Offline memory replay in recurrent neuronal networks emerges from constraints on online dynamics

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Abstract  During spatial exploration, neural circuits in the hippocampus store memories of sequences of sensory events encountered in the environment. When sensory information is absent during ‘offline’ resting periods, brief neuronal population bursts can ‘replay’ sequences of activity.

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that resemble bouts of sensory experience. These sequences can occur in either forward or reverse order, and can even include spatial trajectories that have not been experienced, but are consistent with the topology of the environment. The neural circuit mechanisms underlying this variable and flexible sequence generation are unknown. Here we demonstrate in a recurrent spiking network model of hippocampal area CA3 that experimental constraints on network dynamics such as population sparsity, stimulus selectivity, rhythmicity and spike rate adaptation, as well as associative synaptic connectivity, enable additional emergent properties, including variable offline memory replay. In an online stimulus-driven state, we observed the emergence of neuronal sequences that swept from representations of past to future stimuli on the timescale of the theta rhythm. In an offline state driven only by noise, the network generated both forward and reverse neuronal sequences, and recapitulated the experimental observation that offline memory replay events tend to include salient locations like the site of a reward. These results demonstrate that biological constraints on the dynamics of recurrent neural circuits are sufficient to enable memories of sensory events stored in the strengths of synaptic connections to be flexibly read out during rest and sleep, which is thought to be important for memory consolidation and planning of future behaviour.

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Abstract figure legend During simulated rodent spatial navigation, place cells in hippocampal area CA3 fire at specific locations in space, generating a sequence in the order that the animal traverses. Recurrent network models of excitatory (E) place cells and inhibitory (I) interneurons that included associative synaptic connectivity between E cells, rhythmic synchrony in E and I cells, and spike rate adaptation in E cells were found to generate sequences in an offline state in the absence of structured sensory inputs. These sequences replayed those generated during navigation, but occurred in either forward or reverse order.

Key points
• A recurrent spiking network model of hippocampal area CA3 was optimized to recapitulate experimentally observed network dynamics during simulated spatial exploration.
• During simulated offline rest, the network exhibited the emergent property of generating flexible forward, reverse and mixed direction memory replay events.
• Network perturbations and analysis of model diversity and degeneracy identified associative synaptic connectivity and key features of network dynamics as important for offline sequence generation.
• Network simulations demonstrate that population over-representation of salient positions like the site of reward results in biased memory replay.

Introduction
In mammals, the hippocampus is a brain region involved in the storage and recall of spatial and episodic memories. As an animal explores a spatial environment, different subpopulations of hippocampal neurons known as ‘place cells’ are selectively activated at different positions in space, resulting in sequences of neuronal spiking that are on the seconds-long timescale of locomotor behaviour (O’Keefe & Conway, 1978). The synchronous firing of these sparse neuronal ensembles is coordinated by population-wide oscillations referred to as theta (∼4–10 Hz) and gamma (∼30–100 Hz) rhythms (Colgin, 2016). Within each cycle of the theta rhythm (∼125 ms), the spiking of active neurons is organized into fast timescale sequences such that neurons selective for just-visited positions spike first, then neurons selective for the current position, and finally neurons selective for the next and future positions spike last in the sequence (Drieu & Zugaro, 2019; Foster & Wilson, 2007). These order-preserving fast timescale ‘theta sequences’ are thought to be involved in planning and learning of event order through associative synaptic plasticity (Jensen et al., 1996; Kay et al., 2020).
When an animal stop running, theta and gamma oscillations decrease, and neuronal circuits in the hippocampus instead emit intermittent synchronous bursts of activity that are associated with high-frequency oscillatory activity detectable in local field potential recordings in hippocampal area CA1. These ∼50–150 ms-long events are referred to as ‘sharp wave-ripples’ (SWRs) (Colgin, 2016; Fernández-Ruiz et al., 2019), and they occur during non-locomotor periods of quiet wakefulness, during reward consumption, and during slow-wave sleep, when sensory information about the spatial environment is reduced or absent. During SWRs, sparse subsets of neurons are co-activated, with a tendency for neurons that fire sequentially during exploratory behaviour to also fire sequentially during SWRs, either in the same order, or in reverse, or with a mixture of both directions (Davidson et al., 2009; Pfeiffer, 2020; Stella et al., 2019; Wu & Foster, 2014). The hippocampus can also activate sequences of place cells during SWRs that correspond to possible paths through the environment that have not actually been experienced, suggesting a possible role for offline sequence generation in behavioural planning (Gupta et al., 2010; Igata et al., 2021; Olafsdóttir et al., 2015, 2018; Wu & Foster, 2014). Manipulations that disrupt neuronal activity during SWRs result in deficits in memory recall (Girardeau et al., 2009; JadHAV et al., 2012), supporting a hypothesis that offline reactivation of neuronal ensembles during SWRs is important for the maintenance and consolidation of long-term memories (Buzsáki, 1989; Joo & Frank, 2018).

Hippocampal SWRs are thought to be generated by the synchronous firing of subpopulations of neurons in the CA2 and CA3 regions of the hippocampus (Csicsvari et al., 2000; Oliva et al., 2016), which are characterized by substantial recurrent feedback connectivity (Duigou et al., 2014; Guzman et al., 2016; Okamoto & Ikegaya, 2019). Recurrent networks have long been appreciated for their ability to generate rich internal dynamics (Amit & Brunel, 1997), including oscillations (Ermentrout, 1992). It has also been shown that associative plasticity at recurrent connections between excitatory neurons can enable robust reconstruction of complete memory representations from incomplete or noisy sensory cues (Amit & Brunel, 1997; Griniasty et al., 1993; Guzman et al., 2016; Hopfield, 1982; Marr, 1971; Treves & Rolls, 1994). However, this ‘pattern completion’ function of recurrent networks requires that similarly tuned neurons activate each other via strong synaptic connections, resulting in sustained self-activation, rather than sequential activation of neurons that are selective for distinct stimuli (Lisman et al., 2005; Pfeiffer & Foster, 2015; Renno-Costa et al., 2014). Previous work has shown that, in order for recurrent networks to generate sequential activity, some mechanism must be in place to ‘break the symmetry’ and enable spread of activity from one ensemble of cells to another (Sompolinsky & Kanter, 1986; Tsodyks et al., 1996). During spatial navigation, feedforward sensory inputs carrying information about the changing environment can provide the momentum necessary for sequence generation. However, during hippocampal SWRs, sensory inputs are reduced, and activity patterns are thought to be primarily internally generated by the recurrent connections within the hippocampus. In this study we use a computational model of hippocampal area CA3 to investigate the synaptic, cellular and network mechanisms that enable flexible offline generation of memory-related neuronal sequences in the absence of ordered sensory information.

A number of possible mechanisms for sequence generation in recurrent networks have been proposed:

1. Winner-takes-all network mechanism (Almeida et al., 2007, 2009a; Lisman & Jensen, 2013). Within this framework, the subset of excitatory neurons receiving the most strongly weighted synaptic inputs responds first upon presentation of a stimulus. This active ensemble of cells then recruits feedback inhibition via local interneurons, which in turn prevents other neurons from firing for a brief time window (e.g. the ∼15 ms duration of a single gamma cycle). This highlights the important roles that inhibitory neurons play in regulating sparsity (how many cells are co-active), selectivity (which cells are active) and rhythmicity (when cells fire) in recurrent networks (Almeida et al., 2009b; Rennó-Costa et al., 2019; Stark et al., 2014; Stefanelli et al., 2016). However, while oscillatory feedback inhibition provides a network mechanism for parsing neuronal sequences into discrete elements, additional mechanisms are still required to ensure that distinct subsets of excitatory neurons are activated in a particular order across successive cycles of a rhythm (Lisman et al., 2005; Ramirez-Villegas et al., 2018).

2. Heterogeneous cellular excitability (Luczak et al., 2007; Stark et al., 2015). If the intrinsic properties of neurons in a network are variable and heterogeneous, when a stimulus is presented, those neurons that are the most excitable will fire early, while neurons with progressively lower excitability will fire later, resulting in sequence generation. This mechanism can explain the offline generation of stereotyped, unidirectional sequences, but cannot account for variable generation of sequences in both forward and reverse directions.

3. Asymmetric distributions of synaptic weights (Sompolinsky & Kanter, 1986; Tsodyks et al., 1996). During learning, if changes in synaptic weights are controlled by a temporally asymmetric learning rule, recurrent connections can become biased such that neurons activated early in a sequence have stronger connections onto neurons activated later.
in a sequence (Levy, 1989; Malerba & Bazhenov, 2019; McNaughton & Morris, 1987; Reifenstein et al., 2021). This enables internally generated activity to flow along the direction of the bias in synaptic weights. While this mechanism accounts for offline replay of specific sequences in the same order experienced during learning, it cannot account for reverse replay or the flexible generation of non-experienced sequences (Gupta et al., 2010; Igata et al., 2021; Ólafsdóttir et al., 2015, 2018; Wu & Foster, 2014).

(4) Cellular or synaptic adaptation. It has also been proposed that short-term adaptation of either neuronal firing rate (Ecker et al., 2022; Itskov et al., 2011; Treves, 2004) or synaptic efficacy (Romani & Tsodyks, 2015) can enable neuronal sequence generation in recurrent networks without asymmetric synaptic weights. According to this scheme, recently activated neurons initially recruit connected partners with high efficacy, but continued spiking results in either a decrease in firing rate or a decrease in the probability of neurotransmitter release. This causes connections to fatigue over time, and favours the sequential propagation of activity to more recently activated cells. These mechanisms do allow for the stochastic generation of neuronal sequences in either the forward or reverse direction, though they do not prescribe which or how many neurons will participate in a given replay event.

