Probabilistic Modelling Improves Burst Detection in Thalamic Cells and suggests that non-REM Sleep Correlations are largely due to Bursting.

Summary. The oscillations of non-REM sleep (slow and spindle oscillations in thalamocortical networks, ripples in hippocampus) organize a hippocampo-necortical dialogue that leads to the consolidation of episodic memories (Buzsaki 1996; Wilson et al., 2015; Penagos et al., 2017). Specifically, the cycles of spindles coordinate the occurrence of ripples in the hippocampus and the spiking of thalamocortical cells (Sirota et al., 2003; Peyrache et al., 2011; Yang et al., 2019; Varela & Wilson, 2019). Spiking in the thalamus could thus help integrate recent memories into neocortical networks. Thalamic cells fire in two modes, burst and tonic; although bursts predominate during resting states, both tonic and burst firing are observed during sleep, and have been suggested to contribute to spindle generation (Steriade, 1994; Lee et al., 2013). We sought to investigate the firing patterns and cell population dynamics that organize thalamic firing during spindles. We have developed a model-based algorithm that improves the detection of bursts in thalamic cells, and used it to investigate the firing patterns (burst versus tonic) underlying the correlations between cells in the midline thalamus during natural non-REM sleep. Our preliminary results indicate that cells in the thalamus are sparsely active during sleep and that their pairwise correlations are dominated by bursting. This suggests that memory reactivation in CA1 occurs in a background of thalamic inhibition that correlates with sparse co-activation of bursting thalamocortical cells.

Additional Details

Methods: We analyzed the correlations of 17 single unit pairs simultaneously recorded in midline nuclei of the dorsal thalamus (reuniens, n = 6 pairs; VM = 4; PT/AM border = 4; MD = 1; CM = 1; VL = 1). Extracellular recordings were performed in freely behaving Long Evans rats implanted with tetrodes in these thalamic nuclei, medial prefrontal cortex (mPFC) and in CA1.

We used a Gaussian Mixture Model (GMM) clustering algorithm to model the distribution of inter-spike intervals (ISIs) during sleep and classify spikes as bursts. GMMs were fitted to each unit individually. Initial parameter values for the models were provided from bursts detected using a fixed ISI criterion (70 ms ISI followed by 5 ms).

Result 1. Co-modulation of Thalamic Units during non-REM Sleep: We first calculated auto-correlograms for each single unit and found that none had peaks that would indicate rhythmic firing (Fig. 1A). We then calculated the cross-correlograms of spikes in 17 pairs of units and found that 7 of them (or 41 %) showed a peak (Fig. 1B) that suggested a co-activation of both units within 50 ms of each other, within the timeframe of spindle cycles. Furthermore, the cross-correlogram peaks are also seen when selecting spikes that occur during

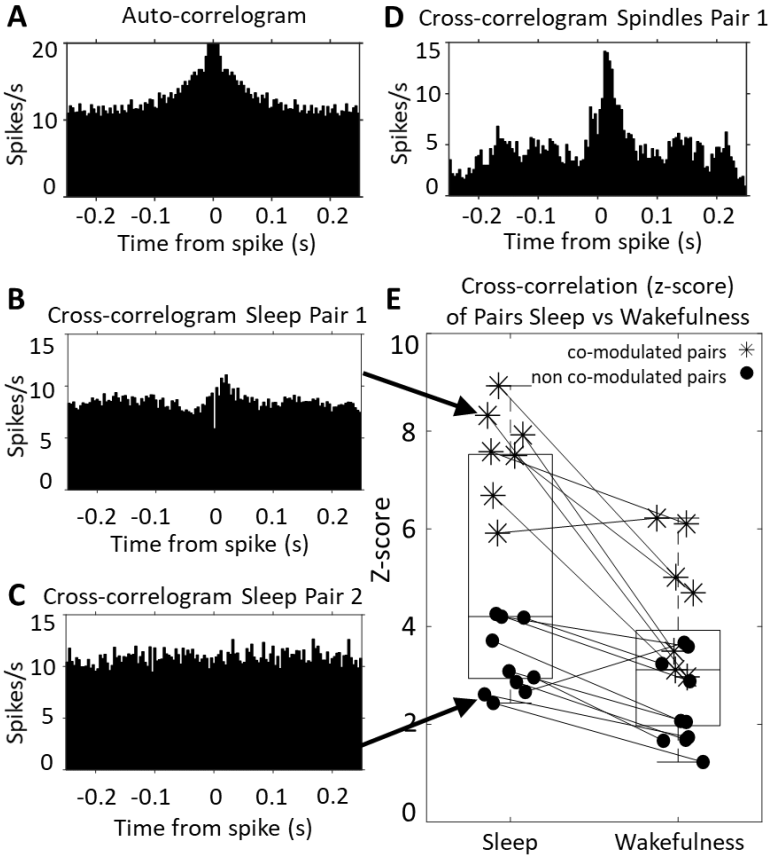

Figure 1: (A) Auto-correlogram of spikes from one thalamic unit during sleep showing no rhythmic firing at spindle frequency. (B) Cross-correlogram of spikes from a pair of units showing increased co-modulation within 50 ms. (C) Cross-correlogram of spikes from an uncorrelated pair. (D) Cross-correlogram showing increased co-modulation when using only spikes during spindles for units in B. (E) Z-score of peaks is higher for 7 out of the 17 pairs during sleep. We refer to these pairs of units as co-modulated pairs. The z-score goes down during wakefulness and this decrease is most substantial for the comodulated pairs.

detected spindle cycles (Fig. 1D), suggesting a functional correlation with the spindle oscillation. To quantify the observed peaks, we z-scored the peaks of the cross-correlogram (Fig 1E) with respect to a shuffled distribution obtained by randomly shifting the two spike trains (by 1-5 s). Seven pairs of units had a higher z-score during sleep compared to rest of the pairs, suggesting that subsets of thalamic cells are selectively correlated during rest. We then explored the firing modes underlying the observed correlations.

