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Dynamic control of sequential retrieval speed in networks with heterogeneous learning rules

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Abstract

Temporal rescaling of sequential neural activity has been observed in multiple brain areas during behaviors involving time estimation and motor execution at variable speeds. Temporally asymmetric Hebbian rules have been used in network models to learn and retrieve sequential activity, with characteristics that are qualitatively consistent with experimental observations. However, in these models sequential activity is retrieved at a fixed speed. Here, we investigate the effects of a heterogeneity of plasticity rules on network dynamics. In a model in which neurons differ by the degree of temporal symmetry of their plasticity rule, we find that retrieval speed can be controlled by varying external inputs to the network. Neurons with temporally symmetric plasticity rules act as brakes and tend to slow down the dynamics, while neurons with temporally asymmetric rules act as accelerators of the dynamics. We also find that such networks can naturally generate separate 'preparatory' and 'execution' activity patterns with appropriate external inputs.

eLife assessment

The authors provide a **valuable** analysis of what neural circuit mechanisms enable varying the speed of retrieval of sequences, as needed for say reproducing motor patterns. Their use of heterogeneous plasticity rules to allow external currents to control speed of sequence recall is a novel alternative to other mechanisms proposed in the literature. They perform a **solid** characterization of relevant properties of recall via simulations and theory, which would benefit from a better mapping to biologically plausible mechanisms.

Introduction

Timing is a critical component in the proper planning and execution of temporally extended motor behaviors. In behaviors consisting of a single motor action, it may be desirable to control the duration of its execution. In behaviors composed of multiple actions, the precise time interval between actions can be a key determinant in the success of the behavior. How can the duration of these intervals be flexibly controlled in a network of neurons?

A simple mechanistic hypothesis for the regulation of motor related timing intervals posits a specialized neural circuit with network dynamics that vary in speed as a consequence of differing levels of constant external input. Several network models utilizing external input as a means of speed control have been proposed to account for cortical and striatal dynamics observed during motor execution [1, 2]. To account for speed control in cortex, a recurrent neural network model has been trained to achieve temporal rescaling of network activity as a function of external input [2]. However, this model relies on supervised learning rules that may not be biologically plausible, and cannot generalize to other speeds from training on just one example timing interval. To explain speed control of sequential activity in striatum, a recurrent inhibitory network model has been proposed with a feedforward structure learned through anti-Hebbian plasticity [1]. This model demonstrates transient winner-take-all dynamics, with short term synaptic depression facilitating transitions in activity from one group of neurons to the next, and external input controlling the duration of each group's transient activation. While experimental evidence for the necessary type of depressive adaptation mechanism exists in the striatum, it may not be present in all cortical areas where rescaling of sequential activity is observed. Whether speed can be controlled in network models constructed using Hebbian learning without this mechanism remains unknown.

Network models with a connectivity generated by temporally asymmetric synaptic plasticity provide a potential framework for explaining how sequential activity can arise from local biologically plausible learning rules [3, 4]. In both rate and spiking networks, the temporal statistics of sequential activity in networks using this type of rule qualitatively match experimental findings made over both short and long timescales of observation in multiple tasks with timing components [5]. However, the speed of sequential dynamics in these models is constrained by the choice of temporal offset in the learning rule and neuronal time constant, and cannot be modulated with external input.

The Hebbian rules explored in this work and previous studies are approximations of various forms of spike-timing dependent plasticity (STDP). The effects of STDP can be quantified through kernels that measure the change in excitatory postsynaptic potential size at a synapse (as a proxy for synaptic strength), as a function of the timing difference between pre and postsynaptic spikes. Experimentally, a large diversity of STDP kernels have been characterized across cortical, subcortical, and cerebellar structures [6, 7]. Kernels measured in cortex and hippocampus typically, but not always, exhibit a temporal asymmetry, in which presynaptic activity must precede postsynaptic activity to elicit a positive change in synaptic strength [8, 9]. Theoretical studies have shown that this temporal asymmetry can be used to store and retrieve sequences of activity [1, 5, 10–20]. However, symmetric kernels, in which coincident activity leads to strengthening regardless of the order of pre and post-synaptic spikes, have also been observed in multiple contexts with high frequency plasticity induction protocols in cortex [21], in hippocampal cultures in the presence of dopamine [22], and at excitatory-to-excitatory synapses in hippocampal CA3 [23]. Hebbian learning rules that are temporally symmetric lead instead to the creation of fixed point attractors [24–28].

It is not known to what degree temporal asymmetry varies across synapses at the scale of local networks, but analysis of a calcium-based plasticity model demonstrates that the degree of asymmetry can be controlled via adjustment of biophysical parameters [29]. We hypothesize that variability in the temporal offset expressed at a synapse may be a key ingredient in permitting the control of retrieval speed, suggesting a potential new role for the observed heterogeneity in STDP kernels.

In this work, we explore a generalization of previously investigated temporally asymmetric learning to multiple temporal offsets that captures this heterogeneity. Specifically, we find that varying the temporally asymmetry of the learning rule across synapses gives rise to network mechanisms that allow for the control of speed as a function of external inputs to the network. We

start by considering a network with a bimodal distribution of heterogeneity in the learning rule, resulting in two distinct populations: one with a symmetric learning rule, and one with an asymmetric rule. We characterize the effect of input strength on retrieval speed and quality in these networks with connectivity generated using linear and nonlinear synaptic plasticity rules. We also find that transitions between fixed-point attractor-like "preparatory" periods and sequential "execution" phases can be realized in this model by rescaling the magnitude of external input. Finally, we demonstrate that networks with a uniform distribution of heterogeneity lead to qualitatively similar findings.

Degree of symmetry in learning rule determines retrieval speed

We explore a network model in which the firing rate dynamics of each neuron r_i in a population of size N is described by the equation

$$\tau \frac{dr_i}{dt} = -r_i + \phi\left(\sum_{j=1}^{N} J_{ij} r_j + I_i^{ext}(t)\right) \qquad (1)$$

where τ is the time constant of firing rate dynamics, J_{ij} is the connectivity matrix, $\phi(x)$ is a sigmoidal neuronal transfer function (see Methods), and $I_i^{ext}(t)$ describes the external input provided to each neuron at time t.

We follow a similar learning procedure as in [5]. A sequence of P random i.i.d standard Gaussian patterns ξ_i^{μ} is presented to the network and stored in network connectivity. This sequence of patterns modifies the strength of synaptic connections J_{ij} from neuron j to i according to a Hebbian learning rule that transforms pre and post synaptic inputs into synaptic weight changes. The resulting connectivity matrix J_{ij} is a generalization of previously studied rules which combines both temporally symmetric and asymmetric learning [5, 28],

$$J_{ij} = A\frac{c_{ij}}{Nc}\left(\sum_{\mu=1}^{P} z_i f(\xi_i^{\mu}) g(\xi_j^{\mu}) + \sum_{\mu=1}^{P-1} (1 - z_i) f(\xi_i^{\mu+1}) g(\xi_j^{\mu})\right) \qquad (2)$$

where c_{ij} is a matrix describing the structural connectivity, whose entries are given by i.i.d. Bernoulli random variables, $p(c_{ij} = 1) = c$, $p(c_{ij} = 0) = 1 - c$, where c is the connection probability; The functions $g(x)$ and $f(x)$ describe how the synaptic plasticity rule depends on pre and postsynaptic input patterns during learning, respectively; The parameter A controls the overall strength of the recurrent connections. And $z_i \in [0, 1]$ describes the degree of temporal symmetry at synapses of neuron i. A neuron with fully temporally symmetric plasticity is described by $z_i = 1$, while $z_i = 0$ indicates a neuron with fully temporally asymmetric plasticity. Note that we focus here to the case of a single sequence stored in synaptic connectivity, but such networks can also store multiple sequences [5].

