Decoupling through Synchrony in Neuronal Circuits with Propagation Delays
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Supplementary Information

S1. Relevance of Theory for the Hippocampus

The results described in the manuscript predict that synchronous bursts, occurring within recurrent circuits with delays, should lead to the selective decoupling of the participating neurons. This result is relevant for circuits meeting the following requirements: (1) presence of recurrent connections, (2) nonzero axonal conduction delays, (3) Hebbian spike-timing-dependent plasticity in the recurrent connections, (4) conditions producing synchronous population activity. Finally, it is assumed that there is no consistent temporal ordering of neuronal firing within synchronous bursts.

The hippocampal CA3 subfield satisfies all the requirements for applicability of our results as described in more detail below.

- **Range and distribution of axonal conduction delays of CA3 recurrent connections:**
  
  **Anatomical evidence:** Based on experiments using the anterograde tracer Phaseolus vulgaris leucoagglutinin (PHA-L), Ishizuka et al. [1] report striking evidence that the CA3 projections to other levels of CA3 (associational connections) and to field CA1 are massively divergent along the septotemporal axis. The extent of the septotemporal axis in their preparation was 8-10 mm and the heaviest CA3 associational fiber and terminal labeling was observed at some distance from the injection site. Thus CA3 neurons in the middle of the septotemporal and transverse axes have axonal collaterals that extend to levels up to 4 mm septally as well as temporally and the full transverse extent of the CA3 field (1.6 mm). Since these collaterals rarely travel in straight lines their actual lengths can be 5-6 mm. The velocity of conduction in the associational connections has been estimated at 0.48 ± 0.08 m/s [2]. Therefore the range of collateral lengths translates into delays ranging up to 10-12 ms. With respect to the distribution of delays, we note that CA3 axon collaterals are characterized by regularly spaced (every 7 µm) axonal varicosities associated with en passant presynaptic terminals, as confirmed by electron microscopy. Therefore if one such non-branching collateral 5 mm long innervated the CA3 subfield the resulting distribution of delays would be uniform between 0 and 10 ms. If branching is present the distribution can be skewed towards longer delays. In particular if the branching produces a uniform density of presynaptic terminals in the plane, the density of delays will be a growing linear function of radial distance, since the area of an annulus of radius $r$ and thickness $dr$ grows as $r$. This skew toward larger delays is counteracted by the higher density of short-range collaterals, experimentally observed within a 1-2 mm radial range. In the absence of detailed knowledge of the branching of the axonal plexus and associated distribution of presynaptic terminals the assumption of a uniform distribution of delays between 1 and 10 ms seems reasonable.

  **Electrophysiological evidence:** Based on the spatial distribution and latencies of EPSPs produced by stimulation at a fixed point in a longitudinal slice from the CA3...
region, Miles et al. [2] observe responses up to 4 mm away from the stimulation site with a corresponding latency of 10 ms. Based on linear regression between distance and latency they estimate the conduction velocity at $0.48 \pm 0.08$ m/s. Based on the spatial distribution of EPSP amplitudes they suggest that connectivity decays exponentially along the septotemporal axis with a space constant of 0.6 mm. However this approximation almost certainly underestimates the fraction of long range connections, as many of the longer collaterals are likely to leave to 400 $\mu$m transverse extent of the slice and therefore fail to contribute to the EPSP amplitude.

- **Hebbian STDP** has been shown to underlie plasticity in CA3 recurrent connections [3]. Furthermore, there is direct experimental evidence that the simultaneous firing of a pair of CA3 neurons decreases the strength of the synaptic connections between them [3].

- **Synchronous activity**: Sharp-wave bursts are some of the most synchronous naturally occurring population events in the brain. Within CA3 these bursts have $\sigma$ estimated between 15 and 20 ms [4] and within CA1 the median $\sigma$ was 26 ms (figure 8c).

- **Absence of temporal order**: Previous studies have demonstrated the presence of a significant bias toward sequential reactivation of activity patterns during population bursts in SWS [5, 6, 7, 8]. Yet the ordered patterns constitute a small fraction of the total number of bursts and therefore do not violate the ordering prerequisite for decoupling. Please refer to section *Sequential firing in the hippocampus in SWS* in the main text for a detailed discussion.

