Propagating Densities of Spontaneous Activity in Cortical Slices

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Slow Oscillations (SO) as The Default Activity Pattern of the Cerebral Cortex [1]

Phenomenology

- Multiscale Slow Oscillations (≲1Hz):
  - from the neuronal level, to the whole brain (slow waves), through the **local network level**.
- Emergent activity under functional disconnection:
  - NREM sleep, deep anaesthesia or **cortical slices**

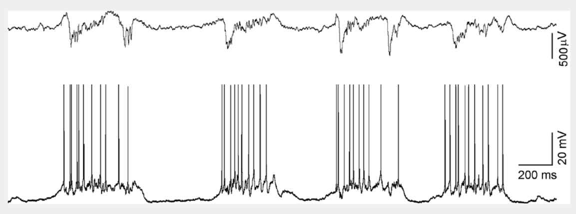

Figure 1: Simultaneous LFP (**top**) and intracellular (**bottom**) recordings from the auditory cortex of the anaesthetized rat, exhibiting slow oscillations [2]

Key Dynamical Features

- Relaxation-oscillator behaviour:
  - Intrinsic fluctuations between two alternating metastable attractors: **UP and DOWN states**.
- Spatio-temporal propagation:
  - The travelling **UP/DOWN wavefront** reveals properties of the underlying network.

Advantages of the SO Cortical State

- Low Connectivity: resilience to perturbances.
- Facilitation of the transition towards more connected, awake-like states (AS).
- UP States: Model of circuit attractor implementing computation and acting as a window into conciousness.

→ **SO is a promising paradigm to study the cortical function and the emergence of conciousness.**

Motivation

- *Can we detect other network states emerging from the SO regime?*
- *Candidates:*
  - *Nested substates within the SO regime (is there only one single type of UP state?)*
  - *States which emerge when the UP/DOWN regime ebbs away.*

Experimental Model and Cortical Slice Recordings

Extracellular recordings in coronal cortical slices of the ferret's primary visual cortex

From SO to an Awake-Like State (AS) [3]

Pharmacological Modulations

- addition of Carbachol (0.5 μM) + Norepinephrine (50 μM)
- reduction of extracellular Calcium (to 0.8-0.9 mM)

→ Experimental model to explore the transitions from the SO state towards an awake-like, largely asynchronous state: emulating the transition from unconciousness to consiousness.

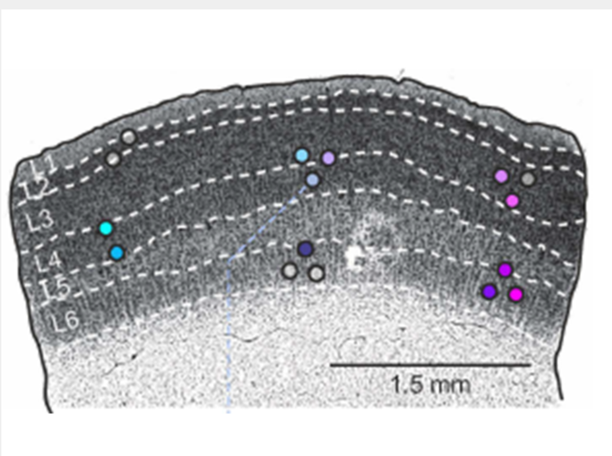

Figure 2: Nissl-stained ferret's V1 cortical slice depicting cortical layers and the location of the multi-electrode array. Electrodes will ideally lie on different layers (supra- and infra-granular), across different cortical columns [4].

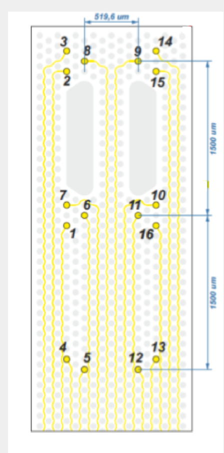

Figure 3: 16-channel flexible multi-electrode array used for the recordings [5].

LFP and MUA

Extracellular Recordings are usually decomposed into Local Field Potentials (LFP) and Multi-Unit Activity (MUA):

- LFP results from afferent neuronal activity (e.g., from the summation of EPSP), as captured by the low-frequency band (<200Hz) of the extracellular recordings.
- Only units in the vicinity of the electrode contribute to the MUA (i.e., efferent activity), represented in the high frequencies of the recording.

Estimating the MUA

Theoretical motivation: high-frequency spectral components of the population firing rate are asymptotically proportional to the individual firing rates of the neurons involved [6].

→ The MUA may be estimated as the relative power change of the high frequencies (200-1500 Hz) of the extracellular recordings [7].

