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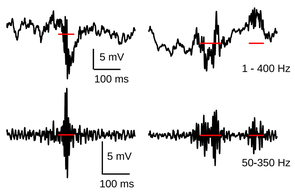
Hippocampal Ripples as Inhibitory Transients

Introduction

Sleep is known to be important for memory consolidation, and memories are thought to be stored in the hippocampus during the wakefulness and "transferred" to cortex during sleep. Recently, memory replay – repeatable sequences of pyramidal cell firing – has been demonstrated during sleep, and associated with characteristic brain oscillations, giving rise to the hypothesis that these may form the critical neural substrate of memory consolidation. Tampering with replay can disrupt memory formation and consolidation, and the mechanisms underlying sequence replay are still unknown.

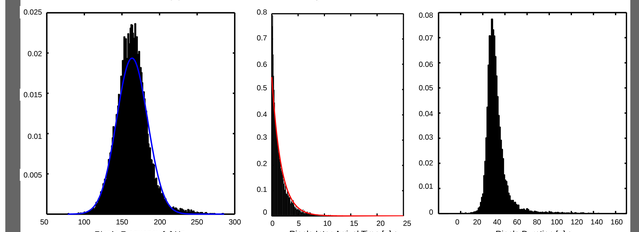


CA1 ripples LFP recordings.

During sleep, replay events are associated with specific patterns of neuronal activity. Replay is seen in cortex during sleep oscillation – a rhythmic (< 1Hz) state in which periods of activity (active or Up states) alternate with quiet periods (silent or Down states), while replay in the hippocampus is associated with sharp-wave ripple events – irregularly brief bouts of high frequency (>150 Hz) firing. It is believed that hippocampal ripples may contribute to the cortical active state generation, however specific interactions between ripples and slow oscillation remain unknown. In the present study, we develop a model of ripple generation to explore interaction between cortical slow oscillation and hippocampal ripples during sleep.

Ripples have many shapes, but only one duration

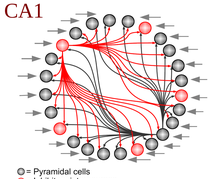
- Ripples are identified by large amplitude excursion of the band-passed LFP.
- Frequencies are quantified as the inverse of the average peak-to-peak time within a ripple event
  - Ripple frequency is normally distributed around ~170Hz
  - Ripple inter-arrival times are approximately exponential, with rate ~1.77Hz
  - The distribution of ripple durations shows high kurtosis around a mean of ~60ms

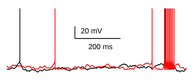


Ripples are very different in frequency and have non-rhythmic arrival times, but their duration is rather stereotyped.

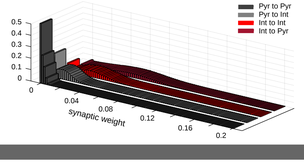
Computational Model of CA1

- Adaptive Exponential Integrate-and-fire model neurons
- Heterogeneity: each neuron receives independent Ornstein-Uhlenbeck noise and a mean DC current
- Fast synaptic time scales
- All-to-all connectivity, with very few and weak Pyr-to-Pyr synapses
- Network: 800 Pyr cells, 160 Int cells.
- Input from CA3 localized in time, with different magnitudes for Pyramidal cells and Interneurons