In this study, we sought to understand how neuronal sequence generation in hippocampal area CA3 depends on the structure and function of the underlying network. To do this, we constructed a computational neuronal network model comprising recurrently connected excitatory and inhibitory spiking neurons, and tuned it to match experimental constraints on the spiking dynamics of CA3 during spatial navigation, including sparsity, selectivity, rhythmicity and spike rate adaptation. We then analysed the direction and content of neuronal sequences generated both ‘online’ during simulated navigation, and ‘offline’ during simulated rest. We found that when the network was driven by ordered sensory information in the online state, it generated forward-sweeping ‘theta sequences’ that depended on the structure of recurrent connectivity in the network. In the offline state driven by noise, the network generated heterogeneous memory replay events that moved in either forward, or reverse, or mixed directions, and depended on network sparsity and rhythmicity, and neuronal stimulus selectivity and spike-rate adaptation. Model degeneracy analysis and network perturbations indicated that offline memory replay does not occur in networks with disrupted recurrent connectivity, or in networks lacking sparsity, selectivity, rhythmicity, or spike rate adaptation. Finally, when particular spatial locations were over-represented by the network, as occurs in the hippocampus at sites of reward (Lee et al., 2006; Turi et al., 2019; Zaremba et al., 2017), memory replay events were biased towards trajectories that included those salient positions (Gillespie et al., 2021; Ólafsdóttir et al., 2015; Singer & Frank, 2009).

Methods

Ethical approval

No animal or human subjects were used in this study. This research was performed in compliance with all institutional policies regarding ethical research practices.

Neuronal network modelling

Simulations of a recurrent network of excitatory and inhibitory spiking neurons were executed using the Python interface for the NEURON simulation software (Hines et al., 2009). Cell models were single-compartment integrate-and-fire neuronal cell models, as defined by Izhikevich (2007), and as implemented for the NEURON simulator by Lytton et al. (2016). Previously calibrated cell models were replicated from those previous reports without modification – the ‘intrinsically bursting cell’ model was used for excitatory neurons (E) with spike rate adaptation, the ‘regular spiking pyramidal cell’ model was used for excitatory neurons without spike rate adaptation, and the ‘fast-spiking interneuron’ model was used for inhibitory neurons (I) (Izhikevich, 2007; Lytton et al., 2016). Individual spikes in presynaptic neurons activated saturable conductance-based synapses with exponential rise and decay kinetics after a constant delay of 1 ms to emulate axonal conduction time (Carnevale & Hines, 2006). Excitatory synapses had a reversal potential of 0 mV (like AMPA-type glutamate receptors), and inhibitory synapses had a reversal potential of −80 mV (like GABA_A-type receptors). In addition to the excitatory (E) and inhibitory (I) neuron populations, a population of feedforward afferent inputs (FF) provided a source of external excitatory synaptic drive to the model network.

The baseline weights of excitatory synapses onto E cells were sampled from a log-normal distribution (Almeida et al., 2009b; Buzsáki & Mizuseki, 2014), while the weights of excitatory synapses onto I cells, and all inhibitory synapses were sampled from a normal distribution (Grienberger et al., 2017). In addition to the random baseline synaptic weights assigned to excitatory synapses onto E cells, input strengths were increased by a variable additive factor that depended on the distance between the place fields of cells with overlapping spatial selectivity (Supplementary Fig. S1B). The place field locations of the FF and E populations were assigned by distributing
Table 1. Model parameter values

| Parameter | Structured $E \rightarrow E$ weights | Random $E \rightarrow E$ weights | Suppressed rhythmicity | No sparsity or selectivity constraints | No spike rate adaptation |
|-----------|-------------------------------------|---------------------------------|------------------------|---------------------------------------|-------------------------|
| $E \leftarrow FF$ weight mean | 0.1–5 | 1.28 | 0.29 | 1.30 | 0.37 | 1.57 | 0.55 |
| $E \leftarrow FF$ weight st. dev. | 0.1–5 | 1.09 | 0.21 | 0.91 | 0.80 | 0.88 | 0.41 |
| $E \leftarrow E$ weight mean | 0.1–5 | 0.75 | 0.50 | 1.43 | 0.90 | 0.54 | 2.45 |
| $E \leftarrow I$ weight mean | 0.1–5 | 0.87 | 0.70 | 2.06 | 0.86 | 0.59 | 0.54 |
| $I \leftarrow FF$ weight mean | 0.1–5 | 0.52 | 0.48 | 0.58 | 0.25 | 0.73 | 1.74 |
| $I \leftarrow E$ weight mean | 0.1–5 | 0.47 | 0.32 | 0.41 | 0.76 | 0.73 | 0.16 |
| $E \leftarrow I$ weight st. dev. | 0.1–5 | 1.50 | 1.83 | 2.44 | 0.38 | 1.53 | 1.60 |
| $I \leftarrow E$ weight st. dev. | 0.1–5 | 0.68 | 0.82 | 0.45 | 0.38 | 0.55 | 0.22 |
| $E \leftarrow E$ decay (ms) | 2–20 | 3.43 | 10.76 | 3.48 | 19.87 | 3.53 | 5.91 |
| $E \leftarrow I$ decay (ms) | 2–30 | 8.09 | 5.65 | 8.12 | 9.24 | 10.19 | 22.35 |
| $I \leftarrow FF$ weight mean | 0.1–5 | 1.5 | 1.83 | 2.44 | 0.38 | 1.53 | 1.60 |
| $I \leftarrow E$ weight mean | 0.1–5 | 1.85 | 1.31 | 1.44 | 1.63 | 1.77 | 0.82 |
| $I \leftarrow I$ weight mean | 0.1–5 | 0.22 | 0.28 | 0.21 | 0.17 | 0.14 | 0.79 |
| $E \leftarrow FF$ no. synapses/pair | 0–2 | 0.62 | 0.96 | 0.70 | 0.57 | 0.73 | 0.18 |
| $E \leftarrow E$ no. synapses/pair | 0–2 | 0.55 | 0.57 | 0.55 | 0.05 | 0.33 | 0.46 |
| $E \leftarrow I$ no. synapses/pair | 0–10 | 0.31 | 0.47 | 0.19 | 0.22 | 0.13 | 0.10 |
| $I \leftarrow FF$ no. synapses/pair | 0–2 | 15.04 | 18.53 | 17.94 | 13.49 | 17.10 | 18.39 |
| $I \leftarrow E$ no. synapses/pair | 0–2 | 8.09 | 5.65 | 8.12 | 9.24 | 10.19 | 22.35 |
| $I \leftarrow I$ no. synapses/pair | 0–10 | 10.04 | 18.53 | 17.94 | 13.49 | 17.10 | 18.39 |

Locations throughout the circular simulated track at equal intervals and randomly assigning them to cells within each population. Random connectivity resulted in each E neuron receiving inputs from many FF and E neurons with heterogeneous selectivity, which produced substantial out-of-field excitation at all positions along the track.

For each of six types of connections between the three cell types (E $\leftarrow$ FF, E $\leftarrow$ E, E $\leftarrow$ I, I $\leftarrow$ FF, I $\leftarrow$ E, I $\leftarrow$ I), a number of parameters were varied and explored during optimization to identify model configurations that produced dynamics comparable to experimental observations. These parameters included: the mean and variance of the synaptic weight distribution for each connection type, the decay time constants of the synaptic conductances, the mean number of synapses made by one presynaptic cell onto one postsynaptic cell for each pair of cell types, and the maximum increase in synaptic weight due to shared selectivity, as mentioned above. Self-connections were not permitted.

Optimization was performed using a population-based iterative multi-objective algorithm. During each of 50 iterations, a population of 600 models with different parameters were simulated for one trial of simulated online run, and for 5 trials of simulated offline rest. During offline rest trials, a random subset of 25% of feed-forward inputs were active with a mean rate of 12.5 Hz for an event duration of 160 ms (8 bins of 20 ms each). Different trials were implemented by using a distinct random number stream to sample unique spike times of the feedforward inputs from an inhomogeneous Poisson process. The following features of the network dynamics were evaluated for each model: average minimum and maximum firing rates of E cells during run, average mean firing rates of I cells during run, average fraction of active E and I cells during run, mean firing rates of E cells during rest, average fraction of active E cells during rest, and finally, features related to the frequency and power of theta and gamma band oscillations in E and I cells during run. These features were compared to target values to obtain a set of multiple objective error values. Models within a population were compared to each other and ranked with a non-dominated sorting procedure (Deb, 2011). Then, a new population of models was generated by making small perturbations to the parameter values of the most highly ranked models from the previous iteration. This algorithm effectively identified model configurations that satisfied multiple objective criteria. In Tables 1 and 2, the final optimized parameter values (Table 1) and measured features of the network dynamics (Table 2) are compared for various model configurations discussed in this study.
### Table 2. Features of model network dynamics