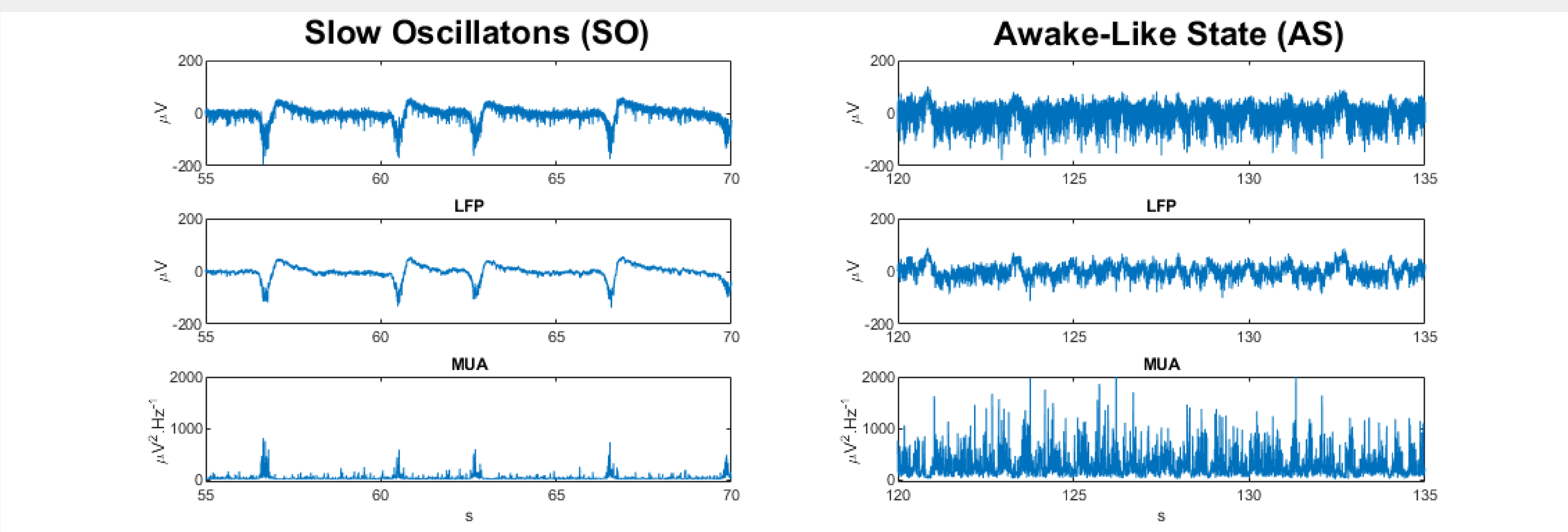

Figure 4: Signals obtained from a sample extracellular recording of an infra-granular electrode in the same cortical slice. **Left:** during the SO regime. **Right:** during the Awake-Like (AS). Note the change of magnitude order over the MUA signals.

Measuring the Evolution of Locally Estimated Densities

Neuronal Network State ≡ MUA's Probability Density.

(Working Definition for Network State)

→ **When estimated from different electrode groups, with varying time baselines, densities reflect different spatial and temporal scales.**

Kolmogorov-Smirnov time-series (KSts). For a set of channels $C = \{c_1, \ldots, c_p\}$, consider f_T^C, the estimated probability density of the values taken by the signals $X_t^{c_i}$, $1 \leq i \leq p$, altogether, over a period T of length h.

- Temporal evolution of these densities to be measured by their relative change against a static density $f_{T_0}^C$, estimated over a baseline period T_0.
- The time-series K_τ^C is defined in a suitable sub-sampling set, as the KS statistic between the evolving and the static densities.

$$K_\tau^C := d_{KS}(f_{T_0}^C, f_{T_\tau}^C), \qquad (1)$$

where T_τ is an interval of length h, containing τ.

→ Acts as a spatio-temporal filter that is distribution-free.

