connected within multiple overlapping clusters that are random with respect to any future, novel environment. Such clustering is a common motif across the brain, including the CA3 region of the hippocampus (Guzman et al., 2016 [DOI](#)) as well as cortex (Song et al., 2005 [DOI](#); Perin et al., 2011 [DOI](#)), naturally arises from a combination of Hebbian and homeostatic plasticity in recurrent networks (Bourjaily and Miller, 2011 [DOI](#); Litwin-Kumar and Doiron, 2014 [DOI](#); Lynn et al., 2022 [DOI](#)), and spontaneously develops in networks of cultured hippocampal neurons (Antonello et al., 2022 [DOI](#)).

As an animal gains experience in an environment, the pattern of recurrent connections of CA3 would be shaped by Hebbian plasticity (Debanne et al., 1998 [DOI](#); Mishra et al., 2016 [DOI](#)). Relative to CA1, which has little recurrent connectivity, CA3 has been found to have both more stable spatial tuning and a stronger functional assembly organization, consistent with the hypothesis that spatial coding in CA3 is influenced by its recurrent connections (Sheintuch et al., 2023 [DOI](#)). Gaining experience in different environments would then be expected to lead to individual place cells participating in multiple formed clusters. Such overlapping clustered connectivity may be a general feature of any hippocampal and cortical region that has typical Hebbian plasticity rules. Sadovsky and MacLean, 2014 [DOI](#), found such structure in the spontaneous activity of excitatory neurons in primary visual cortex, where cells formed overlapping but distinct functional clusters. Further, such preexisting clusters may help explain the correlations that have been found in otherwise seemingly random remapping (Kinsky et al., 2018 [DOI](#); Whittington et al., 2020 [DOI](#)) and support the rapid hippocampal representations of novel environments that are initially generic and become refined with experience (Liu et al., 2021 [DOI](#)). Such clustered connectivity likely underlies the functional assemblies that have been observed in hippocampus, wherein groups of recorded cells have correlated activity that can be identified through independent component analysis (Peyrache et al., 2010 [DOI](#); Farooq et al., 2019 [DOI](#)).

Since our model relies on its random recurrent connections for propagation of activity through the network during spontaneous activity, we also sought to assess the extent to which the internal activity within the network can generate place cells with firing rate peaks at a location where they do not receive a peak in their external input. While the total input to the network is constant as a function of position, each cell only receives a peak in its spatially linearly varying feedforward input at one end of the track. Our reasoning is that landmarks in the environment, such as boundaries or corners, provide location-specific visual input to an animal, but locations between such features are primarily indicated by their distance from them, which in our model is represented by reduction in the landmark-specific input. One can therefore equate our model's inputs as corresponding to boundary cells (Savelli et al., 2008 [DOI](#); Solstad et al., 2008 [DOI](#); Bush et al., 2014 [DOI](#)), and the place fields between boundaries are generated by random internal structure within the network. Further, variations in spatial input forms do not affect the consistency and robustness of the model.

In our implementation of this model, we find that spontaneous sequences of spikes generated by a randomly clustered network can be decoded as spatial trajectories without relying on pre-configured, environment-specific maps. Because the network contains neither a preexisting map of the environment nor experience-dependent plasticity, we refer to the spike-sequences it generates as preplay. However, the model can also be thought of as a preexisting network in which

immediate replay in a novel environment can be expressed and then reinforced through experience-dependent plasticity. We find that preplay in this model occurs most strongly when the network parameters are tuned to generate networks that have a small-world structure (Watts and Strogatz, 1998 [↗](#); Humphries et al., 2006 [↗](#); Humphries et al., 2008). Our results support the idea that preplay and immediate replay could be a natural consequence of the preexisting recurrent structure of the hippocampus.

Results

The model

We propose a model of preplay and immediate replay based on randomly clustered recurrent connections (**Figure 1** [↗](#)). In prior models of preplay and replay, a preexisting map of the environment is typically assumed to be contained within the recurrent connections of CA3 cells, such that cells with nearby place fields are more strongly connected (**Figure 1a** [↗](#)). While this type of model successfully produces replay (Haga and Fukai, 2018 [↗](#); Pang and Fairhall, 2019 [↗](#)), such a map would only be expected to exist in a familiar environment, after experience-dependent synaptic plasticity has had time to shape the network (Theodoni et al., 2018 [↗](#)). It remains unclear how, in the absence of such a preexisting map of the environment, the hippocampus can generate both preplay and immediate replay of a novel environment.

Our proposed alternative model is based on a randomly clustered recurrent network with random feed-forward inputs (**Figure 1b** [↗](#)). In our model, all excitatory neurons are randomly assigned to overlapping clusters that constrain the recurrent connectivity, and they all receive the same linear spatial and contextual input cues which are scaled by randomly drawn, cluster-dependent connection weights (see Methods). This bias causes cells that share cluster memberships to have more similar place fields during the simulated run period, but, crucially, this bias is not present during sleep simulations so that there is no environment-specific information present when the network generates preplay.

An example network with 8 clusters and cluster participation of 1.5 (the mean number of clusters to which an excitatory neuron belongs) is depicted in **Figure 1c** [↗](#). Excitatory neurons are recurrently connected to each other and to inhibitory neurons. Inhibitory cells have cluster-independent connectivity, such that all E-to-I and I-to-E connections exist with a probability of 0.25. Feed-forward inputs are independent Poisson spikes with random connection strength for each neuron (**Figure 1d** [↗](#)). Excitatory cells are randomly, independently assigned membership to each of the clusters in the network. All neurons are first assigned to one cluster, and then randomly assigned additional clusters to reach the target cluster participation (**Figure 1e** [↗](#)). Given the number of clusters and the cluster participation, the within-cluster connection probability is calculated such that the global connection probability matches the parameter $p_c = 0.08$ (**Figure 1f** [↗](#)). The left peak in the distribution shown in **Figure 1f** [↗](#) is from cells in a single cluster and the right peak is from cells in two clusters, with the long tail corresponding to cells in more than two clusters.

For a given p_c , excitatory connectivity is parameterized by the number of clusters in the network and the mean cluster participation. The small-world index (SWI; Neal, 2015 [↗](#); Neal, 2017 [↗](#)) systematically varies across this 2-D parameterization (**Figure 1g** [↗](#)). A high SWI indicates a network with both clustered connectivity and short path lengths (Watts and Strogatz, 1998 [↗](#)). A ring lattice network (**Figure 1—figure supplement 1a** [↗](#)) exhibits high clustering but long path lengths between nodes on opposite sides of the ring. In contrast, a randomly connected network (**Figure 1—figure supplement 1c** [↗](#)) has short path lengths but lacks local clustered structure. A network with small world structure, such as a Watts-Strogatz network (Watts and Strogatz, 1998 [↗](#)) or our randomly clustered model (**Figure 1—figure supplement 1b** [↗](#)), combines both

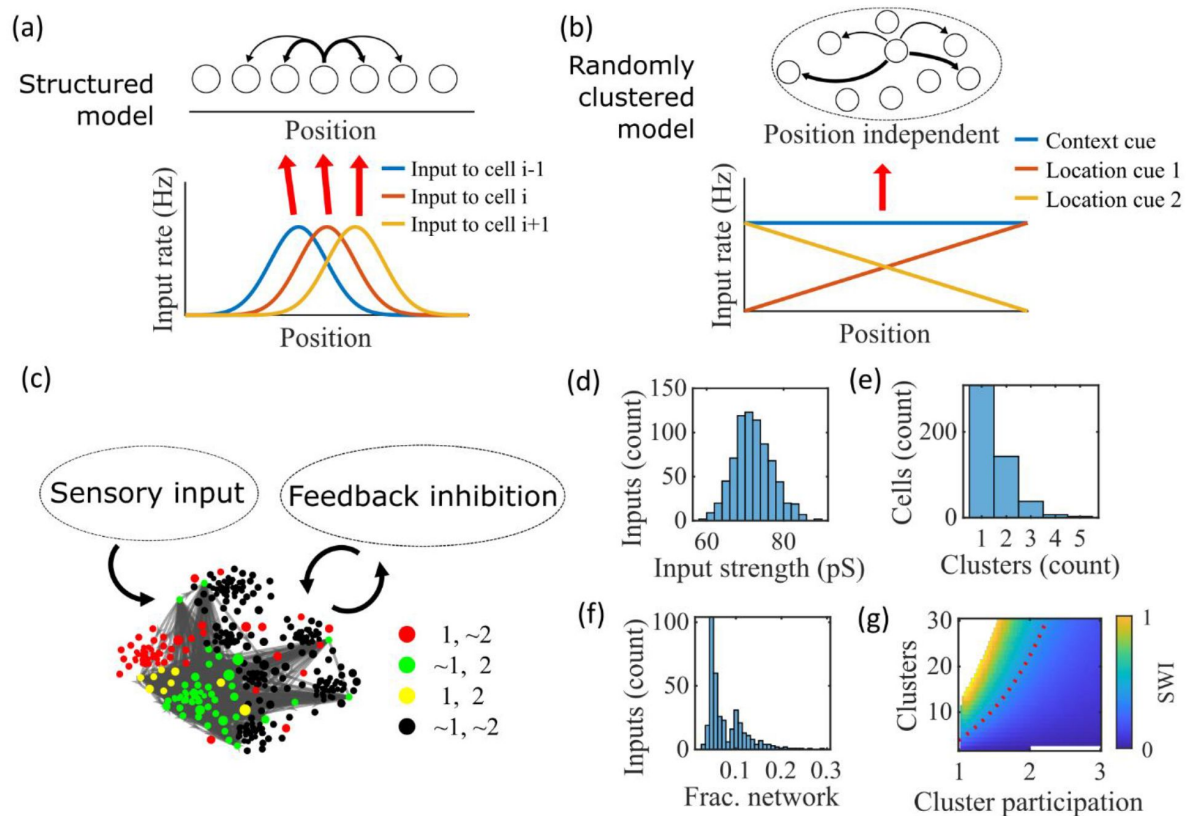


Figure 1

Illustration of the randomly clustered model

(a) Schematic diagram of prior replay models that rely on preexisting environment-specific structure, wherein each cell receives uniquely tuned Gaussian-shaped feed-forward inputs to define the place fields, and cells with nearby place fields are recurrently connected. Pairs of cells with closest place fields are connected most strongly (thicker arrows). (b) Schematic diagram of our model, where neurons are randomly placed into clusters and all neurons receive the same spatial and contextual information but with random, cluster-dependent input strengths. (c) Example representation of the network (8 clusters, mean cluster participation per cell of 1.5). Excitatory cells (each symbol) are recurrently connected with each other and with inhibitory cells ("Feedback inhibition", individual inhibitory cells not shown) and receive feed forward input ("Sensory input"). Symbol color indicates neurons' membership in clusters 1 and 2, with ~ meaning not in the cluster. Symbol size scales with the number of clusters a neuron is in. Lines show connections between neurons that are in cluster 2. Symbol positions are plotted based on a t-distributed stochastic neighbor embedding (t-SNE) of the connection matrix, which reveals the randomly overlapping clusters. (d-f) Histograms based on the network in (c) of: (d) the distribution of input strengths; (e) the number of clusters that each neuron is a member of; and (f) the fraction of the excitatory cells to which each excitatory cell connects. (g) The Small-World Index (SWI) of the excitatory connections varies with the number of clusters and the mean number of clusters of which each neuron is a member ("cluster participation"). The median value of the SWI from 10 networks at each parameter point is plotted. The red dashed line shows a contour line where $SWI = 0.4$. Regions in white are not possible due to either cluster participation exceeding the number of clusters (lower right) or cells not being able to connect to enough other cells to reach the target global connectivity p_c (upper left).

clustered connectivity and short path lengths. In our clustered networks, for a fixed connection probability, SWI increases with more clusters and lower cluster participation, so long as cluster participation is greater than one to ensure sparse overlap of (and hence connections between) clusters. Networks in the top left corner of **Figure 1g** are not possible, since in that region all within-cluster connections are not sufficient to match the target global connectivity probability, p_c . Networks in the bottom right are not possible because otherwise mean cluster participation would exceed the number of clusters. The dashed red line shows an example contour line where $SWI = 0.4$.

Example activity

Our randomly clustered model produces both place fields and preplay with no environment-specific plasticity or preexisting map of the environment (**Figure 2**). Example place cell activity shows spatial specificity during linear track traversal (**Figure 2a-c**).

Although the spatial tuning is noisy, this is consistent with the experimental finding that the place fields that are immediately expressed in a novel environment require experience in the environment to stabilize and improve decoding accuracy (Tang and Jadhav, 2022; Shin et al., 2019; Hwaun and Colgin, 2019). Raster plots of network spiking activity (**Figure 2a**) and example cell membrane potential traces (**Figure 2b**) demonstrate selective firing in specific track locations. Place fields from multiple networks generated from the same parameters, but with different input and recurrent connections, show spatial tuning across the track (**Figure 2c**).

To test the ability of the model to produce preplay, we simulated sleep sessions in the same networks. Sleep sessions were simulated in a similar manner to the running sessions but with no location cue inputs active and a different, unique set of context cue inputs active to represent the sleep context. The strength of the context cue inputs to the excitatory and inhibitory cells were scaled in order to generate an appropriate level of network activity, to account for the absence of excitatory drive from the location inputs (see Methods). During simulated sleep, sparse, stochastic spiking spontaneously generates sufficient excitement within the recurrent network to produce population burst events resembling preplay (**Figure 2d-f**). Example raster and population rate plots demonstrate spontaneous transient increases in spiking that exceed 1 standard deviation above the mean population rate denoting population burst events (PBEs; **Figure 2d**). We considered PBEs that lasted at least 50 ms and contained at least 5 participating cells candidates for Bayesian decoding (Shin et al., 2019). Bayesian decoding of an example PBE using the simulated place fields reveals a spatial trajectory (**Figure 2e**). We use the same two statistics as Farooq et al. (2019) to quantify the quality of the decoded trajectory: the absolute weighted correlation (r) and the maximum jump distance (jd ; **Figure 2f**). The absolute weighted correlation of a decoded event is the absolute value of the linear Pearson's correlation of space-time weighted by the event's derived posteriors. Since sequences can correspond to either direction along the track, the sign of the correlation simply indicates direction while the absolute value indicates the quality of preplay. The maximum jump distance of a decoded event is the maximum jump in the location of peak probability of decoded position across any two adjacent 10-ms time bins of the event's derived posteriors. A high-quality event will have a high absolute weighted correlation and a low maximum jump distance.

Together, these results demonstrate that the model can reproduce key dynamics of hippocampal place cells, including spatial tuning and preplay, without relying on environment-specific recurrent connections.

Place Fields

To compare the place fields generated by the model to those from hippocampal place cells of rats, we calculated several place-field statistics for both simulated and experimentally recorded place fields (**Figure 3**). Because our model assumes no previous environment-specific plasticity, we

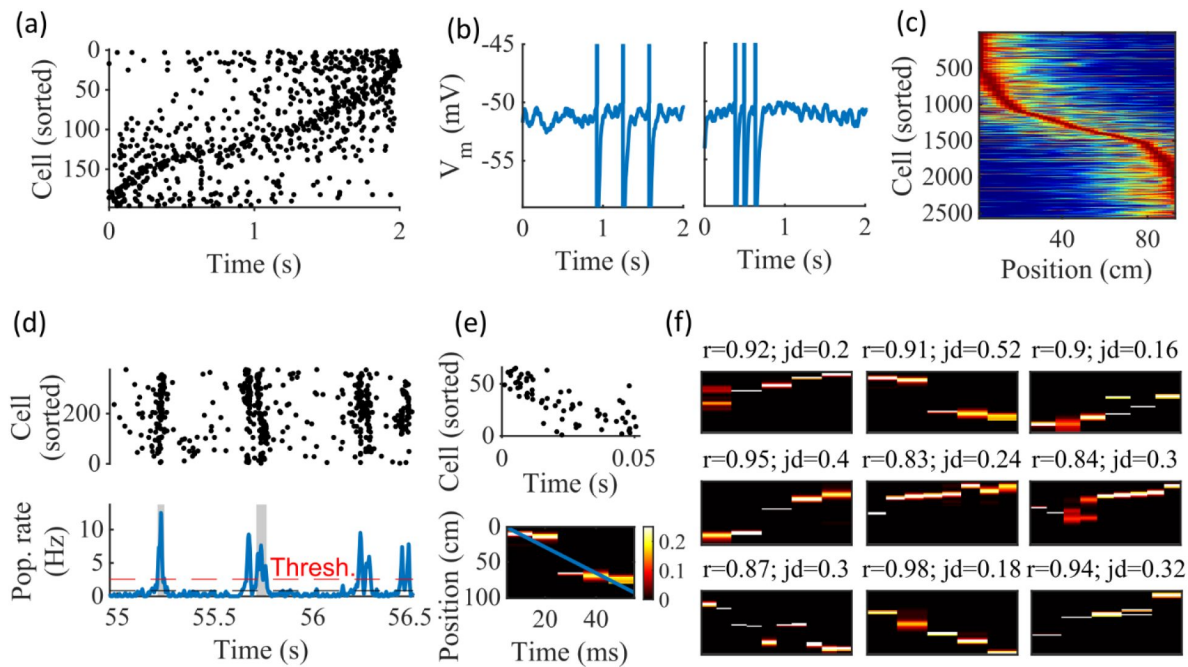


Figure 2

Spatially correlated reactivations in networks without environment-specific connectivity or plasticity

(a-f) Example activity from the fiducial parameter set (15 clusters, mean cluster participation of 1.25). (a) Example raster plot from one place-field trial. Cells sorted by trial peak. (b) Example membrane traces from two of the cells in (a). (c) Place fields from 10 different networks generated from the same parameter set, sorted by peak location and normalized by peak rate. (d) Example raster plot (top) and population firing rate (bottom; blue line) showing preplay in a simulation of sleep. Horizontal dashed black line is the mean population rate across the simulation. Horizontal dashed red line is the threshold for detecting a population-burst event (PBE). PBEs that exceeded the threshold for at least 50 ms and had at least 5 participating cells were included in the preplay decoding analysis. Grey bars highlight detected events. (e) Example preplay event (Top, raster plot. Bottom, Bayesian decoding of position). Event corresponds to the center event in (d). Raster includes only participating cells. The blue line shows the weighted correlation of decoded position across time. (f) Nine example decoded events from the same networks in (c). The width of each time bin is 10 ms. The height spans the track length. Same color scale as in (e). r is each event's absolute weighted correlation. jd is the maximum normalized jump in peak position probability between adjacent time bins. The same event in (e) is shown with its corresponding statistics in the center of the top row. Preplay statistics calculated as in Farooq et al., 2019 [Farooq et al., 2019 \[DOI\]\(https://doi.org/10.7554/eLife.93981.2\)](https://doi.org/10.7554/eLife.93981.2).

analyzed data from place cells in rats on their first exposure to a W-track (Shin et al., 2019). Equivalent statistics of place-field peak rate, sparsity, and spatial information are shown for experimental data (Figure 3a) and simulations (Figure 3b). We found that the model produces qualitatively similar (but not quantitatively identical) distributions for the fiducial parameter set.

These place-field properties depend on the network parameters (Figure 3c). With fewer clusters and lower cluster overlap (lower cluster participation), place fields have higher peak rates, sparsity, and spatial information (Figure 3c, top row and bottom left). However, lower overlap reduces the uniformity of place-field locations, measured by KL-divergence (Figure 3c bottom middle) and the fraction of place fields in the central third of the track (Figure 3c bottom right).

To verify that our simulated place cells were more strongly coding for spatial location than for elapsed time, we performed simulations with additional track traversals at different speeds and compared the resulting place fields and time fields in the same cells. We find that there is significantly greater place information than time information (Figure 3—figure supplement 1)

Preplay

Having found that the model produces realistic place-field representations with neither place-field like inputs nor environment-specific spatial representation in the internal network connectivity (Figure 3), we next examined whether the same networks could generate spontaneous preplay of novel environments. To test this, for the same set of networks characterized by place-field properties in Figure 3, we simulated sleep activity by removing any location-dependent input cues and analyzed the resulting spike patterns for significant sequential structure resembling preplay trajectories (Figure 4). We find significant preplay in both our reference experimental data set (Shin et al., 2019; Figure 4a, b; see Figure 4—figure supplement 1 for example events) and our model (Figure 4c, d) when analyzed by the same methods as Farooq et al., 2019, wherein the significance of preplay is determined relative to time-bin shuffled events (see Methods). The distribution of absolute weighted correlations of actual events was significantly greater than the distribution of absolute weighted correlations of shuffled events for both the experimental data (Figure 4a, KS-test, $p=2 \times 10^{-12}$, KS-statistic=0.078) and the simulated data (Figure 4c, KS-test, $p=3 \times 10^{-16}$, KS-statistic=0.29). Additionally, we found that this result is robust to random subsampling of cells in our simulated data (Figure 4—figure supplement 2). Our analyses of the hippocampal data produce similar results when analyzing each trajectory independently (Figure 4—figure supplement 3).

For each event, we also calculated the maximum spatial jump of the peak probability of decoded position between any two adjacent time bins as a measure of the continuity of the decoded trajectory. The absolute weighted correlation (high is better) and maximum jump (low is better) were then two different measures of the quality of a decoded trajectory. We performed a bootstrap test that took both of these measures into account by setting thresholds for a minimum absolute weighted correlation and a maximum jump distance and then calculating the fraction of events meeting both criteria of quality. The significance of the fraction of events meeting both criteria was then determined by comparing it against a distribution of such fractions generated by sets of the time-bin shuffled events. We systematically varied both thresholds and found that the actual events are of significantly higher quality than chance for a wide range of thresholds in both the hippocampal (Figure 4b) and simulated (Figure 4d) data. The upper right corner of these grids cannot be significant since 100% of all possible events would be included in any shuffle or actual set. Points in the left-most column are not all significant because the strictness of the maximum jump distance means that very few events in either the actual or shuffled data sets meet the criterion, and therefore the analysis is underpowered. This pattern is similar to that seen in Farooq et al., 2019 (as shown in their Figure 1e).