We first explore the bilinear learning rule scenario ($f(x) = g(x) = x$) with homogeneous synaptic plasticity, i.e. $z_i = z$ for all $i = 1, \ldots, N$. At the two extremes of this variable we can recover previously studied learning rules. When $z = 0$, only the second term in Eq. 2 is present, resulting in a purely temporally asymmetric rule. Networks with connectivity constructed using such a rule can recall a sequence of stored patterns, and their sequential retrieval dynamics have been extensively characterized [5]. When $z = 1$, synaptic plasticity is temporally symmetric, potentially leading to fixed point attractor dynamics [28]. If z is instead fixed to a value between 0 and 1, then the asymmetric component in the plasticity rule leads to the retrieval of the whole sequence, but the speed at which the sequence is retrieved strongly depends on z. For instance, in **Fig. 1b** we demonstrate retrieval for an intermediate value of $z = 0.5$. Retrieval is quantified by plotting the Pearson correlation of the instantaneous firing rate $r(t)$ with each stored pattern ξ^{μ} as a function of time (see Methods). During sequence retrieval, correlations with individual patterns in the sequence increase, peak and decrease one after the other, indicating the network transiently visit states close to each of the patterns in succession. We find that in such a network,

retrieval speed strongly depends on z. For the parameters in **Fig. 1b**, retrieval proceeds nearly twice as slowly as compared to a network with connectivity arising from a purely asymmetric learning rule, where retrieval speed is fixed by the time constant of the firing rate dynamics [5]. However, retrieval speed is fixed by the choice of z (see **Fig. 1c** showing a linear dependence of speed on z), and cannot be dynamically modulated in response to changes in the external input I_a^{ext}.

Heterogeneity in synaptic plasticity temporal asymmetry gives rise to a speed control mechanism

We next explored whether adding heterogeneity to this learning rule, allowing z_i to differ across synapses, can produce networks capable of both recalling stored sequences of patterns and modulating the speed of recall. We initially consider a bimodal distribution of degrees of temporal symmetry across the network. For each neuron, z_i was drawn randomly and independently as a Bernoulli random variable with probability $p(z_i = 1) = 0.5$, $p(z_i = 0) = 0.5$. As a result, the network of N neurons can be divided into two subpopulations of approximately equal sizes $N_a = N_s = \frac{N}{2}$ neurons, according to the learning rule present at their synapses:

$$\tau \frac{dr_i^a}{dt} = -r_i^a + \phi\left(\sum_{j=1}^{N_a} J_{ij}^{aa} r_j^a + \sum_{j=1}^{N_s} J_{ij}^{as} r_j^s + I_a^{ext}(t)\right) \tag{3}$$

$$\tau \frac{dr_i^s}{dt} = -r_i^s + \phi\left(\sum_{j=1}^{N_s} J_{ij}^{ss} r_j^s + \sum_{j=1}^{N_a} J_{ij}^{sa} r_j^a + I_s^{ext}(t)\right) \tag{4}$$

where the connectivity matrix is given by

$$J_{ij}^{aX} = \frac{c_{ij}^{aX}}{N_a c} \sum_{\mu}^{P-1} f(\xi_i^{a,\mu+1}) g(\xi_j^{X,\mu}) \tag{5}$$

$$J_{ij}^{sX} = \frac{c_{ij}^{sX}}{N_s c} \sum_{\mu}^{P} f(\xi_i^{s,\mu}) g(\xi_j^{X,\mu}) \tag{6}$$

and where $X = a, s$ denotes the presynaptic population. Note that the external input I_X^{ext} now depends on the population. To reduce the space of possible learning rules, we have assumed that the type of learning at a synapse depends only on the identity of the postsynaptic neuron. The bimodal distribution of z_i restricts synapses to only one of the two types of plasticity, but in the final section entitled “Retrieval with a broad distribution of learning rules” we relax this constraint.

In **Fig. 1e**, we show an example of how the stored sequence can be retrieved under different input conditions. In both the top and bottom panels of 1e, network activity is initialized to the first pattern in the sequence, and a constant external input is provided to each subpopulation (“asymmetric” input I_a^{ext}, and “symmetric” input I_s^{ext}). In the top panel, the symmetric population is effectively silenced with strongly negative input, resulting in retrieval that lasts approximately τP, consistent with the dynamics being driven purely by the asymmetric component in the learning rule [5]. In the bottom panel, this input is no longer strongly negative, causing retrieval time to more than double, due to the effect of the symmetric population that tends to slow down the dynamics.

To characterize how retrieval time depends on these two sources of external input, we explored the space of the parameters defining the inputs to the network, I_a and I_s. In **Fig. 2**, we show the dependence of retrieval quality and speed on these variables. Retrieval quality is quantified by measuring the maximal correlation of the final pattern in the retrieved sequence. Retrieval speed is measured in units of the inverse of the neural time constant, τ^{-1}. It is computed by measuring

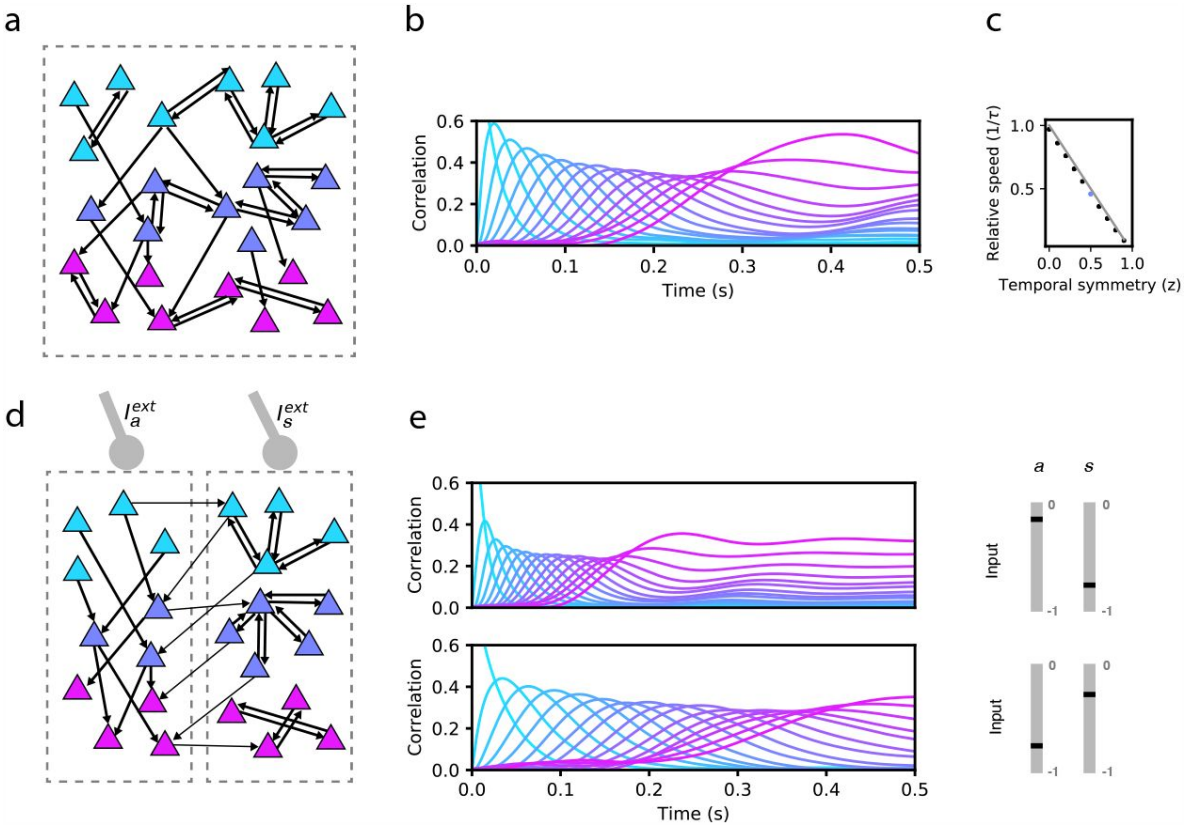

Fig. 1.