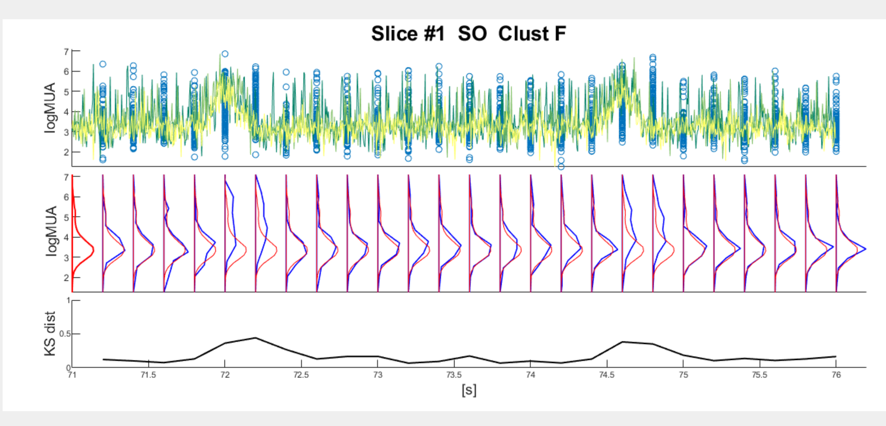

Figure 5: Example of KS-timeseries computation for 3 channels from the same node during SO. **Top:** log(MUA) signals of distinct channels superposed (green hues); values taken during the sample period (blue dots) **Middle:** estimated densities (blue) superposed to the baseline static density (red). **Bottom:** KS-timeseries.

Spatial Clustering of Multi-Unit Activity Densities

Static Densities

Density estimation during long baseline periods (≥ 300 s) offers a static spatial image of the network.

- SO's static densities are a mixture of DOWN- and UP-states' densities.
- Whilst SO are dominated by DOWNs' subdensities, very similar across channels, UPs' exhibit a richer variety, which depends on their cortical location.
- Differences between groups of electrodes on different layers tend to increase in the AS condition, namely for IG-layer's signals.
- Interestingly, UP-densities' variability prefigures AS's.

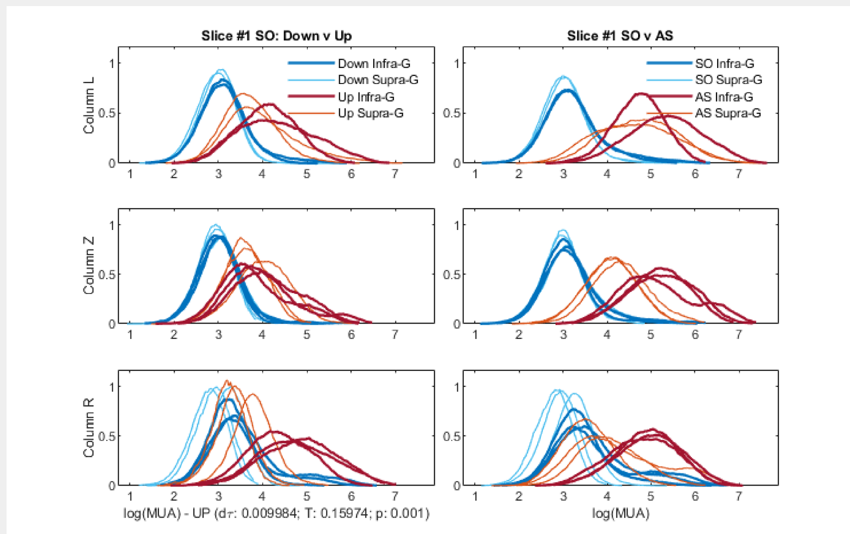

Figure 6: MUA's static densities comparison across electrode groups (by column and layer position). **Left:** within SO for two states (Down and Up). **Right:** for two distinct regimes (SO and AS)

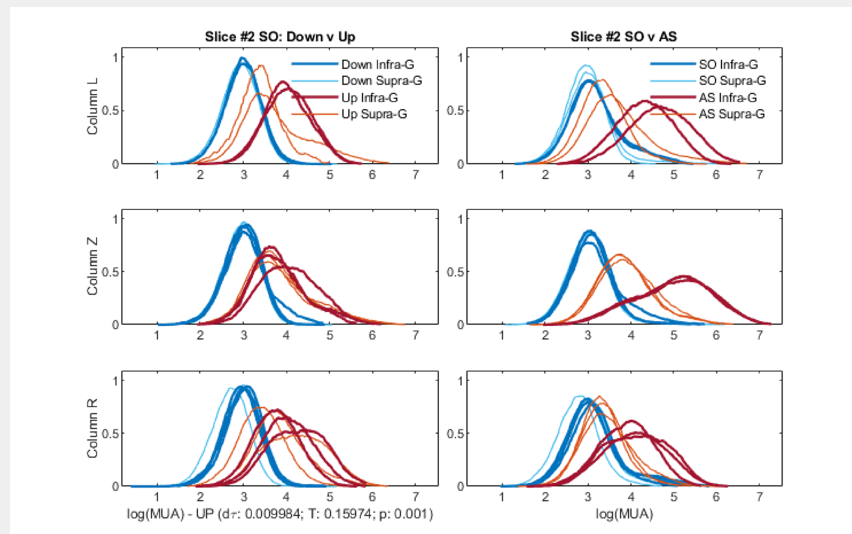

Figure 7: Same as *fig 6* for a different slice. Inasmuch as the position of the MEA may slightly vary from one preparation to another, so the actual layer-relative location of the electrodes cannot be ascertained *a priori*.