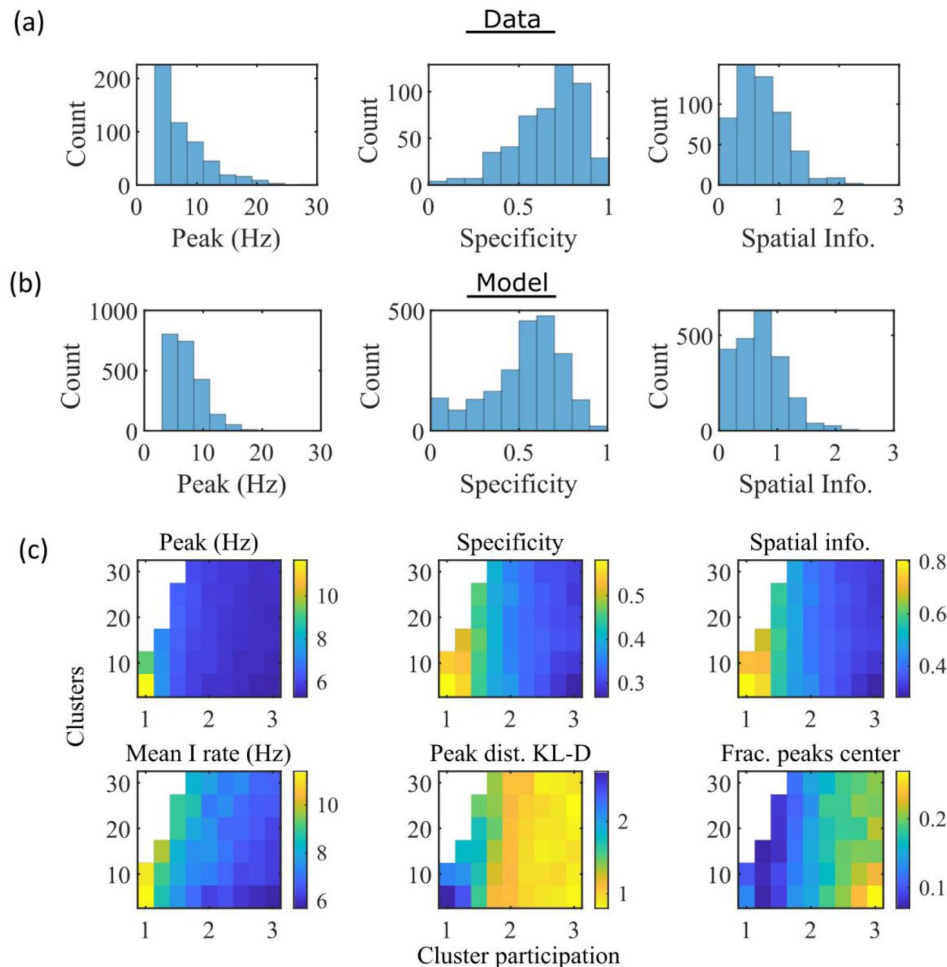


Figure 3

The model produces place fields with similar properties to hippocampal place fields

(a) Place field statistics for hippocampal place fields recorded in rats upon their first exposure to a W-track (Shin et al., 2019). Left, place-field peak rate (Hz). Center, place-field specificity (fraction of track). Right, place-field spatial information (bits/spike). **(b)** Same as (a) but for place fields from a set of 10 simulated networks at one parameter point (15 clusters and mean cluster participation of 1.25). **(c)** Network parameter dependence of place-field statistics. For each parameter point, the color indicates the mean over all place fields from all networks. Top row: mean statistics corresponding to the same measures of place fields used in panels (a, b). Bottom left: mean firing rate of the inhibitory cells. Bottom center: the KL-divergence of the distribution of place-field peaks relative to a uniform spatial distribution. Bottom right: fraction of place-field peaks peaked in the central third of the track.

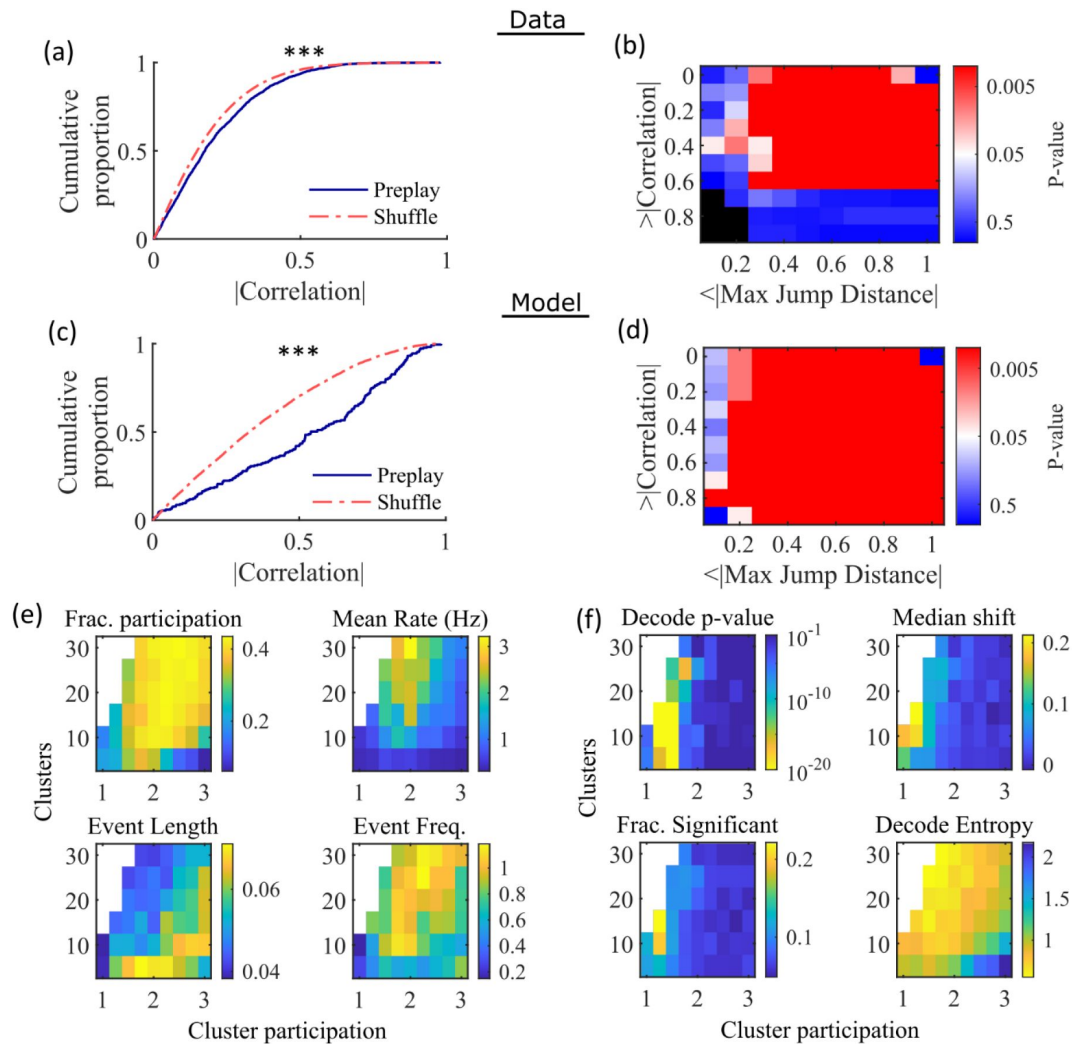


Figure 4

Preplay depends on modest cluster overlap

(a,c) The cumulative distribution function (CDF) of the absolute weighted correlations for actual events (blue line) versus shuffled events (red dashed line) of experimental data from Shin et al., 2019 (a; KS-test, $p=2 \times 10^{-12}$, KS-statistic=0.078) and simulated data (c; KS-test, $p=3 \times 10^{-16}$, KS-statistic=0.29) reveal results similar to those in Figure 1h of Farooq et al., 2019. *** $p < 0.001$. (b,d) P-value grids (p-value indicated logarithmically by color) showing that the actual decoded events are higher quality sequences than shuffles across a wide range of quality thresholds for both experimental data from Shin et al., 2019 (b) and simulated data (d). For each point on the grid the fraction of events that exceed the absolute weighted correlation threshold (y-axis) and don't exceed the maximum jump distance (x-axis) is calculated, and the significance of this fraction is determined by comparison against a distribution of corresponding fractions from shuffled events. Black squares indicate criteria that were not met by any events (either shuffled or actual). The panel is equivalent to Figure 1e of Farooq et al., 2019. (e) Network parameter dependence of several statistics quantifying the population-burst events. Top left, fraction of excitatory cells firing per event. Top right, mean excitatory cell firing rate (Hz). Bottom left, mean event duration (s). Bottom right, mean event frequency (Hz). Each point is the mean of data combined across all population-burst events of all networks at each parameter point. Data from the same simulations as Figure 3. (f) Network parameter dependence of several statistics quantifying the Bayesian decoding. Top left, p-value of the absolute weighted correlations (from a KS-test as calculated in (c)). Top right, the shift in the median absolute weighted correlation of actual events relative to shuffle events. Bottom left, the fraction of events with significant absolute weighted correlations relative to the distribution of absolute weighted correlations from time bin shuffles of the event. Bottom right, the mean entropy of the position probability of all time bins in decoded trajectories.

Both PBEs and preplay are significantly affected by the two network parameters (**Figure 4e**, f). The number of clusters and the extent of cluster overlap (indicated via mean cluster participation) affects PBE participation (**Figure 4e**, top left), firing rates (**Figure 4e**, top right), event durations (**Figure 4e**, bottom left), and event frequency (**Figure 4e**, bottom right). We find that significant preplay occurs only at moderate cluster overlap (**Figure 4f**, top left), where we also find the greatest increase from chance in the linearity of decoded trajectories (**Figure 4f**, top right). The fraction of events that are individually significant (determined by comparing the absolute weighted correlation of each decoded event against the set of absolute weighted correlations of its own shuffles) is similarly highest for modest cluster overlap (**Figure 4f**, bottom left). The mean entropy of position probability of each time bin of decoded trajectories is also highest for modest cluster overlap (**Figure 4f**, bottom right), meaning that high cluster overlap leads to more diffuse, less precise spatial decoding.

To test the robustness of our results to variations in input types, we simulated alternative forms of spatially modulated feedforward inputs. We found that with no parameter tuning or further modifications to the network, the model generates robust preplay with variations on the spatial inputs, including inputs of three linearly varying cues (**Figure 4—figure supplement 4a**) and two stepped cues (**Figure 4—figure supplement 4b-c**). The network is impaired in its ability to produce preplay with binary step location cues (**Figure 4—figure supplement 4d**), when there is no cluster bias (**Figure 4—figure supplement 4e**), and at greater values of cluster participation (**Figure 4—figure supplement 4f**).

Preplay is due to successive activations of individual clusters

Figure 4f indicates that PBEs are best decoded as preplay when cluster participation is only slightly above one, indicating a small, but non-zero, degree of cluster overlap. We hypothesized that this can be explained as balancing two counteracting requirements: 1) Sufficient cluster overlap is necessary for a transient increase in activity in one cluster to induce activity in another cluster, so as to extend any initiated trajectory; and 2) Sufficient cluster isolation is necessary so that, early in a transient, spikes from an excited cluster preferentially add excitement to the same cluster. A network with too much cluster overlap will fail to coherently excite individual clusters—rendering decoded positions to be spread randomly throughout the track—while a network with too little cluster overlap will fail to excite secondary clusters—rendering decoded positions to remain relatively localized.

We find that the dependence of preplay on cluster overlap can indeed be explained by the manner in which clusters participate in PBEs (**Figure 5**). An example PBE (**Figure 5a**) shows transient recruitment of distinct clusters, with only one cluster prominently active at a time. We define a cluster as ‘active’ if its firing rate exceeds twice the rate of any other cluster. We calculated the number of active clusters per event (**Figure 5b**) and the duration of each active cluster period (**Figure 5d**). We find that these statistics vary systematically with the network parameters (**Figure 5c**, e), in a manner consistent with the dependence of preplay on cluster overlap (**Figure 4f**). When there is modest overlap of an intermediate number of clusters, events involve sequential activation of multiple clusters that are each active sufficiently long to correspond to at least one of the time bins used for decoding (10 ms). **Figures 4** and **5** together indicate that high-quality preplay arises via a succession of individually active clusters. Such succession requires a moderate degree of cluster overlap, but this must be combined with sufficient cluster isolation to promote independent activation of just one cell assembly for the duration of each time-bin used for decoding.

The results of **Figure 5** suggest that cluster-wise activation may be crucial to preplay. One possibility is that the random overlap of clusters in the network spontaneously produces biases in sequences of cluster activation which can be mapped onto any given environment. To test this, we looked at the pattern of cluster activations within events. We found that sequences of three active clusters were not more likely to match the track sequence than chance (**Figure 5—figure**

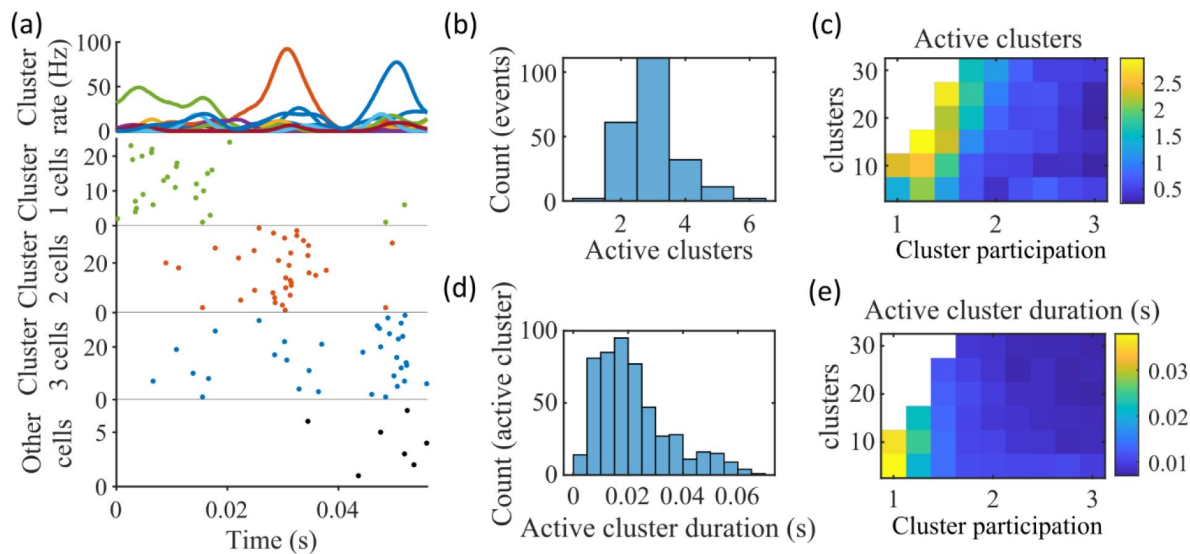


Figure 5

Coherent spiking within clusters supports preplay

(a) Example event. Top, spike rates averaged across neurons of individual clusters: Each firing rate curve is the smoothed mean firing rate across the population of cells belonging to each cluster. We defined clusters as “active” if at any point their rates exceed twice that of any other cluster. Three clusters meet the criterion of being active (green, then red, then blue). Bottom, raster plots: Cells belonging to each of the active clusters are plotted separately in the respective colors. Cells in multiple clusters contribute to multiple population curves, and cells in multiple active clusters appear in multiple rows of the raster plot. Cells that participate but are not in any active clusters are labeled “Other cells” and plotted in black. Only active cells are plotted. **(b)** For the fiducial parameter set (15 clusters, mean cluster participation of 1.25), the distribution over events of the number of active clusters per event. **(c)** The mean number of active clusters per event as a function of the network parameters. Same data as that used for the parameter grids in earlier figures. **(d)** For the fiducial parameter set (15 clusters, mean cluster participation of 1.25), the distribution of durations of active clusters for all active cluster periods across all events. The active duration was defined as the duration for which an active cluster remained the most-active cluster. **(e)** The mean active cluster duration as a function of the network parameters.

supplement 1a [↗](#)). This suggests that preplay is not dependent on a particular biased pattern in the sequence of cluster activation. We then asked if the number of clusters that were active influenced preplay quality. We split the preplay events by the number of clusters that were active during each event and found that the median preplay shift relative to shuffled events with the same number of active clusters decreased with the number of active clusters (Spearman's rank correlation, $p=0.0019$, $\rho=-0.13$; **Figure 5—figure supplement 1b** [↗](#)).

Cluster identity is sufficient for preplay

The pattern of preplay significance across the parameter grid in **Figure 4f** [↗](#) shows that preplay only occurs with modest cluster overlap, and the results of **Figure 5** [↗](#) show that this corresponds to the parameter region that supports transient, isolated cluster-activation.

This raises the question of whether cluster-identity is sufficient to explain preplay. To test this, we took the sleep simulation population burst events from the fiducial parameter set and performed decoding after shuffling cell identity in three different ways. We found that when the identity of all cells within a network are randomly permuted the resulting median preplay correlation shift is centered about zero (t-test 95% confidence interval, -0.2018 to 0.0012) and preplay is not significant (distribution of p-values is consistent with a uniform distribution over 0 to 1, chi-square goodness-of-fit test $p=0.4436$, chi-square statistic=2.68; **Figure 6a** [↗](#)). However, performing decoding after randomly shuffling cell identity between cells that share membership in a cluster does result in statistically significant preplay for all shuffle replicates, although the magnitude of the median correlation shift is reduced for all shuffle replicates (**Figure 6b** [↗](#)). The shuffle in **Figure 6b** [↗](#) does not fully preserve cell's cluster identity because a cell that is in multiple clusters may be shuffled with a cell in either a single cluster or with a cell in multiple clusters that are not identical. Performing decoding after doing within-cluster shuffling of only cells that are in a single cluster results in preplay statistics that are not statistically different from the unshuffled statistics (t-test relative to median shift of un-shuffled decoding, $p=0.1724$, 95% confidence interval of -0.0028 to 0.0150 relative to the reference value; **Figure 6c** [↗](#)). Together these results demonstrate that cluster-identity is sufficient to produce preplay.

Mean relative spike rank correlates with place field location

While cluster-identity is sufficient to produce preplay (**Figure 6b** [↗](#)), the shuffle of **Figure 6c** [↗](#) is incomplete in that cells belonging to more than one cluster are not shuffled. Together, these two shuffles leave room for the possibility that individual cell-identity may contribute to the production of preplay. It might be the case that some cells fire earlier than others, both on the track and within events. To test the contribution of individual cells to preplay, we calculated for all cells in all networks of the fiducial parameter point their mean relative spike rank and tested if this is correlated with the location of their mean place field density on the track (**Figure 7** [↗](#)). We find that there is no relationship between a cell's mean relative within-event spike rank and its mean place field density on the track (**Figure 7a** [↗](#)). This is the case when the relative rank is calculated over the entire network (**Figure 7** [↗](#), “Within-network”) and when the relative rank is calculated only with respect to cells with the same cluster membership (**Figure 7** [↗](#), “Within-cluster”). However, because preplay events can proceed in either track direction, averaging over all events would average out the sequence order of these two opposite directions. We performed the same correlation but after reversing the spike order for events with a negative slope in the decoded trajectory (**Figure 7b** [↗](#)). To test the significance of this correlation, we performed a bootstrap significance test by comparing the slope of the linear regression to the slope that results when performing the same analysis after shuffling cell identities in the same manner as in **Figure 6c** [↗](#). We found that the linear regression slope is greater than expected relative to all three shuffling methods for both the within-network mean relative rank correlation (**Figure 6c** [↗](#)) and the within-cluster mean relative rank correlation (**Figure 6d** [↗](#)).

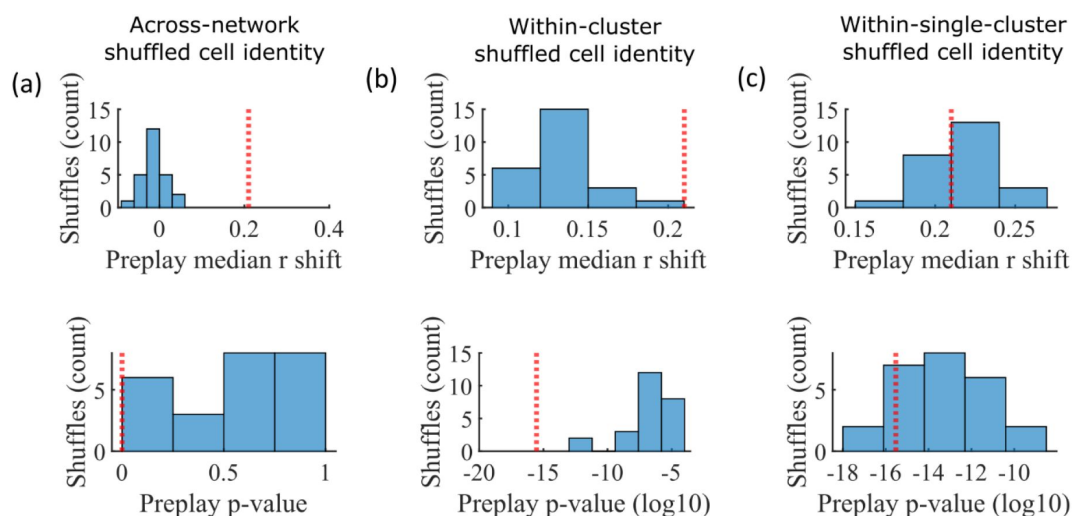


Figure 6

Preplay is abolished when events are decoded with shuffled cell identities but is preserved if cell identities are shuffled only within clusters.