Network model and sequence retrieval. **a**. Schematic of network connectivity after learning with a plasticity rule that combines temporally symmetric and asymmetric components. The network stores a sequence of patterns that activate non-overlapping sets of neurons (colored according to the pattern that activates them). Note connections both within each set, and from one set to the next. **b**. Correlation of each stored pattern with network activity following initialization to the first pattern. Retrieval speed is fixed by the balance of symmetry/asymmetry at the synapse. **c**. Relative retrieval speed as a function of temporal symmetry (z), showing linear relationship. Solid line: 1 − *z*, the speed computed from MFT (see Methods). Black dots: Network simulations. **d**. Connectivity of a network with two types of neurons, asymmetric (left) and symmetric (right). Note that the connections from left neurons project to neurons active in the next pattern in the sequence, while connections from right neurons project to neurons active in the same pattern as the pre-synaptic neuron. The two types of neurons can be driven differentially by external inputs (I_a^{ext} and I_s^{ext}, respectively) **e**. Correlations as in (a) for two distinct pairs of input strengths (in the range [-1,0] for I_a^{ext} and I_s^{ext}), demonstrating two different retrieval speeds. In the simulations shown on the center and right panels, N = 80,000, c = 0.005, τ = 10ms, P = 16, A = 2, θ = 0, and σ = 0.1. For simplicity, we depict only 3 of the 16 stored patterns in the left schematics.

the average inverse time between the peaks of consecutive correlations of the network state with consecutive patterns in the sequence. For example, a speed of 0.5 corresponds to an average time difference of 2τ between the peaks of the correlations of two consecutive retrieved patterns with network state. In the upper left quadrant of **Fig. 2b**, speed depends primarily on the strength of input to the symmetric population. Moving away from this region in the direction of increasing symmetric input, retrieval speed slows down to approximately 0.5. In the lower right quadrant, retrieval speed instead depends primarily on the strength of external input provided to the asymmetric population. As this negative input grows, retrieval speed becomes approximately four times slower than the speed of the purely asymmetric network. While we have focused on negative input in **Fig. 2**, retrieval speed is also modulated by positive input. Interestingly, it is the magnitude, not sign, of the input that determines retrieval speed. Expanding the phase diagram in panel (b) to positive input shows that the same dependence holds: values for retrieval speed are approximately symmetric about the I_a^{ext} and I_s^{ext} axes (not shown).

Flexible retrieval with a non-linear plasticity rule

We next considered the consequences of a nonlinear learning rule implemented by the following presynaptic and postsynaptic functions in **Eq. 2**:

$$f(x) = q_f - 1 + \Theta(x - x_f) \tag{7}$$

$$g(x) = q_g - 1 + \Theta(x - x_g) \tag{8}$$

where $\Theta(x)$ is the Heaviside function. This rule binarizes the activity patterns ξ according to a threshold, and its effects on persistent and sequential network activity have been studied extensively [5, 28, 30]. The parameter q_g is chosen such that $\int Dz g(z) = 0$, which keeps the mean connection strength at zero. The general dependency of retrieval speed on asymmetric and symmetric inputs in a network utilizing this rule is similar to that of the bilinear rule (see **Fig. 2**). One key difference is that a much wider range of speeds can be achieved using a nonlinear rule within the same retrieval quality bounds (see Methods). In fact, retrieval speed can now be arbitrarily slowed down, and even completely stopped when the input to the asymmetric population is sufficiently negative (see white dots in **Fig. 3b**). In this region, persistent activity is stable, and there exists a fixed point attractor correlated with any of the patterns in any stored sequence. There also exists a region in which sequential activity stops in the middle of retrieval and switches to stable persistent activity (see hatched diagonal lines in **Fig. 3b**).

Temporally varying external inputs can lead to transitions between persistent and sequential activity

We next explored how this heterogeneity might be used not only to control the speed of dynamics, but also to trigger transitions between qualitatively different dynamics. In **Fig. 4** we use the same nonlinear model as in the previous section, and present discrete, time-dependent inputs intended to achieve persistent retrieval of a single pattern, followed by sequential retrieval of the remaining patterns at a specified time. To initiate persistent activity, we briefly present the first pattern as an input to the symmetric population. This elicits persistent activity in this population, as reflected by the sustained positive correlation of the symmetric population with the first pattern during the first 200ms (**Fig. 4b**). This activity does not recruit sequential activity in either population, however, as the asymmetric population responsible for that transition is presented with sufficiently strong negative input during this period. To initiate sequential activity, inhibition to the asymmetric population is released after t = 0.2s, prompting the network to retrieve the stored sequence in both populations.

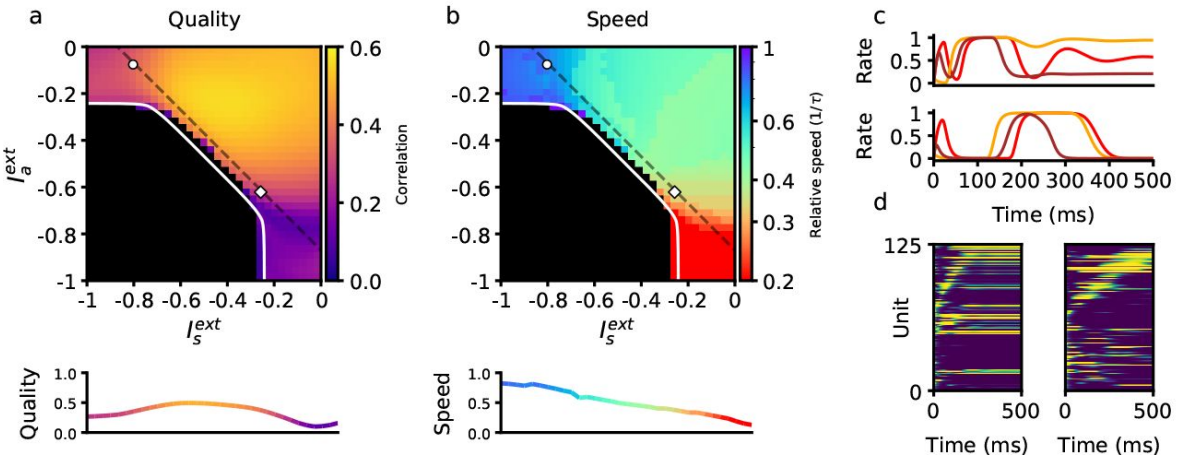

Fig. 2.

Retrieval properties depend on external inputs. **a**. Retrieval quality, defined as the peak correlation m^P of the final pattern in the sequence, as a function of external inputs to asymmetric population I_a^{ext}, and to symmetric population I_s^{ext}. The white line bounds the region of successful retrieval. Below this line (black region), retrieval is not possible, regardless of initial condition (see Methods). **b**. Retrieval speed, measured by averaging the inverse time between consecutive pattern correlation peaks (see Methods). **c**. Firing rates of three randomly selected neurons during retrieval for parameters corresponding to the circle (left) and diamond (right) in panels (a-b). Note the approximate (but not exact) temporal scaling by a factor ~ 3 between these two sets of external inputs. **d**. Activity of 125 units (from a total of 80,000), sorted by peak firing rate time, for parameters corresponding to the circle (left) and diamond (right) in panels (a-b). All other parameters are as in **Fig. 1b**.

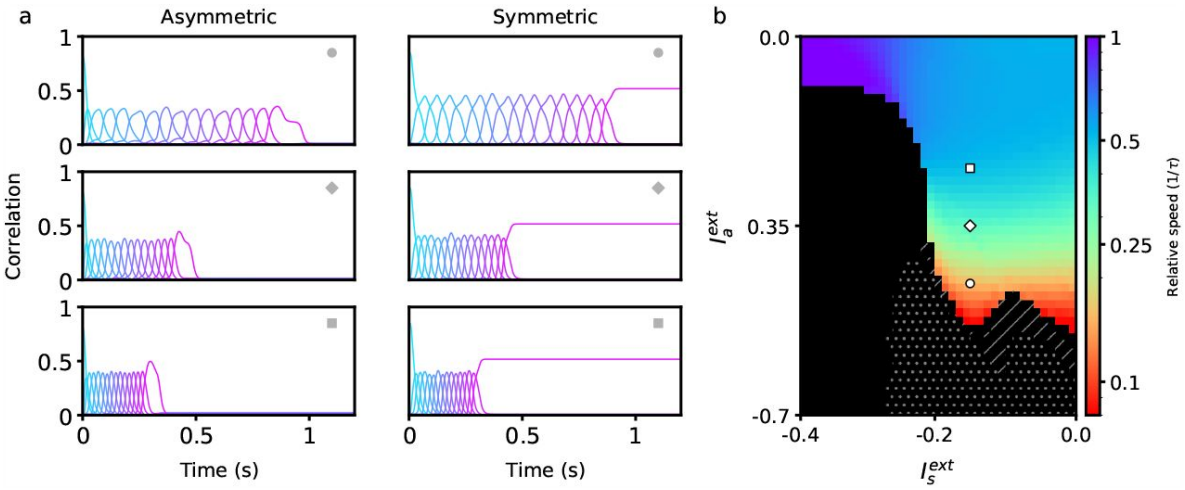

Fig. 3.