### S2. Conditions for Mixture States and Persistent Synchrony

As discussed in the main text, the convergence of networks to mixture states is a consequence of the coupling and decoupling forces of STDP that applies to randomly driven networks for which the level of synchronous activity is principally controlled by the strength of the recurrent excitatory connections. Therefore, we do not expect all recurrent circuits to have mixture state dynamics at all times. For example, the presence of strong thalamo-cortical interactions during sleep likely precludes neocortex from exhibiting the mixture-like activity patterns that characterize spontaneous hippocampal firing in slow-wave sleep. Furthermore, the hippocampus itself exhibits rhythmic theta activity when driven by entorhinal and septal inputs during active exploration and REM sleep. Therefore, the fact that recurrent circuits may exhibit population dynamics different from mixture states does not contradict our results. Below, we consider how a state of persistent synchrony can exist even in the simple network models we study.

It is important to emphasize that the mixture states corresponding to certain STDP rules are actually characterized by a high level of synchrony. This is certainly the case for rules with a large positive integral (e.g. red points in figure 5). Such rules are
generally considered non-physiological, precisely because of their tendency to saturate synapses [9] and therefore lock networks in oscillatory states. Thus one explanation of persistent synchrony that is compatible with mixture states being the global attractor of network dynamics is such an abnormal STDP rule shape. This scenario in essence represents a misregulation of plasticity that may be relevant for understanding the pathogenesis of an epileptic focus, for example.

However, persistent synchrony can also be induced experimentally in vitro, in cases where there may be no reason to suspect that the shape of the STDP rule has been altered [10, 11, 12]. This implies that there must be circumstances under which the decoupling force of STDP is absent. Indeed, the maps of relative synaptic change as a function of delay $\mu$ and population burst width $\sigma$ (figures 1, S3, S8) reveal the existence of parameter ranges under which population bursts can produce coupling. Under all-to-all STDP implementations (Experimental Procedures), these coupling ranges are small compared to their corresponding decoupling ranges even for STDP rules with a large positive integral (figure S3 a4, b4), hence the dominant nature of the decoupling force. Under nearest-neighbor implementations these coupling ranges can be substantially larger (figure S3 c1, c4) and furthermore can increase in size as a function of the firing rate within the population burst (figure S8b). Since increased coupling usually produces bursts of longer duration and higher firing rate, this results in a positive-feedback mechanism and implies that under certain rules and initial conditions of strong coupling, networks can converge to a state different than the mixture state, namely a high coupling/high order state of persistent synchrony (figure S9). The mixture state is still an attractor under these conditions, but it is no longer the global attractor (figure S9). It is therefore possible to take a network that has settled into a mixture state and push it into the attractor basin of persistent synchrony (not only by strengthening synapses [11, 12], but also by suddenly altering the duration and firing rate within population bursts. This can be accomplished by rapidly increasing the excitability of individual neurons or by disinhibiting the circuit (simulation data not shown). Such bistable behavior and persistent synchrony have been indeed experimentally observed in vitro [13, 10, 11]. This scenario represents a large sudden perturbation to the network and reveals the vulnerability of highly recurrent plastic circuits to such drastic manipulations, that may be relevant for understanding brain trauma, for example.

S3. Burst and background rate dependence on network size

For a synchronous burst to develop, a critical fraction, $c = t/(sm)$, of neurons must become co-active within a time window, $w$, of a few milliseconds. Here $t$ is the distance between the expected membrane potential and firing threshold, $s$ is the expected synaptic weight, and $m$ is the expected number of inputs a neuron receives. The rate of burst occurrence will therefore depend on how often the network exceeds this critical fraction. On the other hand, the expected fraction, $e$, of co-active neurons is simply $e = wf$, where $f$ is the spontaneous neuronal firing rate, a free parameter in the model. The convergence to mixture state can be understood as the tuning of $s$ by the STDP rule, so that the critical
threshold $c$ is brought close to the expected fraction, $e$.

Since $f$ is a free parameter in the simulation in principle it can be set arbitrarily low in order to match the experimentally observed inter-burst firing rates. In the models we consider it was set to either 1 Hz or 0.5 Hz. Why can’t it then be lowered further in order to quantitatively match the real system? If lowered further, the network of figure S4 does not produce bursts. The reason is that since the dynamic range of the synapse is limited, i.e. $0 < s < s_{\text{max}}$, $c$ can never be lower than $(t/m)(1/s_{\text{max}})$. Therefore if $e$ is set too low the network can never produce bursts. So for mixture states to be possible we must have:

$$e > \frac{t}{m s_{\text{max}}}$$

Then in order to match the experimentally observed inter-burst firing rate we must have a large enough network, so that $m > (t/e)(1/s_{\text{max}}) = 5,000$. With 5% connectivity this means the network must have in the order of 100,000 neurons. Hence, this theoretical analysis indicates that such a network will converge to a mixture state with low firing rates, and will still be capable of synchronous burst generation.