| Feature                                      | Target                  | Structured E ← E weights | Random E ← E weights | Shuffled E ← E weights | Suppressed rhythmicity | No sparsity or selectivity constraints | No spike rate adaptation |
|----------------------------------------------|-------------------------|---------------------------|----------------------|-------------------------|------------------------|----------------------------------------|-------------------------|
| E peak rate (run) (Hz)                       | 20.                     | 17.20                     | 19.96                | 10.42                   | 20.07                  | 19.73                                  | 7.30                    |
| E min rate (run) (Hz)                        | 0.                      | 0.24                      | 0.25                 | 0.27                    | 0.25                   | 12.37                                  | 0.39                    |
| I mean rate (run) (Hz)                       | 20.                     | 19.58                     | 32.05                | 12.08                   | 2.77                   | 19.90                                  | 6.17                    |
| E fraction active (run)                      | 0.6                     | 0.59                      | 0.60                 | 0.61                    | 0.60                   | 1.00                                   | 0.60                    |
| I fraction active (run)                      | 0.95                    | 1.00                      | 1.00                 | 0.95                    | 0.23                   | 0.98                                   | 0.87                    |
| E theta amplitude (run)                      | 0.5                     | 0.78                      | 0.37                 | 0.63                    | 0.15                   | 0.77                                   | 1.29                    |
| I theta amplitude (run)                      | 0.5                     | 0.48                      | 0.14                 | 0.19                    | 0.26                   | 0.53                                   | 1.15                    |
| E gamma amplitude (run)                      | 0.25                    | 0.53                      | 0.40                 | 0.66                    | 0.20                   | 0.59                                   | 0.27                    |
| I gamma amplitude (run)                      | 0.25                    | 1.19                      | 1.85                 | 1.33                    | 1.67                   | 1.39                                   | 1.27                    |
| E theta frequency (run) (Hz)                 | 7.                      | 7.09                      | 7.45                 | 7.64                    | 11.27                  | 7.09                                   | 6.73                    |
| I theta frequency (run) (Hz)                 | 7.                      | 6.91                      | 7.27                 | 7.45                    | 12.55                  | 6.91                                   | 6.73                    |
| E gamma frequency (run) (Hz)                 | 70.                     | 71.06                     | 72.93                | 71.06                   | 57.98                  | 72.93                                  | 39.29                   |
| I gamma frequency (run) (Hz)                 | 70.                     | 71.06                     | 72.93                | 69.19                   | 87.88                  | 76.67                                  | 69.19                   |
| E theta frequency tuning index                | >5.                     | 6.40                      | 6.30                 | 7.00                    | 0.00                   | 29.05                                  | 150.67                  |
| I theta frequency tuning index                | >5.                     | 9.83                      | 6.10                 | 3.99                    | 0.00                   | 34.16                                  | 150.59                  |
| E gamma frequency tuning index (run)         | >5.                     | 10.67                     | 10.90                | 5.08                    | -0.37                  | 10.18                                  | -0.01                   |
| I gamma frequency tuning index (run)         | >5.                     | 16.16                     | 4.14                 | 31.65                   | 0.36                   | 6.02                                   | 3.43                    |
| E fraction active (rest)                     | 0.25                    | 0.37                      | 0.20                 | 0.53                    | 0.36                   | 1.00                                   | 0.40                    |
| E mean rate (rest) (Hz)                      | 12.5                    | 7.11                      | 6.56                 | 7.12                    | 7.65                   | 17.77                                  | 6.97                    |

In Tables 1 and 2, theta and gamma amplitudes were quantified as follows. Average population firing rates were band-pass filtered, and the envelopes of the filtered traces were computed from the Hilbert transformation. Then power was expressed as a ratio of the average envelope amplitude to the average population firing rate. To quantify theta and gamma frequency, bandpass filtered traces were subject to frequency decomposition, and the frequency corresponding to the centroid or centre-of-mass of the power spectral density distribution was taken as the dominant frequency within the band. The area of the power spectral density distribution was also used to compute a ‘frequency tuning index’ which quantified how concentrated the power distribution was around the centroid frequency. This metric was akin to a signal-to-noise ratio in the frequency domain instead of the time domain, and was computed as follows:

\[ \text{FTI} = \frac{S - N}{2 \times \sigma \times w} \quad (1) \]

where \( S \) is the average power at frequencies within the centre of mass quartile containing the centroid frequency (signal), \( N \) is the average power at frequencies in the extreme high and low quartiles outside the centre of mass quartile (noise), \( \sigma \) is the standard deviation of the power distribution, and \( w \) is the half-width of the power distribution in the frequency domain normalized to the width of the bandpass filter. This metric has values near zero when power is distributed uniformly within the filter band, and values larger than 1 when power is concentrated around the centroid frequency.

Following parameter optimization, each variant of the network was evaluated by simulating five trials of online run, and 1000 trials of offline rest for each of five independent network instances. For a given set of model parameters, independent instances of each network variant were constructed by using distinct random number streams to assign place field locations, input spike times, synaptic connections and synaptic weights for all cells in the network.

Bayesian decoding of spatial position from spike times recorded during a single trial (Figs 2, 3, 5 and 6, and Supplementary Figs S3–S6) was performed using the procedure described in Davidson et al. (2009). The spatial firing rates of all cells were averaged across five trials of simulated online run to compute the spiking probabilities of each neuron in 20 ms bins. Then, spiking data were taken from either a held-out set of five trials of simulated run (Fig. 2), or offline rest trials (Figs 3, 5 and 6, and Supplementary Figs S3–S6). The numbers of spikes emitted by each cell in 20 ms bins were used to
Network mechanisms of offline memory replay

Determine a likelihood distribution over spatial positions. The position with maximum likelihood was used as the decoded position estimate for each temporal bin. In Fig. 2A, decoded positions of E and I cells sweep smoothly from past to future positions, and then relax back to the current position on the timescale of the ongoing theta rhythm. To quantify this form of online neuronal sequence generation, a theta sequence score (Figs 2E and 4H) was computed as follows: decoded position error was first bandpass filtered in the theta band (4–10 Hz). Then the contribution of this oscillation to the total variance in decoded position error was calculated as the square of the correlation ($R^2$) between the original mean-subtracted error signal and the theta filtered signal. In Figs 3F, M, 4I, 5G and 6G, and Supplementary Figs S3H, S4F, S5K, S6K and S8E, offline sequences were categorized as consistent with a continuous trajectory through space if they met the following criteria: (1) at least one cell in a population must emit at least one spike in each temporal bin, (2) the change in decoded position between any two adjacent bins must not exceed 35% of the track length, (3) the total path length of the decoded trajectory must not exceed 100% of the track length, and (4) the net speed of the trajectory (absolute value of net change in position divided by the 160 ms offline event duration) must exceed 50% of the run speed of 0.33 track lengths/s used during simulation of online exploration.

In Fig. 4 and Supplementary Fig. S8, the diversity and degeneracy of various model configurations was explored as follows: for each model configuration, 30,000 models were evaluated during parameter optimization, and the model with the lowest multi-objective error score was considered the ‘best’ model. The remaining models were sorted by their Euclidean distance from the ‘best’ model in the space of model parameters. This resulted in an error landscape (e.g. Fig. 4A) in which models with similar parameters resulted in similar multi-objective error scores. We then identified models located at local minima in this error landscape, which as a group comprised models that were distant from each other in parameter space, but similar to each other in terms of overall multi-objective error. We further enforced that selected models had to be a minimum distance of 0.15 from each other in parameter space, and selected five such models with the lowest error score to be included in a ‘Marder group’ of models for further analysis. For each alternative network model configuration (i.e. network models with and without structured recurrent excitatory connections), each of five ‘Marder group’ model variants with different parameters were evaluated for offline sequence generation by simulating 1000 trials for each of five independent network instances.

In box and whisker plots in Figs 2D, E, 3F, M, 4D–I, 5G and 6G, and Supplementary Figs S1C, D, S3H, S4F, S5K, S6K and S8A–E, centre lines indicate median, boxes span the first and third quartile of the data, and whiskers extend to 1.5 times the inter-quartile range.

Statistics

Differences in mean values between cell populations (e.g. E vs. FF) across $n = 5$ instances of a single variant (e.g. ‘best’ model) of a single network model configuration (e.g. model with structured recurrent excitatory synaptic weights in Fig. 1) were evaluated with a one-sided paired Student’s t test. Differences in mean values for one cell population between two model configurations ($n = 5$ instances each from a single model variant) (e.g. structured weights vs. random weights in Fig. 2) were evaluated with two-sided t tests. Differences in the distributions of data across trials either between two model configurations or between cell populations for a single model configuration ($n = 5$ instances each from a single model variant) were evaluated using the Kolmogorov–Smirnov (K-S) test. Differences in mean values between two model configurations across $n = 5$ model variants (data averaged over five instances of each variant) were evaluated using two-sided t tests. P-values were adjusted for multiple comparison using the Bonferroni method for small numbers of comparisons, and using the Benjamini–Hochberg method to reduce false discovery rate (FDR) for large numbers of comparisons.