Retrieval properties in networks with nonlinear learning rules. **a**. Correlations between stored patterns and network states in asymmetric (left) and symmetric (right populations, for three different external input combinations (denoted by the inset symbol, see right panel). **b**. Retrieval speed as a function of parameters describing external inputs, similarly as in **Fig. 2**. White dots indicate the region in which stable persistent activity of the first pattern is present. Hatched diagonal lines indicate the region in which incomplete sequential activity terminates in stable persistent activity. All parameters are as in **Fig. 2**, except $A = 20$ and $\sigma = 0.05$. The parameters of the learning rule are $x_f = 1.5$, $x_g = 1.5$, $q_f = 0.8$, and $q_g = 0.933$.

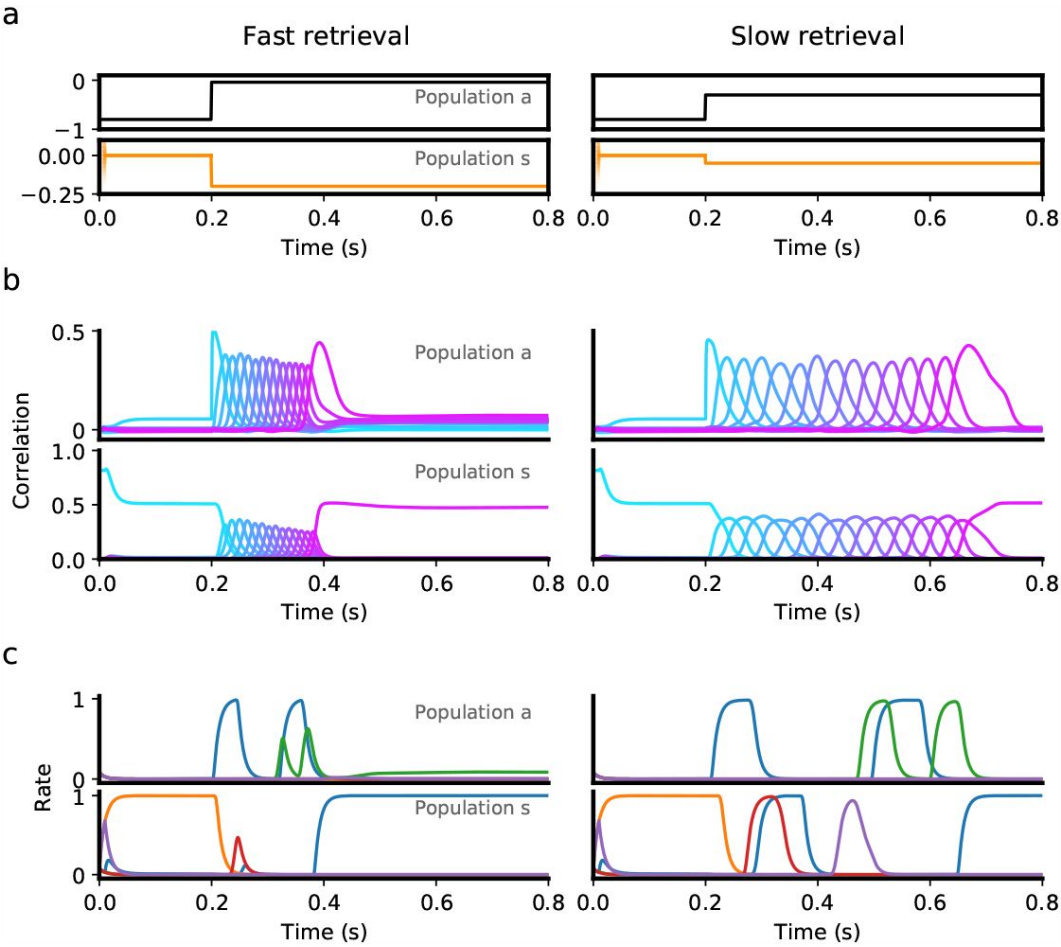

Fig. 4.

Transition from persistent activity ('preparatory' period) to sequence retrieval ('execution' period) mediated by external input **a**. Inputs provided to the asymmetric (black) and symmetric population (orange) consist of a "preparatory period" input lasting 200ms, followed by an "execution period" input that is fixed for the rest of the interval. During a 200ms preparatory period, a brief input is presented to the symmetric population for the first 10ms, which drives the network to a state which is strongly correlated with the first pattern in a sequence. This input is removed after 10ms, but the network remains in a persistent activity state corresponding the the first pattern, because a strong negative input is presented to the asymmetric population throughout the entire 200ms, which prevents the network from retrieving the sequence. At the end of this period, the input to the symmetric population is decreased, while the asymmetric population is increased, which leads to retrieval of the sequence ('execution period'). Sequence retrieval can happen at different speeds, depending on the inputs to the asymmetric and symmetric populations. **b**. Correlations with stored patterns in the sequence in each population, in each input scenario. Note correlations in the slow retrieval case are temporally scaled by a factor ~ 2.5 compared to the fast retrieval case. **c**. Example single unit firing rates in each population. Note that for some neurons firing rates do not follow a simple temporal rescaling for instance the purple neuron in the symmetric population is active at around $t = 0.45$ in the slow retrieval case, but is not active in the fast retrieval case. All parameters are as in **Fig. 3**, except $\theta = 0.07$ and $\sigma = 0.05$.

Note that in this scenario also, a sequence can be retrieved at various speeds, using the same inputs during the persistent period, but changing the level of constant stimulation provided during retrieval (compare left and right panels in **Fig. 4b**). As in a network with only a single asymmetric population, single neuron activity in this network is temporally sparse, with many neurons being active only at specific time intervals (**Fig. 4c**).

In our network, stability of persistent activity requires the dependence of the plasticity rule on pre and/or post synaptic firing rates to be non-linear. With a bilinear learning rule and Gaussian patterns, the network dynamics does not converge to fixed-point attractors that are correlated with a single pattern, but rather to mixed states correlated with multiple patterns [31].

The dynamics shown in **Fig. 4** reproduces some of the landmark features observed in electrophysiological recordings during delayed motor tasks. In such tasks, a preparatory period follows presentation of a cue (e.g. instructing a target direction or a desired response speed), during which the animal can prepare the motor response, but not execute it [32]. This period is typically characterized by persistent activity of specific groups of neurons, whereas during motor execution those same neurons instead display transient activity [33].

Flexible sequence retrieval in networks with a continuous distribution of degrees of temporal symmetry

Up to this point, we have analyzed a network model in which neurons are separated in two discrete classes distinguished by their plasticity rule (symmetric or asymmetric). For a given postsynaptic neuron, the learning rule present at all presynaptic synapses was chosen to be either temporally symmetric or asymmetric with equal probability, defining two distinct subpopulations of neurons. Can retrieval speed still be modulated by external input when synapses do not fall into such a binary classification, but have more heterogeneous properties? To model this heterogeneity, we chose to embed a continuum of learning rules. Instead of a bimodal distribution for z_i in Eq. 2, we choose a uniform distribution on the interval [0, 1]. The input I_i^{ext} provided to each neuron i in Eq. 1 is a linear combination of symmetric and asymmetric input components: $I_i^{ext} = z_i I_s^{ext} + (1 - z_i) I_a^{ext}$. We also choose to investigate a network with the previously described non-linear plasticity rule. **Fig. 5** shows that a network with these modifications also exhibits flexible sequence retrieval, and that speed decreases as the asymmetric input component becomes more negative. However, as shown in **Fig. 5c**, to reach slower speeds a positive I_s^{ext} is now required. Note that a region of stable persistent activity is no longer present in this scenario, as stable persistent activity requires that a finite fraction of neurons in the network have a symmetric plasticity rule.

Discussion

In this paper, we have introduced a new mechanism for flexible control of retrieval speed in networks storing sequences. This mechanism relies on heterogeneity of synaptic plasticity rules across neurons in the network, with different degrees of temporal asymmetry. Neurons with temporally symmetric plasticity act as brakes of the dynamics, as they stabilize network activity in its current state, while neurons with temporally asymmetric plasticity act instead as accelerators, as they push the network towards the next pattern in the sequence. The speed of retrieval can then be modified in a flexible way by changing external inputs driving these two types of neurons. Furthermore, we found that this mechanism can be used to gate transitions between persistent and sequential activity.