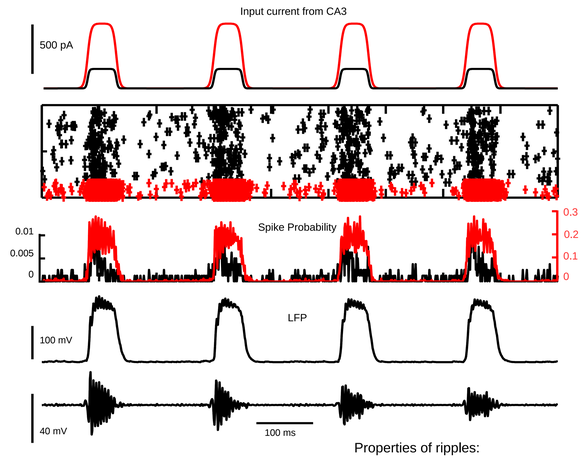




$$C\dot{v} = -g_L(v - E_L) + g_L\Delta\exp((v - V_t)/\Delta) - w + I(t)$$
$$\dot{w} = (a(v - E_L) - w)/\tau_w$$
$$v(t) = V_{thr} \Rightarrow v(t + dt) = V_{reset}$$
$$w(t + dt) = w(t) + b$$
$$I(t) = I_{DC} + \beta\eta_t + I_{syn}(t) + I_{inp}(t)$$
$$\tau\, d\eta_t = -\eta_t dt + dW_t$$
$$I_{inp}(t) = \left(1 + \exp\left(-\frac{t - t_{on}}{k}\right)\right)^{-1}\left(1 + \exp\left(\frac{t - t_{off}}{k}\right)\right)^{-1}$$



Model of Ripple Activity



In the Model:

- CA3 input is higher on Int (red) than on Pyr Cells (black).
- Interneurons show oscillatory behavior.
- LFP computed averaging across all Pyramidal Cells their incoming synaptic currents.
- Band-passed LFP filtered (50-350Hz).

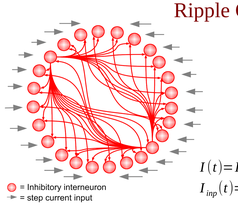
Properties of ripples:

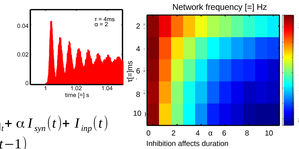
- Ripple frequency ~180Hz
- Ripple duration ~60ms

Properties of Pyramidal Cells during a ripple:

- ~15% of Pyramidal cells spike
- Each Pyramidal cell spikes once
- Pyramidal cells tend to fire before Interneurons

Ripple Oscillation Mechanism





$$I(t) = I_{DC} + \sigma\beta\eta_t + \alpha I_{syn}(t) + I_{inp}(t)$$
$$I_{inp}(t) = k\, Heav(t - 1)$$

τ = decay time scale of inhibitory synapses
σ = scaling of noise size
α = scaling of synaptic input

Purely inhibitory network:

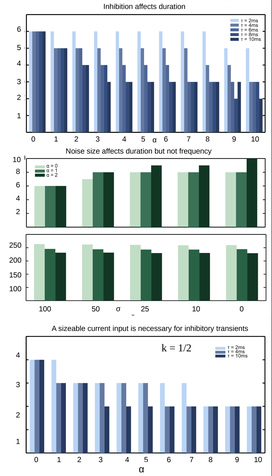
- Common input organizes initial network firing.
- Intrinsic noise promotes de-synchronization.
- Synaptic currents
  - promote synchrony if enough synaptic inputs are aligned
  - propagate de-synchronization if enough neurons are asynchronous

We find that:

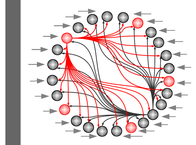
- Oscillation frequency and duration depend on size of inhibitory currents
- Frequency stays within ripple ranges for τ up to 6ms if synapses are weak.
- Noise size controls duration, but not frequency.
- Initial portion of synchronized neurons is crucial for transient occurrence.

Synchronous input organizes transient oscillatory patterns.

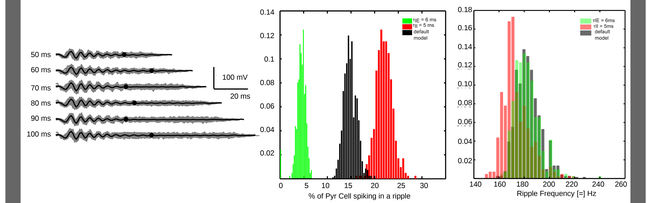
Triggering a transient oscillation is a "faster than gamma" property.



Model Predictions



- Ripple duration independent of duration of ripple-trigger depolarization events in CA3
- Ratio of CA1 Pyr cells recruited in a ripple is modulated by both excitatory drive from CA3 and inhibitory currents within CA1
- Increasing τ onto Int vs onto Pyr Cells has competing effects on Pyr Cell recruitment
- Ripple frequency is not strongly modulated by τ



With every ripple, CA1 produces a stereotyped "package" of information to project downstream.