We decoded the population burst events from the fiducial parameter set simulations after randomly shuffling cell identities in three different manners (a-c, 25 replicates for each condition) and compared the resulting preplay statistics to the unshuffled result (red line). (a) Randomly shuffling cell identities results in median preplay correlation shifts near zero (top, 100th percentile of shuffles), with p-values distributed approximately uniformly (bottom, 0th percentile of shuffles). (b) Randomly shuffling cell identities within clusters reduces the magnitude of the median preplay correlation shifts (top, 100th percentile of shuffles) but preserves the statistical significance of preplay (bottom, 0th percentile of shuffles). (c) Randomly shuffling cell identities within clusters for only cells that belong to a single cluster results in median preplay correlation shifts that are similar to the unshuffled result (top, 36th percentile of shuffles) and are all statistically significant (bottom, 12th percentile of shuffles).

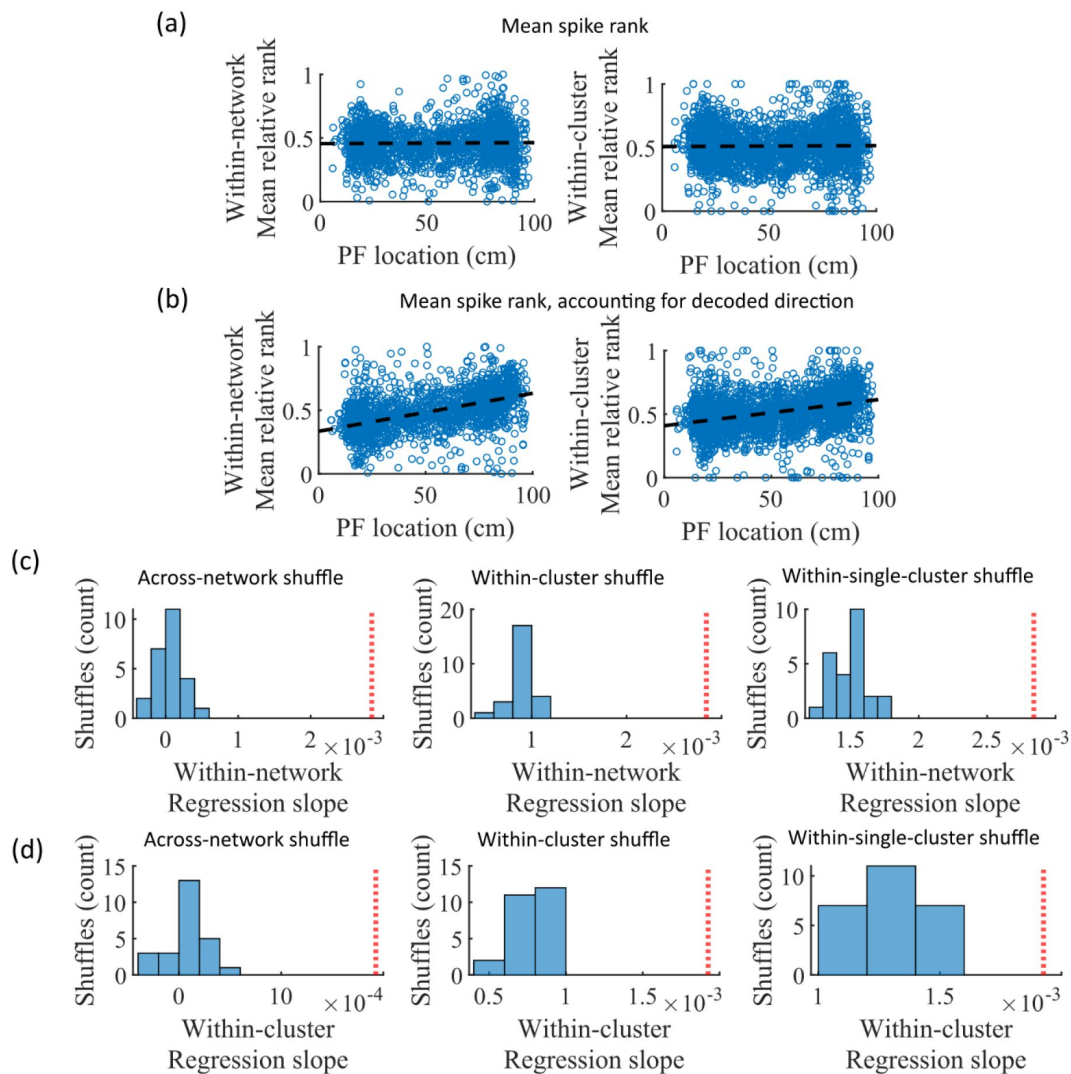


Figure 7

Place cells' mean event rank are correlated with their place field location when accounting for decode direction.

(a) Mean within-event relative spike rank of all place cells as a function of the location of their mean place field density on the track for networks at the fiducial parameter set. Left, mean relative rank with respect to all cells in each network. Right, mean relative rank with respect to only cells that share cluster membership. **(b)** Same as (a), but after accounting for the direction of each events' decoded trajectory. If the decoded slope for a given event was negative, then the order of spiking in that event was reversed. **(c-d)** Comparison of the regression slopes from (b) to the distribution of slopes that results from applying the same analysis after shuffling cell identities as in [Figure 6](#). **(c)** The within-network regression slope is significant relative to all three methods of shuffling cell identity. **(d)** Same as (c), but for the within-cluster regression slope.

Small-world index correlates with preplay

We noticed that the highest quality of decoded trajectories ([Figure 4f](#)) seemed to arise in networks with the highest small-world index (SWI; [Figure 1g](#)). In order to test this, we simulated different sets of networks with both increased and decreased global E-to-E connection probability, p_c . Changing p_c , in addition to varying the number of clusters and the mean cluster participation, impacted the SWI of the networks ([Figure 8](#), left column).

We hypothesized that independent of p_c , a higher SWI would correlate with improved preplay quality. To test this, we simulated networks across a range of parameters for three p_c values: a decrease of p_c by 50% to 0.04, the fiducial value of 0.08, and an increase by 50% to 0.12 ([Figure 8a-c](#), respectively). For the decreased and increased p_c cases, the E-to-E connection strength was respectively doubled or reduced to 2/3 of the fiducial strength to keep total E-to-E input constant. For each parameter combination, we quantified preplay quality as the rightward shift in median absolute weighted correlation of decoded preplay events versus shuffled events (as in [Figure 4f](#), top right). We then asked if there was a correlation between that quantification of preplay quality and SWI.

Across all three p_c values, SWI significantly correlated with improved preplay both across parameter sets ([Figure 8](#), center column) and across individual networks ([Figure 8](#), right column). These results support our prediction that higher small-world characteristics correspond to higher-quality preplay dynamics regardless of average connectivity.

Preplay significantly decodes to linear trajectories in arbitrary environments

Information about each environment enters the network via the feed-forward input connection strengths, which contain cluster-dependent biases. A new environment is simulated by re-ordering those input biases. We first wished to test that a new environment simulated in such a manner produced a distinct set of place fields. We therefore simulated place maps for leftward and rightward trajectories on linear tracks in two distinct environments ([Figure 9a](#)). The two maps with different directions of motion showed very high correlations when in the same environment ([Figure 9b](#), blue) while the comparisons of trajectories across environments show very low correlations ([Figure 9b](#), red). Cells that share membership in a cluster will have some amount of correlation in their remapping due to the cluster-dependent cue bias, which is consistent with experimental results (Hampson et al., 1996; Pavlides et al., 2019), but the combinatorial nature of cluster membership renders the overall place field map correlations low ([Figure 9b](#)). We also performed simulations with extra laps of running and calculated the correlations between paired sets of place fields produced by random, independent splits of trials of the same trajectory. The distribution of these correlations was similar to the distribution of within-environment correlations (comparing opposite trajectories with the same spatial input), showing no significant *de novo* place-field directionality. This is consistent with hippocampal data in which place-field directionality is initially low in novel environments and increases with experience (Frank et al., 2004; Navratilova et al., 2012; Shin et al., 2019).

Because we simulated preplay without any location-specific inputs, we expected that the set of spiking events that significantly decode to linear trajectories in one environment ([Figure 4](#)) should decode with a similar fidelity in another environment. Therefore, we decoded each PBE four times, once with the place fields of each trajectory ([Figure 9c-e](#)). Since the place field map correlations are high for trajectories on the same track and near zero for trajectories on different tracks, any individual event would be expected to have similar decoded trajectories when decoding based on the place fields from different trajectories in the same environment and dissimilar decoded trajectories when decoding based on place fields from different environments.

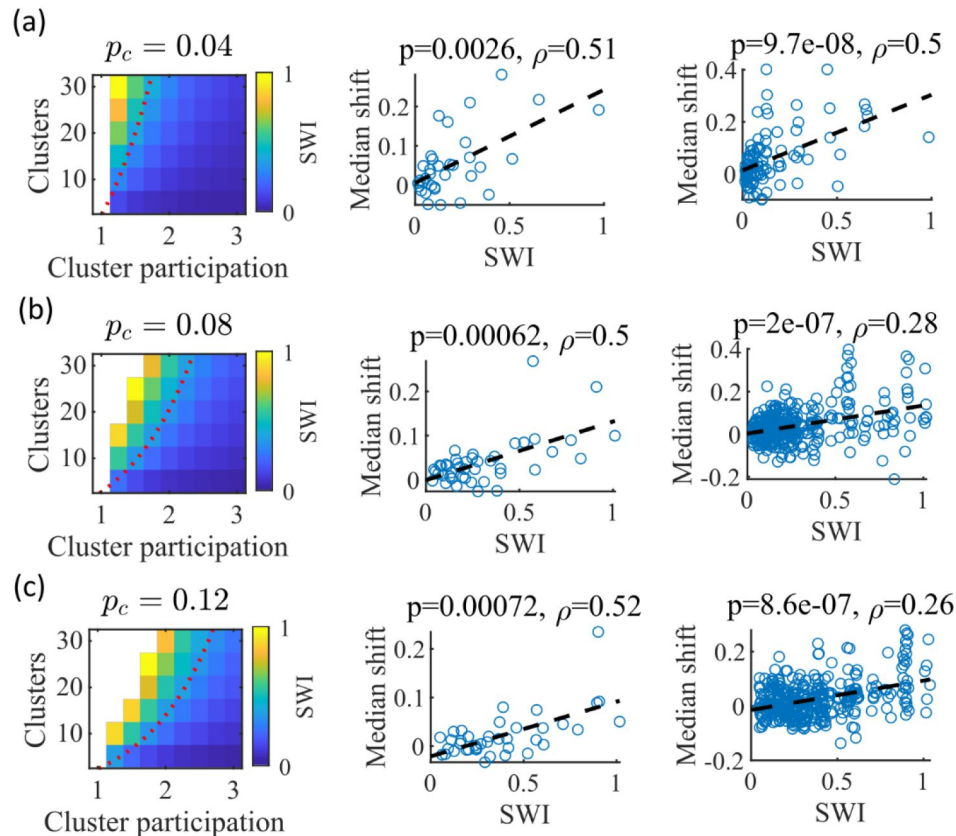


Figure 8

The Small-World Index of networks correlates with preplay quality

(a-c) Left column, the Small-World Index (SWI; plotted as color) is affected by the global E-to-E connection probability, p_c . Red dotted line indicates a contour line of SWI = 0.4. This boundary shifts downward as p_c increases. Center column, across parameter points in the network parameter grid, SWI correlates with an increase in the median absolute weighted correlation of decoded trajectories relative to shuffles (e.g. this corresponds in [Figure 4c](#) to the rightward shift of the CDF of measured absolute weighted correlations relative to the shuffle events). Each point is produced by analysis of all events across 10 networks from one parameter point in the grid on the left. Right column, same as the center column but each point is data from each of the 10 individual networks per parameter set. P-value and correlation, ρ , are calculated from Spearman's rank-order correlation test. Dashed line is the least-squares fit. **(a)** Data from a parameter grid where the E-to-E connection probability was decreased by 50% and the E-to-E connection strength was doubled from their fiducial values used in prior figures. **(b)** Data from the same parameter grid as [Figures 3-5](#). **(c)** Data from a parameter grid where the E-to-E connection probability was increased by 50% and the E-to-E connection strength scaled by two-thirds from their fiducial values.

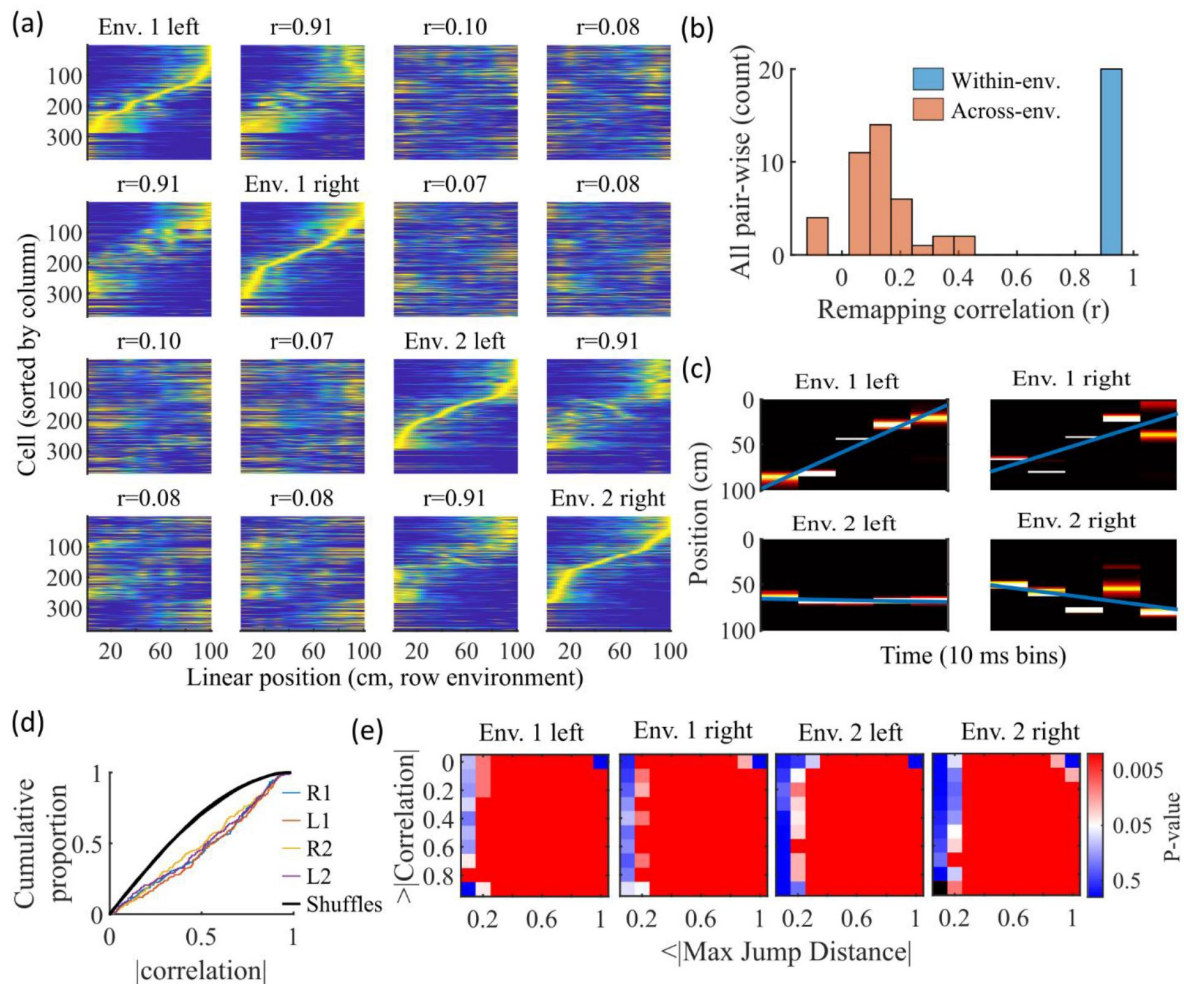


Figure 9

Trajectories decoded from population-burst events are significantly correlated with linear trajectories in arbitrary environments

(a) Place fields from a single network with simulated runs in both directions of travel on a linear track in two different environments. Each column of panels is the set of place fields for the trajectory labeled on the diagonal. Each row of panels has cells sorted by the order of place-field peaks for the trajectory labeled on the diagonal. The r values are the correlations between the corresponding remapped trajectory with its comparison on the diagonal. Note that correlations mirrored across the diagonal are equal because they correspond only to a change in the labels of the dimensions of the population rate vectors, which does not affect the vector correlation. **(b)** Distribution of the place-field map correlations across trajectories from both directions of travel on a linear track in two environments for 10 networks. Blue is the distribution of correlations for all left vs right place-field maps from the same environment. Red is the correlations from all pair-wise comparisons of trajectories from different environments. **(c)** An example event with a statistically significant trajectory when decoded with place fields from Env. 1 left (absolute correlation at the 99th percentile of time-bin shuffles) but not when decoded with place fields of the other trajectories (78th, 45th, and 63rd percentiles for Env. 1 right, Env. 2 left, and Env. 2 right, respectively). **(d)** An entire set of PBEs shows similar levels of absolute weighted correlations when decoded with different sets of place fields. In color are CDFs of absolute weighted correlations of decoded trajectories with leftward and rightward linear trajectories in each of the two environments (R1 and L1 are the rightward and leftward trajectories of environment one. R2 and L2 are the rightward and leftward trajectories of environment two). In black (all overlapping) are the corresponding absolute weighted correlations with each of the 4 trajectories arising from decoding of shuffled events. **(e)** The significance of linearity of decoded trajectories indicated by p-value in color (as in Figure 4b) from decoding the same PBEs with the four different environment place fields. Black squares indicate criteria that were not met by any events (either shuffled or actual). Env. 1 left is the same as that shown in Figure 4d.

A given event with a strong decoded trajectory based on the place fields of one environment would then be expected to have a weaker decoded trajectory when decoded with place fields from an alternative environment (**Figure 9c**). The distributions of absolute weighted correlations arising from decoding of PBEs according to each of the four sets of place fields was consistent across environments (**Figure 9d**, colored lines) and all were significantly rightward shifted (indicating greater absolute weighted correlation) when compared to those absolute weighted correlations arising from the corresponding shuffled events (**Figure 9d**, overlapping black lines). If we consider both absolute weighted correlation and jump-distance thresholds as in **Figure 4d**, we find that the matrices of p-values are consistent across environments (**Figure 9e**). In summary, without environment-specific or place-field dependent pre-assigned internal wiring, the model produces population-burst events, which, as an ensemble, show significant preplay with respect to any selected environment.

Discussion

Our work shows that spontaneous population bursts of spikes that can be decoded as spatial trajectories can arise in networks with clustered random connectivity without pre-configured maps representing the environment. In our proposed model, excitatory neurons were randomly clustered with varied overlap and received feed-forward inputs with random strengths that decayed monotonically from the boundaries of a track (**Figure 1**). Even though the model neural circuit lacked place-field like input and lacked environment-specific internal wiring, the network exhibited both realistic place fields (**Figures 2, 3**) and spontaneous preplay of novel, future environments (**Figures 2, 4**).

We validated our modeling results by applying the same analyses to a previously collected experimental data set (Shin et al., 2019). Indeed, we replicated the general finding of hippocampal preplay found previously in Farooq et al., 2019, although the p-value matrix for our experimental data (**Figure 4b**) is significant across a smaller range of threshold values than found in their prior work. This is likely due to differences in statistical power. The pre-experience sleep sessions of Shin et al., 2019 were not longer than half an hour for each animal, while the pre-experience sleep sessions of Farooq et al., 2019 lasted 2-4 hours. However, finding statistically significant hippocampal preplay in an experiment not designed for studying preplay shows that the general result is robust to a number of methodological choices, including shorter recording sessions, use of a W-track rather than linear track, and variations in candidate event detection criterion.

Although our model is a model of the recurrently connected CA3 region and the data set we analyze (Shin et al., 2019) comes from CA1 cells, the qualitative comparisons we make here are nevertheless useful. Despite some statistically significant quantitative differences, the general properties of place fields that we consider are qualitatively similar across CA1 and CA3 (Sheintuch et al., 2023; Harvey et al., 2020), and CA3 and CA1 generally reactivate in a coordinated manner (O'Neil et al., 2008; Karlsson and Frank, 2009).

The model parameters that controlled the clustering of the recurrent connections strongly influenced preplay and place-field quality. Moderate overlap of clusters balanced the competing needs for both a) sufficiently isolated clusters to enable cluster-wise activation and b) sufficiently overlapping clusters to enable propagation of activity across clusters (**Figure 5**). In our clustered network structure, such a balance in cluster overlap produces networks with small-world characteristics (Watts and Strogatz, 1998) as quantified by a small-world index (SWI; Neal, 2015; Neal, 2017). Networks with a high SWI, indicating high clustering (if two neurons are connected to the same third neuron, they are more likely than chance to be connected to each other) yet short paths (the mean number of connections needed to traverse from one neuron to any other), showed optimal preplay dynamics (**Figure 8**). The same networks could flexibly

represent distinct remapped environments (Leutgeb et al., 2004 [↗](#); Leutgeb et al., 2005 [↗](#); Alme et al., 2014 [↗](#)) solely through differences in scaling of feed-forward spatially linear input (**Figure 9** [↗](#)).

Across many species, small-world properties can be found at both the local neuronal network scale and the gross scale of the network of brain regions. At the neuronal connection scale, small-world properties have been reported in a number of networks, such as the *C. elegans* connectome (Watts and Strogatz, 1998 [↗](#); Humphries et al., 2008), the brainstem reticular formation (Humphries et al., 2006 [↗](#)), mouse visual cortex (Sadovsky and MacLean, 2014 [↗](#)), cultured rat hippocampal neurons (Antonello et al., 2022 [↗](#)), mouse prefrontal cortex (Luongo et al., 2016 [↗](#)), and connectivity within the entorhinal-hippocampal region in rats (She et al., 2016 [↗](#)). At the level of connected brain regions, small-world properties have been reported across the network of brain regions activated by fear memories in mice (Vetere et al., 2016), in the hippocampal-amygdala network in humans (Zhang et al., 2022 [↗](#)), and across the entire human brain (Liao et al., 2010).