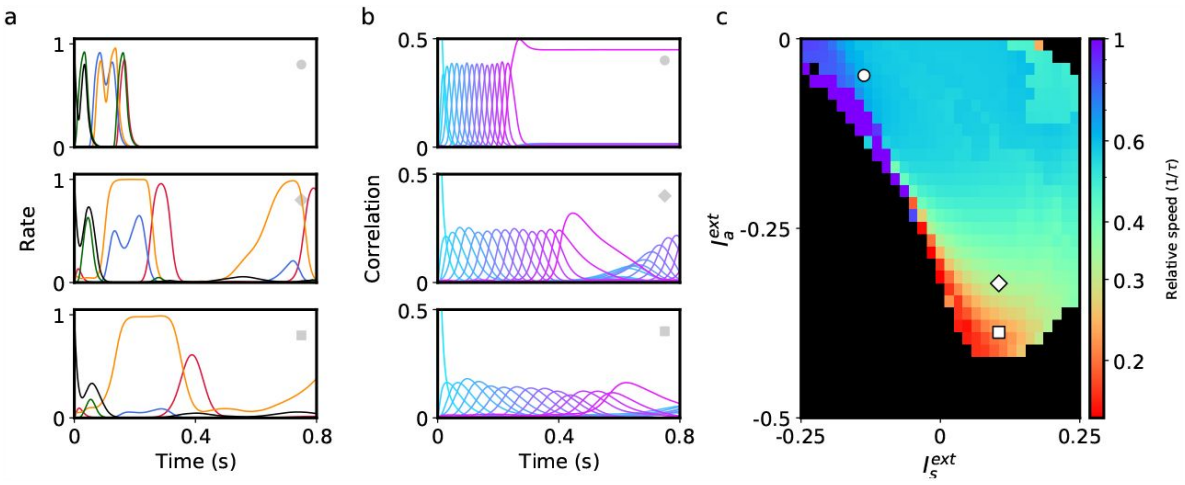

Fig. 5.

Retrieval of sequences in networks with heterogeneous learning rules described by a continuum of degrees of symmetry. **a**. Firing rate dynamics of five representative neurons during retrieval for each external input configuration (see inset symbols in panel c). **b**. Correlation of network activity with each stored pattern during retrieval for each external input configuration. **c**. Retrieval speed as described in **Fig. 2**. All parameters are as in **Fig. 3** except $A = 10$.

Heterogeneity of synaptic plasticity

Our findings suggest a potential functional role for the experimentally observed diversity in synaptic plasticity rules [6–8, 21, 23]. In particular, a wide diversity of spike-timing dependent plasticity (STDP) curves have been reported in various brain structures, and sometimes in the same structure. In the hippocampus, temporally asymmetric STDP is typically observed in cultures [8] and at CA3 to CA1 connections in slices [34, 35], but temporally symmetric STDP is observed in area CA3 [23]. In the cerebellum, synaptic plasticity rules with diverse temporal requirements on the time difference between parallel fiber and climbing fiber inputs have been found in Purkinje cells in different zones of this structure [7]. While this heterogeneity has been found so far across structures or across different regions in the same structure, this heterogeneity could also be present within local networks, as current experimental methods for probing plasticity only have access to a single delay between pre and post-synaptic spikes in each recorded neuron, and would therefore miss this heterogeneity.

For simplicity, the degree of temporal asymmetry was chosen in our model to depend only on the identity of the postsynaptic neuron. This is consistent with the observation that a model of synaptic plasticity that depends only on the postsynaptic concentration of calcium can account for a range of experimentally observed STDP curves [29]. This suggests that heterogeneities in temporal asymmetry could arise due to heterogeneities in biophysical parameters that control calcium dynamics in post-synaptic spines.

Comparison with other mechanisms of speed control

The mechanism investigated here has major differences with previously described models of input-driven speed control. It does not require adaptation mechanisms or delays to slow down retrieval of subsequent patterns [1, 3]. It also does not require presentation of multiple exemplars spanning the desired range of retrieval speeds in order to find the appropriate network structure [2]. However, the mapping between external input strength and retrieval speed must be learned in order for the network to be able to perform retrieval at desired speeds. Unlike the model explored in [2], however, once this mapping is learned, it can be used to control the speed of other stored sequences.

Another recent study [36] has investigated how a recurrent network could flexibly control its temporal dynamics using a different approach. They trained a low-rank recurrent network using back-propagation through time to produce specific dynamics with flexible timing, and showed that the resulting network can then be flexibly controlled by a one-dimensional input. It would be interesting to investigate whether the low-rank structure found in such a manner exhibits similarities with the synaptic connectivity structure in our model.

The low-dimensional external inputs used to regulate speed are unrelated to the stored sequential input patterns, and suggest that a mapping to retrieval speed can be learned independently from a particular set of sequential patterns. We demonstrated that a reinforcement learning rule can be used to arrive at external input values implementing a desired speed (**Fig. 6**). By using a reward signal measuring how similar retrieval is to the desired speed, the rule adjusts initially random external inputs to the appropriate values over the course of multiple trial repetitions. Critically, once these external input values are learned, they can be used to modulate the retrieval speed of other stored sequences without having to relearn this mapping. Future experimental work could analyze the evolution of neural activity across the training of interval timing tasks, and evaluate whether it is consistent with such a reinforcementbased rule.

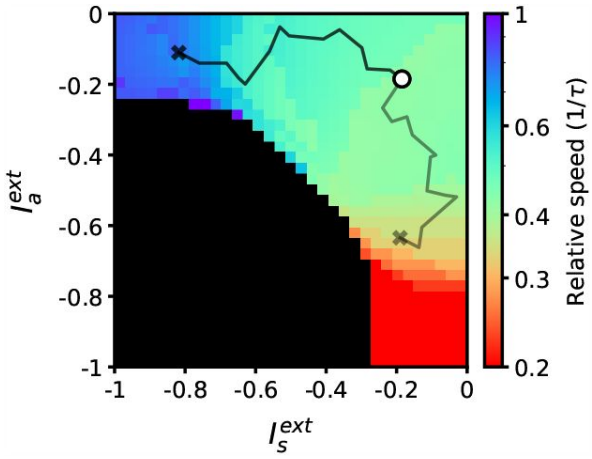

Fig. 6.

Desired target speeds can be reached by adjusting external inputs using a rewardbased learning rule. The black and grey lines denote the trajectories for two learning trials targeting different speeds. External inputs start at − 0.2 (marked with a circle) and terminate at values implementing desired target speeds of 0.8 and 0.3 (marked with crosses). All parameters are as in **Fig. 2**.

Experimental predictions

This mechanism presented here makes several predictions regarding the relationship between plasticity rules, external input, and the speed of network dynamics. One prediction is that retrieval speed could be modified by providing different external inputs to each population (asymmetric and symmetric). In vivo, these populations could be identified using the dependence of mean firing rates on speed of retrieval - neurons who increase their rates with slower/faster retrieval speeds would be predicted to be the symmetric/asymmetric neurons, respectively. Targeting one class of neurons or the other, using holographic techniques (see e.g. [37]) would then be expected to increase or decrease the speed of retrieval. Another prediction is that these cells have distinct profiles of temporal asymmetry in their synaptic plasticity. The model presented here also predicts the existence of "null" input directions, for which no change in retrieval speed is expected as external input is changed. When moving along these "null" directions, single neurons would only be expected to change their temporal firing patterns, but without affecting the speed of retrieval.

Transitions between persistent and sequential activity

Heterogeneity in the learning rule also provides a mechanism that enables input changes to drive transitions in activity states. An example of such a transition is frequently reported in primary motor cortex (M1) during delayed reaching tasks, where a preparatory period with persistent activity or ramping dynamics is followed by an execution period with transient, sequential dynamics [38, 39]. We demonstrated how an input change can gate such a transition in a simple network model composed of neurons with two distinct plasticity rules, the first temporally symmetric, and the second temporally asymmetric. At the start of the preparatory period, asymmetric neurons are inhibited, and a transient specific input elicits persistent activity in symmetric neurons. When inhibition is removed, asymmetric neurons become activated and drive a transition to sequential activity in both types of neurons.