Results

To investigate how sequential activity in the hippocampus generated ‘online’ during spatial exploration can be recapitulated ‘offline’ in the absence of sensory cues, we constructed a simple spiking neuronal network model of rodent hippocampal area CA3 (Methods). Neural circuits in the hippocampus and cortex typically comprise a majority of excitatory neurons that project information to downstream circuits, and a minority of primarily locally connected inhibitory interneurons. We included populations of excitatory (1000) and inhibitory (200) neurons in proportion to experimental observations (Pelkey et al., 2017; Tremblay et al., 2016) (Fig. 1A). Cells models were single-compartment, integrate-and-fire neurons with saturable, conductance-based excitatory and inhibitory synapses (Carnevale & Hines, 2006; Izhikevich, 2007; Izhikevich & Edelman, 2008). Excitatory neurons were endowed with spike-rate adaptation to support punctuated bursting behaviour during theta oscillations (O’Keefe & Recce, 1993; Scharfman, 1993), and inhibitory neurons exhibited fast-spiking dynamics to sustain continuous high frequency firing during gamma oscillations (Csisvári et al., 2003; Ylinen et al., 1995) (Supplementary Fig. S1A, Methods).
To simulate the sensory experience of locomotion in a spatial environment, we provided both excitatory and inhibitory neurons with external afferent inputs from a population of 1000 excitatory neurons, each of which was selectively activated at distinct but overlapping positions within a simulated circular track that took 3 s to traverse (Fig. 1A–C, Methods). Recurrent connections within and between excitatory and inhibitory cell populations were also included (Fig. 1A), as they are hallmark features of hippocampal area CA3, and have been shown to support rich network dynamics (Renno-Costa et al., 2014; Stark et al., 2014). Specifically, inhibitory feedback connections have been shown to regulate the number of simultaneously active neurons (sparsity) (Stefanelli et al., 2016), and to contribute to the generation of theta and gamma network oscillations (Bezaire et al., 2016; Geisler et al., 2005; Renno-Costa et al., 2019; Stark et al., 2014; Wang, 2010). Plastic excitatory connections between excitatory neurons

Figure 1. Sparsity, selectivity, and rhythmicity in a recurrent spiking neuronal network model of hippocampal area CA3

A, diagram illustrating connectivity of network model. Feedforward (FF) external excitatory inputs contact excitatory (E) and inhibitory (I) neurons. E and I neurons are recurrently connected to other E and I neurons. B, simulations of rodent ‘online exploration’ emulating the response of the hippocampus during unidirectional locomotion along a circular linear track that takes 3 s to traverse at constant run velocity. C, firing rates vs. time of all neurons in each cell population (average of five trials from one example network instance). Cells in each population are sorted by the location of maximum firing. D, population sparsity (active fraction of neurons) vs. time shown for each cell population. E, mean firing rate of active neurons vs. time shown for each cell population. F, average stimulus selectivity of each cell population. Trial-averaged activity of each cell was centred around the location of maximum firing, and then averaged across cells. G, the average activity of each population on a single trial (top row) was bandpass filtered in the theta (middle row) and gamma (bottom row) frequency bands. Coloured traces show filtered signals (theta: green, gamma: purple). Traces derived from one example network instance. H, power spectrum of average population activity indicates dominant frequency components in the theta and gamma bands (one-sided paired t tests: theta: E vs. FF, P<0.00001; I vs. FF, P<0.00001; gamma: E vs. FF, P<0.00001; I vs. FF, P<0.00001). In C, D, F and H, data were first averaged across five trials per network instance. Means (continuous line) ± SEM (shading) were computed across five independent instances of each network model. P-values reflect FDR correction for multiple comparisons.
have long been implicated in stimulus selectivity and the storage and recall of memories (Almeida et al., 2007; Hopfield, 1982; Lisman & Jensen, 2013). It has been proposed that strong connections between ensembles of co-active neurons could arise through a combination of biased connectivity during brain development (Buzsáki et al., 2021; Dragoi & Tonegawa, 2013; Farooq & Dragoi, 2019; Grosmark & Buzsáki, 2016), and experience-driven synaptic plasticity during learning (Bittner et al., 2015, 2017; Brunel & Trullier, 1998; Káli & Dayan, 2000; Milstein et al., 2021; O’Neill et al., 2008). While here we did not simulate these dynamic processes explicitly, we implemented the structured connectivity that is the end result of these processes by increasing the strengths of synaptic connections between excitatory cells that share overlapping selectivity for spatial positions in the environment (Table 1, Supplementary Fig. S1B, Methods) (Arkhipov et al., 2018).

Despite the relatively simple architecture of this network model, a wide range of networks with distinct dynamics could be produced by varying a number of parameters, including (1) the probabilities of connections between cell types (Káli & Dayan, 2000), (2) the kinetics and strengths of synaptic connections between cell types (Brunel & Wang, 2003), and (3) the magnitude of the above-mentioned increase in synaptic strengths between neurons with shared selectivity (Brunel, 2016; Dorkenwald et al., 2019). To calibrate the network model to produce dynamics that matched experimentally derived targets, we performed an iterative stochastic search over these parameters (see Methods, Table 1 for complete list of parameters), and optimized the following features of the activity of the model network: (1) population sparsity – the fraction of active neurons of each cell type, (2) the mean firing rates of active neurons of each cell type, (3) stimulus-selective firing of excitatory cells, and (4) the frequency and amplitude of theta and gamma oscillations in the synchronous spiking activity of each cell population (Methods).

This procedure identified a model with dynamics that met all of the above constraints. Given sparse and selective feedforward inputs during simulated navigation (Fig. 1B and C), the excitatory neurons in the network responded with a fraction of active cells (Fig. 1D) and with average firing rates comparable to the those of the feedforward input population (Fig. 1E). The majority of inhibitory neurons were activated continuously (Fig. 1C and D) at high firing rates (Fig. 1E). While excitatory neurons received random connections from feedforward afferents and from other excitatory neurons with heterogeneous spatial tuning, excitatory cells exhibited a high degree of spatial selectivity (Fig. 1C and F). This selective increase in firing rate at specific spatial locations within the ‘place field’ of each excitatory neuron was supported by enhanced synaptic connection strengths between excitatory neurons with overlapping tuning (Supplementary Fig. S1B). While substantial background excitation occurred in all cells at all spatial positions, firing outside the place field of each cell was suppressed by sufficiently strong inhibitory input (Bittner et al., 2015; Grienberger et al., 2017). Interestingly, inhibitory neurons also exhibited spatial selectivity, albeit to a weaker degree and with a higher background firing rate (Fig. 1C and F). This feature of the network dynamics was an emergent property that was not explicitly designed or optimized. While excitatory connections onto inhibitory cells were random and not weighted according to shared selectivity (Supplementary Fig. S1B), the total amount of excitatory input arriving onto individual inhibitory cells fluctuated across spatial positions, and predicted a small degree of spatial selectivity (Supplementary Fig. S1C). Inhibitory inputs received by inhibitory cells reduced their average activity, effectively enabling fluctuations in excitation above the mean to stand out from the background excitation (Supplementary Fig. S1C and D). This mechanism of background subtraction by inhibitory synaptic input may explain the partial spatial selectivity previously observed in subpopulations of hippocampal inhibitory neurons (Ego-Stengel & Wilson, 2007; Geiller et al., 2020; Grienberger et al., 2017; Hangya et al., 2010; Marshall et al., 2002; Wilent & Nitz, 2007).

The tuned network model also exhibited oscillatory synchrony in the firing of the excitatory and inhibitory neuron populations, despite being driven by an asynchronous external input (Fig. 1G and H). The requirement that the network self-generate rhythmic activity in the theta band constrained recurrent excitatory connections to be relatively strong, as this input provided the only source of rhythmic excitation within the network (Supplementary Fig. S1E). Interestingly, as the firing rates of inhibitory cells increased within each cycle of the theta rhythm, their synchrony in the gamma band increased, resulting in an amplitude modulation of gamma paced at the theta frequency (Fig. 1G and Supplementary Fig. S1F). This ‘theta-nested gamma’ is a well-known feature of oscillations in the hippocampus (Soltesz & Deschesnes, 1993; Ylinen et al., 1995), and here emerged from fundamental constraints on dual band rhythmicity without requiring additional mechanisms or tuning.

Position decoding reveals ‘theta sequences’ during simulated navigation

Next, we analysed neuronal sequence generation within the network during simulated navigation. First, we simulated multiple trials and computed trial-averaged spatial firing rate maps for all neurons in the network (Fig. 1C). We then used these rate maps to perform Bayesian decoding of spatial position given the spiking...
activity of all cells in the network from individual held-out trials not used in constructing the decoding template (Fig. 2A, Methods) (Davidson et al., 2009; Zhang et al., 1998). For the population of feedforward excitatory inputs, the underlying spatial firing rates were imposed, and the spikes of each cell were generated by sampling from an inhomogeneous Poisson process. Thus, decoding position from the activity of this population served to validate our decoding method, and indeed simulated position could be decoded from the spiking activity of the feedforward input population with very low reconstruction error (Fig. 2B and E). When we applied this method to the population of excitatory neurons within the network, reconstruction error was increased (Fig. 2A and D). This reflected an increased fraction of temporal bins (20 ms) where the decoded position was either behind or in advance of the actual position (Fig. 2A). However, rather than simply reflecting reconstruction noise or poor spatial selectivity of individual cells (Fig. 1F), these divergences from actual position resulted from consistent sequential structure in the spiking activity of cells in the excitatory population (Fig. 2A, bottom row). Ordered neuronal firing resulted in decoded positions that continuously swept from past positions, through the current actual position, to future positions, and then reset to past positions, on the timescale of the ongoing theta rhythm. These ‘theta sequences’ caused decoded position estimates to oscillate around the actual position (Fig. 2A, bottom row), and this theta timescale oscillation accounted for a large proportion of the variance in decoded position (Fig. 2E, Methods). Interestingly, we found that position could also be accurately decoded from the moderately spatially tuned activity of inhibitory cells in the network (Fig. 2A and D), and that the spiking activity of the inhibitory population was also organized into theta sequences (Fig. 2A, bottom row and E).