Densities' Spatial Clustering

Electrode grouping: hierarchical cluster analysis of the MUA densities over a long baseline period.

- Clusters are farer apart in the AS condition than in the SO's.
- AS's clusters tend to be organised longitudinally, according to alleged cortical layers.
- UP's clusters lie on a deformation path between SO's and AS's.

→ The clustering of high-activity states (UPs and AS) seems to reflect the laminar structure of the slice.
→ UP-states activity anticipates the awake-like state.

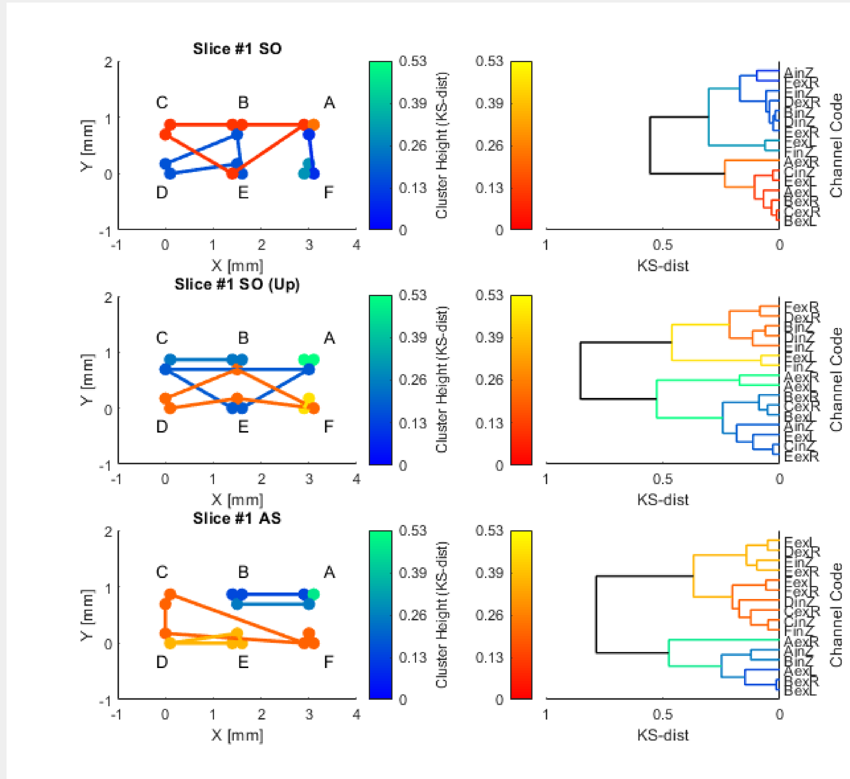

Figure 8: Hierarchical clustering of static densities' similarity. Comparison for individual slices under different regimes (**top:** SO (overall), **middle:** SO (Up), **bottom:** AS). Groups of similar static densities are outlined.