Inhibitory gating has been previously hypothesized as a mechanism to control the initiation of execution period activity. Analysis of M1 activity suggests that local inhibitory interneurons do not engage in this gating, as putative inhibitory neurons do not appear to be preferentially active during the preparatory period compared to the execution period [40]. However, this does not rule out the possibility that the necessary inhibition could arise from other external inputs to M1. It is also possible that inhibition may not be required at all. Effective silencing of the asymmetric neurons could occur by a reduction of excitatory input during the preparatory period. Recent work in mice suggests that thalamocortical interactions may be a potential candidate for driving the required transition. Recorded activity in motor thalamus during a reaching task shows that at movement onset, thalamus activity is negatively correlated with premotor activity, but positively correlated with activity in M1 [41]. In a separate directional licking task, thalamus projections were shown to be required for initiating cued movement, and mimicked presentation of the cue when optogenetically stimulated [42]. An alternative model for transitions between preparatory and execution activity has recently been proposed [43], in which external inputs trigger a switch between a preparatory state and a nearly orthogonal execution state. However, in the model of ref. [43], the execution epoch is described by a single pattern, and any temporal dynamics within this epoch is inherited from external inputs.

Methods

Neuronal transfer function

The neuronal transfer function is given by the sigmoidal function

$$\phi(h) = \frac{r_{\max}}{2}\left(1 + \mathrm{erf}\left(\frac{h-\theta}{\sqrt{2}\sigma}\right)\right), \tag{9}$$

where θ determines the input at which the neuron fires at half the maximal value r_{max}, and σ is inversely proportional to the gain. This function was chosen for continuity with previous work [5]. We expect that using qualitatively similar functions should not alter the results of this paper.

Measuring pattern correlations

To compute the Pearson pattern correlation $m_\mu(t)$, we compute the overlap of each of the stored patterns ξ_μ with the instantaneous firing rates for the entire population and divide by the standard deviation of firing rate activity: $m_\mu(t) = \frac{1}{N}\sum_{i=1}^{N} r_i \xi_i^\mu / \sigma_r(t)$. In **Figs. 3** and **4**, we compute the correlations separately for each subpopulation.

Measuring retrieval speed

To measure retrieval speed v in **Figs. 2**, **3**, and **5**, we recorded the times at which each pattern correlation attained its peak value, and computed the average time difference between the peaks of successive patterns in a sequence. We then divided the time constant of the rate dynamics by this averaged value in order to convert speed into units of τ^{-1}:

$$v = \frac{\tau}{\frac{1}{P-1}\sum_{l=2}^{P} \mathrm{argmax}_t\big(m_l(t)\big) - \mathrm{argmax}_t\big(m_{l-1}(t)\big)} \tag{10}$$

To account for simulations with dynamics that did not have well-defined correlation peaks (typically observed at extreme storage loads or with persistent activity), we excluded peak time differences that exceeded two standard deviations of the average difference value. If no peak time difference passed this criteria, the sequence was considered not retrieved (black regions in **Figs. 2**, **3**, and **5**).

Mean-field theory of single-population network with variable degree of temporal asymmetry

In this section we derive a mean-field theory for the single population network with homogeneous synaptic plasticity. This is a generalization of the theory derived for a purely temporally asymmetric network [5]. We define order parameters $q_\mu(t) = \mathbb{E}\,(r(t)\xi^\mu$ and $M = \mathbb{E}\,((r)^2(t)$, describing the average overlap of network activity with pattern ξ^μ and the average squared firing rate, respectively.

Using equations (1,2), we derive equations describing the temporal evolution of the overlaps (for $l \in \{2, .., P\}$),

$$\tau\frac{dq_l}{dt} = -q_l + \int D\xi^l Dx \xi^l \phi\big((1-z)\xi^l q_{l-1} + z\xi^l q_l + R_l x + I^{\mathrm{ext}}\big) \tag{11}$$

where R_l is a 'noise' term due to patterns $\mu \neq l$ in the sequence (see [5] for details) By making the following change of variables:

$$v = \frac{q_l^z \xi_l + x R_l}{\sqrt{(q_l^z)^2 + R_l^2}} \tag{12}$$

$$u = \frac{\xi_l R_l - q_l^z x}{\sqrt{(q_l^z)^2 + R_l^2}} \tag{13}$$

in which we have defined $q_l^z = (1-z)q_{l-1} + z q_l$, we obtain

$$\tau\frac{dq_l}{dt} = -q_l + q_l^z G\Big((q_l^z)^2 + R_l^2\Big), \tag{14}$$

where

$$G(x) = \frac{\int DuDv\phi\left(v\sqrt{x} + I_{ext}\right)}{\sqrt{x}}. \tag{15}$$

Assuming that $G(x) \approx 1$, which is the case during successful retrieval (see also [5]), then we can simplify to:

$$\frac{\tau}{1-z}\frac{dq_l}{dt} = -q_l + q_{l-1} \tag{16}$$

This equation makes it clear that retrieval speed depends linearly on z, i.e. on the balance between the symmetric and asymmetric components of synaptic plasticity.

Mean-field theory of heterogeneous network and conditions for retrieval

Mean-field theory can be used to further analyze retrieval speed dynamics, along the lines of [5]. We define order parameters $q_\mu^X(t) = \mathbb{E}\left(r^X(t)\xi^{X,\mu}\right)$ and $M_X = \mathbb{E}\,(r^X)^2(t)$, describing the average overlap of network activity in subpopulation X with pattern $\xi^{X,\mu}$ and the average squared firing rate in subpopulation X, respectively. The equations for the overlaps are given by:

$$\tau\frac{dq_l^a}{dt} = -q_l^a + \left(q_{l-1}^a + q_{l-1}^s\right)\cdot G_a\left((q_{l-1}^a + q_{l-1}^s)^2 + (R_l^a)^2\right) \tag{17}$$

$$\tau\frac{dq_l^s}{dt} = -q_l^s + \left(q_l^s + q_l^a\right)\cdot G_s\left((q_l^a + q_l^s)^2 + (R_l^s)^2\right) \tag{18}$$

where G is given, for arbitrary transfer functions ϕ by:

$$G_X(x) = \frac{\int DuDv\phi\left(v\sqrt{x} + I_X^{ext}\right)}{\sqrt{x}}. \tag{19}$$

For the transfer function used in this paper, Eq. (9), the expression simplifies,

$$G_X(x) \equiv \frac{1}{\sqrt{2\pi(\sigma^2 + x)}}\exp\left(-\frac{(\theta + I_X^{ext})^2}{2(\sigma^2 + x)}\right). \tag{20}$$

As in the previous section, R_l^a and R_l^s are 'noise' terms due to patterns $\mu \neq l$ in the sequence, which also depends on the average squared firing rates M_a and M_s. Using Eqs. 17-18, we can derive the dynamics of the combined population overlap $q_l(t) = q_l^a(t) + q_l^s(t)$:

$$\tau\frac{dq^l}{dt} = -q^l + q_{l-1}G_a\left((q_{l-1})^2 + (R_l^a)^2\right) + q_l G_s\left((q_l)^2 + (R_l^s)^2\right) \tag{21}$$

To compute the boundary for successful retrieval given by the white line in **Fig. 2**, we analyze this equation when the gains are constant: $G_X(t) = G_X$. Plugging in and rearranging, we find:

$$\frac{\tau}{1-G_s}\frac{dq_l}{dt} = -q_l + \frac{G_a}{1-G_s}q_{l-1} \tag{22}$$

This equation shows that the sequence can only be retrieved if $G_a/(1 - G_s) > 1$, otherwise the peak of the overlaps decay to zero with increasing l. Thus retrieval of an asymptotically long sequence is successful if the gain converges to a value greater or equal to one during retrieval. This condition can only be satisfied if

$$\max_x\left[G_a(x;\ \theta,\sigma,I_{ext}^a) + G_s(x;\ \theta,\sigma,I_{ext}^s)\right] \geq 1 \tag{23}$$

To test for successful sequence retrieval in **Fig. 2**, we computed the maximal correlation value of the final pattern $m_P(t)$, and compared this value to a threshold $\theta_P = 0.05$. If the value fell below this threshold, then retrieval was considered unsuccessful, and was denoted by a black square. This threshold criterion was also used in **Figures 3** and **5**.