Our results suggest that the preexisting hippocampal dynamics supporting preplay may reflect general properties arising from randomly clustered connectivity, where the randomness is with respect to any future, novel experience. The model predicts that preplay quality will depend on the network's balance of cluster isolation and overlap, as quantified by small-world properties. Synaptic plasticity in the recurrent connections of CA3 may primarily serve to reinforce and stabilize intrinsic dynamics, which could be established through a combination of developmental programming (Perin et al., 2011 [↗](#); Druckmann et al., 2014; Huszar et al., 2022) and past experiences (Bourjaily and Miller, 2011 [↗](#)), rather than creating spatial maps *de novo*. The particular neural activity associated with a given experience would then selectively reinforce the relevant intrinsic dynamics, while leaving the rest of the network dynamics unchanged.

Our model provides a general framework for understanding the origin of pre-configured hippocampal dynamics. Hebbian plasticity on independent, previously experienced place maps would produce effectively random clustered connectivity. The spontaneous dynamics of such networks would influence expression of place fields in future, novel environments. Together with intrinsic sequence generation, this could enable preplay and immediate replay generated by the preexisting recurrent connections.

Future modeling work should explore how experience-dependent plasticity may leverage and reinforce the dynamics initially expressed through preexisting clustered recurrent connections to produce higher-quality place fields and decoded trajectories during replay (Shin et al., 2019 [↗](#); Farooq et al., 2019 [↗](#)). Plasticity may strengthen connectivity along frequently reactivated spatiotemporal patterns. Clarifying interactions between intrinsic dynamics and experience-dependent plasticity will provide key insights into hippocampal neural activity. Additionally, the *in vivo* microcircuitry of CA3 is complex and includes aspects such as nonlinear dendritic computations and a variety of inhibitory cell types (Rebola et al., 2017 [↗](#)). This microcircuitry is crucial for explaining certain aspects of hippocampal function, such as ripple and gamma oscillogenesis (Ramirez-Villegas et al., 2017), but here we have focused on a minimal model that is sufficient to produce place cell spiking activity that is consistent with experimentally measured place field and preplay statistics.

Methods

To investigate what network properties could support preplay, we simulated recurrently connected networks of spiking neurons and analyzed their dynamics using standard hippocampal place cell analyses.

Neuron model

We simulate networks of Leaky Integrate-and-Fire (LIF) neurons, which have leak conductance, g_L , excitatory synaptic conductance, g_E , inhibitory synaptic conductance, g_I , spike-rate adaptation (SRA) conductance, g_{SRA} , and external feed-forward input synaptic conductance, g_{ext} . The membrane potential, V , follows the dynamics

$$\tau_m \frac{dV}{dt} = -g_L(V - E_L) - g_E(V - E_E) - g_I(V - E_I) - g_{SRA}(V - E_{SRA}) - g_{ext}(V - E_E)$$

where τ_m is the membrane time constant, E_L is the leak reversal potential, E_E is the excitatory synapse reversal potential, E_I is the inhibitory synapse reversal potential, E_{SRA} is the SRA reversal potential, and E_{ext} is the external input reversal potential. When the membrane potential reaches the threshold V_{th} , a spike is emitted and the membrane potential is reset to V_{reset} .

The changes in SRA conductance and all synaptic conductances follow

$$\tau_i \frac{dg_i}{dt} = -g_i$$

to produce exponential decay between spikes for any conductance i . A step increase in conductance occurs at the time of each spike by an amount corresponding to the connection strength for each synapse (W_{E-E} for E-to-E connections, W_{E-I} for E-to-I connections, and W_{I-E} for I-to-E connections), or by δ_{SRA} for g_{SRA} . Initial feed-forward input conductances were set to values approximating their steady-state values by randomly selecting values from a Gaussian with a mean of $W_{in} r_G \tau_E$ and a standard deviation of $\sqrt{W_{in}^2 r_G \tau_E}$. Initial values of the recurrent conductances and the SRA conductance were set to zero.

<u>Parameter</u>	<u>Value</u>	<u>Description</u>
τ_m	40 ms	Membrane time constant
C_m	0.4 nF	Membrane capacitance
d_t	0.1 ms	Simulation time step
g_L	10 nS	Leak conductance
E_L	−70 mV	Leak reversal potential
E_E	0 mV	Excitatory synaptic reversal potential
E_I	−70 mV	Inhibitory synaptic reversal potential
E_{SRA}	−80 mV	SRA reversal potential

V_{th}	−50 mV	Spike threshold
V_{reset}	−70 mV	Reset potential
τ_E	10 ms	Excitatory time constant
τ_I	3 ms	Inhibitory time constant
τ_{SRA}	30 ms	Spike-rate adaptation time constant
δ_{SRA}	3 pS	Spike-rate adaptation strength

Network structure

We simulated networks of $n = 500$ neurons, of which 75% were excitatory. Excitatory neurons were randomly, independently assigned membership to each of n_c clusters in the network. First, each neuron was randomly assigned membership to one of the clusters. Then, each cluster was assigned a number— $n_E(\mu_c - 1)/n_c$ rounded to the nearest integer—of additional randomly selected neurons such that each cluster had identical numbers of neurons, $n_{E,clust} = n_E(\mu_c/n_c)$, and mean cluster participation, μ_c , reached its goal value.

E-to-E recurrent connections were randomly assigned on a cluster-wise basis, where only neurons that shared membership in a cluster could be connected. The within-cluster connection probability was configured such that the network exhibited a desired global E-to-E connection probability p_c . Given the total number of possible connections between excitatory neurons is $C_{tot} = n_E(n_E - 1)$ and the total number of possible connections between excitatory neurons within all clusters is $C_{clust} = n_{E,clust}(n_{E,clust} - 1)n_c$, we calculated the within-cluster connection probability as $p_c(C_{tot}/C_{clust})$. That is, given the absence of connections between clusters (clusters were coupled by the overlap of cells) the within-cluster connection probability was greater than p_c so as to generate the desired total number of connections equal to $p_c C_{tot}$.

All E-to-I and I-to-E connections were independent of cluster membership and existed with a probability p_{cI} . There were no I-to-I connections. p_c , n_c , and μ_c were varied for some simulations. Except where specified otherwise, all parameters took the fiducial value shown in the table below.

The network visualization in **Figure 1c** [↗](#) was plotted based on the first 2 dimensions of a t-distributed stochastic neighbor embedding of the connectivity between excitatory cells using the MATLAB function *tsne*. The feature vector for each excitatory cell was the binary vector indicating the presence of both input and output connections.

<u>Parameter</u>	<u>Fiducial</u>	
	<u>Value</u>	<u>Description</u>
n	500	Number of neurons
n_E	375	Number of excitatory neurons
n_c or "clusters"	15	Number of clusters
μ_c or "cluster participation"	1.25	Mean cluster membership per neuron
p_c	0.08	E-to-E connection probability
p_{cI}	0.25	E-to-I and I-to-E connection probability
W_{E-E}	220 pS	E-to-E synaptic conductance step increase
W_{E-I}	400 pS	E-to-I synaptic conductance step increase
W_{I-E}	400 pS	I-to-E synaptic conductance step increase

Network inputs

All excitatory neurons in the network received three different feed-forward inputs (**Figure 1b** [↗](#)). Two inputs were spatially modulated, with rates that peaked at either end of the track and linearly varied across the track to reach zero at the opposite end. One input was a context cue that was position independent. All excitatory cells received unique Poisson spike trains from each of the three inputs at their position-dependent rates. Inhibitory cells received only the context input.

The connection strength of each feed-forward input to each neuron was determined by an independent and a cluster-specific factor.

First, strengths were randomly drawn from a log-normal distribution $e^{\mu+\sigma N}$, where N is a zero-mean, unit variance Normal distribution, $\mu = \ln\left(\frac{W_{in}^2}{\sigma_{in}^2 + W_{in}^2}\right)$ and $\sigma = \sqrt{\ln\left(\frac{\sigma_{in}^2}{W_{in}^2 + 1}\right)}$ for mean strength W_{in} and standard deviation σ_{in} for the location cues, with σ_{in} replaced by $\sigma_{context}$ for the context cue. Each environment and the sleep session had unique context cue input weights. For model simplicity, the mean input strength W_{in} for all inputs was kept the same for both E and I cells in both the awake and sleep conditions, but the strength of the resulting context input was then scaled by some factor f_x for each of the 4 cases to accommodate for the presence, or lack thereof, of the additional current input from the location cues. These scaling factors were set at a level that generated appropriate levels of population activity. During simulation of linear track traversal, the context cue to excitatory cells was scaled down by $f_{E-awake}$ to compensate for the added excitatory drive of the location cue inputs, and the context cue input to I cells was not changed ($f_{I-awake} = 1$). During sleep simulation, the context cue input to E cells was not scaled ($f_{E-sleep} = 1$) but the context cue input to I cells was scaled down by $f_{I-sleep}$.

Second, to incorporate cluster-dependent correlations in place fields, a small ($\leq 4\%$) location cue bias was added to the randomly drawn feed-forward weights based on each neuron's cluster membership. For each environment, the clusters were randomly shuffled and assigned a normalized rank bias value, such that the first cluster had a bias of -1 (corresponding to a rightward cue preference) and the last cluster had a bias of +1 (leftward cue preference). A neuron's individual bias was calculated as the mean bias of all clusters it belonged to, multiplied by the scaling factor σ_{bias} . The left cue weight for each neuron was then scaled by 1 plus its bias, and the right cue weight was scaled by 1 minus its bias. In this way, the feed-forward input tuning was biased based on the mean rank of a neuron's cluster affiliations for each environment. The addition of this bias produced correlations in cells' spatial tunings based on cluster membership, but, importantly, this bias was not present during the sleep simulations, and it did not lead to high correlations of place-field maps between environments (**Figure 9b** [↗](#)).

Parameter	Value	Description
r_G	5000 Hz	Peak Poisson input rate
W_{in}	72 pS	Mean strength of the input synapses
σ_{in}	5 pS	Standard deviation of the location cue input synapses
$\sigma_{context}$	1.25 pS	Standard deviation of the context cue input synapses
σ_{bias}	0.04	Location bias scale
$f_{E-awake}$	0.1	E-cell context cue input scaling during awake simulation
$f_{E-sleep}$	1	E-cell context cue input scaling during sleep simulation
$f_{I-awake}$	1	I-cell context cue input scaling during awake simulation
$f_{I-sleep}$	0.75	I-cell context cue input scaling during sleep simulation

Simulation

For a given parameter set, we generated 10 random networks. We simulated each network for one sleep session of 120 s and for five 2-s long traversals of each of the two linear trajectories on each track. For the parameter grids in **Figures 3** and **4** we simulated 20 networks with 300 s long sleep sessions in order to get more precise empirical estimates of the simulation statistics. For analysis comparing place-field reliability, we simulated 10 traversals of each trajectory.

To compare coding for place vs time, we performed repeated simulations for the same networks at the fiducial parameter point with 1.0x and 2.0x of the original track traversal speed. We then combined all trials for both speed conditions to calculate both place fields and time fields for each cell from the same linear track traversal simulations. The place fields were calculated as described below (average firing rate within each of the fifty 2-cm long spatial bins across the track) and the time fields were similarly calculated but for fifty 40-ms time bins across the initial two seconds of all track traversals.

Place field analysis

Place-field rate maps

We followed the methods of [Shin et al., 2019](#) to generate place fields from the spike trains. We calculated for each excitatory cell its trial-averaged occupancy-discounted firing rate in each 2 cm spatial bin of the 1 m long linear track. Note that the occupancy-discounting term is uniform across bins, so it has no impact in our model, because we simulated uniform movement speed. We then smoothed this with a Gaussian kernel with a 4 cm standard deviation. For statistics quantifying place-field properties and for Bayesian decoding, we considered only excitatory cells with place-field peaks exceeding 3 Hz as in [Shin et al., 2019](#).

Place-field specificity

Place-field specificity was defined as 1 minus the fraction of the spatial bins in which the place field's rate exceeded 25% of its maximum rate ([Shin et al., 2019](#)).

Place-field spatial information

The spatial information of each cells' place field was calculated as

$$\text{Spatial Information} = \sum_i p_i \left(\frac{r_i}{\bar{r}} \right) \log_2 \left(\frac{r_i}{\bar{r}} \right)$$

where p_i is the probability of being in spatial bin i , r_i is the place field's rate in spatial bin i , and $\bar{r}$ is the mean rate of the place field ([Sheintuch et al., 2023](#)). Given the division of the track into 50 spatial bins, spatial information could vary between 0 for equal firing in all bins and $\log_2(50) \cong 5.6$ for firing in only a single bin. Spatial information of 1 is equivalent, for example, to equal firing in exactly one half of the bins and no firing elsewhere.

Distribution of peaks

We used two measures to quantify the extent to which place-field peaks were uniformly distributed across the track. In our first measure, we calculated the Kullback-Leibler divergence of the distribution of peaks from a uniform distribution, as

$$D_{KL} = - \sum_i p_i^{\text{data}} \log_2 \left(\frac{p_i^{\text{uniform}}}{p_i^{\text{data}}} \right)$$

where p_i^{data} is the fraction of cells with peak firing rates in the i^{th} spatial bin and p_i^{uniform} is $1/50$, i. e., the fraction expected from a uniform distribution (Sheintuch et al., 2023 [↗](#)). Similarly, the range for spatial information, D_{KL} is bounded between zero for a perfectly uniform distribution of peaks and $\log_2(50) \cong 5.6$ if all peaks were in a single bin. D_{KL} of 1 is equivalent, for example, to all peaks being uniformly spread over one half of the bins in the track.

For our second measure, we calculated the fraction of place cells whose peak firing rate was in the central third of the track. Since inputs providing spatial information only peaked at the boundaries of the track, the central third was ubiquitously the most depleted of high firing rates.

Place-field map correlations

To compare the similarity of place fields across different trajectories, we calculated the correlation between the place-field rate maps of each pair of trajectories. For each spatial bin, we calculated the Pearson correlation coefficient between the vector of the population place-field rates of the two trajectories. We then averaged the correlation coefficients across all spatial bins to get the correlation between the two trajectories.

PBE detection

We detected candidate preplay events in the simulated data by identifying population-burst events (PBEs). During the simulated sleep period, we calculated the mean rate of the population of excitatory cells, which defines the population rate, smoothed with a Gaussian kernel (15 ms standard deviation). We then detected PBEs as periods of time when the population rate exceeded 1 standard deviation above the mean population rate for at least 30 ms. We also required the peak population rate to exceed 0.5 Hz (corresponding to 5-6 spikes per 30ms among excitatory cells) in order for the rate fluctuation to qualify as a PBE. We then combined PBEs into a single event if their start and end times were separated by less than 10 ms.

Sharp-wave ripple detection

Because of the reduced number of recorded cells relative to the simulated data, we detected candidate events in the Shin et al., 2019 [↗](#) data with a method that incorporated the ripple band oscillation power in the local field potential (LFP) in addition to the population spiking activity. We first calculated the smoothed firing rate for each excitatory neuron by convolving its spikes with a Gaussian kernel (100 ms standard deviation) and capping at 1 to prevent bursting dominance. We then computed the z-scored population firing rate from the capped, smoothed single-neuron rates. Additionally, we calculated the z-scored, ripple-filtered envelope of the tetrode-averaged LFP. We then summed these two z-scores and detected peaks that exceeded 6 for at least 10 ms and exceeded the neighboring regions by at least 6 (*MinPeakHeight*, *MinPeakWidth*, and *MinPeakProminence* of the MATLAB function *findpeaks*, respectively). Candidate events were defined as periods around detected peaks, spanning from when the z-score sum first dipped below 0 for at least 5 ms before the peak to after the peak when it again dipped below 0 for at least 5 ms. We additionally required that the animal be immobile during the event.

Bayesian decoding

We performed Bayesian decoding of candidate preplay events following the methods of [Shin et al., 2019](#). We performed decoding on all candidate events that had at least 5 active cells and exceeded at least 50 ms in duration. Spikes in the event were binned into 10 ms time bins. We decoded using the place fields for each trajectory independently. The description provided below is for the decoding using the place fields of one particular trajectory.

For each time bin of each event, we calculated the location on the track represented by the neural spikes based on the place fields of the active cells using a memoryless Bayesian decoder

$$P(x|s) = \frac{P(s|x)P(x)}{P(s)}$$

where $P(x|s)$ is the probability of the animal being in spatial bin x given the set of spikes s that occurred in the time bin, $P(s|x)$ is the probability of the spikes s given the animal is in spatial bin x (as given by the place fields), $P(x)$ is the prior probability of the animal being in spatial bin x , and $P(s)$ is the probability of the spikes s .

We assumed a uniform prior probability of position, $P(x)$. We assumed that the N cells firing during the event acted as independent Poisson processes in order to calculate

$$P(s|x) = \prod_i^N \frac{(\tau r_i(x))^{s_i} e^{-\tau r_i(x)}}{s_i!}$$

where τ is the time bin window duration (10 ms), $r_i(x)$ is the place-field rate of cell i in spatial bin x and s_i is the number of spikes from cell i in the time bin.

This allows us to calculate the posterior probability of position for each time bin as

$$P(x|s) = C \left(\prod_i^N r_i(x)^{s_i} \right) e^{-\tau \sum_i^N r_i(x)}$$

where C is a normalization constant, which accounts for the position-independent term, $P(s)$.

Bayesian decoding statistical analyses

We analyzed the significance of preplay using the methods of [Farooq et al., 2019](#) (see also [Silva et al., 2015](#)). We computed two measures of the sequence quality of each decoded event: the event's absolute weighted correlation and its jump distance. The absolute weighted correlation is the absolute weighted Pearson's correlation of decoded position across the event's time bins. For each decoded event, we calculate the weighted correlation between space and time with MATLAB's *fitlm* function using the decoded probability in each space-time bin (10 ms by 2 cm) as the weight for the corresponding location in the correlation. The absolute value of the weighted correlation is used in order to account for both forward and reverse preplay. The jump distance is the maximum of the distance between the positions of peak probability for any two adjacent 10-ms time bins in the event, quantified as fraction of the track length.

For each event, we generated 100 shuffled events by randomly permuting the order of the 10-ms time bins. We then calculated the weighted correlation and jump distance for each shuffled event in the same manner as for the actual events. For each simulated parameter set, we combined all events from the 10 simulated networks.

Following the methods of Farooq et al., 2019 [\[1\]](#), we calculated the statistical significance of the population of preplay events using two different methods. First, we used the Kolmogorov-Smirnov (KS) test to compare the distributions of absolute weighted correlations obtained from the actual events and the shuffled events (**Figure 4a** [\[1\]](#), c).

Second, we used a bootstrap test to compare the fraction of high-quality events—defined as having both high absolute weighted correlations and low maximum jump distance—relative to shuffles (**Figure 4b,d** [\[1\]](#)). To perform the bootstrap test, we created a grid of thresholds for minimum absolute weighted correlation and maximum jump distance, and for each combination of thresholds we calculated the fraction of actual events that exceeded the minimum absolute weighted correlation threshold and did not exceed the maximum jump distance threshold. Then, we generated 100 data sets of shuffled events by randomly permuting the order of the 10-ms time bins for each actual event and calculated the fraction of events meeting the same pairs of thresholds for each shuffled data set. The p-value of the fraction of high-quality events was then calculated as the fraction of shuffled data sets with a higher fraction of high-quality events.

To test the significance of each event's absolute weighted correlation individually, we calculated the event's p-value as the fraction of the event's own shuffles that had a higher absolute weighted correlation than the un-shuffled event (**Figure 4f** [\[1\]](#), bottom left).

The spatial entropy H of a decoded event was calculated as the mean over its time bins of the entropy of the decoded position probability in each time bin, using the equation

$$H = - \sum_i p_i \log_2(p_i)$$

for each time bin, where p_i is the decoded position probability for spatial bin i .

Cell identity shuffled decoding

We performed Bayesian decoding on the fiducial parameter set after shuffling cell identities in three different manners (**Figures 6** [\[1\]](#) and **7** [\[1\]](#)). To shuffle cells in a cluster-independent manner (“Across-network shuffle”), we randomly shuffled the identity of cells during the sleep simulations. To shuffle cells within clusters (“Within-cluster shuffle”), we randomly shuffled cell identity only between cells that shared membership in at least one cluster. To shuffle cells within only single clusters (“Within-single-cluster shuffle”), we shuffled cells in the same manner as the within-cluster shuffle but excluded any cells from the shuffle that were in multiple clusters.

To test for a correlation between spike rank during sleep PBEs and the order of place fields on the track (**Figure 7** [\[1\]](#)), we calculated for each excitatory cell in each network of the fiducial parameter set its mean relative spike rank and correlated that with the location of its mean place field density on the track (**Figure 7a** [\[1\]](#)). To account for event directionality, we calculated the mean relative rank after inverting the rank within events that had a negatively sloped decoded trajectory (**Figure 7b** [\[1\]](#)). We calculated mean relative rank for each cell relative to all cells in the network (“Within-network mean relative rank”) and relative to only cells that shared cluster membership with the cell (“Within-cluster mean relative rank”). We then compared the slope of the linear regression between mean relative rank and place field location against the slope that results when applying the same analysis to each of the three methods of cell identify shuffles for both the within-network regression (**Figure 7c** [\[1\]](#)) and the within-cluster regression (**Figure 7d** [\[1\]](#)).