A number of possible mechanisms have been proposed to account for theta sequence generation in vivo, including synaptic, cell-intrinsic and network-level mechanisms (Chadwick et al., 2015, 2016; Drieu & Zugaro, 2019; Foster & Wilson, 2007; Grienberger et al., 2017; Kang & DeWeese, 2019; Mehta et al., 2002; Skaggs et al., 1996). That theta sequences in the model emerged in both excitatory and inhibitory neuron populations implicates recurrent interactions within the network (Chadwick et al., 2016). To further investigate, we analysed neuronal sequence generation in a variant of the model in which the strengths of recurrent connections between excitatory neurons were randomized and no longer depended on shared spatial selectivity between connected pairs of cells (Supplementary Fig. S2A). This alternative model could still be tuned to match experimental targets, including sparsity, selectivity and rhythmicity (Supplementary Fig. S2B–F). In this case the spatial selectivity of excitatory cells was entirely determined by the synaptic weights of the feedforward afferent inputs (Supplementary Fig. S2A), while the recurrent excitatory input supported synchronization in the theta and gamma bands (Supplementary Fig. S2F). However, in this model, theta timescale neuronal sequence generation in both excitatory and inhibitory cells was suppressed (Fig. 2B and E). Decoding of position from spikes on single trials produced lower reconstruction error (Fig. 2D), as neuronal population activity more faithfully followed the current spatial position provided by the feedforward inputs, and was not organized into the sweeps from past to future positions characteristic of theta sequences (Fig. 2B, bottom row and E). We also tested a related variant of the model in which the skewed distribution of recurrent excitatory synaptic weights used in the structured weights model (Figs 1 and 2A, and Supplementary Fig. 1) was randomly shuffled (Fig. 2C and Supplementary Fig. S2G–L). Theta sequence generation was also reduced in this network model variant (Fig. 2E).

These results indicate that structure in the synaptic strengths of recurrent excitatory connections is required for the generation of fast timescale (~125 ms) neuronal sequences when network activity is driven by behavioural timescale (>1 s) sequences of sensory inputs, as occurs during spatial exploration.

Emergence of offline memory replay

The above results show that the same network structure that enables population dynamics in CA3 to exhibit sparsity, selectivity, and rhythmicity also supports neuronal sequence generation in the online state when ordered sensory information is present. We next sought to understand how neuronal sequences consistent with the sensory environment are generated offline when sensory inputs are reduced. To mimic the transient (~50–150 ms) increase in population activity that occurs during a hippocampal SWR (Fernández-Ruiz et al., 2019), we transiently stimulated the network by randomly choosing sparse subsets of cells from the feedforward input population to emit spikes (Fig. 3A and B). We then used the same decoding templates as above, constructed from the trial-averaged activity during simulated run, to decode spatial position from spiking activity during these transient offline events (Methods).

Given that the place field locations of the stimulated neurons in the feedforward input population were heterogeneous and unordered, the spatial positions decoded from their spiking were typically discontinuous across adjacent temporal bins (Fig. 3A, B and F). This input pattern evoked spiking in sparse subsets of both the excitatory and the inhibitory populations in the network (Fig. 3A and B). In contrast with the feedforward
Figure 2. Online neuronal sequence generation depends on recurrent excitatory synaptic connectivity

A, ‘online exploration’ was simulated for the same network model as in Fig. 1, in which recurrent excitatory connections between E cells were structured such that neurons with shared selectivity have elevated synaptic weights. Top row: spike times of all neurons in each cell population on a single trial of simulated ‘online exploration’ are marked. A separate set of five trials was used to construct a spatial firing rate template for each neuron (shown in Fig. 1C). Cells in each population are sorted by the location of maximum average spatial firing rate. Bottom row: the spatial firing rate templates for all neurons were used to perform Bayesian decoding of spatial position from the single trial spiking data shown in the top row. For each cell population, the likelihood of each spatial position in each time bin (20 ms) is indicated by grayscale intensity.

B, same as A for alternative network model with random synaptic strengths at recurrent excitatory connections between E cells. Spatial firing rate templates used for decoding are shown in Supplementary Fig. S2B.

C, same as A for alternative network model in which the structured excitatory recurrent synaptic weights between E cells were randomly shuffled. Spatial firing rate templates used for decoding are shown in Supplementary Fig. S2H.

D, decoded position error is quantified as the difference between actual and predicted position. The absolute value of decoded position error is expressed as a fraction of the track length (one-sided paired $t$-tests: structured E $\leftrightarrow$ E weights: E vs. FF, $P < 0.00001$; I vs. FF, $P < 0.00001$; random E $\leftrightarrow$ E weights: E vs. FF, $P = 0.00001$; I vs. FF, $P = 0.00001$; shuffled E $\leftrightarrow$ E weights: E vs. FF, $P = 0.00001$; I vs. FF, $P = 0.00001$; two-sided $t$-tests vs. data from model with structured E $\leftrightarrow$ E weights: random E $\leftrightarrow$ E weights: E, $P < 0.00001$, I, $P = 0.00001$; shuffled E $\leftrightarrow$ E weights: E, $P < 0.00001$, I, $P = 0.00001$).

E, in the model with structured E $\leftrightarrow$ E weights, decoded positions of E and I cell populations oscillated between past, current and future positions at the timescale of the population theta oscillation. A theta sequence score was computed as the proportion of the variance in the decoded position error explained by a theta timescale oscillation (see Methods) (one-sided paired $t$-tests: structured E $\leftrightarrow$ E weights: E vs. FF, $P = 0.00005$; I vs. FF, $P = 0.00005$; random E $\leftrightarrow$ E weights: E vs. FF, $P = 0.00001$; I vs. FF, $P = 0.28287$; shuffled E $\leftrightarrow$ E weights: E vs. FF, $P = 0.00010$; I vs. FF, $P = 0.99600$; two-sided $t$-tests vs. data from model with structured E $\leftrightarrow$ E weights: random E $\leftrightarrow$ E weights: E, $P < 0.00001$, I, $P < 0.00001$; shuffled E $\leftrightarrow$ E weights: E, $P < 0.00001$, I, $P < 0.00001$). In (D) and (E), data were first averaged across five trials per network instance. Box and whisker plots depict data from five independent instances of each network model (see Methods). $P$-values reflect FDR correction for multiple comparisons.
Figure 3. Forward and reverse offline memory replay depends on recurrent excitatory synaptic connectivity

A–B: ‘offline rest’ was simulated for the network model with structured E ← E weights (Fig. 1). Top row: spike times of all neurons in each cell population on a single trial of simulated ‘offline rest’ are marked. Data from five trials of simulated ‘online exploration’ were used to construct a spatial firing rate template for each neuron (Fig. 1C). Cells in each population are sorted by the location of maximum average spatial firing rate. Bottom row: the spatial firing rate templates for all neurons were used to perform Bayesian decoding of spatial position from the single trial spiking data shown in the top row. For each cell population, the likelihood of each spatial position in each time bin (20 ms) is indicated by grayscale intensity. A and B correspond to two example trials from one example network.

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instance. C–G, this procedure was repeated for 1000 trials for each of five instances of the network. C, histogram of spatial positions decoded from each cell population across all simulated replay events (two-sided K-S tests: E vs. FF, \( P = 0.99974 \); l vs. FF, \( P = 0.99974 \)). D, histogram of the path length of spatial sequences decoded from each cell population (two-sided K-S tests: E vs. FF, \( P < 0.00001 \); l vs. FF, \( P < 0.00001 \)). E, histogram of the mean velocity of spatial sequences decoded from each cell population (two-sided K-S tests: E vs. FF, \( P = 0.00235 \); l vs. FF, \( P = 0.73515 \)). F, fraction of events that met criterion for sequences consistent with continuous spatial trajectories (see Methods) (one-sided paired t tests: E vs. FF, \( P < 0.00001 \), l vs. FF, \( P = 0.00084 \)). G, power spectrum of average population activity indicates high frequency components (one-sided paired t tests: 75–300 Hz frequency band: E vs. FF, \( P = 1 \); l vs. FF, \( P < 0.00001 \)). H–N, same as A–G for an alternative network model with random E \( \leftrightarrow \) E weights. H and I correspond to two example trials from one example network instance. J, decoded positions (two-sided K-S tests: E vs. FF, \( P = 0.99974 \); l vs. FF, \( P = 0.99974 \)); two-sided K-S tests vs. data from model with structured E \( \leftrightarrow \) E weights in C: \( E, P = 0.85869 \); I, \( P = 0.87577 \)). K, offline sequence path length (two-sided K-S tests: E vs. FF, \( P < 0.00001 \); l vs. FF, \( P = 0.99997 \)); two-sided K-S tests vs. data from model with structured E \( \leftrightarrow \) E weights in D: \( E, P < 0.00001 \); I, \( P < 0.00001 \)). L, offline sequence velocity (two-sided K-S tests: E vs. FF, \( P = 0.99877 \); l vs. FF, \( P = 0.99877 \)); two-sided K-S tests vs. data from model with structured E \( \leftrightarrow \) E weights in E: \( E, P = 0.01591 \); I, \( P = 0.76837 \)). M, fraction of events that met criterion for sequences consistent with continuous spatial trajectories (see Methods) (one-sided paired t tests: E vs. FF, \( P = 0.00005 \); l vs. FF, \( P = 0.86564 \)); two-sided t tests vs. data from model with structured E \( \leftrightarrow \) E weights in F: \( E, P < 0.00001 \); l, \( P < 0.00001 \)). N, offline high-frequency rhythmicity (one-sided paired t tests: 75–300 Hz frequency band: E vs. FF, \( P = 0.97708 \); l vs. FF, \( P < 0.00001 \)); two-sided t tests vs. data from model with structured E \( \leftrightarrow \) E weights in G: \( E, P = 0.64948 \); I, \( P < 0.00001 \). In C–E, G, J–L, and N, means (continuous line) \( \pm \) SEM (shading) were computed across five independent instances of each network. In F and M, box and whisker plots depict data from five independent instances of each network model (see Methods). P-values reflect FDR correction for multiple comparisons.