Reward-driven learning

A simple perturbation-based reinforcement learning rule is used to demonstrate that external inputs can be generated that produce network dynamics at a desired target speed over the course of multiple trial repetitions. We simulate a series of trials with stochastically varying external inputs. At each trial n, the external inputs used in the previous trial are perturbed randomly,

$$I_{\text{pert}}^{ext,a} = I_{n-1}^{ext,a} + \lambda \Delta x_n^a \tag{24}$$

$$I_{\text{pert}}^{ext,s} = I_{n-1}^{ext,s} + \lambda \Delta x_n^s \tag{25}$$

where λ is the strength of the perturbation, and Δx_n^p are uniformly distributed random variables over the interval [−1, 1], drawn independently for each population $p \in \{a, s\}$ at each trial n. If these external inputs lead to an improvement in speed compared to previous trials, then

$$I_n^{ext,a} = I_{\text{pert}}^{ext,a} \tag{26}$$

$$I_n^{ext,s} = I_{\text{pert}}^{ext,s}; \tag{27}$$

else,

$$I_n^{ext,a} = I_{n-1}^{ext,a} \tag{28}$$

$$I_n^{ext,s} = I_{n-1}^{ext,s}. \tag{29}$$

In **Fig. 6**, the correlation threshold $\theta_m = 0.05$, the target speed $v_{target} = \{0.3, 0.8\}$, and $\lambda = 0.1$. On the first trial ($n = 0$), the external inputs are taken to be $I_0^{ext,a} = -0.2$ and $I_0^{ext,s} = -0.2$ (see open circle).

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Reviewer #1 (Public Review):

While there are many models for sequence retrieval, it has been difficult to find models that vary the speed of sequence retrieval dynamically via simple external inputs. While recent works [1,2] have proposed some mechanisms, the authors here propose a different one based on heterogeneous plasticity rules. Temporally symmetric plasticity kernels (that do not distinguish between the order of pre and post spikes, but only their time difference) are expected to give rise to attractor states, asymmetric ones to sequence transitions. The authors incorporate a rate-based, discrete-time analog of these spike-based plasticity rules to learn the connections between neurons (leading to connections similar to Hopfield networks for attractors and sequences). They use either a parametric combination of symmetric and asymmetric learning rules for connections into each neuron, or separate subpopulations having only symmetric or asymmetric learning rules on incoming connections. They find that the latter is conducive to enabling external inputs to control the speed of sequence retrieval.

Strengths:
The authors have expertly characterised the system dynamics using both simulations and theory. How the speed and quality of retrieval varies across phases space has been well-studied. The authors are also able to vary the external inputs to reproduce a preparatory followed by an execution phase of sequence retrieval as seen experimentally in motor control. They also propose a simple reinforcement learning scheme for learning to map the two external inputs to the desired retrieval speed.

Weaknesses:
1. The authors translate spike-based synaptic plasticity rules to a way to learn/set connections

for rate units operating in discrete time, similar to their earlier work in [5]. The bio-plausibility issues of learning in [5] carry over here, for e.g. the authors ignore any input due to the recurrent connectivity during learning and effectively fix the pre and post rates to the desired ones. While the learning itself is not fully bio-plausible, it does lend itself to writing the final connectivity matrix in a manner that is easier to analyze theoretically.

2. While the authors learn to map the set of two external input strengths to speed of retrieval, they still hand-wire one external input to the subpopulation of neurons with temporally symmetric plasticity and the other external input to the other subpopulation with temporally asymmetric plasticity. The authors suggest that these subpopulations might arise due to differences in the parameters of Ca dynamics as in their earlier work [29]. How these two external inputs would connect to neurons differentially based on the plasticity kernel / Ca dynamics parameters of the recurrent connections is still an open question which the authors have not touched upon.

3. The authors require that temporally symmetric and asymmetric learning rules be present in the recurrent connections between subpopulations of neurons in the same brain region, i.e. some neurons in the same brain region should have temporally symmetric kernels, while others should have temporally asymmetric ones. The evidence for this seems thin. Though, in the discussion, the authors clarify 'While this heterogeneity has been found so far across structures or across different regions in the same structure, this heterogeneity could also be present within local networks, as current experimental methods for probing plasticity only have access to a single delay between pre and post-synaptic spikes in each recorded neuron, and would therefore miss this heterogeneity'.

4. An aspect which the authors have not connected to is one of the author's earlier work: Brunel, N. (2016). Is cortical connectivity optimized for storing information? Nature Neuroscience, 19(5), 749-755. https://doi.org/10.1038/nn.4286
which suggests that the experimentally observed over-representation of symmetric synapses suggests that cortical networks are optimized for attractors rather than sequences.

Despite the above weaknesses, the work is a solid advance in proposing an alternate model for modulating speed of sequence retrieval and extends the use of well-established theoretical tools. This work is expected to spawn further works like extending to a spiking neural network with Dale's law, more realistic learning taking into account recurrent connections during learning, and experimental follow-ups. Thus, I expect this to be an important contribution to the field.

Reviewer #2 (Public Review):

Sequences of neural activity underlie most of our behavior. And as experience suggests we are (in most cases) able to flexibly change the speed for our learned behavior which essentially means that brains are able to change the speed at which the sequence is retrieved from the memory. The authors here propose a mechanism by which networks in the brain can learn a sequence of spike patterns and retrieve them at variable speed. At a conceptual level I think the authors have a very nice idea: use of symmetric and asymmetric learning rules to learn the sequences and then use different inputs to neurons with symmetric or asymmetric plasticity to control the retrieval speed. The authors have demonstrated the feasibility of the idea in a rather idealized network model. I think it is important that the idea is demonstrated in more biologically plausible settings (e.g. spiking neurons, a network with exc. and inh. neurons with ongoing activity).

Summary

In this manuscript authors have addressed the problem of learning and retrieval sequential activity in neuronal networks. In particular, they have focussed on the problem of how

sequence retrieval speed can be controlled?
They have considered a model with excitatory rate-based neurons. Authors show that when sequences are learned with both temporally symmetric and asymmetric Hebbian plasticity, by modulating the external inputs to the network the sequence retrieval speed can be modulated. With the two types of Hebbian plasticity in the network, sequence learning essentially means that the network has both feedforward and recurrent connections related to the sequence. By giving different amounts of input to the feed-forward and recurrent components of the sequence, authors are able to adjust the speed.

Strengths
- Authors solve the problem of sequence retrieval speed control by learning the sequence in both feedforward and recurrent connectivity within a network. It is a very interesting idea for two main reasons: 1. It does not rely on delays or short-term dynamics in neurons/synapses 2. It does not require that the animal is presented with the same sequences multiple times at different speeds. Different inputs to the feedforward and recurrent populations are sufficient to alter the speed. However, the work leaves several issues unaddressed as explained below.

Weaknesses
- The main weakness of the paper is that it is mostly driven by a motivation to find a computational solution to the problem of sequence retrieval speed. In most cases they have not provided any arguments about the biological plausibility of the solution they have proposed e.g.:

-- Is there any experimental evidence that some neurons in the network have symmetric Hebbian plasticity and some temporally asymmetric? In the references authors have cited some references to support this. But usually the switch between temporally symmetric and asymmetric rules is dependent on spike patterns used for pairing (e.g. bursts vs single spikes). In the context of this manuscript, it would mean that in the same pattern, some neurons burst and some don't and this is the same for all the patterns in the sequence. As far as I see here authors have assumed a binary pattern of activity which is the same for all neurons that participate in the pattern.

-- How would external inputs know that they are impinging on a symmetric or asymmetric neuron? Authors have proposed a mechanism to learn these inputs. But that makes the sequence learning problem a two stage problem -- first an animal has to learn the sequence and then it has to learn to modulate the speed of retrieval. It should be possible to find experimental evidence to support this?

-- Authors have only considered homogeneous DC input for sequence retrieval. This kind of input is highly unnatural. It would be more plausible if the authors considered fluctuating input which is different from each neuron.

-- All the work is demonstrated using a firing rate based model of only excitatory neurons. I think it is important that some of the key results are demonstrated in a network of both excitatory and inhibitory spiking neurons. As the authors very well know it is not always trivial to extend rate-based models to spiking neurons.

I think at a conceptual level authors have a very nice idea but it needs to be demonstrated in a more biologically plausible setting (and by that I do not mean biophysical neurons etc.).

Author Respone

Reviewer #1 (Public Review):

While there are many models for sequence retrieval, it has been difficult to find models that vary the speed of sequence retrieval dynamically via simple external inputs. While recent works [1,2] have proposed some mechanisms, the authors here propose a different one based on heterogeneous plasticity rules. Temporally symmetric plasticity kernels (that do not distinguish between the order of pre and post spikes, but only their time difference) are expected to give rise to attractor states, asymmetric ones to sequence transitions. The authors incorporate a rate-based, discrete-time analog of these spike-based plasticity rules to learn the connections between neurons (leading to connections similar to Hopfield networks for attractors and sequences). They use either a parametric combination of symmetric and asymmetric learning rules for connections into each neuron, or separate subpopulations having only symmetric or asymmetric learning rules on incoming connections. They find that the latter is conducive to enabling external inputs to control the speed of sequence retrieval.