Small-world index

The small-world index (SWI) was calculated following the method of Neal, 2015 (see also Neal, 2017). It was defined as

$$\text{SWI} = \frac{(L - L_l)}{(L_r - L_l)} \times \frac{(C - C_r)}{(C_l - C_r)}$$

where L is the mean path distance and C is the clustering coefficient of the network. We calculate L as the mean over all ordered pairs of excitatory cells of the shortest directed path length from the first to the second cell. We calculate C as the ratio of the number of all triplets of excitatory cells that are connected in either direction over the number of all triplets that could form, following the methods of Fagiolo, 2007 for directed graphs. L_l and C_l are the expected values for a one-dimensional ring lattice network with the same size and connection probability (in which connections are local such that there are no connections between cells with a greater separation on the ring than that of any pairs without a connection). And L_r and C_r are the expected values for a random network of the same size and connection probability. A network with a high SWI index is therefore a network with both a high clustering coefficient, similar to a ring lattice network, and small mean path length, similar to a random network.

For directed graphs of size n , average degree k , and global connection probability p

$$C_r = p \text{ (Fagiolo, 2007),}$$

$$L_r = \frac{\ln(n) - \gamma}{\ln(k)} + 0.5 \text{ (Fronczak et al., 2004),}$$

$$C_l = \frac{3(k-2)}{4(k-1)} \text{ (Neal, 2015)}$$

$$L_l = \frac{n}{2k} + 0.5 \text{ (Neal, 2015; Fronczak et al., 2004)}$$

where γ is the Euler-Mascheroni constant.

Active cluster analysis

To quantify cluster activation (figure 5), we calculated the population rate for each cluster individually as the mean firing rate of all excitatory cells belonging to the cluster smoothed with a Gaussian kernel (15 ms standard deviation). A cluster was defined as ‘active’ if at any point its population rate exceeded twice that of any other cluster during a PBE. The active clusters’ duration of activation was defined as the duration for which it was the most active cluster.

To test whether the sequence of activation in events with three active clusters matched the sequence of place fields on the track, we performed a bootstrap significance test (Figure 5—figure supplement 1). For all events from the fiducial parameter set that had three active clusters, we calculated the fraction in which the sequence of the active clusters matched the sequence of the clusters’ left vs right bias on the track in either direction. We then compared this fraction to the distribution expected from randomly sampling sequences of three clusters without replacement.

To determine if there was a relationship between the number of active clusters within an event and its preplay quality we performed a Spearman’s rank correlation between the number of active clusters and the normalized absolute weighted correlation across all events at the fiducial parameter set. The absolute weighted correlations were z-scored based on the absolute weighted correlations of the time-bin shuffled events that had the same number of active clusters.

Experimental data

Electrophysiological data was reanalyzed from the hippocampal CA1 recordings first published in Shin et al., 2019 [↗](#). All place-field data (**Figure 3a** [↗](#)) came from the six rats' first experience on the W-track spatial alternation task. All preplay data (**Figure 4a,b** [↗](#)) came from the six rats' first sleep-box session, which lasted 20-30 minutes and occurred immediately before their first experience on the W-track.

Code

Simulations and analysis were performed in MATLAB with custom code. Code available at https://github.com/primon23/Preplay_paper [↗](#).

Impact Statement

Neural circuits with small-world connectivity spontaneously emit sequences of spikes that are correlated with any of the distinct sequences of realistic place fields produced by location-modulated, monotonically varying input.

Contributions

Jordan Breffle: Conceptualization, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing

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Shantanu P. Jadhav: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing

Paul Miller: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing

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Figure 1—figure supplement 1

Comparison of the randomly clustered network and the canonical Watts-Strogatz small-world network

(a) A small ring-lattice network. **(b)** Example small-world networks. Top, a Watts-Strogatz network with re-wiring parameter $\beta = 0.2$. Bottom, a randomly clustered network with two clusters and a cluster participation of 1.25. **(c)** Example randomly connected network.

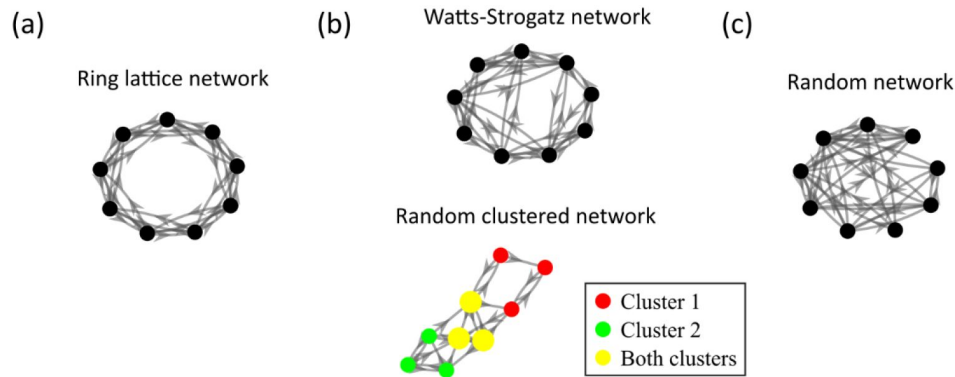


Figure 3—figure supplement 1

The simulated cells have greater place information than time information.

(a) Place fields (left) and time fields (right) for an example cell calculated from simulated trajectories that took 2 seconds (solid line) or 4 seconds (dotted line) to traverse the track. **(b)** CDFs of the information content of the place fields ("Place") and time fields ("Time") of all cells. The spatial information is significantly greater than the temporal information (KS-test, $p=6.4e-23$). **(c)** Scatter plot of the data in **(b)**, with the median values marked in red.

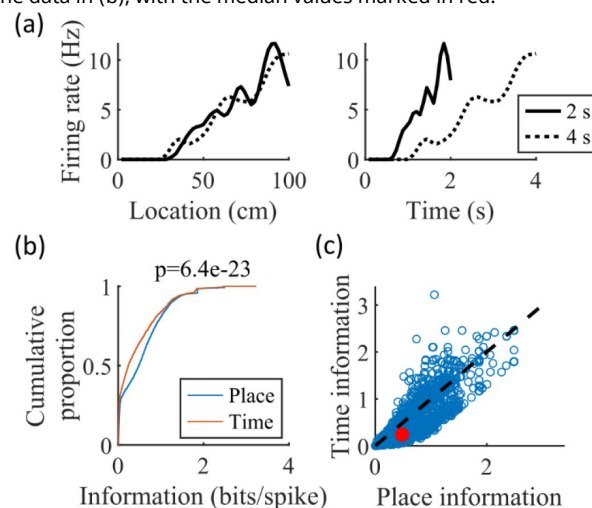


Figure 4—figure supplement 1

Example preplay events from the Shin et al., 2019 [data](#)

Example preplay events. Same as **Figure 2f** [but](#) for events from the hippocampal data from Shin et al., 2019 [data](#). The height of each plot spans the length of the trajectory used for decoding, divided into 2 cm spatial bins. The width of each plot spans the duration of the detected event, divided into 10 ms time bins. Probability is shown in color.

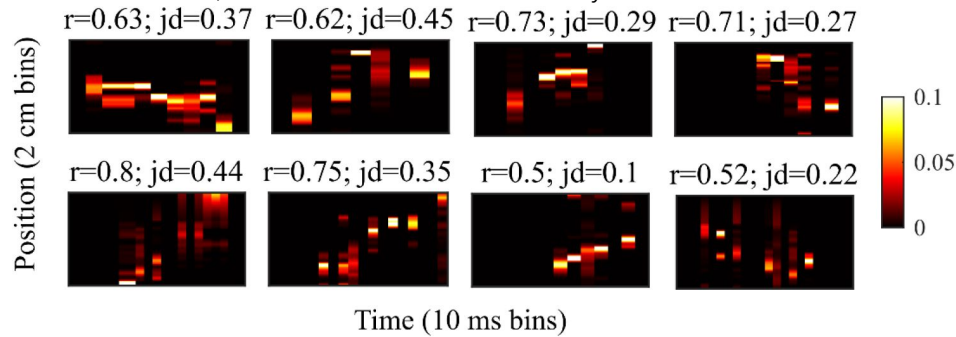
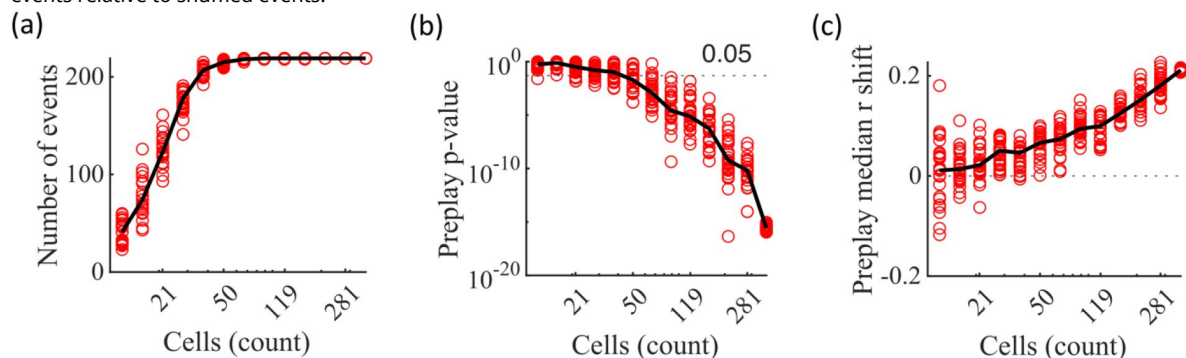


Figure 4—figure supplement 2

Significant preplay can typically be identified with as few as 50 cells

(a-c) Results from performing the same Bayesian decoding on the same simulated population burst events (PBEs) in **Figure 4c** [but](#) using only random subsets of the excitatory cells for performing the decoding analysis. Each circle is the result of an analysis performed on one random subset of the cells. 25 random subsets were analyzed for each analyzed cell count. The subset sizes are logarithmically spaced. Black lines show the median value. The variability at $N=375$ is due to the variation in the randomness of the time-bin shuffles. (a) Number of events meeting the inclusion criterion for decoding analysis. (b) P-value of the KS-test comparing actual vs shuffled event absolute weighted correlations. A majority of the random subsets of 50 cells (17 out of 25) produce preplay p-values below 0.05. (c) Shift in the median absolute weighted correlation of actual events relative to shuffled events.



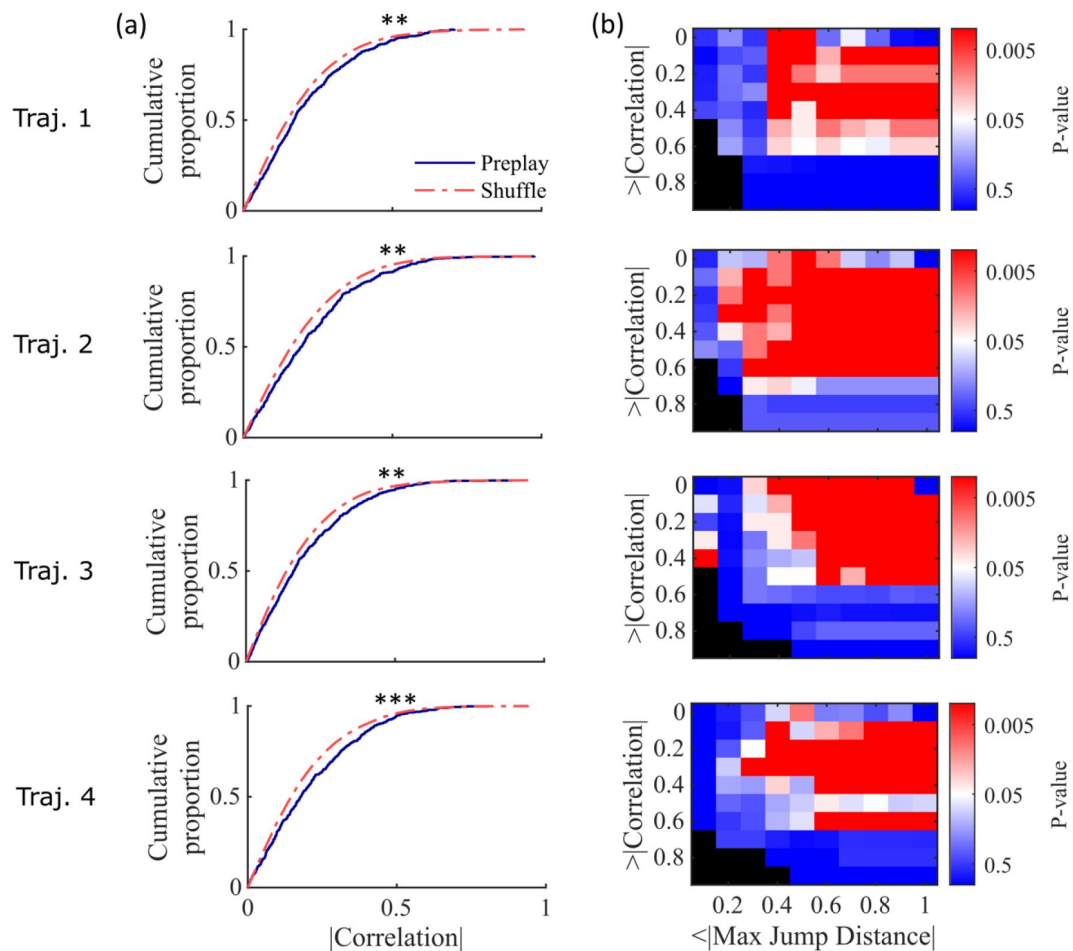


Figure 4—figure supplement 3

Preplay statistics by trajectory for Shin et al., 2019 data.

(a) Same as Figure 4a but separated by results from decoding by each of the 4 trajectories of the W-track individually (trajectory 1, center arm to right arm; trajectory 2, right arm to center arm; trajectory 3, center arm to left arm; trajectory 4, left arm to center arm). KS-test for each trajectory: trajectory 1, $p=0.0030$; trajectory 2, $p=0.0028$; trajectory 3, $p=0.0027$; trajectory 4, $p=5.461 \times 10^{-5}$. ** $p < 0.01$, *** $p < 0.001$. **(b)** Same as Figure 4b but separated by results from decoding by each of the 4 trajectories individually.

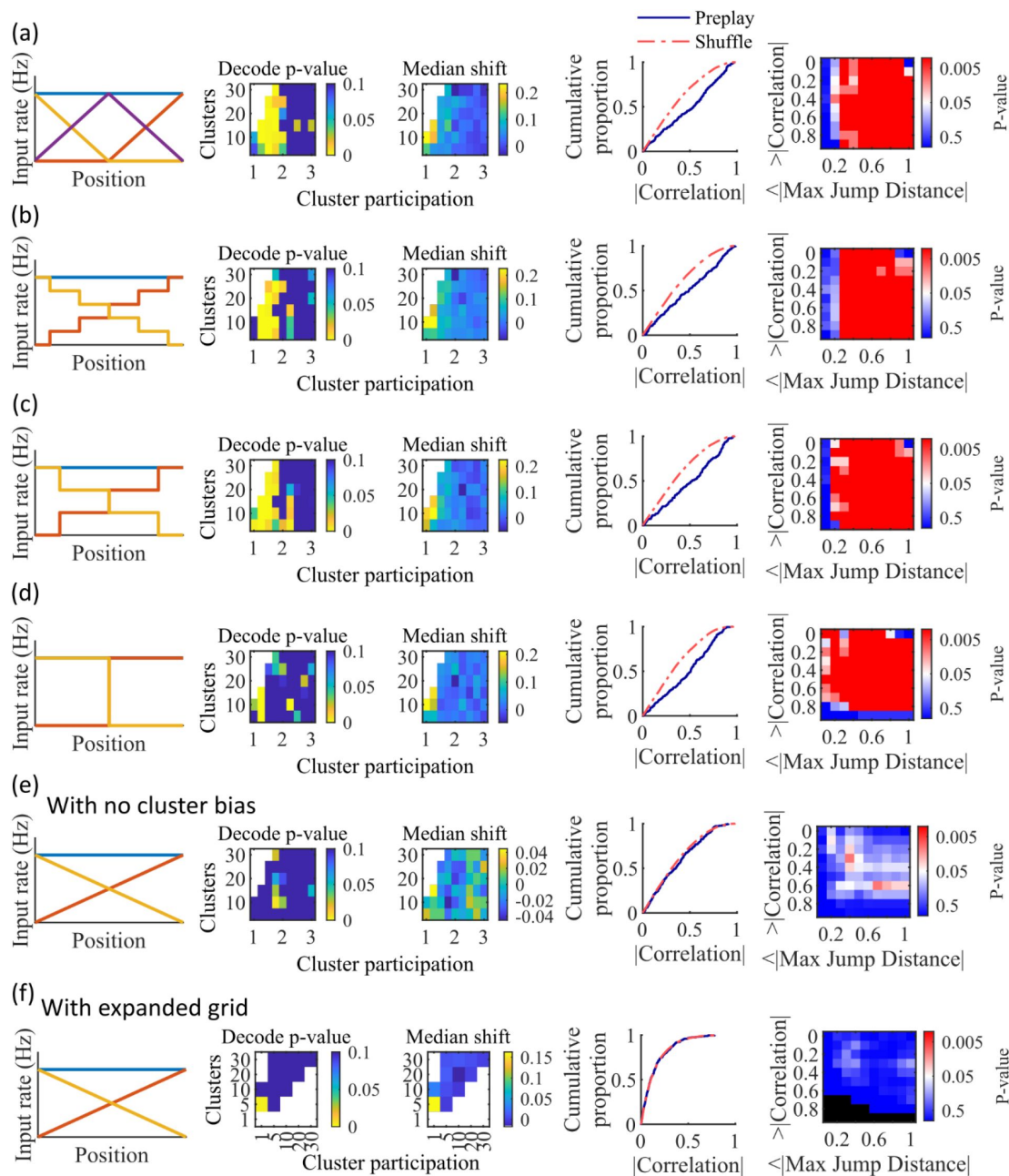


Figure 4—figure supplement 4

Additional simulations support the consistency and robustness of the model to variations in spatial input forms. Each row corresponds to a different parameter grid simulation, with statistics calculated as in the corresponding panel from **Figure 4**. (a) Preplay statistics are similar to the main simulation results when a third linearly varying spatial cue is included in the inputs to the network (CDF KS-test, $p=3.9 \times 10^{-13}$, KS-statistic=0.26). (b) Preplay statistics are similar to the main simulation results when a stepped input is used (CDF KS-test, $p=2.5 \times 10^{-8}$, KS-statistic=0.20). The stepped input is less spatially informative since stretches of adjacent locations on the track have identical spatial input. (c) Same as (b), but with three step increments (CDF KS-test, $p=6.2 \times 10^{-13}$, KS-statistic=0.26). (d) Same as (c), but with a single step increment (CDF KS-test, $p=4.9 \times 10^{-13}$, KS-statistic=0.26). With this input the fiducial parameter set still shows significant preplay (right two columns), but most of the parameter grid loses significant preplay. (e) When the bias in cluster spatial input location is removed preplay is no longer significant (CDF KS-test, $p=0.34$, KS-statistic=0.063). (f) A parameter grid that shows greater values of cluster participation do not have significant preplay. Values along the diagonal where clusters equals cluster participation are equivalent to a random cluster-less network. Example parameter point is at clusters=5 and cluster participation=5 (CDF KS-test, $p=0.99$, KS-statistic=0.02).

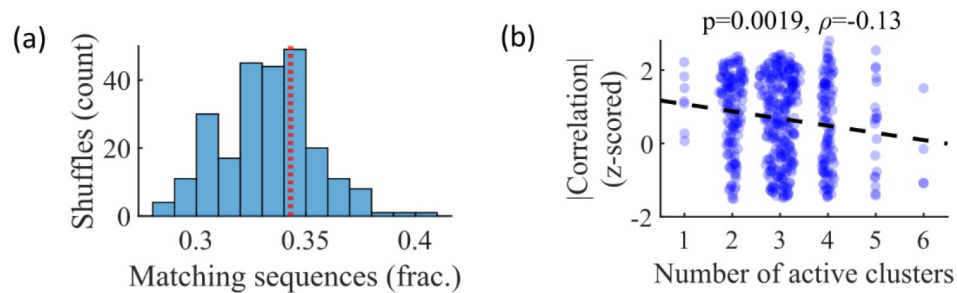


Figure 5—figure supplement 1

Relationship between cluster activation and preplay.

(a) Out of all events from the fiducial parameter set simulations where 3 unique clusters were active, the fraction of those events with sequences that match the order of cluster biases on the track (red line) is consistent with the values expected by randomly sampling clusters (blue). (b) Z-scored absolute weighted preplay correlation is negatively correlated with the number of active clusters (Spearman's rank correlation).