References


Figure S1: Order Parameter. (a) Spike rasters from a network of 100 neurons over a 5 second period. The instantaneous firing rate $r$ in the network was computed by dividing the time axis into adjacent bins of equal size and counting the number of spikes falling in each bin. The bin size $dt$ was set so that the expected count in each bin under the null hypothesis of random firing was equal to $\lambda = 25$, i.e. $dt = \frac{\lambda T}{N}$, where $T$ is the duration of the given period and $N$ is the total number of spikes. Under the null hypothesis $r$ at each time lag follows a Poisson distribution with parameter $\lambda$. Since $dt$ was set so that $\lambda = 25$ the normal approximation to the Poisson distribution holds. In this example, $dt = 34.5 ms$. (b) The normalized instantaneous firing rate $n$ (grey trace under the spike rasters) was obtained by rescaling $r$ as $n = \frac{r-\lambda}{\sqrt{\lambda}}$. Values of $n$ more than 3 standard deviations away from the zero mean (dotted horizontal lines) indicate significant departures from the null hypothesis of random firing. (c) The order parameter $\psi$ was defined as the fraction of $n$ values that were outside the interval $(-3, 3)$ (red dots and horizontal bars) or equivalently as 1 minus the fraction of $n$ values in the interval $(-3, 3)$ (blue dots and horizontal bar). The order parameter for the given example is $\psi = 0.32$. 
Figure S2: Order parameter $\psi$ compared to $r^2$ synchrony measure. (a) Evolution of the order parameter $\psi$ (red) and the Pinsky and Rinzel $r^2$ synchrony measure (blue) [14] for the simulation in figure 4. The two measures disagree when the network shows regular oscillations, i.e. before 120 s and after 480 s, but appear very correlated in the mixture state, i.e. between 120 s and 480 s. Scatter plots of order parameter versus $r^2$ synchrony measure for the entire run (correlation coefficient $r = 0.38$) (b), from 120 s to the end of the run ($r = 0.96$) (c), and from 120 s to 480 s ($r = 0.96$) (d).
Figure S3: Decoupling force under different STDP implementations. Maps of relative synaptic change as a function of delay $\mu$ and burst width $\sigma$ for (1-4) four different STDP rules under (a) all-to-all (b) all-to-all with $Z = 5$ ms, i.e. $\Delta t \in (-5, 5)$ ms ignored (c) nearest-neighbor implementations. The rules were (1) negatively biased with $A_+ = 1$, $A_- = 0.5$, $\tau_+ = 13$ ms, $\tau_- = 35$ ms, $\tau_{\text{stdp}} = 1$ s (2) negatively biased with $A_+ = 1$, $A_- = 1.4$, $\tau_+ = \tau_- = 20$ ms, $\tau_{\text{stdp}} = 1$ s (3) neutral with $A_+ = A_- = 1$, $\tau_+ = \tau_- = 20$ ms, $\tau_{\text{stdp}} = 1$ s (4) positively biased with $A_+ = 1.4$, $A_- = 1$, $\tau_+ = \tau_- = 20$ ms, $\tau_{\text{stdp}} = 1$ s. In each panel the thick blue line indicates the cross-over boundary between strengthening and weakening. In the case of all-to-all implementations the kernels multiplying the STDP rule for a given burst width $\sigma$ have the same shape, but are shifted with respect to each other by the delay $\mu$. In the nearest-neighbor case this is no longer true and the kernels tend to emphasize the central portion of the STDP rule around $\Delta t = 0$. Notice that (a) and (b) are very similar under all rules, indicating that the decoupling force does not depend on the presence of a sharp discontinuity in the STDP rule at 0. Notice also that the nearest-neighbor implementation accentuates the features of the maps obtained with the all-to-all implementation when $\tau_+ = \tau_-$, (c2-c4), but can introduce a significant coupling parameter range under a negatively biased rule when $\tau_+ < \tau_-$, (c1).
Figure S4: Effects of STDP in more realistic network. The manipulations shown in Figure 4 were carried out in a more realistic network with parameters consistent with the structure of the hippocampal CA3 field. There was a total of 1000 neurons, 900 excitatory and 100 inhibitory, with 5% divergence and a uniform distribution of delays between 1 and 10 ms. Half of the excitatory neurons were regular spiking (RS, \( a = 0.02, b = 0.2, c = -65, d = 8 \)) and the other half were intrinsically bursting (IB, \( a = 0.02, b = 0.2, c = -55, d = 4 \)). All inhibitory neurons were fast spiking (FS, \( a = 0.1, b = 0.2, c = -65, d = 2 \)). All three populations were further diversified by perturbing the parameters controlling neuronal dynamics by Gaussian noise with standard deviation of 2.5% of the corresponding means. A balanced STDP rule with \( A_+ = A_- = 1, \tau_+ = \tau_- = 20 \text{ ms}, \tau_{stdp} = 