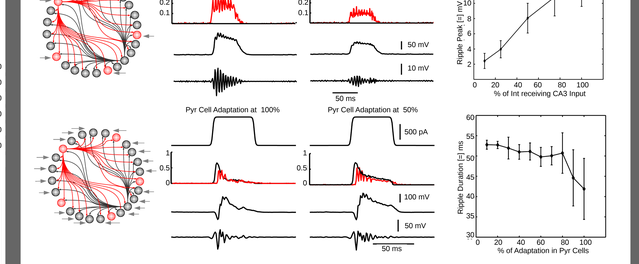
Within this package, Pyramidal cells spiking is organized by selectivity of CA3 input more than local inhibitory mechanisms.

If only Interneurons receive CA3 input,

- oscillations show a much reduced amplitude.

If only Pyramidal cells receive CA3 input,

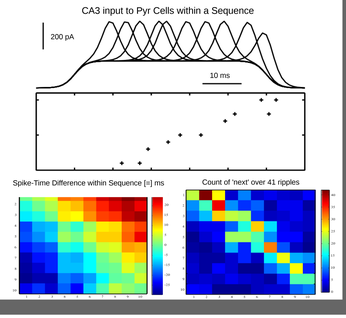
- Both population firing probabilities decay in time.
- The high frequency event quickly (<30ms) defaults to a gamma frequency oscillation.
- Spike-frequency adaptation in Pyramidal cells regulates the duration of HFO



Driving only Pyramidal cells or only Interneurons does not lead to ripple oscillations

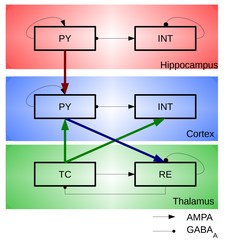
CA1 inherits and refines CA3 sequential activation

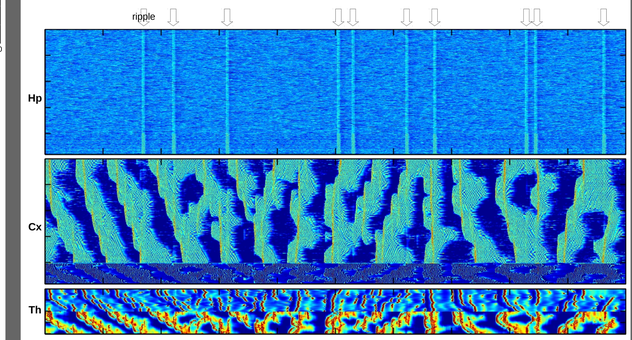
- Topologically organized CA3 input to CA1 induces sequential activation of some CA1 Pyr cells during ripple activity.
- Plastic synapses between CA3 Pyr Cells and CA1 Pyr Cells enhanced by learning.
- Sequential reactivation in CA3 gives rise to refined sequential activation within CA1 ripples.



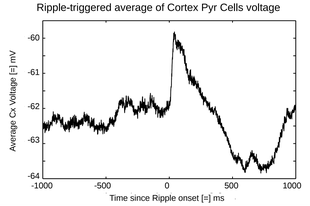
Ripple Input to Cortex during Slow-Wave Sleep affects Timing of Up-Down state transitions

- Previously developed Thalamo-Cortical model of Slow-wave sleep
  - Cortex: 200 Pyr, 50 Int. Thalamus: 50 TC, 50 RE.
- CA1-to-Cortex functional connectivity:
  - CA1 Pyr to Cortex Pyr.
- Following a Ripple event, Cortical Pyr Cells are more likely to be depolarized
- Framework where sequential cell activation during ripples can be mirrored by Cortex





SWS Activity of Thalamo-Cortical model with Hippocampal Input



In the open-loop configuration, a ripple is likely to initiate/prolong an UP state

Conclusions

- In vivo ripples have broad frequency distribution and very stereotyped duration.
- We design a model of CA1 ripple generation in which synchronization of inhibitory neurons is due to common input from CA3. In the model:
  - Activity of inhibitory interneurons regulates the windows of opportunity for pyramidal cells to spike.
  - Ripple frequency and duration depend on CA1 architecture
  - Phase-dispersion induced by noise constrains the duration of a ripple event
  - Sequential activation of pyramidal cells is directly derived from CA3 input.
  - Hence, CA1 optimizes CA3 output for downstream transmission.
- In a preliminary, open-loop configuration, ripple input biases cortical UP states during slow oscillations

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