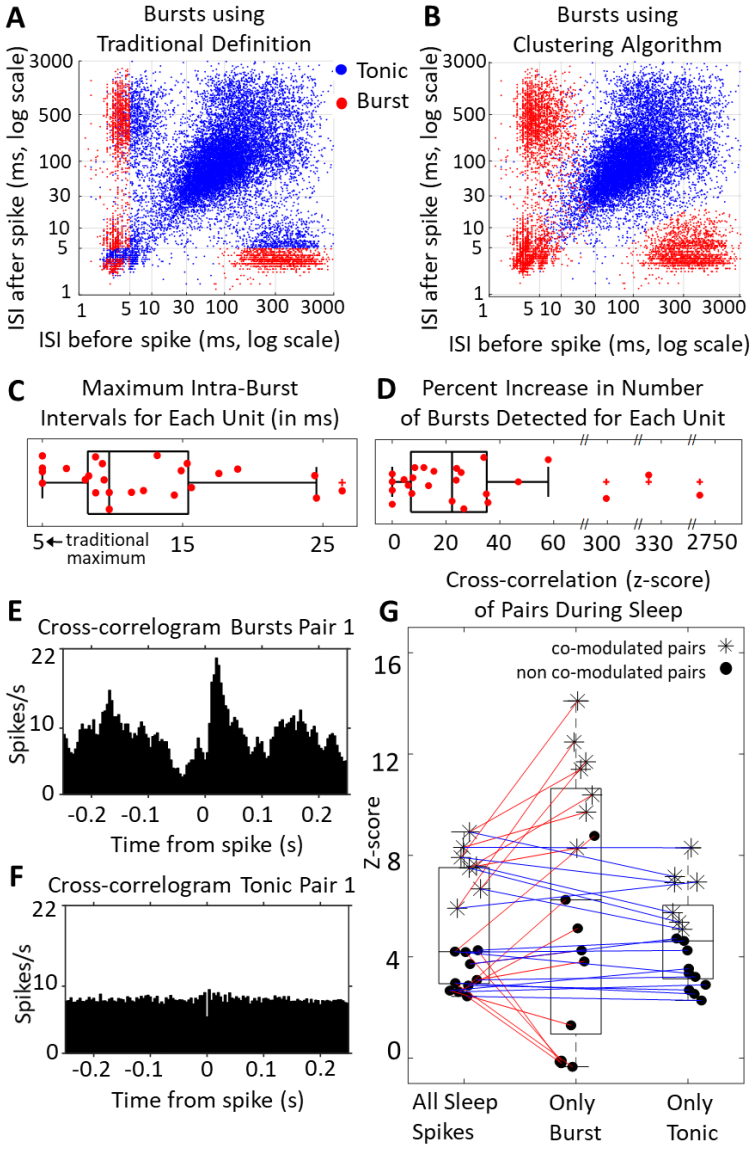

Figure 2: (A) Spikes classified as bursts (red dots) and tonic (blue) using fixed, standard, criterion. (B) Spikes clustered as bursts based on inter-spike interval (ISI) GMM distribution. (C) Distribution of the minimum intra-burst spike intervals, found using GMM clustering method, extend to a higher range than those found with the traditional definition of 5 ms. (D) Distribution of percent increase in number of new bursts for all units. (E) Cross-correlogram using only burst spikes from a pair of units shows a more distinct peak compared to sleep. (F) Cross-correlogram using only tonic spikes for the same pair of units shows no peaks, indicating that the co-modulation occurs only when both units are bursting. (G) The sleep cross-correlation (each dot one pair) tends to increase during bursting (red) and remains constant or decreases during tonic mode (blue).

Result 2. Sleep co-modulation largely due to bursting: Thalamic cells can fire in two modes, burst or tonic. Bursting is more frequent in resting states like sleep, when thalamic cells are thought to be hyperpolarized, which de-inactivates the T-current responsible for burst firing.

Thalamic burst detection is commonly based on a fixed classification of ISIs: spikes are termed as bursts if they are preceded by quiescence for ≥ 70 ms and intra-burst intervals are ≤ 5 ms (Lu et al. 1992). However, burst firing has been less studied outside of sensory thalamic nuclei, and it is possible that the bursting properties are different in the midline. In fact, we find that applying this fixed criterion artificially crops clusters in the ISI plots and misses many bursty spikes (Fig. 2A). Therefore, we developed a data-driven burst detection algorithm that takes into account each unit's ISI distribution. We used a Gaussian Mixture Model (GMM) to find the bottom right cluster in the ISI plot (which contains the first spike in bursts), which, along with the newfound maximum intra-burst ISI, was used to find the remaining spikes in bursts (Fig. 2B). In 25 units this new method increased the number of detected bursts by a median of 22 % (Fig. 2D). The minimum quiescence period before bursts in these units lies between 41-675 ms (median = 73.49 ms) and maximum intra-burst interval lies between 5-26 ms (median = 9.76 ms). These results suggest that traditional methods are not sufficient to capture burst spikes and that burst characteristics are highly variable among the cells of the midline thalamus.

The 7 pairs of co-modulated units showed stronger peaks in their cross-correlograms when only burst spikes during sleep are included in the analysis (Fig. 2E, same units as in 1B), as demonstrated by the increase in the peak z-score (Fig. 2G, red lines). Contrarily, the cross-correlogram of tonic spikes during sleep does not show a peak (Fig. 2F, Fig. 2G, blue lines). These results suggest that the co-modulation we observe between a subset of the thalamic units occurs prominently when they are in burst mode i.e. when they are inhibited.