1 \text{ s} \) was used under nearest-neighbor implementation. Inhibitory connections were not plastic and were set to \( s_{\text{max}} = -10 \). The system was driven by 1 Hz uncorrelated Poisson inputs modeling spontaneous activity. (a) The time evolution of the mean weight for all excitatory-to-excitatory connections is shown in red and for all excitatory-to-inhibitory connections in gray. The order parameter based on the activity of all RS cells is displayed in blue and all IB cells in black. (b-d) Five second rasters of spikes illustrating the patterns of network activity at select time points (arrows). Notice the rapid decoupling following the turning on of plasticity and the gradual transition into a mixture state, demonstrating qualitative agreement with the simpler system studied in Figure 4.
Figure S5: Evolution of $\langle s \rangle$ and $\psi$ under different STDP implementations. Evolution of the mean synaptic weight $\langle s \rangle$ (red trace) and order parameter $\psi$ (blue trace) in the same network as in Figure 4 (100 regular spiking neurons, 45% divergence, uniform distribution of delays between 1 and 20 ms, balanced STDP rule with $A_+ = A_- = 1$, $\tau_+ = \tau_- = 20$ ms, $\tau_{\text{stdp}} = 1$ s under four different STDP implementations: (a) all-to-all, (b) all-to-all with $\Delta t$ in the interval $(-5, 5)$ ms ignored, (c) all-to-all with spike suppression, $\tau_{\text{pre}} = 28$ ms, $\tau_{\text{post}} = 88$ ms, (d) nearest-neighbor. Notice the rapid decoupling in all cases as soon as STDP is turned on. All systems settle into mixture states, but the transition in (a-b) is associated with an undershoot in both $\langle s \rangle$ and $\psi$, in (c) the undershoot is only evident in $\psi$ and in (d) there is no undershoot.
Figure S6: Order parameter surface projections. (a) Side view and (b) top down view of the order parameter surface of Figure 5. Notice that the transitions from randomness to order become sharper as the connectivity $M$ increases and the inflection point $\langle s \rangle_c \to 0$. The mean weight and order parameter associated with steady state (colored dots) lie slightly to the left of their corresponding order transition curves, indicating that STDP can tune synaptic weights to produce more order than random weights with the same mean. Notice that in (b) most colored dots lie on the edge between the blue and the red regions, demonstrating that STDP adjusts the mean synaptic weight $\langle s \rangle$, so as to place most networks in the narrow transition regime between randomness and synchrony.
Figure S7: Origin of mixture states. (a) The level of synchrony in the system, reflected in the order parameter $\psi$, depends on the strength of the interactions between individual elements, reflected in the mean synaptic strength $\langle s \rangle$. At the two extremes of coupling the behavior of the system is intuitively obvious: (blue) $\langle s \rangle \to 0 \Rightarrow \psi \to 0$, no coupling implies absence of interactions and precludes the possibility of any emergent synchronization; (red) $\langle s \rangle \to \infty \Rightarrow \psi \to 1$, infinite coupling precludes the independent behavior of individual elements and implies total synchronization. What is striking is that in the networks described in this study the transition between randomness (blue) and synchronization (red) is very sharp (green) and can thus be characterized by some critical level of coupling $\langle s \rangle_c$ (black target). (b-c) When activity in the network is random (blue), $\langle s \rangle$ is controlled by weight diffusion and evolves toward the equilibrium value $\langle s \rangle_\infty$ (yellow target). When the system generates population bursts (green and red), a decoupling force is present pushing $\langle s \rangle$ toward 0. (b) When $\langle s \rangle_\infty < \langle s \rangle_c$, (yellow target lies within the blue region), $\langle s \rangle \to \langle s \rangle_\infty$ and random activity is the global attractor for the system. (c) In most cases $\langle s \rangle_\infty > \langle s \rangle_c$, (yellow target lies within the red region), under these circumstances weight diffusion pushes $\langle s \rangle$ outside the blue region, while the decoupling force pushes $\langle s \rangle$ outside the red region and as a result the system settles in the green mixture state region with $\langle s \rangle \approx \langle s \rangle_c$. In this example the mixture state is a global attractor of the system, but under nearest-neighbor implementations and certain asymmetric STDP rules, strongly coupled system can diverge into a highly ordered state.