population, the activity evoked in excitatory neurons was structured such that neurons with nearby place field locations spiked in adjacent temporal bins, resulting in decoded spatial trajectories that were continuous (Fig. 3A, B and F). Inhibitory neuron activity during these events was organized into high-frequency oscillations (Fig. 3A, B and G). This procedure was repeated to produce thousands of offline events evoked by stimulation of different random ensembles of inputs (Methods). Across these events, each position along the track was decoded with equal probability (Fig. 3C). For each event, the length and mean velocity of the decoded trajectory was calculated from the differences in decoded positions between adjacent bins (Fig. 3D and E). A mean velocity of zero corresponds to events with equal steps in the forward and reverse directions, while positive velocities correspond to net forward-moving trajectories, and negative velocities correspond to net backwards-moving trajectories. While the trajectories decoded from the random feedforward input population comprised large, discontinuous steps that traced out large path lengths with an average velocity near zero, the excitatory neuron population generated shorter, more continuous sequences that progressed in either the forward or reverse directions (Fig. 3D–F). These trajectories on average covered \( \sim 0.5 \) of the length of the track in the short (\( \sim 150 \) ms) duration of the offline event. Compared to the run trajectory, which took 3 s to cover the full track length, this corresponded to a \( \sim 10 \)-fold temporal compression (Fig. 3E), similar to experimental data (Davidson et al., 2009). Spatial trajectories decoded from the inhibitory neuron population were intermediate in length, but with little forward or reverse momentum, similar to the feedforward inputs. However, the inhibitory cells exhibited high-frequency synchrony (Fig. 3A, B and G), similar to experimentally recorded CA3 interneurons during hippocampal SWRs (Csicsvari et al., 2000; Tukker et al., 2013).

These data demonstrate that random, unstructured input can evoke sequential activity in a CA3-like recurrent spiking network, with sequences corresponding to forward, reverse, or mixed direction trajectories through an experienced spatial environment. This self-generated memory-related activity implicates information stored in the synaptic weights of the recurrent connections within the network as being important for offline replay of experience. However, in most previous models, sequence generation was unidirectional, and was enabled by an asymmetric bias in the strengths of recurrent connections such that neurons encoding positions early in a sequence formed stronger synapses onto neurons encoding later positions (Levy, 1989; Malerba & Bazhenov, 2019; McNaughton & Morris, 1987; Reifenstein et al., 2021; Sompolinsky & Kaner, 1986; Tsodyks et al., 1996). In contrast, the current network flexibly generated sequences in forward, reverse or mixed directions, and had symmetric recurrent connections such that synaptic strengths between pairs of excitatory neurons depend only on overlapping selectivity, not on sequence order. Does sequence generation in the present network still depend on recurrent connectivity? To test this, we first verified that including an asymmetric bias in the strengths of excitatory connections produced offline replay events that were biased towards forward sequences (Supplementary Fig. S3). We next analysed the sequence content of offline events generated in the variants of the network model with random (Fig. 3H–N and Supplementary Fig. S2A–F) or shuffled Supplementary Fig. S2G–L and S4).
Figure 4. Exploration of model parameter diversity and degeneracy

A, during network model optimization, 30,000 model variants with different parameters were evaluated. To explore model diversity and degeneracy, for each network model configuration, a subset of model variants termed a 'Marder group' were selected based on their large distance from each other in the space of parameters, but their similar performance with respect to multiple optimization objectives (see Methods). This selection procedure is illustrated here for the model with random E ← E weights as an example. The five 'Marder group' members with the lowest multi-objective error (labelled ‘best’ and ‘M1’–’M4’) were selected for further evaluation. B, for the network model configuration with structured E ← E weights, the range of parameter values across five distinct 'Marder group' models is shown. C, same as B for the model with random E ← E weights. D–I, features of the simulated network dynamics produced by distinct model variants within a ‘Marder group’ are compared across network model configurations. Each data point (grey circles) depicts one ‘Marder group’ model. D, spatial selectivity of the excitatory neuron population during simulated ‘online exploration’ is computed as a ratio of maximum to mean activity (two-sided t tests vs. data from model with structured E ← E weights: random E ← E weights: P = 1; shuffled E ← E weights: P = 0.00224). E, the fraction of the excitatory neuron population that is synchronously active during simulated ‘online exploration’ is shown (two-sided t tests vs. data from model with structured E ← E weights: random E ← E weights: P = 1; shuffled E ← E weights: P = 0.12079). F, gamma rhythmicity of the excitatory neuron population is computed as the integrated power spectral density in the gamma frequency band (two-sided t tests vs. data from model with structured E ← E weights: random E ← E weights: P = 0.03552; shuffled E ← E weights: P = 0.03952).
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G, theta rhythmicity of the excitatory neuron population is computed as the integrated power spectral density in the theta frequency band (two-sided t tests vs. data from model with shuffled E ← E weights: random E ← E weights: P = 0.0027; shuffled E ← E weights: P = 0.0147). H, theta sequence score (see Fig. 2 and Methods) (two-sided t tests vs. data from model with structured E ← E weights: random E ← E weights: P = 0.0281; shuffled E ← E weights: P = 0.0147). I, fraction of events during simulated ‘offline rest’ that met criterion for sequences consistent with continuous spatial trajectories (see Fig. 3, Supplementary Fig. S3 and Methods) (two-sided t tests vs. data from model with structured E ← E weights: random E ← E weights: P < 0.0001; shuffled E ← E weights: P = 0.0004). In D–I, for each network model configuration, box and whisker plots depict five distinct ‘Marder group’ model variants with different parameters (see Methods). Data for each model variant (grey circles) were first averaged across five independent instances of that model variant. In F–I, grey dashed lines indicate value for the feedforward input to the network for reference. P-values reflect Bonferroni correction for multiple comparisons.

recurrent connection weights. Indeed, without structure in the recurrent connection weights, spatial trajectories decoded from the activity of excitatory neurons was more similar to those of the feedforward inputs, consisting of large, discontinuous steps without forward or reverse momentum (Fig. 3H–M and Supplementary Fig. S4A–F). Still, these networks exhibited high-frequency oscillatory synchrony during these offline events (Fig. 3N and Supplementary Fig. S4G).

Exploration of model diversity and degeneracy

The above results strongly supported the hypothesis that recurrent connectivity is important for offline sequence generation. During optimization of each of the alternative network model configurations shown above to meet the multiple objectives of sparsity, selectivity and rhythmicity, we evaluated 30,000 variants of each model with different parameters (Methods). For each model configuration, the model with the lowest overall multi-objective error was chosen as the ‘best’ model for further analysis, as shown in Figs 2 and 3 and Supplementary Figs S1, S2 and S4. However, we noted that the parameter values that specified these ‘best’ models were variable across the multiple network configurations (Table 1). This raised the possibility that while many models with diverse parameters may produce networks with similar online dynamics (referred to as model degeneracy; Marder & Taylor, 2011), perhaps only a smaller subset of models would additionally support the emergence of offline sequence generation. The fact that sequence generation was not observed for either of the ‘best’ models with disrupted recurrent excitatory synaptic weights could reflect an incomplete sampling of the parameter space and a failure to identify models that both meet the objective criteria for online dynamics and produce offline sequences. Therefore, in order to explore the diversity and degeneracy of models evaluated during optimization, we devised a method to identify models that performed similarly with respect to multiple optimization objectives, but were specified by divergent sets of parameters (Methods). For each model configuration, all model variants evaluated during parameter optimization were sorted by their Euclidean distance from the ‘best’ model in the space of model parameters. This resulted in an error landscape (e.g. Fig. 4A) in which models with similar parameters resulted in similar multi-objective error scores. We then identified models located at local minima in this error landscape, which formed a group of models that were distant from each other in parameter space, but similar to each other in terms of overall multi-objective error. We termed a set of such models as a ‘Marder group’ after pioneering work characterizing degeneracy in biological systems (Marder & Taylor, 2011). For each alternative network model configuration, we selected the five members of this ‘Marder group’ with the lowest multi-objective error (labelled ‘best’ and ‘M1’–’M4’ in Fig. 4A), and evaluated their network dynamics during simulations of both online exploration and offline rest. We first verified that for all model configurations with and without structured recurrent excitatory connectivity analysed above (Figs 1–3 and Supplementary Figs S1, S2 and S4), model variants within a ‘Marder group’ exhibited considerable diversity across model parameters (Fig. 4B and C), and met all objective criteria for neuronal stimulus selectivity (Fig. 4D), population sparsity (Fig. 4E), and rhythmogenesis in the theta and gamma bands (Fig. 4F and G). However, only model variants with synaptic weights structured by shared stimulus selectivity exhibited theta sequences during online run (Fig. 4H) and generated offline sequences consistent with continuous spatial trajectories (Fig. 4I). This analysis demonstrated that generation of memory-related neuronal sequences by recurrent networks requires that information about the topology of the sensory environment is stored in the strengths of recurrent excitatory connections between excitatory neurons.