References

1. Alme CB, Miao C, Jezek K, Treves A, Moser EI, Moser M-B (2014) **Place cells in the hippocampus: Eleven maps for eleven rooms** *Proceedings of the National Academy of Sciences* **111**:18428–18435 <https://doi.org/10.1073/pnas.1421056111>
2. Antonello PC, Varley TF, Beggs J, Porcionatto M, Sporns O, Faber J (2022) **Self-organization of in vitro neuronal assemblies drives to complex network topology** *eLife* **11** <https://doi.org/10.7554/eLife.74921>
3. Azizi AH, Wiskott L, Cheng S (2013) **A computational model for preplay in the hippocampus** *Front Comput Neurosci* **7** <https://doi.org/10.3389/fncom.2013.00161>
4. Battaglia FP, Treves A (1998) **Attractor neural networks storing multiple space representations: A model for hippocampal place fields** *Phys Rev E* **58**:7738–7753 <https://doi.org/10.1103/PhysRevE.58.7738>
5. Berners-Lee A, Feng T, Silva D, Wu X, Ambrose ER, Pfeiffer BE, Foster DJ (2022) **Hippocampal replays appear after a single experience and incorporate greater detail with more experience** *Neuron*:S <https://doi.org/10.1016/j.neuron.2022.03.010>
6. Bourjaily MA, Miller P (2011) **Excitatory, Inhibitory, and Structural Plasticity Produce Correlated Connectivity in Random Networks Trained to Solve Paired-Stimulus Tasks** *Front Comput Neurosci* **5** <https://doi.org/10.3389/fncom.2011.00037>
7. Bush D, Barry C, Burgess N (2014) **What do grid cells contribute to place cell firing?** *Trends in Neurosciences* **37**:136–145 <https://doi.org/10.1016/j.tins.2013.12.003>
8. Carr MF, Jadhav SP, Frank LM (2011) **Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval** *Nature Neuroscience* **14**:147–153 <https://doi.org/10.1038/nn.2732>
9. Chenkov N, Sprekeler H, Kempster R (2017) **Memory replay in balanced recurrent networks.** **Gutkin BS, editor** *PLOS Computational Biology* **13** <https://doi.org/10.1371/journal.pcbi.1005359>
10. Csicsvari J, Hirase H, Mamiya A, Buzsáki G (2000) **Ensemble Patterns of Hippocampal CA3-CA1 Neurons during Sharp Wave-Associated Population Events** *Neuron* **28**:585–594 [https://doi.org/10.1016/S0896-6273\(00\)00135-5](https://doi.org/10.1016/S0896-6273(00)00135-5)
11. Debanne D, Gähwiler BH, Thompson SM (1998) **Long-term synaptic plasticity between pairs of individual CA3 pyramidal cells in rat hippocampal slice cultures** *The Journal of Physiology* **507**:237–247 <https://doi.org/10.1111/j.1469-7793.1998.237bu.x>
12. Diesmann M, Gewaltig M-O, Aertsen A (1999) **Stable propagation of synchronous spiking in cortical neural networks** *Nature* **402**:529–533 <https://doi.org/10.1038/990101>
13. Dragoi G, Tonegawa S (2011) **Preplay of future place cell sequences by hippocampal cellular assemblies** *Nature* **469**:397–401 <https://doi.org/10.1038/nature09633>

14. 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 <https://doi.org/10.1073/pnas.1306031110>
15. Farooq Usman, Sibille Jeremie, Liu Kefei, Dragoi George (2019) **Strengthened Temporal Coordination within Pre-Existing Sequential Cell Assemblies Supports Trajectory Replay** *Neuron* **103**:719–733 <https://doi.org/10.1016/j.neuron.2019.05.040>
16. Fagiolo G (2007) **Clustering in complex directed networks** *Phys Rev E* **76** <https://doi.org/10.1103/PhysRevE.76.026107>
17. Foster DJ, Wilson MA (2006) **Reverse replay of behavioural sequences in hippocampal place cells during the awake state** *Nature* **440**:680–683 <https://doi.org/10.1038/nature04587>
18. Frank LM, Stanley GB, Brown EN (2004) **Hippocampal Plasticity across Multiple Days of Exposure to Novel Environments** *J Neurosci* **24**:7681–7689 <https://doi.org/10.1523/JNEUROSCI.1958-04.2004>
19. Fronczak A, Fronczak P, Holyst JA (2004) **Average path length in uncorrelated random networks with hidden variables** *Phys Rev E* **70** <https://doi.org/10.1103/PhysRevE.70.056110>
20. Grosmark AD, Buzsaki G (2016) **Diversity in neural firing dynamics supports both rigid and learned hippocampal sequences** *Science* **351**:1440–1443 <https://doi.org/10.1126/science.aad1935>
21. Guzman SJ, Schlogl A, Frotscher M, Jonas P (2016) **Synaptic mechanisms of pattern completion in the hippocampal CA3 network** *Science* **353**:1117–1123 <https://doi.org/10.1126/science.aaf1836>
22. Haga T, Fukai T (2018) **Recurrent network model for learning goal-directed sequences through reverse replay** *eLife* **7** <https://doi.org/10.7554/eLife.34171>
23. Humphries MD, Gurney K, Prescott TJ. (2006) **The brainstem reticular formation is a small-world, not scale-free, network** *Proc R Soc B*. **273**:503–511 <https://doi.org/10.1098/rspb.2005.3354>
24. Harvey RE, Berkowitz LE, Savage DD, Hamilton DA, Clark BJ (2020) **Altered Hippocampal Place Cell Representation and Theta Rhythmicity following Moderate Prenatal Alcohol Exposure** *Current Biology* **30**:3556–3569 <https://doi.org/10.1016/j.cub.2020.06.077>
25. Humphries MD, Gurney K (2008) **Network ‘Small-World-Ness’: A Quantitative Method for Determining Canonical Network Equivalence**. Sporns O, editor *PLoS ONE* **3** <https://doi.org/10.1371/journal.pone.0002051>
26. Hwaun E, Colgin LL (2019) **CA3 place cells that represent a novel waking experience are preferentially reactivated during sharp wave-ripples in subsequent sleep** *Hippocampus* **29**:921–938 <https://doi.org/10.1002/hipo.23090>
27. Jahnke S, Timme M, Memmesheimer R-M (2015) **A Unified Dynamic Model for Learning, Replay, and Sharp-Wave/Ripples** *Journal of Neuroscience* **35**:16236–16258 <https://doi.org/10.1523/JNEUROSCI.3977-14.2015>
28. Karlsson MP, Frank LM (2009) **Awake replay of remote experiences in the hippocampus** *Nature Neuroscience* **12**:913–918 <https://doi.org/10.1038/nn.2344>

29. Kinsky NR, Sullivan DW, Mau W, Hasselmo ME, Eichenbaum HB (2018) **Hippocampal Place Fields Maintain a Coherent and Flexible Map across Long Timescales** *Current Biology* **28**:3578–3588 <https://doi.org/10.1016/j.cub.2018.09.037>
30. Leutgeb S, Leutgeb JK, Treves A, Moser M-B, Moser EI (2004) **Distinct Ensemble Codes in Hippocampal Areas CA3 and CA1** *Science* **305**:1295–1298 <https://doi.org/10.1126/science.1100265>
31. Leutgeb S, Leutgeb JK, Barnes CA, Moser EI, McNaughton BL, Moser M-B (2005) **Independent Codes for Spatial and Episodic Memory in Hippocampal Neuronal Ensembles** *Science* **309**:619–623 <https://doi.org/10.1126/science.1114037>
32. Liao W, Ding J, Marinazzo D, Xu Q, Wang Z, Yuan C, Zhang Z, Lu G, Chen H (2011) **Small-world directed networks in the human brain: Multivariate Granger causality analysis of resting-state fMRI** *NeuroImage* **54**:2683–2694 <https://doi.org/10.1016/j.neuroimage.2010.11.007>
33. Litwin-Kumar A, Doiron B (2014) **Formation and maintenance of neuronal assemblies through synaptic plasticity** *Nat Commun* **5** <https://doi.org/10.1038/ncomms6319>
34. Liu K, Sibille J, Dragoi G (2019) **Preconfigured patterns are the primary driver of offline multi-neuronal sequence replay** *Hippocampus* **29**:275–283 <https://doi.org/10.1002/hipo.23034>
35. Liu K, Sibille J, Dragoi G (2021) **Orientation selectivity enhances context generalization and generative predictive coding in the hippocampus** *Neuron*:S 896627321006103 <https://doi.org/10.1016/j.neuron.2021.08.013>
36. Luongo FJ, Zimmerman CA, Horn ME, Sohal VS (2016) **Correlations between prefrontal neurons form a small-world network that optimizes the generation of multineuron sequences of activity** *Journal of Neurophysiology* **115**:2359–2375 <https://doi.org/10.1152/jn.01043.2015>
37. Lynn CW, Holmes CM, Palmer SE (2022) **Heavy-tailed neuronal connectivity arises from Hebbian self-organization**
38. Mishra RK, Kim S, Guzman SJ, Jonas P (2016) **Symmetric spike timing-dependent plasticity at CA3–CA3 synapses optimizes storage and recall in autoassociative networks** *Nat Commun* **7** <https://doi.org/10.1038/ncomms11552>
39. Morris RGM, Garrud P, Rawlins JNP, O’Keefe J (1982) **Place navigation impaired in rats with hippocampal lesions** *Nature* **297**:681–683 <https://doi.org/10.1038/297681a0>
40. Moser EI, Kropff E, Moser M-B (2008) **Place Cells, Grid Cells, and the Brain’s Spatial Representation System** *Annu Rev Neurosci* **31**:69–89 <https://doi.org/10.1146/annurev.neuro.31.061307.090723>
41. Muller R, Kubie J, Ranck J (1987) **Spatial firing patterns of hippocampal complex-spike cells in a fixed environment** *J Neurosci* **7**:1935–1950 <https://doi.org/10.1523/JNEUROSCI.07-07-01935.1987>
42. Nakashiba T, Young JZ, McHugh TJ, Buhl DL, Tonegawa S (2008) **Transgenic Inhibition of Synaptic Transmission Reveals Role of CA3 Output in Hippocampal Learning** *Science* **319**:1260–1264 <https://doi.org/10.1126/science.1151120>

43. Nakashiba T, Buhl DL, McHugh TJ, Tonegawa S (2009) **Hippocampal CA3 Output Is Crucial for Ripple-Associated Reactivation and Consolidation of Memory** *Neuron* **62**:781–787 <https://doi.org/10.1016/j.neuron.2009.05.013>
44. Navratilova Z, Hoang LT, Schwindel CD, Tatsuno M, McNaughton BL (2012) **Experience-dependent firing rate remapping generates directional selectivity in hippocampal place cells** *Front Neural Circuits* **6** <https://doi.org/10.3389/fncir.2012.00006>
45. Neal Z (2015) **Making Big Communities Small: Using Network Science to Understand the Ecological and Behavioral Requirements for Community Social Capital** *American Journal of Community Psychology* **55**:369–380 <https://doi.org/10.1007/s10464-015-9720-4>
46. Neal ZP (2017) **How small is it? Comparing indices of small worldliness.** *Net Sci* **5**:30–44 <https://doi.org/10.1017/nws.2017.5>
47. Nitzan N, Swanson R, Schmitz D, Buzsáki G (2022) **Brain-wide interactions during hippocampal sharp wave ripples** *Proc Natl Acad Sci USA* **119** <https://doi.org/10.1073/pnas.2200931119>
48. O'Keefe J, Nadel L (1978) **The hippocampus as a cognitive map**
49. O'Neill J, Senior TJ, Allen K, Huxter JR, Csicsvari J (2008) **Reactivation of experience-dependent cell assembly patterns in the hippocampus** *Nature Neuroscience* **11**:209–215 <https://doi.org/10.1038/nn2037>
50. Pang R, Fairhall AL (2019) **Fast and flexible sequence induction in spiking neural networks via rapid excitability changes** *eLife* **8** <https://doi.org/10.7554/eLife.44324>
51. Perin R, Berger TK, Markram H (2011) **A synaptic organizing principle for cortical neuronal groups** *Proc Natl Acad Sci USA* **108**:5419–5424 <https://doi.org/10.1073/pnas.1016051108>
52. Peyrache A, Benchenane K, Khamassi M, Wiener SI, Battaglia FP (2010) **Principal component analysis of ensemble recordings reveals cell assemblies at high temporal resolution** *J Comput Neurosci* **29**:309–325 <https://doi.org/10.1007/s10827-009-0154-6>
53. Ramirez-Villegas JF, Willeke KF, Logothetis NK, Besserve M (2018) **Dissecting the Synapse- and Frequency-Dependent Network Mechanisms of In Vivo Hippocampal Sharp Wave-Ripples** *Neuron* **100**:1224–1240 <https://doi.org/10.1016/j.neuron.2018.09.041>
54. Rebola N, Carta M, Mülle C (2017) **Operation and plasticity of hippocampal CA3 circuits: implications for memory encoding** *Nat Rev Neurosci* **18**:208–220 <https://doi.org/10.1038/nrn.2017.10>
55. Sadovskiy A, MacLean J (2014) **Mouse Visual Neocortex Supports Multiple Stereotyped Patterns of Microcircuit Activity** *Journal of Neuroscience* **34**:7769–7777 <https://doi.org/10.1523/JNEUROSCI.0169-14.2014>
56. Samsonovich A, McNaughton BL (1997) **Path Integration and Cognitive Mapping in a Continuous Attractor Neural Network Model** *J Neurosci* **17**:5900–5920 <https://doi.org/10.1523/JNEUROSCI.17-15-05900.1997>
57. Savelli F, Yoganarasimha D, Knierim JJ (2008) **Influence of boundary removal on the spatial representations of the medial entorhinal cortex** *Hippocampus* **18**:1270–1282 <https://doi.org/10.1002/hipo.20511>

58. She Q, Chen G, Chan RHM (2016) **Evaluating the Small-World-Ness of a Sampled Network: Functional Connectivity of Entorhinal-Hippocampal Circuitry** *Sci Rep* 6 <https://doi.org/10.1038/srep21468>
59. Sheintuch L, Geva N, Deitch D, Rubin A, Ziv Y (2023) **Organization of hippocampal CA3 into correlated cell assemblies supports a stable spatial code** *Cell Reports* 42 <https://doi.org/10.1016/j.celrep.2023.112119>
60. Shin JD, Tang W, Jadhav SP (2019) **Dynamics of Awake Hippocampal-Prefrontal Replay for Spatial Learning and Memory-Guided Decision Making** *Neuron* 104:1110–1125 <https://doi.org/10.1016/j.neuron.2019.09.012>
61. Silva D, Feng T, Foster DJ (2015) **Trajectory events across hippocampal place cells require previous experience** *Nat Neurosci* 18:1772–1779 <https://doi.org/10.1038/nn.4151>
62. Solstad T, Boccara CN, Kropff E, Moser M-B, Moser EI (2008) **Representation of Geometric Borders in the Entorhinal Cortex** *Science* 322:1865–1868 <https://doi.org/10.1126/science.1166466>
63. Song S, Sjöström PJ, Reigl M, Nelson S, Chklovskii DB (2005) **Highly Nonrandom Features of Synaptic Connectivity in Local Cortical Circuits.** Friston KJ, editor *PLoS Biology* 3 <https://doi.org/10.1371/journal.pbio.0030068>
64. Squire LR, Stark CEL, Clark RE (2004) **The medial temporal lobe** *Annual Review of Neuroscience* 27:279–306 <https://doi.org/10.1146/annurev.neuro.27.070203.144130>
65. Tang W., Jadhav S. P (2022) **Multiple-Timescale Representations of Space: Linking Memory to Navigation** *Annual Review of Neuroscience* 45:1–21 <https://doi.org/10.1146/annurev-neuro-111020-084824>
66. Theodoni P, Rovira B, Wang Y, Roxin A (2018) **Theta-modulation drives the emergence of connectivity patterns underlying replay in a network model of place cells** *eLife* 7 <https://doi.org/10.7554/eLife.37388>
67. Vaz AP, Wittig JH, Inati SK, Zaghloul KA (2023) **Backbone spiking sequence as a basis for preplay, replay, and default states in human cortex** *Nat Commun* 14 <https://doi.org/10.1038/s41467-023-40440-5>
68. Vetere G, Kenney JW, Tran LM, Xia F, Steadman PE, Parkinson J, Josselyn SA, Frankland PW (2017) **Chemogenetic Interrogation of a Brain-wide Fear Memory Network in Mice** *Neuron* 94:363–374 <https://doi.org/10.1016/j.neuron.2017.03.037>
69. Watts DJ, Strogatz SH (1998) **Collective dynamics of ‘small-world’ networks** *Nature* 393:440–442 <https://doi.org/10.1038/30918>
70. Whittington JCR, Muller TH, Mark S, Chen G, Barry C, Burgess N, Behrens TEJ (2020) **The Tolman-Eichenbaum Machine: Unifying Space and Relational Memory through Generalization in the Hippocampal Formation** *Cell* 183:1249–1263 <https://doi.org/10.1016/j.cell.2020.10.024>
71. Wilson MA, McNaughton BL (1994) **Reactivation of Hippocampal Ensemble Memories During Sleep** *Science* 265:676–679 <https://doi.org/10.1126/science.8036517>

72. Yamamoto J, Tonegawa S (2017) **Direct Medial Entorhinal Cortex Input to Hippocampal CA1 Is Crucial for Extended Quiet Awake Replay** *Neuron* **96**:217–227 <https://doi.org/10.1016/j.neuron.2017.09.017>
73. Zhang L, Hu X, Hu Y, Tang M, Qiu H, Zhu Z, Gao Y, Li H, Kuang W, Ji W (2022) **Structural covariance network of the hippocampus–amygdala complex in medication-naïve patients with first-episode major depressive disorder** *Psychoradiology* **2**:190–198 <https://doi.org/10.1093/psyrad/kkac023>

Editors

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Reviewer #1 (Public review):

Summary:

An investigation of the dynamics of a neural network model characterized by sparsely connected clusters of neuronal ensembles. The authors found that such a network could intrinsically generate sequence preplay and place maps, with properties like those observed in the real-world data.

Strengths:

Computational model and data analysis supporting the hippocampal network mechanisms underlying sequence preplay of future experiences and place maps.
The revised version of the manuscript addressed all my comments and as a result is significantly improved.

Weaknesses:

None noted

<https://doi.org/10.7554/eLife.93981.2.sa3>

Reviewer #2 (Public review):

Summary:

The authors show that a spiking network model with clustered connectivity produces intrinsic spike sequences when driven with an ramping input, which are recapitulated in the absence of input. This behavior is only seen for some network parameters (neuron cluster participation and number of clusters in the network), which correspond to those that produce a small world network. By changing the strength of ramping input to each network cluster, the network can show different sequences.

Strengths:

A strength of the paper is the direct comparison between the properties of the model and neural data.

Weaknesses:

My main critique of the paper relates to the form of the input to the network. Specifically, it's unclear how much the results depend on the choice of a one-dimensional environment with ramping input. While this is an elegant idealization that allows the authors to explore the representation and replay properties of their model, it is a strong and highly non-physiological constraint. In order to address this concern, the authors would need to test the spatial tuning of their network in 2-dimensional environments, and with different kinds of input from a population of neurons that have a range of degree of spatial tuning and physiological plausibility. A method for systematically producing input with varying degrees of spatial tuning in both 1D and 2D environments has been previously used in (Fang et al 2023, eLife, see Figures 4 and 5), which could be readily adapted for the current study; and behaviorally plausible trajectories in 2D can be produced using the RatInABox package (George et al 2022, bioRxiv), which can also generate e.g. grid cell-like activity that could be used as physiologically plausible input to the network.

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Reviewer #3 (Public review):

This work offers a novel perspective to the question of how hippocampal networks can adaptively generate different spatial maps and replays of the corresponding place cells, without any such maps pre-existing in the network architecture or its inputs. And how can these place cells preplay their sequences even before the environment is experienced? Previous models required pre-existing spatial representations to be artificially introduced, limiting their adaptability to new environments. Others depended on synaptic plasticity rules which made remapping slower than what is seen in recordings. In contrast, this modeling study proposes that quickly-adaptive intrinsic spiking sequences (preplays) and spatially tuned spiking (place cells) can be generated in a network through randomly clustered recurrent connectivity. By simulating spatial exploration through border-cell-like synaptic inputs, the model generates place cells for different "environments" without the need to reconfigure its synaptic connectivity or introduce plasticity. By simulating sleep-like random synaptic inputs, the model generates sequential activations of cells, mimicking preplays. These "preplays" require small-world connectivity, so that cell clusters are activated in sequence. Using a set of electrophysiological recordings from CA1, the authors confirm that the modeled place cells and replays share many features with recorded ones.

Many features of the model are thoroughly examined, and conclusions are overall convincing (within the simple architecture of the model). Even though the modeled connectivity applies more closely to CA3, it remains unclear whether CA3 recapitulates the proposed small world architecture.

In any case, the proposal that a small-world-structured, clustered network can generate flexible place cells and replays without the need for pre-configured maps is novel and of potential interest to a wide computational and experimental community.

<https://doi.org/10.7554/eLife.93981.2.sa1>

Author response:

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

Public Reviews:

Reviewer #1 (Public Review):

In this manuscript, the authors investigated the dynamics of a neural network model characterized by sparsely connected clusters of neuronal ensembles. They found that such a network could intrinsically generate sequence preplay and place maps, with properties like those observed in the real-world data. Strengths of the study include the computational model and data analysis supporting the hippocampal network mechanisms underlying sequence preplay of future experiences and place maps.

Previous models of replay or theta sequences focused on circuit plasticity and usually required a pre-existing place map input from the external environment via upstream structures. However, those models failed to explain how networks support rapid sequential coding of novel environments or simply transferred the question to the upstream structure. On the contrary, the current proposed model required minimal spatial inputs and was aimed at elucidating how a preconfigured structure gave rise to preplay, thereby facilitating the sequential encoding of future novel environments.

In this model, the fundamental units for spatial representation were clusters within the network. Sequential representation was achieved through the balance of cluster isolation and their partial overlap. Isolation resulted in a self-reinforced assembly representation, ensuring stable spatial coding. On the other hand, overlap-induced activation transitions across clusters, enabling sequential coding.

This study is important when considering that previous models mainly focused on plasticity and experience-related learning, while this model provided us with insights into how network architecture could support rapid sequential coding with large capacity, upon which learning could occur efficiently with modest modification via plasticity.

I found this research very inspiring and, below, I provide some comments aimed at improving the manuscript. Some of these comments may extend beyond the scope of the current study, but I believe they raise important questions that should be addressed in this line of research.

(1) The expression 'randomly clustered networks' needs to be explained in more detail given that in its current form risks to indicate that the network might be randomly organized (i.e., not organized). In particular, a clustered network with future functionality based on its current clustering is not random but rather pre-configured into those clusters. What the authors likely meant to say, while using the said expression in the title and text, is that clustering is not induced by an experience in the environment, which will only be later mapped using those clusters. While this organization might indeed appear as randomly clustered when referenced to a future novel experience, it might be non-random when referenced to the prior (unaccounted) activity of the network. Related to this, network organization based on similar yet distinct experiences (e.g., on parallel linear tracks as in Liu, Sibille, Dragoi, Neuron 2021) could explain/configure, in part, the hippocampal CA1 network organization that would appear otherwise 'randomly clustered' when referenced to a future novel experience.