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Weaknesses:

1. *The authors translate spike-based synaptic plasticity rules to a way to learn/set connections for rate units operating in discrete time, similar to their earlier work in [5]. The bio-plausibility issues of learning in [5] carry over here, for e.g. the authors ignore any input due to the recurrent connectivity during learning and effectively fix the pre and post rates to the desired ones. While the learning itself is not fully bio-plausible, it does lend itself to writing the final connectivity matrix in a manner that is easier to analyze theoretically.*

We agree with the reviewer that learning is not fully bio-plausible'. However, we believe that extending the results to a model in which synaptic plasticity depends on recurrent inputs is beyond the scope of this work. We will address this issue in the Discussion in a revised manuscript.

1. *While the authors learn to map the set of two external input strengths to speed of retrieval, they still hand-wire one external input to the subpopulation of neurons with temporally symmetric plasticity and the other external input to the other subpopulation with temporally asymmetric plasticity. The authors suggest that these subpopulations might arise due to differences in the parameters of Ca dynamics as in their earlier work [29]. How these two external inputs would connect to neurons differentially based on the plasticity kernel / Ca dynamics parameters of the recurrent connections is still an open question which the authors have not touched upon.*

The issue of how external inputs could self-organize to drive the network to retrieve sequences at appropriate speeds is addressed in the last part of the Results section. We believe this issue is independent from how different forms of synaptic plasticity can be achieved using different parameters that describe how calcium triggers synaptic plasticity. We will discuss these issues more clearly in the revised manuscript.

1. *The authors require that temporally symmetric and asymmetric learning rules be present in the recurrent connections between subpopulations of neurons in the same brain region, i.e. some neurons in the same brain region should have temporally symmetric kernels, while others should have temporally asymmetric ones. The evidence for this seems thin. Though, in the discussion, the authors clarify 'While this heterogeneity has been found so far across structures or across different regions in the same structure, this heterogeneity could also be present within local networks, as current experimental methods for probing plasticity only have access to a single delay between pre and post-synaptic spikes in each recorded neuron, and would therefore miss this heterogeneity'.*

We agree with the reviewer that this is currently an open question. We will describe this issue in more detail in the Discussion of a revised manuscript.

1. *An aspect which the authors have not connected to is one of the author's earlier work: Brunel, N. (2016). Is cortical connectivity optimized for storing information? Nature Neuroscience, 19(5), 749-755. https://doi.org/10.1038/nn.4286 which suggests that the experimentally observed over-representation of symmetric synapses suggests that cortical networks are optimized for attractors rather than sequences.*

We thank the reviewer for this suggestion. We will add a paragraph in discussion that discusses work on statistics of synaptic connectivity in optimal networks. We expect that in networks that contain two subpopulations of neurons, the degree of symmetry should be intermediate between a network storing fixed point attractors exclusively, and a network storing sequences exclusively. We will also elaborate on predictions our scenario makes on higher order network motifs.

Despite the above weaknesses, the work is a solid advance in proposing an alternate model for modulating speed of sequence retrieval and extends the use of well-established theoretical tools. This work is expected to spawn further works like extending to a spiking neural network with Dale's law, more realistic learning taking into account recurrent connections during learning, and experimental follow-ups. Thus, I expect this to be an important contribution to the field.

We thank the reviewer for the insightful comments.

Reviewer #2 (Public Review):

Sequences of neural activity underlie most of our behavior. And as experience suggests we are (in most cases) able to flexibly change the speed for our learned behavior which essentially means that brains are able to change the speed at which the sequence is retrieved from the memory. The authors here propose a mechanism by which networks in the brain can learn a sequence of spike patterns and retrieve them at variable speed. At a conceptual level I think the authors have a very nice idea: use of symmetric and asymmetric learning rules to learn the sequences and then use different inputs to neurons with symmetric or asymmetric plasticity to control the retrieval speed. The authors have demonstrated the feasibility of the idea in a rather idealized network model. I think it is important that the idea is demonstrated in more biologically plausible settings (e.g. spiking neurons, a network with exc. and inh. neurons with ongoing activity).

Summary

In this manuscript authors have addressed the problem of learning and retrieval sequential activity in neuronal networks. In particular, they have focussed on the problem of how sequence retrieval speed can be controlled?

They have considered a model with excitatory rate-based neurons. Authors show that when sequences are learned with both temporally symmetric and asymmetric Hebbian plasticity, by modulating the external inputs to the network the sequence retrieval speed can be modulated. With the two types of Hebbian plasticity in the network, sequence learning essentially means that the network has both feedforward and recurrent connections related to the sequence. By giving different amounts of input to the feed-forward and recurrent components of the sequence, authors are able to adjust the speed.

Strengths

- *Authors solve the problem of sequence retrieval speed control by learning the sequence in both feedforward and recurrent connectivity within a network. It is a very interesting idea for two main reasons: 1. It does not rely on delays or short-term dynamics in neurons/synapses 2. It does not require that the animal is presented with the same sequences multiple times at different speeds. Different inputs to the feedforward and recurrent populations are sufficient to alter the speed. However, the work leaves several issues unaddressed as explained below.*

Weaknesses

- *The main weakness of the paper is that it is mostly driven by a motivation to find a computational solution to the problem of sequence retrieval speed. In most cases they have not provided any arguments about the biological plausibility of the solution they have proposed e.g.:*

- *Is there any experimental evidence that some neurons in the network have symmetric Hebbian plasticity and some temporally asymmetric? In the references authors have cited some references to support this. But usually the switch between temporally symmetric and asymmetric rules is dependent on spike patterns used for pairing (e.g. bursts vs single spikes). In the context of this manuscript, it would mean that in the same pattern, some neurons burst and some don't and this is the same for all the patterns in the sequence. As far as I see here authors have assumed a binary pattern of activity which is the same for all neurons that participate in the pattern.*

There is currently only weak evidence for heterogeneity of synaptic plasticity rules within a single network, though there is plenty of evidence for such a heterogeneity across networks or across locations within a particular structure (see references in our Discussion). The reviewer suggests another interesting possibility, that the temporal asymmetry could depend on the firing pattern on the post-synaptic neuron. An example of such a behavior can be found in a paper by Wittenberg and Wang in 2006, where they show that pairing single spikes of pre and post-synaptic neurons lead to LTD at all time differences in a symmetric fashion, while pairing a pre-synaptic spike with a burst of post-synaptic spikes lead to temporally asymmetric plasticity, with a LTP window at short positive time differences. We will mention this possibility in the Discussion, but we believe exploring fully this scenario is beyond the scope of the paper.

- *How would external inputs know that they are impinging on a symmetric or asymmetric neuron? Authors have proposed a mechanism to learn these inputs. But that makes the sequence learning problem a two stage problem -- first an animal has to learn the sequence and then it has to learn to modulate the speed of retrieval. It should be possible to find experimental evidence to support this?*

Our model does not assume that the two processes necessarily occur one after the other. Importantly, once the correct external inputs that can modulate sequence retrieval are learned, sequence retrieval modulation will automatically generalize to arbitrary new sequences that are learned by the network.

- *Authors have only considered homogeneous DC input for sequence retrieval. This kind of input is highly unnatural. It would be more plausible if the authors considered fluctuating input which is different from each neuron.*

In a revised manuscript, we will add an additional panel to Figure 1 to demonstrate that fluctuating inputs do not qualitatively affect our results.

- *All the work is demonstrated using a firing rate based model of only excitatory neurons. I think it is important that some of the key results are demonstrated in a network of both excitatory and inhibitory spiking neurons. As the authors very well know it is not always trivial to extend rate-based models to spiking neurons.*

I think at a conceptual level authors have a very nice idea but it needs to be demonstrated in a more biologically plausible setting (and by that I do not mean biophysical neurons etc.).

We are confident that our results can be reproduced in networks of excitatory and inhibitory spiking networks, since previous studies have shown that such networks can exhibit attractor dynamics (e.g. Amit and Brunel 1997, Brunel and Wang 2001) and sequential activity (e.g. Gillett, Pereira, and Brunel 2020). We plan to include a new section with an associated figure to a revised manuscript demonstrating how the flexible speed control can be achieved in an excitatory-inhibitory (E-I) spiking network containing two excitatory populations with distinct plasticity mechanisms.