Constraints on online sparsity, selectivity and rhythmicity enable offline memory replay

Our above findings suggest that experimental constraints on the online dynamics of hippocampal area CA3 during spatial exploration are sufficient to enable the emergence of offline memory replay. We next sought to determine whether all or only a subset of these constraints were...
required for generation of memory-related sequences. To
determine the importance of rhythmicity, we removed
the optimization criteria that excitatory and inhibitory
neuron populations synchronize in the theta and gamma
bands, and instead added an objective to minimize
power density across the full frequency spectrum
(Supplementary Fig. S5E). Following optimization, this
alternative network model exhibited reduced rhythmicity,
but still met objectives related to sparsity and selectivity
(Supplementary Fig. S5A–D). However, when challenged
with random stimuli during simulated offline rest, this
model with suppressed rhythmicity failed to generate
continuous forward or reverse sequences (Supplementary
Fig. S5F–L). Rather, spatial trajectories decoded from
offline population activity contained large discontinuous
jumps in position, and most events had zero net velocity in
either the forward or the reverse direction. This indicated
that the same reciprocal interactions between excitatory
and inhibitory neurons that support rhythogenesis
in the theta and gamma bands also contribute to the
sequential organization of neuronal activity during offline
memory replay.

We next optimized a network model variant without
constraints on population sparsity and neuronal stimulus
selectivity (see Methods). In this network model, while
feedforward excitatory inputs remained spatially tuned,
their connectivity with excitatory neurons was shuffled to
prevent inheritance of spatial selectivity. This resulted
in a complete loss of sparsity of excitatory neuron
activity (Supplementary Fig. S6A and B), and suppressed
stimulus selectivity in excitatory neurons even below
the level exhibited in the inhibitory neuron population
(Supplementary Fig. S6C and D). Rhythogenesis in the
theta and gamma bands in excitatory and inhibitory
neurons was maintained (Supplementary Fig. S6E).
During simulation of offline rest, this network generated
highly synchronous population bursts that tended to
either hover at one decoded position or make large
discontiguous jumps between positions (Supplementary
Fig. S6F–K). These results suggest that the network
connectivity parameters that support highly sparse and
selective neuronal activity in the online stimulus-driven
state, also enable sparse reactivation of neuronal
sequences in the offline state. We also repeated the
model degeneracy analysis described above (Fig. 4) for
multiple model variants with compromised sparsity,
selectivity or rhythmicity, which corroborated these
findings (Supplementary Fig. S8).

Role of neuronal spike rate adaptation in forward
and reverse offline memory replay

Above we showed that structure in the synaptic
connectivity of the CA3 network is important for
neuronal sequence generation. However, unlike previous
models of sequence generation where asymmetry
in connection strengths biased the direction of neuronal
sequences (Levy, 1989; Malerba & Bazhenov, 2019;
McNaughton & Morris, 1987; Reifenstein et al., 2021;
Sompolinsky & Kanter, 1986; Tsodyks et al., 1996), here
synaptic connectivity was symmetric, and yet variable
neuronal sequences were flexibly generated in both
forward and reverse directions (Fig. 3A, B and E). If this
symmetric connectivity enables recurrent networks to
generate either forward or backward steps, what ‘breaks’
this symmetry and produces sequences that make net
progress in either the forward or backward direction?
We next wondered if directionality of offline sequences
in our network model was facilitated by our choice of
‘bursty’ excitatory cell model, which exhibited spike-rate
adaptation (Fig. 5A). As mentioned before, use-dependent
deCREASES in either firing rate or synaptic transmission
over time can provide momentum to neuronal sequences
by favouring the recruitment of new neurons that have
not yet been activated during a network population event
(Itskov et al., 2011; Romani & Tsodyks, 2015; Treves,
2004). To test a possible role for cellular adaptation in
sequence generation in our model network, we replaced
the ‘bursting’ excitatory cell model with a ‘regular spiking’
model without spike rate adaptation (Fig. 5A). This cell
model did not support the high instantaneous firing rates
of the bursting cell model, which compromised the peak
firing rates of excitatory cells in the network and their
entrainment by higher frequency gamma oscillations
during simulated online navigation (Supplementary Fig.
S7). Otherwise, this variant of the network did meet
the criterion for sparsity, selectivity and rhythmicity
(Supplementary Figs S7 and S8A–D). However, during
simulated offline rest, random feedforward inputs evoked
a truncated response from the network (Fig. 5B and C),
with the high frequency rhythmic activity of the inhibitory
neurons diminishing before the end of the stimulus period
(Fig. 5B, C and H). Spatial trajectories decoded from the
activity of excitatory neurons in the network comprised
large steps that did not progress in either forward or
reverse direction, similar to the random feedforward
inputs (Fig. 5E–G and Supplementary Fig. S8E). These
data show that adaptation of neuronal spiking provides
a cellular-level mechanism for flexible and reversible
sequence generation in recurrent spiking networks.

Preferential replay of reward location

Thus far, we have simulated network activity during
spatial navigation, and identified features of the network
that enable offline replay of behavioural sequences
stored in memory. However, in these simulations all
spatial positions were visited with equal occupancy,
and considered to be of equal salience or relevance to the virtual animal. This resulted in all positions being replayed with equal probability offline (Fig. 3C), mimicking experimental conditions where all spatial positions contain discriminable sensory cues, and opportunities for reward are provided at random times and positions (Turi et al., 2019; Zaremba et al., 2017). However, it has been shown that when a reward is provided at a fixed location that the animal must discover through learning, offline memory replay events become biased towards

**Figure 5. Neuronal spike rate adaptation supports offline memory replay**

A, intracellular voltage recordings of three neuronal cell models with distinct spiking dynamics in response to simulated square-shaped intracellular current injections. B–H, same as Figs 3A–2G for an alternative network model in which E cells are regular-spiking cell models without spike rate adaptation. B and C correspond to two example trials from one example network instance. D, decoded positions (two-sided K-S tests: E vs FF, P = 0.99974; I vs FF, P = 0.89825; two-sided K-S tests vs. data from model with structured E ← E weights in Fig. 3C: E, P = 0.84875; I, P = 0.85869). E, offline sequence length (two-sided K-S tests: E vs FF, P < 0.00001; I vs FF, P < 0.00001; two-sided K-S tests vs. data from model with structured E ← E weights in Fig. 3D: E, P < 0.00001; I, P = 0.99997). F, offline sequence velocity (two-sided K-S tests: E vs FF, P = 0.15282; I vs FF, P = 0.73515; two-sided K-S tests vs. data from model with structured E ← E weights in Fig. 3E: E, P = 0.93099; I, P = 0.91017). G, fraction of events that met criterion for sequences consistent with continuous spatial trajectories (see Methods) (one-sided paired t tests: E vs FF, P = 0.00038, I vs FF, P = 0.00119; two-sided t tests vs. data from model with structured E ← E weights in Fig. 3F: E, P < 0.00001; I, P = 0.03860). H, offline high-frequency rhythmicity (one-sided paired t tests: 75–300 Hz frequency band: E vs FF, P = 0.00114; I vs FF, P = 0.00003; two-sided t tests vs. data from model with structured E ← E weights in Fig. 3G: E, P < 0.00001; I, P = 0.00027). In D–F and H, means (continuous lines) ± SEM (shading) were computed across five independent instances of each network. In G, box and whisker plots depict data from five independent instances of each network model (see Methods). P-values reflect FDR correction for multiple comparisons.
Figure 6. Offline memory replay is biased towards reward positions over-represented by the network

A, in the variant of the network, an increased proportion of E cells are selective for spatial positions near the site of a simulated reward. Firing rates vs. time of all neurons in each cell population are shown (average of five trials from one example network instance). Cells in each population are sorted by the location of maximum firing. The simulated reward site is marked with red dashed line. B–H, same as Figs 3A–G for an alternative network model with population-level over-representation of reward location in E cells. B and C correspond to two example trials from one example network instance. The simulated reward site is marked with red dashed line. D, decoded positions (two-sided K-S tests: E vs. FF, \( P < 0.00001 \); I vs. FF, \( P = 0.41580 \); two-sided K-S tests vs. data from model with structured E ← E weights in Fig. 3C: E, \( P < 0.00001 \); I, \( P = 0.84875 \)). E, offline sequence length (two-sided K-S tests: E vs. FF, \( P < 0.00001 \); I vs. FF, \( P < 0.00001 \); two-sided K-S tests vs. data from model with structured E ← E weights in Fig. 3D: E, \( P = 0.25150 \); I, \( P < 0.00001 \)). F, offline sequence velocity (two-sided K-S tests: E vs. FF, \( P = 0.02742 \); I vs. FF, \( P = 0.73515 \); two-sided K-S tests vs. data from model with structured E ← E weights in Fig. 3E: E, \( P = 0.16847 \); I, \( P = 0.62023 \)). G, fraction of events that met criterion for sequences consistent with continuous spatial trajectories (see Methods) (one-sided paired \( t \)-tests: E vs. FF, \( P < 0.00001 \); I vs. FF, \( P = 0.00754 \)). H, offline high-frequency rhythmicity (one-sided paired \( t \)-tests: 75–300 Hz frequency band: E vs. FF, \( P = 0.00067 \); I vs. FF, \( P = 0.00006 \); two-sided \( t \)-tests vs. data from model with structured E ← E weights in Fig. 3F: E, \( P = 0.00003 \); I, \( P = 0.00001 \)). In D–F and H, means (continuous line) ± SEM (shading) were computed across five independent instances of each network. In G, box and whisker plots depict data from five independent instances of each network model (see Methods). P-values reflect FDR correction for multiple comparisons.
sequences of place cells that encode positions nearby and including the site of the reward (Gillespie et al., 2021; Ölafsdóttir et al., 2018; Pfeiffer, 2020; Singer & Frank, 2009). In parallel with the development of this bias in offline memory replay during learning, it has been shown that the fraction of hippocampal pyramidal cells that selectively fire along the path to reward increases (Lee et al., 2006; Turi et al., 2019; Zaremba et al., 2017). Here we sought to test the hypothesis that this network-level over-representation of reward location is sufficient to bias the content of offline memory replay.