As suggested by the reviewer, we have revised the text to clarify that the random clustering is random with respect to any future, novel environment (lines 111-114 and 710-712).

Lines 111-114: “To reconcile these experimental results, we propose a model of intrinsic sequence generation based on randomly clustered recurrent connectivity, wherein place cells are connected within multiple overlapping clusters that are random with respect to any future, novel environment.”

Lines 710-712: “Our results suggest that the preexisting hippocampal dynamics supporting preplay may reflect general properties arising from randomly clustered connectivity, where the randomness is with respect to any future, novel experience.”

The cause of clustering could be prior experiences (e.g. Bourjaily and Miller, 2011) or developmental programming (e.g. Perin et al., 2011; Druckmann et al., 2014; Huszar et al., 2022), and we have modified lines 116 and 714-718 to state this.

Lines 116: Added citation of “Perin et al., 2011”

Lines 714-718: “Synaptic plasticity in the recurrent connections of CA3 may primarily serve to reinforce and stabilize intrinsic dynamics, which could be established through a combination of developmental programming (Perin et al., 2011; Druckmann et al., 2014; Huszar et al., 2022) and past experiences (Bourjaily and Miller, 2011), rather than creating spatial maps de novo.”

We thank the reviewer for suggesting that the results of Liu et al., 2021 strengthen the support for our modeling motivations. We agree, and we now cite their finding that the hippocampal representations of novel environments emerged rapidly but were initially generic and showed greater discriminability from other environments with repeated experience in the environment (lines 130-134).

Lines 130-134: “Further, such preexisting clusters may help explain the correlations that have been found in otherwise seemingly random remapping (Kinsky et al., 2018; Whittington et al., 2020) and support the rapid hippocampal representations of novel environments that are initially generic and become refined with experience (Liu et al., 2021).”

(2) The authors should elaborate more on how the said 'randomly clustered networks' generate beyond chance-level preplay. Specifically, why was there preplay stronger than the time-bin shuffle? There are at least two potential explanations:

(1) When the activation of clusters lasts for several decoding time bins, temporal shuffle breaks the continuity of one cluster's activation, thus leading to less sequential decoding results. In that case, the preplay might mainly outperform the shuffle when there are fewer clusters activating in a PBE. For example, activation of two clusters must be sequential (either A to B or B to A), while time bin shuffle could lead to non-sequential activations such as a-b-a-b-a-b where a and b are components of A and B;

(2) There is a preferred connection between clusters based on the size of overlap across clusters. For example, if pair A-B and B-C have stronger overlap than A-C, then cluster sequences A-B-C and C-B-A are more likely to occur than others (such as A-C-B) across brain states. In that case, authors should present the distribution of overlap across clusters, and whether the sequences during run and sleep match the magnitude of overlap. During run simulation in the model, as clusters randomly receive a weak location cue bias, the activation sequence might not exactly match the overlap of clusters due to the external drive. In that case, the strength of location cue bias (4% in the current setup) could change the balance between the internal drive and external drive of the representation. How does that parameter influence the preplay incidence or quality?

Explanation 1 is correct: Our cluster-activation analyses (Figure 5) showed that the parameter values that generate preplay correspond to the parameter regions that support sustained cluster activity over multiple decoding time bins, which led us to the conclusion of the reviewer's first proposed explanation.

We have now added additional analyses supporting the conclusion that cluster-wise activity is the main driver of preplay rather than individual cell-identity (Figures 6 and 7). In Figure 6

we show that cluster-identity alone is sufficient to produce significant preplay by performing decoding after shuffling cell identity within clusters, and in Figure 7 we show that this result holds true when considering the sequence of spiking activity within population bursts rather than the spatial decoding.

Lines 495-515: The pattern of preplay significance across the parameter grid in Figure 4f shows that preplay only occurs with modest cluster overlap, and the results of Figure 5 show that this corresponds to the parameter region that supports transient, isolated cluster-activation. This raises the question of whether cluster-identity is sufficient to explain preplay. To test this, we took the sleep simulation population burst events from the fiducial parameter set and performed decoding after shuffling cell identity in three different ways. We found that when the identity of all cells within a network are randomly permuted the resulting median preplay correlation shift is centered about zero (t-test 95% confidence interval, -0.2018 to 0.0012) and preplay is not significant (distribution of p-values is consistent with a uniform distribution over 0 to 1, chi-square goodness-of-fit test $p=0.4436$, chi-square statistic=2.68; Figure 6a). However, performing decoding after randomly shuffling cell identity between cells that share membership in a cluster does result in statistically significant preplay for all shuffle replicates, although the magnitude of the median correlation shift is reduced for all shuffle replicates (Figure 6b). The shuffle in Figure 6b does not fully preserve cell's cluster identity because a cell that is in multiple clusters may be shuffled with a cell in either a single cluster or with a cell in multiple clusters that are not identical. Performing decoding after doing within-cluster shuffling of only cells that are in a single cluster results in preplay statistics that are not statistically different from the unshuffled statistics (t-test relative to median shift of un-shuffled decoding, $p=0.1724$, 95% confidence interval of -0.0028 to 0.0150 relative to the reference value; Figure 6c). Together these results demonstrate that cluster-identity is sufficient to produce preplay.

Lines 531-551: While cluster-identity is sufficient to produce preplay (Figure 6b), the shuffle of Figure 6c is incomplete in that cells belonging to more than one cluster are not shuffled. Together, these two shuffles leave room for the possibility that individual cell-identity may contribute to the production of preplay. It might be the case that some cells fire earlier than others, both on the track and within events. To test the contribution of individual cells to preplay, we calculated for all cells in all networks of the fiducial parameter point their mean relative spike rank and tested if this is correlated with the location of their mean place field density on the track (Figure 7). We find that there is no relationship between a cell's mean relative within-event spike rank and its mean place field density on the track (Figure 7a). This is the case when the relative rank is calculated over the entire network (Figure 7, "Within-network") and when the relative rank is calculated only with respect to cells with the same cluster membership (Figure 7, "Within-cluster"). However, because preplay events can proceed in either track direction, averaging over all events would average out the sequence order of these two opposite directions. We performed the same correlation but after reversing the spike order for events with a negative slope in the decoded trajectory (Figure 7b). To test the significance of this correlation, we performed a bootstrap significance test by comparing the slope of the linear regression to the slope that results when performing the same analysis after shuffling cell identities in the same manner as in Figure 6. We found that the linear regression slope is greater than expected relative to all three shuffling methods for both the within-network mean relative rank correlation (Figure 6c) and the within-cluster mean relative rank correlation (Figure 6d).

Lines 980-1000:

"Cell identity shuffled decoding

We performed Bayesian decoding on the fiducial parameter set after shuffling cell identities in three different manners (Figures 6 and 7). To shuffle cells in a cluster-independent manner ("Across-network shuffle"), we randomly shuffled the identity of cells during the sleep

simulations. To shuffle cells within clusters (“Within-cluster shuffle”), we randomly shuffled cell identity only between cells that shared membership in at least one cluster. To shuffle cells within only single clusters (“Within-single-cluster shuffle”), we shuffled cells in the same manner as the within-cluster shuffle but excluded any cells from the shuffle that were in multiple clusters.

To test for a correlation between spike rank during sleep PBEs and the order of place fields on the track (Figure 7), we calculated for each excitatory cell in each network of the fiducial parameter set its mean relative spike rank and correlated that with the location of its mean place field density on the track (Figure 7a). To account for event directionality, we calculated the mean relative rank after inverting the rank within events that had a negatively sloped decoded trajectory (Figure 7b). We calculated mean relative rank for each cell relative to all cells in the network (“Within-network mean relative rank”) and relative to only cells that shared cluster membership with the cell (“Within-cluster mean relative rank”). We then compared the slope of the linear regression between mean relative rank and place field location against the slope that results when applying the same analysis to each of the three methods of cell identify shuffles for both the within-network regression (Figure 7c) and the within-cluster regression (Figure 7d).”

We also now show that the sequence of cluster-activation in events with 3 active clusters does not match the sequence of cluster biases on the track above chance levels and that events with fewer active clusters have the largest increase in median weighted decode correlation (Figure 5—figure supplement 1), showing that the reviewer’s second explanation is not the case.

Lines 466-477: “The results of Figure 5 suggest that cluster-wise activation may be crucial to preplay. One possibility is that the random overlap of clusters in the network spontaneously produces biases in sequences of cluster activation which can be mapped onto any given environment. To test this, we looked at the pattern of cluster activations within events. We found that sequences of three active clusters were not more likely to match the track sequence than chance (Figure 5—figure supplement 1a). This suggests that preplay is not dependent on a particular biased pattern in the sequence of cluster activation. We then we asked if the number of clusters that were active influenced preplay quality. We split the preplay events by the number of clusters that were active during each event and found that the median preplay shift relative to shuffled events with the same number of active clusters decreased with the number of active clusters (Spearman’s rank correlation, $p=0.0019$, $=-0.13$; Figure 5—figure supplement 1b).”

Lines 1025-1044:

“Active cluster analysis

To quantify cluster activation (figure 5), we calculated the population rate for each cluster individually as the mean firing rate of all excitatory cells belonging to the cluster smoothed with a Gaussian kernel (15 ms standard deviation). A cluster was defined as ‘active’ if at any point its population rate exceeded twice that of any other cluster during a PBE. The active clusters’ duration of activation was defined as the duration for which it was the most active cluster.

To test whether the sequence of activation in events with three active clusters matched the sequence of place fields on the track, we performed a bootstrap significance test (Figure 5—figure supplement 1). For all events from the fiducial parameter set that had three active clusters, we calculated the fraction in which the sequence of the active clusters matched the sequence of the clusters’ left vs right bias on the track in either direction. We then compared this fraction to the distribution expected from randomly sampling sequences of three clusters without replacement.

To determine if there was a relationship between the number of active clusters within an event and its preplay quality we performed a Spearman's rank correlation between the number of active clusters and the normalized absolute weighted correlation across all events at the fiducial parameter set. The absolute weighted correlations were z-scored based on the absolute weighted correlations of the time-bin shuffled events that had the same number of active clusters."

We also now add control simulations showing that without the cluster-dependent bias the population burst events no longer significantly decode as preplay (Figure 4—figure supplement 4e).

(3) The manuscript is focused on presenting that a randomly clustered network can generate preplay and place maps with properties similar to experimental observations. An equally interesting question is how preplay supports spatial coding. If preplay is an intrinsic dynamic feature of this network, then it would be good to study whether this network outperforms other networks (randomly connected or ring lattice) in terms of spatial coding (encoding speed, encoding capacity, tuning stability, tuning quality, etc.)

We agree that this is an interesting future direction, but we see it as outside the scope of the current work. There are two interesting avenues of future work: 1) Our current model does not include any plasticity mechanisms, but a future model could study the effects of synaptic plasticity during preplay on long-term network dynamics, and 2) Our current model does not include alternative approaches to constructing the recurrent network, but future studies could systematically compare the spatial coding properties of alternative types of recurrent networks.

(4) The manuscript mentions the small-world connectivity several times, but the concept still appears too abstract and how the small-world index (SWI) contributes to place fields or preplay is not sufficiently discussed.

For a more general audience in the field of neuroscience, it would be helpful to include example graphs with high and low SWI. For example, you can show a ring lattice graph and indicate that there are long paths between points at opposite sides of the ring; show randomly connected graphs indicating there are no local clustered structures, and show clustered graphs with several hubs establishing long-range connections to reduce pair-wise distance.

How this SWI contributes to preplay is also not clear. Figure 6 showed preplay is correlated with SWI, but maybe the correlation is caused by both of them being correlated with cluster participation. The balance between cluster overlap and cluster isolation is well discussed. In the Discussion, the authors mention "...Such a balance in cluster overlap produces networks with small-world characteristics (Watts and Strogatz, 1998) as quantified by a small-world index..." (Lines 560-561). I believe the statement is not entirely appropriate, a network similar to ring lattice can still have the balance of cluster isolation and cluster overlap, while it will have small SWI due to a long path across some node pairs. Both cluster structure and long-range connection could contribute to SWI. The authors only discuss the necessity of cluster structure, but why is the long-range connection important should also be discussed. I guess long-range connection could make the network more flexible (clusters are closer to each other) and thus increase the potential repertoire.

We agree that the manuscript would benefit from a more concrete explanation of the small-world index. We have added a figure illustrating different types of networks and their

corresponding SWI (Figure 1—figure supplement 1) and a corresponding description in the main text (lines 228-234).

Lines 228-234: “A ring lattice network (Figure 1—figure supplement 1a) exhibits high clustering but long path lengths between nodes on opposite sides of the ring. In contrast, a randomly connected network (Figure 1—figure supplement 1c) has short path lengths but lacks local clustered structure. A network with small world structure, such as a Watts-Strogatz network (Watts and Strogatz, 1998) or our randomly clustered model (Figure 1—figure supplement 1b), combines both clustered connectivity and short path lengths. In our clustered networks, for a fixed connection probability the SWI increases with more clusters and lower cluster participation...”

We note that while our most successful clustered networks are indeed those with small-world characteristics, there are other ways of producing small-world networks which may not show good place fields or preplay. We have modified lines 690-692 to clarify that that statement is specific to our model.

Lines 690-692: “In our clustered network structure, such a balance in cluster overlap produces networks with small-world characteristics (Watts and Strogatz, 1998) as quantified by a small-world index (SWI, Figure 1g; Neal, 2015; Neal, 2017).”

(5) What drives PBE during sleep? Seems like the main difference between sleep and run states is the magnitude of excitatory and inhibitory inputs controlled by scaling factors. If there are bursts (PBE) in sleep, do you also observe those during run? Does the network automatically generate PBE in a regime of strong excitation and weak inhibition (neural bifurcation)?

During sleep simulations, the PBEs are spontaneously generated by the recurrent connections in the network. The constant-rate Poisson inputs drive low-rate stochastic spiking in the recurrent network, which then randomly generates population events when there is sufficient internal activity to transiently drive additional spiking within the network.

During run simulations, the spatially-tuned inputs drive greater activity in a subset of the cells at a given point on the track, which in turn suppress the other excitatory cells through the feedback inhibition.

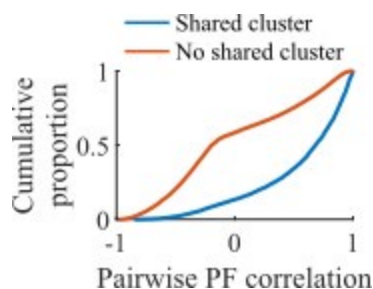
We have added a brief explanation of this in the text in lines 281-284.

Lines 281-284: “During simulated sleep, sparse, stochastic spiking spontaneously generates sufficient excitement within the recurrent network to produce population burst events resembling preplay (Figure 2d-f)”

(6) Is the concept of 'cluster' similar to 'assemblies', as in Peyrache et al, 2010; Farooq et al, 2019? Does a classic assembly analysis during run reveal cluster structures?

Our clusters correspond to functional assemblies in that cells that share a cluster membership have more-similar place fields and are more likely to reactivate together during population burst events. In the figure to the right, we show for an example network at the fiducial parameter set the Pearson correlation between all pairs of place fields split by whether the cells share membership in a cluster (blue) or do not (red).

Author response image 1.



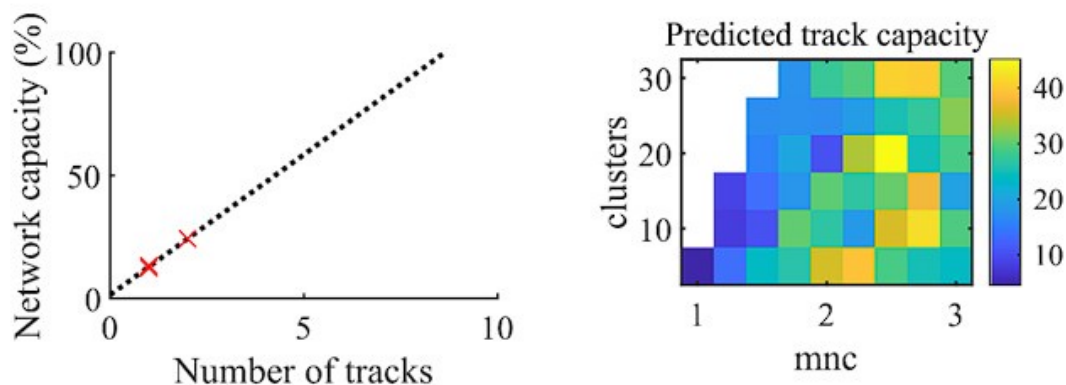
We expect an assembly analysis would identify assemblies similarly to the experimental data, but we see this additional analysis as a future direction. We have added a description of this correspondence in the text at lines 134-137.

Lines 134-137: “Such clustered connectivity likely underlies the functional assemblies that have been observed in hippocampus, wherein groups of recorded cells have correlated activity that can be identified through independent component analysis (Peyrache et al., 2010; Farooq et al., 2019).”

(7) Can the capacity of the clustered network to express preplay for multiple distinct future experiences be estimated in relation to current network activity, as in Dragoi and Tonegawa, PNAS 2013?

We agree this is an interesting opportunity to compare the results of our model to what has been previously found experimentally. We report here preliminary results supporting this as an interesting future direction.

Author response image 2.



We performed a similar analysis to that reported in Figure 3C of Dragoi and Tonegawa, 2013. We determined the statistical significance of each event individually for each of the two environments by testing whether the decoded event’s absolute weighted correlation exceeded that 99th percentile of the corresponding shuffle events. We then fit a linear regression to the fraction of events that were significant for each of the two tracks and that were significant to either of the two tracks (left panel of above figure). We then estimated the track capacity as the number of tracks at the point where the linear regression reached 100% of the network capacity. We find that applying this analysis to our fiducial parameter set returns an estimate of ~8.6 tracks (Dragoi and Tonegawa, 2013, found ~15 tracks).

We performed this same analysis for each parameter point in our main parameter grid (right panel of above figure). The parameter region that produces significant preplay (Figure 4f) corresponds to the region that has a track capacity of approximately 8-25 tracks. In the parameter grid region that does not produce preplay, the estimated track capacity approaches the high values that this analysis would produce when applied to events that are significant only at the false-positive rate. This analysis is based on the assumption that each preplay event would significantly correspond to at least one future event. Interesting interpretation issues arise when applying this analysis to parameter regions that do not produce statistically significant preplay, which we leave to future directions to address.

We note two differences between our analysis here and that in Dragoi and Tonegawa, 2013. First, their track capacity analysis was performed on spike sequences rather than decoded spatial sequences, which is the focus of our manuscript. Second, they recorded rats exploring three novel tracks, while in our manuscript we only simulated two novel tracks, which reduces the accuracy of our linear extrapolation of track capacity.

Reviewer #2 (Public Review):

Summary:

The authors show that a spiking network model with clustered neurons produces intrinsic spike sequences when driven with a ramping input, which are recapitulated in the absence of input. This behavior is only seen for some network parameters (neuron cluster participation and number of clusters in the network), which correspond to those that produce a small world network. By changing the strength of ramping input to each network cluster, the network can show different sequences.

Strengths:

A strength of the paper is the direct comparison between the properties of the model and neural data.

Weaknesses:

My main critiques of the paper relate to the form of the input to the network.

First, because the input is the same across trials (i.e. all traversals are the same duration/velocity), there is no ability to distinguish a representation of space from a representation of time elapsed since the beginning of the trial. The authors should test what happens e.g. with traversals in which the animal travels at different speeds, and in which the animal's speed is not constant across the entire track, and then confirm that the resulting tuning curves are a better representation of position or duration.

We thank the reviewer for pointing out this important limitation. We see extensive testing of the time vs space coding properties of this network as a future direction, but we have performed simulations that demonstrate the robustness of place field coding to variations in traversal speeds and added the results as a supplemental figure (Figure 3—figure supplement 1).

Lines 332-336: “To verify that our simulated place cells were more strongly coding for spatial location than for elapsed time, we performed simulations with additional track traversals at different speeds and compared the resulting place fields and time fields in the same cells. We find that there is significantly greater place information than time information (Figure 3—figure supplement 1).

Lines 835-841: “To compare coding for place vs time, we performed repeated simulations for the same networks at the fiducial parameter point with 1.0x and 2.0x of the original track traversal speed. We then combined all trials for both speed conditions to calculate both place fields and time fields for each cell from the same linear track traversal simulations. The place fields were calculated as described below (average firing rate within each of the fifty 2-cm long spatial bins across the track) and the time fields were similarly calculated but for fifty 40-ms time bins across the initial two seconds of all track traversals.”

Second, it's unclear how much the results depend on the choice of a one-dimensional environment with ramping input. While this is an elegant idealization that allows the authors to explore the representation and replay properties of their model, it is a strong and highly non-physiological constraint. The authors should verify that their results do not depend on this idealization. Specifically, I would suggest the authors also test the spatial coding properties of their network in 2-dimensional environments, and with different kinds of input that have a range of degrees of spatial tuning and physiological plausibility. A method for systematically producing input with varying degrees of spatial tuning in both 1D and 2D environments has been previously used in (Fang et al 2023, eLife, see Figures 4 and 5), which could be readily adapted for the current study; and behaviorally plausible trajectories in 2D can be produced using the RatInABox package (George et al 2022, bioRxiv), which can also generate e.g. grid cell-like activity that could be used as physiologically plausible input to the network.

We agree that testing the robustness of our results to variations in feedforward input is important. We have added new simulation results (Figure 4—figure supplement 4) showing that the existence of preplay in our model is robust to variations in the form of input.

Testing the model in a 2D environment is an interesting future direction, but we see it as outside the scope of the current work. To our knowledge there are no experimental findings of preplay in 2D environments, but this presents an interesting opportunity for future modeling studies.