**Figure S8: Rate dependence of decoupling force under nearest-neighbor implementation.** Maps of relative synaptic change for (a-b) two different STDP rules under nearest-neighbor implementation as a function of delay $\mu$, burst width $\sigma$, and burst firing rate: (1) 10 Hz (2) 20 Hz (3) 50 Hz (4) 100 Hz. The rules were (a) negatively biased with $A_+ = 1$, $A_- = 1.4$, $\tau_+ = \tau_- = 20$ ms, $\tau_{stdp} = 1$ s (b) negatively biased with $A_+ = 1$, $A_- = 0.5$, $\tau_+ = 13$ ms, $\tau_- = 35$ ms, $\tau_{stdp} = 1$ s. Unlike all-to-all implementations, the maps above are qualitatively different under different burst firing rates. In particular higher rates accentuate the central portion of the STDP rule and any asymmetries there get amplified. This implies that manipulations affecting the excitability of neurons or the balance of excitation and inhibition can make systems diverge from mixture states into highly ordered states, by changing the characteristics of the bursts associated with mixture states. This can explain the presence of persistent synchrony observed experimentally and clinically under certain circumstances.
Figure S9: Limited attractor basin of mixture state. The network of Figure 4 was studied under nearest-neighbor implementation of an asymmetric negatively biased STDP rule with $A_+ = 1$, $A_- = 0.5$, $\tau_+ = 13$ ms, $\tau_- = 35$ ms, $\tau_{stdp} = 1$ s. Depending on the initial value of the mean synaptic weight $\langle s \rangle$ (red and orange curves) the system decoupled (red curve) into the familiar mixture state with low order parameter $\psi$ (blue curve) or got further coupled (orange curve) into a high order state with $\psi \approx 1$ (cyan curve). Thus the mixture state is not a global attractor of the dynamics under these conditions and stable attractor characterized by persistent synchrony is also present.
Figure S10: Decay in pairwise firing rate correlations in SWS: Mean pairwise correlations based on (a) all activity, (b) activity during ripples only, (c) activity during inter-ripple intervals only. Each panel shows the results from 8 sessions (A1-4, B1-2, C1-2) recorded from 3 animals (A, B, C). In each panel the boxplots illustrate the sampling distributions $\langle r \rangle_i$, $\langle r \rangle_{Ri}$, and $\langle r \rangle_{II}$ for each dataset. The red triangles show the mean correlations obtained from the first halves of SWS epochs, $\langle r \rangle_1$, $\langle r \rangle_{R1}$, and $\langle r \rangle_{II1}$, and the blue triangles show the corresponding means from the second halves, $\langle r \rangle_2$, $\langle r \rangle_{R2}$, and $\langle r \rangle_{II2}$. A significant decay in correlations is present when the red triangles fall in the upper whiskers of their boxplots and the blue triangles fall in the lower whiskers underneath. Significance is indicated by an asterisk ($p < 0.05$). Notice that when activity during ripples only is considered (b), there is a decay in correlations, $\langle r \rangle_{R1} > \langle r \rangle_{R2}$, in all datasets and the difference is significant whenever the mean correlation is sufficiently high. When all activity is considered (a), the decay in correlations is statistically significant in all datasets, demonstrating that the decay in (b) is not an artifact of ripple identification. Finally, when activity in inter-ripple intervals only is considered (c), there is no decay in correlations, $\langle r \rangle_{R1} \approx \langle r \rangle_{R2}$, except for B1.
**Figure S11: Role of causality and temporal order within bursts:** The left side of each panel depicts two neurons, labeled 5 and 6, as well as their inputs within a recurrent network consisting of six neurons, labeled 1 through 6. On the right are spike rasters (cell 1 on top) showing the order of cell firing within population bursts. (a,b) Two different spontaneous bursts are considered and the synapses causally responsible for firing cells 5 and 6 are marked with circles on the left. Notice that in (a) neurons 1 and 2 make neurons 5 and 6 fire and only 4 out of the 10 synapses displayed are causally responsible for the burst generation. Consequently only these four synapses will be potentiated, while the remaining 6 synapses will be de-potentiated as a result of this burst. In contrast, in (b) it is neurons 3 and 4 that make 5 and 6 fire and the sets of synapses that will be (de)-potentiated are different. In both cases more than half of the input synapses to 5 and 6 will be weakened, i.e. 2 out of 5.