We chose a position along the virtual track to be the fixed location of a simulated reward, and biased the allocation of place field locations such that an increased fraction of excitatory neurons in the network were selectively activated at positions near the reward (Fig. 6A). As before, feedforward and recurrent synaptic connection strengths were increased between neurons with overlapping selectivity (Supplementary Fig. S9A). Aside from an enhanced fraction of active excitatory neurons near the reward site (Supplementary Fig. S9B), this produced network dynamics during simulated navigation that conformed to experimental constraints for sparsity, selectivity and rhythmicity (Fig. 6A and Supplementary Fig. S9B–E). During simulated offline rest, the network responded to random feedforward inputs by generating neuronal sequences corresponding to forward, reverse and mixed direction trajectories through the environment (Fig. 6B–G), paced by high frequency oscillations in the inhibitory cells (Fig. 6H), as before (Fig. 3A–G). However, new positions near the simulated reward site were replayed in a higher proportion of replay events (Fig. 6D). This preferential replay of locations over-represented by the network recapitulated experimental findings and supported the hypothesis that non-uniform place cell allocation and biased memory replay are causally linked (Levy, 1989).

**Discussion**

In this study we used a simple recurrent spiking network model of hippocampal area CA3 to investigate the structural and functional requirements for offline replay of spatial memories. We optimized synaptic, cellular and network parameters of the network to produce population dynamics that match experimentally observed sparsity, selectivity and rhythmicity. We found that networks that fit these constraints exhibit additional emergent properties, including the ability to generate fast timescale memory-related neuronal sequences. During simulated spatial navigation, when ordered sensory information was provided on the seconds-long timescale of locomotion behaviour, the network produced neuronal sequences that swept from past to future positions on the faster timescale (~125 ms) of the theta rhythm (‘theta sequences’). During simulated offline rest, the network responded to transient noisy activation of random, sparse inputs by generating neuronal sequences that corresponded to forward, reverse or mixed direction trajectories through the spatial environment.

Both online and offline sequence generation depended on structure in the strengths of excitatory synaptic connections such that pairs of neurons with overlapping spatial tuning were more strongly connected. In the online phase, different sparse subsets of excitatory neurons were activated at different spatial positions due to structure in the strengths of connections from spatially tuned feedforward afferent inputs. The constraint that recurrent excitation must drive rhythmic synchronization in the theta band resulted in relatively strong recurrent connections. During each cycle of the theta rhythm, when the firing rates of the excitatory neurons were at their maximum, synaptic excitation from recurrent connections exceeded that from the feedforward afferents (Supplementary Fig. S1E). This caused the sum of forward-moving feedforward inputs and symmetric mixed-direction feedback inputs to favour activation of cells encoding positions at or ahead of the current position. This generated forward-sweeping sequences that outpaced the speed of locomotion. However, at the opposite phase of the theta rhythm, when the firing rates of the excitatory cells reached their minimum, the non-rhythmic feedforward input became greater than recurrent excitation (Supplementary Fig. S1E), causing theta sequences to reverse direction and relax back towards the current position encoded by the feedforward inputs.

In the offline phase, the feedforward inputs were not activated in a sequence, so momentum had to be entirely internally generated by the network. In this case, the particular subset of active feedforward inputs initially selected a sparse subset of excitatory neurons to begin to fire, which set a starting position for the replayed trajectory. Slight biases in the feedforward input could then influence whether the active ensemble of excitatory neurons next recruited neurons encoding spatial positions in either the forward or reverse direction. Once activity began moving in one direction, spike-rate adaptation facilitated continued sequence movement along that direction. However, depending on fluctuations in the feedforward inputs, sequences were also generated that included changes in direction. Interestingly, this process is akin to interpolation or smoothing – the recurrent connections within the network served to bridge large, discontinuous jumps in position encoded by the recurrent feedforward inputs with smaller, more continuous steps. This produced offline sequences that were consistent with the topology of the spatial environment, but did not necessarily replay exact experienced trajectories. These
findings are consistent with a recent report that neuronal sequences activated during hippocampal SWRs in vivo resembled Brownian motion, or a random walk through the sensory space, rather than precise replay of experience (Stella et al., 2019). This suggests that, rather than serving mainly to consolidate specific episodic memories of ordered sensory experiences, neuronal sequences during SWRs could also explore possible associations within the environment that had not been fully sampled during experience. Our modelling results showing that increased population representations of goal sites bias the content of offline memory replay also corroborate recent findings that previously rewarded locations are replayed more readily than immediate past or immediate future trajectories (Gillespie et al., 2021). Within this framework, synaptic plasticity during offline replay could modify connection strengths to increase the chance that a new path will be taken that is likely to lead to a desired outcome (Ólafsdóttir et al., 2015).

In summary, our modelling results identified a minimal set of elements sufficient to enable flexible and bidirectional memory replay in neuronal networks: spike rate adaptation, recurrent connectivity between excitatory and inhibitory neuron populations with strengths and kinetics optimized for rhythmogenesis and sparse and selective stimulus representations, and associative structure in the synaptic strengths at recurrent synapses between excitatory neurons. In previous models of neuronal sequence generation, additional network components were proposed to enable unidirectional sequences stored in memory to be reversed during offline recall, including neuromodulation (Gauy et al., 2018), excitability of neuronal dendrites (Gauy et al., 2018; Jahnke et al., 2015), coordinated plasticity at both excitatory and inhibitory synapses (Ramirez-Villegas et al., 2018) and functional specialization of diverse subpopulations of inhibitory interneurons (Cutsuridis & Hasselmo, 2011). While these mechanisms may regulate and enhance memory replay, our results suggest that they are not necessarily required.

This model also makes some experimentally testable predictions. First, it implies that ion channel mutations that disrupt neuronal spike rate adaptation may also degrade neuronal sequence generation and memory consolidation (Peters et al., 2005). Secondly, while the direction and content of offline sequences may be largely controlled by internal dynamics and information stored in the synaptic weights within a recurrent neuronal circuit, the model network still required a small amount of random feedforward afferent input to evoke an offline population burst, suggesting that experimental manipulations of afferent projections to hippocampal area CA3 may alter the frequency or content of memory replay events (Chenani et al., 2019; Sasaki et al., 2018). Recent work has also begun to explore the advantages of generative replay for learning in artificial neural networks (Roscow et al., 2021). In addition to better understanding the biological mechanisms of memory consolidation and flexible planning of behaviour, characterising the minimal mechanisms of memory replay could facilitate the engineering of artificial systems that can refine their internal representations of the environment during periods of offline rest (Buzsáki, 1989).

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Additional information

Data availability statement
All code necessary to reproduce the data and analysis presented in this work are available here: Network simulation and analysis code: https://github.com/neurosutras/optimize_simple_network. Network optimization code: https://github.com/neurosutras/nested.

Competing interests
None.

Author contributions
Conception or design of the work: A.M. and I.S. Acquisition or analysis or interpretation of data for the work: A.M., S.T. and G.N. Drafting the work or revising it critically for important intellectual content: A.M., S.T., G.N. and I.S. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information
Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Figure S1. Related to Figs 1–3. Structure and online dynamics of network model with excitatory synaptic connectivity structured by shared stimulus selectivity.

Figure S2. Related to Figs 1–3. Structure and online dynamics of alternative network models with random recurrent excitatory connectivity.

Figure S3. Related to Figs 1 and 3. Offline replay is unidirectional in an alternative network model with asymmetric synaptic connectivity.

Figure S4. Related to Fig. 3. Offline replay is disrupted in an alternative network model with structured, but shuffled recurrent excitatory connectivity.

Figure S5. Related to Figs 1 and 3. Offline replay is disrupted in an alternative network model optimized to suppress rhythmicity.

Figure S6. Related to Figs 1 and 3. Offline replay is disrupted in an alternative network model optimized without sparsity or selectivity constraints.

Figure S7. Related to Figs 1 and 5. Online dynamics in network model without spike rate adaptation.

Figure S8. Related to Figs 1, 3, 4, and 5. Exploration of model parameter diversity and degeneracy in additional alternative network models.

Figure S9. Related to Figs 1 and 6. Online activity in network model with population over-representation of reward.

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