Lines 413-420: To test the robustness of our results to variations in input types, we simulated alternative forms of spatially modulated feedforward inputs. We found that with no parameter tuning or further modifications to the network, the model generates robust preplay with variations on the spatial inputs, including inputs of three linearly varying cues (Figure 4—figure supplement 4a) and two stepped cues (Figure 4—figure supplement 4b-c). The network is impaired in its ability to produce preplay with binary step location cues (Figure 4—figure supplement 4d), when there is no cluster bias (Figure 4—figure supplement 4e), and at greater values of cluster participation (Figure 4—figure supplement 4f).

Finally, I was left wondering how the cells' spatial tuning relates to their cluster membership, and how the capacity of the network (number of different environments/locations that can be represented) relates to the number of clusters. It seems that if clusters of cells tend to code for nearby locations in the environment (as predicted by the results of Figure 5), then the number of encodable locations would be limited (by the number of clusters). Further, there should be a strong tendency for cells in the same cluster to encode overlapping locations in different environments, which is not seen in experimental data.

Thank you for making this important point and giving us the opportunity to clarify. We do find that subsets of cells with identical cluster membership have correlated place fields, but as we show in Figure 9b (original Figure 7b) the network place map as a whole shows low remapping correlations across environments, which is consistent with experimental data (Hampson et al., 1996; Pavlides, et al., 2019).

Our model includes a relatively small number of cells and clusters compared to CA3, and with a more realistic number of clusters, the level of correlation across network place maps should reduce even further in our model network. The reason for a low level of correlation in the model is because cluster membership is combinatorial, whereby cells that share membership in one cluster can also belong to separate/distinct other clusters, rendering their activity less correlated than might be anticipated.

We have added text at lines 627-630 clarifying these points.

Lines 628-631: "Cells that share membership in a cluster will have some amount of correlation in their remapping due to the cluster-dependent cue bias, which is consistent with experimental results (Hampson et al., 1996; Pavlides et al., 2019), but the combinatorial nature of cluster membership renders the overall place field map correlations low (Figure 9b)."

Reviewer #3 (Public Review):

Summary:

This work offers a novel perspective on the question of how hippocampal networks can adaptively generate different spatial maps and replays/preplays of the corresponding place cells, without any such maps pre-existing in the network architecture or its inputs. Unlike previous modeling attempts, the authors do not pre-tune their model neurons to any particular place fields. Instead, they build a random, moderately-clustered network of excitatory (and some inhibitory) cells, similar to CA3 architecture. By simulating spatial exploration through border-cell-like synaptic inputs, the model generates place cells for different "environments" without the need to reconfigure its synaptic connectivity or introduce plasticity. By simulating sleep-like random synaptic inputs, the model generates sequential activations of cells, mimicking preplays. These "preplays" require small-world connectivity, so that weakly connected cell clusters are activated in sequence. Using a set of electrophysiological recordings from CA1, the authors confirm that the modeled place cells and replays share many features with real ones. In summary, the model demonstrates that spontaneous activity within a small-world structured network can generate place cells and replays without the need for pre-configured maps.

Strengths:

This work addresses an important question in hippocampal dynamics. Namely, how can hippocampal networks quickly generate new place cells when a novel environment is introduced? And how can these place cells preplay their sequences even before the environment is experienced? Previous models required pre-existing spatial representations to be artificially introduced, limiting their adaptability to new environments. Other models depended on synaptic plasticity rules which made remapping slower than what is seen in recordings. This modeling work proposes that quickly-adaptive intrinsic spiking sequences (preplays) and spatially tuned spiking (place cells) can be generated in a network through randomly clustered recurrent connectivity and border-cell inputs, avoiding the need for pre-set spatial maps or plasticity rules. The proposal that small-world architecture is key for place cells and preplays to adapt to new spatial environments is novel and of potential interest to the computational and experimental community.

The authors do a good job of thoroughly examining some of the features of their model, with a strong focus on excitatory cell connectivity. Perhaps the most valuable conclusion is that replays require the successive activation of different cell clusters. Small-world architecture is the optimal regime for such a controlled succession of activated clusters.

The use of pre-existing electrophysiological data adds particular value to the model. The authors convincingly show that the simulated place cells and preplay events share many important features with those recorded in CA1 (though CA3 ones are similar).

Weaknesses:

To generate place cell-like activity during a simulated traversal of a linear environment, the authors drive the network with a combination of linearly increasing/decreasing synaptic inputs, mimicking border cell-like inputs. These inputs presumably stem from the entorhinal cortex (though this is not discussed). The authors do not explore how the model would behave when these inputs are replaced by or combined with grid cell inputs which would be more physiologically realistic.

We chose the linearly varying spatial inputs as the minimal model of providing spatial input to the network so that we could focus on the dynamics of the recurrent connections. We agree our results will be strengthened by testing alternative types of border-like input. We show in Figure 4—figure supplement 4 that our preplay results are robust to several variations in the location-cue inputs. However, given that a sub-goal of our model was to show that place fields could arise in locations at which no neurons receive a peak in external input, whereas combining input from multiple grid cells produces peaked place-field like input, adding grid cell input (and the many other types of potential hippocampal input) is beyond the scope of the paper.

Even though the authors claim that no spatially-tuned information is needed for the model to generate place cells, there is a small location-cue bias added to the cells, depending on the cluster(s) they belong to. Even though this input is relatively weak, it could potentially be driving the sequential activation of clusters and therefore the preplays and place cells. In that case, the claim for non-spatially tuned inputs seems weak. This detail is hidden in the Methods section and not discussed further. How does the model behave without this added bias input?

We apologize for a lack of clarity if we have caused confusion about the type of inputs and if we implied an absence of spatially-tuned information in the network. In order for place fields to appear the network must receive spatial information, which we model as linearly-varying cues and illustrate in Figure 1b and describe in the caption (original lines 156-157), Results (original lines 189-190 & 497-499), and Methods (original lines 671-683). Such input is not place-field like, as the small bias to any cell linearly decreases from one boundary of the track or the other.

The cluster-dependent bias, which is also described in the same lines (Figure 1 caption (original lines 156-157), Results (original lines 189-190 & 497-499), and Methods (original lines 671-683)), only affects the strength of the spatial cues that are present during simulated run periods. Crucially, this cluster-dependent bias is absent during sleep simulations when preplay occurs, which is why preplay can equally correlate with place field sequences in any context.

We have modified the text (lines 207-210, 218, and 824-827) to clarify these points. We have also added results from a control simulation (Figure 4—figure supplement 4e) showing that preplay is not generated in the absence of the cluster-dependent bias.

Lines 207-210: “This bias causes cells that share cluster memberships to have more similar place fields during the simulated run period, but, crucially, this bias is not present during sleep simulations so that there is no environment-specific information present when the network generates preplay.”

Lines 218: “Second, to incorporate cluster-dependent correlations in place fields, a small...”

Lines 824-827: “The addition of this bias produced correlations in cells’ spatial tunings based on cluster membership, but, importantly, this bias was not present during the sleep simulations, and it did not lead to high correlations of place-field maps between environments (Figure 9b).”

Unlike excitation, inhibition is modeled in a very uniform way (uniform connection probability with all E cells, no I-I connections, no border-cell inputs). This goes against a long literature on the precise coordination of multiple inhibitory subnetworks, with different interneuron subtypes playing different roles (e.g. output-suppressing perisomatic inhibition vs input-gating dendritic inhibition). Even though no model is meant to capture every detail of a real neuronal circuit, expanding on the role of inhibition in this clustered architecture would greatly strengthen this work.

This is an interesting future direction, but we see it as outside the scope of our current work. While inhibitory microcircuits are certainly important physiologically, we focus here on a minimal model that produces the desired place cell activity and preplay, as measured in excitatory cells. We have added a brief discussion of this to the manuscript.

Lines 733-739: “Additionally, the *in vivo* microcircuitry of CA3 is complex and includes aspects such as nonlinear dendritic computations and a variety of inhibitory cell types (Rebola et al., 2017). This microcircuitry is crucial for explaining certain aspects of hippocampal function, such as ripple and gamma oscillogenesis (Ramirez-Villegas et al., 2017), but here we have focused on a minimal model that is sufficient to produce place cell spiking activity that is consistent with experimentally measured place field and preplay statistics.”

For the modeling insights to be physiologically plausible, it is important to show that CA3 connectivity (which the model mimics) shares the proposed small-world architecture. The authors discuss the existence of this architecture in various brain regions but not in CA3, which is traditionally thought of and modeled as a random or fully connected recurrent excitatory network. A thorough discussion of CA3 connectivity would strengthen this work.

We agree this is an important point that is missing, and we have modified lines 114-116 to address the clustered connectivity reported in CA3.

Lines 114-116: “Such clustering is a common motif across the brain, including the CA3 region of the hippocampus (Guzman et al., 2016) as well as cortex (Song et al., 2005), ...”

Recommendations for the authors:

Reviewer #1 (Recommendations For The Authors):

(1) Based on Figure 3, the place fields are not uniformly distributed in the maze. Meanwhile, based on Figure 1b and Methods, the total input seems to be uniform across the maze. Why does the uniform total external input lead to nonuniform network activities?

While the total input to the network is constant across the maze, the input to any individual cell can peak only at either end of the track. All excitatory cells receive input from both the left-cue and the right-cue with different input strengths. By chance and due to the cluster-dependent bias some cells will have stronger input from one cue than the other and will therefore be more likely to have a place field toward that side of the track. However, no cell

receives a peak of input in the center of the track. We have modified lines 141-143 to clarify this.

Lines 141-143: “While the total input to the network is constant as a function of position, each cell only receives a peak in its spatially linearly varying feedforward input at one end of the track.”

(2) I find these sentences confusing: "...we expected that the set of spiking events that significantly decode to linear trajectories in one environment (Figure 4) should decode with a similar fidelity in another environment..." (Lines 513-515) and "As expected... but not with the place fields of trajectories from different environments (Figure 7c)" (Line 517-520). What is the expectation for cross-environment decoding? Should they be similar or different? Also, in Figure 7c, the example is not fully convincing. In the figure caption, it states that decoding is significant in the top row but not in the bottom row, but they look similar across rows.

Original lines 513-515 refer to the entire set of events, while original lines 517-520 refer to one example event. The sleep events are simulated without any track-specific information present, so the degree to which preplay occurs when decoding based on the place fields of a specific future track should be independent of any particular track when considering the entire set of decoded PBEs, as shown in Figure 9d (original Figure 7). However, because there is strong remapping across tracks (Figure 9b), an individual event that shows a strong decoded trajectory based on the place fields of one track (Figure 9c, top row) should show chance levels of a decoded trajectory when decoded with the place fields of an alternative track (Figure 9c, bottom row).

We have revised lines 643-650 for clarity, and we have added statistics for the events shown in Figure 9c.

Lines 644-651: “Since the place field map correlations are high for trajectories on the same track and near zero for trajectories on different tracks, any individual event would be expected to have similar decoded trajectories when decoding based on the place fields from different trajectories in the same environment and dissimilar decoded trajectories when decoding based on place fields from different environments. A given event with a strong decoded trajectory based on the place fields of one environment would then be expected to have a weaker decoded trajectory when decoded with place fields from an alternative environment (Figure 9c).

Lines 604-608: “(c) An example event with a statistically significant trajectory when decoded with place fields from Env. 1 left (absolute correlation at the 99th percentile of time-bin shuffles) but not when decoded with place fields of the other trajectories (78th, 45th, and 63rd percentiles, for Env. 1 right, Env. 2 left, and Env. 2 right, respectively). shows a significant trajectory when it is decoded with place fields from one environment (top row), but not when it is decoded with place fields from another environment (bottom row). “

(3) In Methods, the equation at line 610, E in the last term should be E_{ext} .

We modeled the feedforward inputs as excitatory connections with the same reversal potential as the recurrent excitatory connections, so is the proper value.

(4) Equation line 617 states that conductances follow exponential decay, but the initial conductances of $g_{I.g.E}$ and g_{SRA} are not specified.

We have added a description of the initial values in lines 760-764.

Lines 760-764: “Initial feed-forward input conductances were set to values approximating their steady-state values by randomly selecting values from a Gaussian with a mean of and a standard deviation of $\sqrt{W_{in}^2 \tau_G \tau_E}$. Initial values of the recurrent conductances and the SRA conductance were set to zero.”

(5) In the parameter table below line 647, W_{E-E} , W_{E-I} , and W_{I-E} are not described in the text.

We have clarified in lines 757-760 that the step increase in conductance corresponds to these parameter values.

Lines 757-760: “A step increase in conductance occurs at the time of each spike by an amount corresponding to the connection strength for each synapse (for E-to-E connections, for E-to-I connections, and for I-to-E connections), or by for .”

(6) On line 660, “...Each environment and the sleep session had unique context cue input weights...”. Does that mean that within a sleep session, the network received the same context input? How strongly are the sleep dynamics driven by that context input rather than by intrinsic dynamics? Usually, sleep activity is high dimensional, what would happen if the input during sleep is more stochastic?

Yes, within a sleep session each network receives a single set of context inputs, which are implemented as independent Poisson spike trains (so being independent, in small time-windows the dimensionality is equal to the number of neurons). The effects of any particular set of sleep context cue inputs should be minor, since the standard deviation of the input weights, , is small. Further, because the preplay analysis is performed across many networks at each parameter point, the observation of preplay is independent of any particular realization of either the recurrent network or the sleep context inputs.

Further exploring the effects of more biophysically realistic neural dynamics during simulated sleep is an interesting future direction.

(7) One bracket is missing in the denominator in line 831.

We have fixed this error.

Line 1005: “)” -> “()”

Reviewer #2 (Recommendations For The Authors):

- I would suggest the authors cite Chenkov et al 2017, PLOS Comp Bio, in which “replay” sequences were produced in clustered networks, and discuss how their work differs.

We have included a contrast of our model to that of Chenkov et al., 2017 in lines 73-78.

Lines 73-78: “Related to replay models based on place-field distance-dependent connectivity is the broader class of synfire-chain-like models. In these models, neurons (or clusters of neurons) are connected in a 1-dimensional feed-forward manner (Diesmann et al., 1999; Chenkov et al., 2017). The classic idea of a synfire-chain has been extended to included recurrent connections, such as by Chenkov et al., 2017, however such models still rely on an underlying 1-dimensional sequence of activity propagation.”

- Figure legend 2e says “replay”, should be “preplay”.

We have fixed this error.

Line 255: “(e) Example preplay event...”

- How much does the context cue affect the result? e.g. Is sleep notably different with different sleep context cues?

As discussed above in our response to Reviewer 1, the context cue weights have a small standard deviation, which means that differences in the effects of different realizations of the context inputs are small. Different sets of context cues will cause cells to have slightly higher or lower spiking rates during sleep simulations, but because there is no correlation between the sleep context cue and the place field simulations there should be no effect on preplay quality.

- Figure 4 should include a control with a single cluster.

We thank the reviewer for this suggestion and have added additional control simulations.

In our model, the recurrent structure of a network with a single cluster is equivalent to a cluster-less random network. Additionally, any network where cluster participation equals the number of clusters is equivalent to a cluster-less random network, since all neurons belong to all clusters and can therefore potentially connect to any other neuron. Such a condition corresponds to a diagonal boundary where the number of clusters equals the cluster participation, which occurs at higher values of cluster participation than we had shown in our primary parameter grid.

We now include simulation results that extend to this boundary, corresponding to cluster-less networks (Figure 4—figure supplement 4f). Networks at these parameter points do not show preplay. See our earlier response for the new text associated with Figure 4—figure supplement 4.

- The results of Figure 4 are very noisy. I would recommend increasing the sampling, both in terms of the number of population events in each condition and the number of conditions.

We have run simulations for longer durations (300 seconds) and with more networks (20) to produce more accurate empirical values for the statistics calculated across the parameter grids in Figures 3 and 4. Our additional simulations (Figure 4—figure supplement 4) provide support that the parameter region of preplay significance is reliable.

Lines 831-833: “For the parameter grids in Figures 3 and 4 we simulated 20 networks with 300 s long sleep sessions in order to get more precise empirical estimates of the simulation statistics.”

- It's not entirely clear what's different between the analysis described in lines 334-353, and the preplay analysis in Figure 2. In general, the description of this result was difficult to follow, as it included a lot of text that would be better served in the methods.

In Figure 2 we first introduce the Bayesian decoding method, but it is not until Figure 4 that the shuffle-based significance testing is first introduced. We have simplified the description of the shuffle comparison in lines 371-375 and now refer the reader to the methods for details.

Lines 371-375: “We find significant preplay in both our reference experimental data set (Shin et al., 2019; Figure 4a, b; see Figure 4—figure supplement 1 for example events) and our model (Figure 4c, d) when analyzed by the same methods as Farooq et al., 2019, wherein the

significance of preplay is determined relative to time-bin shuffled events (see Methods). For each detected event we calculated its absolute weighted correlation. We then generated 100 time-bin shuffles of each event, and for each shuffle recalculated the absolute weighted correlation to generate a null distribution of absolute weighted correlations.”

- Many of the figures have low text resolution (e.g. Figure 6).

We have now fixed this.

- How does the clustered small world network compare to e.g. a small world ring network as used in Watts and Strogatz 1998?

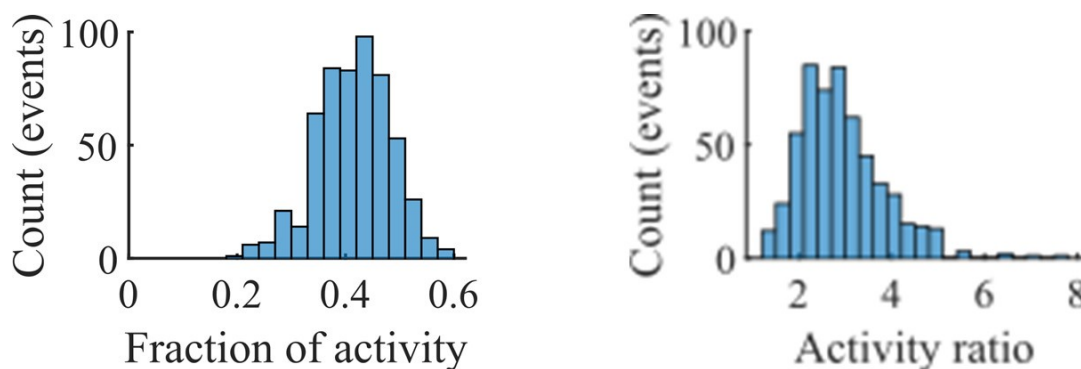
As described in our above response to Reviewer 1's fourth point, we have added a supplementary figure (Figure 1—figure supplement 1, with corresponding text) comparing our model with the Watts-Strogatz model.

Reviewer #3 (Recommendations For The Authors):

Figure 5 would benefit from a plot of the overlap of activated clusters per event.

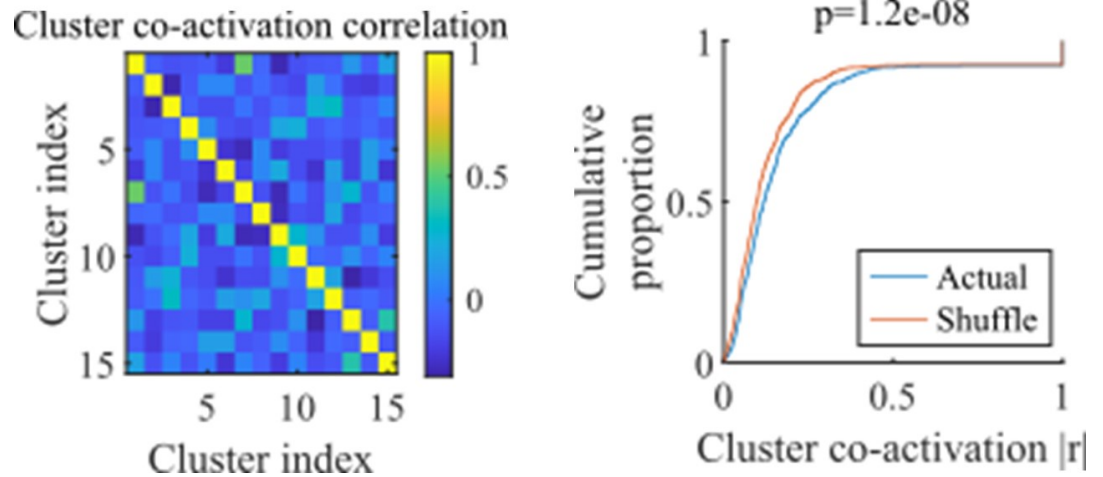
In our cluster activation analysis in Figure 5, we defined a cluster as “active” if at any point in the event its population rate was twice that of any other clusters’. We used this definition—which permits no overlap of activated clusters—rather than a definition based on a z-scoring of the rate, because we determined that preplay required periods of spiking dominated by individual clusters.

Author response image 3.



The choice of such a definition is supported by our observation that most spiking activity within an event is dominated by whichever cluster is most active at each point in time. In the left panel of the above figure we show the distribution of the average fraction of spikes within each event that came from the most active cluster at each point in time. The right panel shows the distribution of the average across time within each event of the ratio of the population activity rate of the most active cluster to the second most active cluster. The data for both panels comes from all events at the fiducial parameter set.

Author response image 4.



Rather than overlapping at a given moment in time, clusters might have overlap in their probability of being active at some point within an event. We do find that there is a small but significant correlation in cluster co-activation. For each network we calculated the activation correlation across events for each pair of clusters (example network show in the left panel). We compared the distribution of resulting absolute correlations against the values that results after shuffling the correlations between cluster activations (right panel, all correlations for all networks from the fiducial parameter point).

| Figures 4e/f are referred to as 4c/d in the text (pg 14).

We have fixed this error.

Lines 400-412: “4c” -> “4e” and “4d” -> “4f”

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