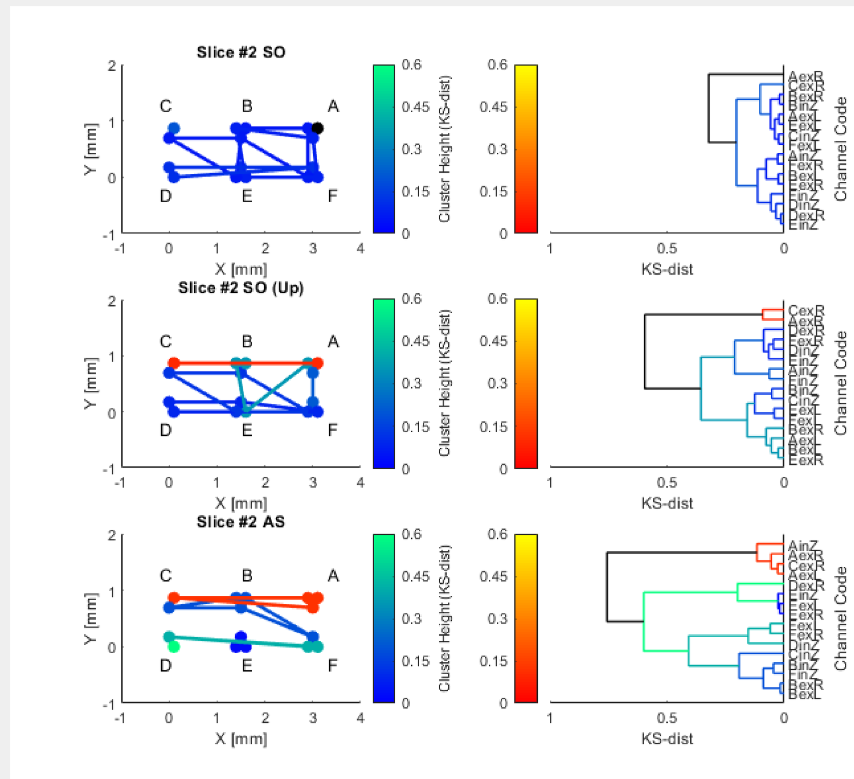

Figure 9: Same as *fig 8* for a different slice. **Right:** Dendrograms exhibiting clusters distances. **Left:** Schematic projection of the dedrograms onto MEA. Letters refer to nodes of electrodes in the MEA.

A Glimpse on the Spatio-Temporal Propagation of MUA Densities

Unified analysis of the MUA's spatio-temporal evolution under different dynamical regimes: in absence of wave-front (AS) and poorly stationary signals (SO).

SO: a whimsical propagating wave

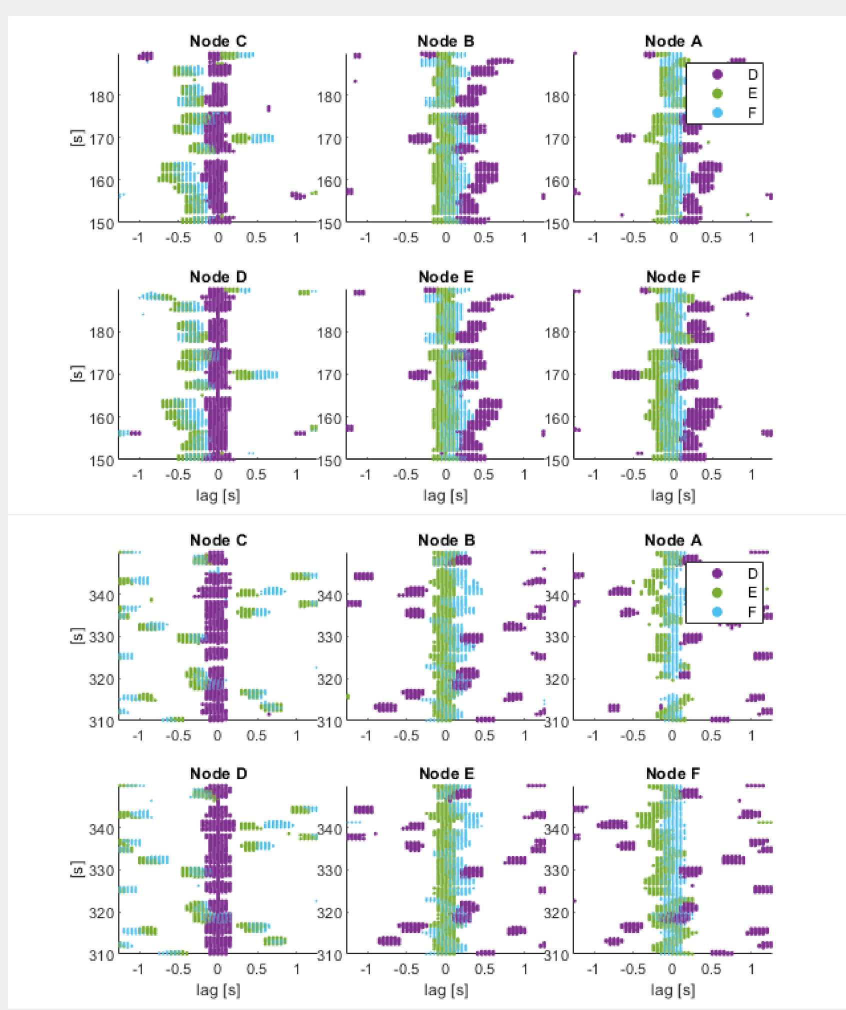

Figure 10: Merged cross-correlograms of KSts during SO, at two different epochs from the same slice as (*figs 6&8*). Colours represent target nodes **D**, **E** and **F**.

AS: ephemeral coordinated activity arises amid asynchrony

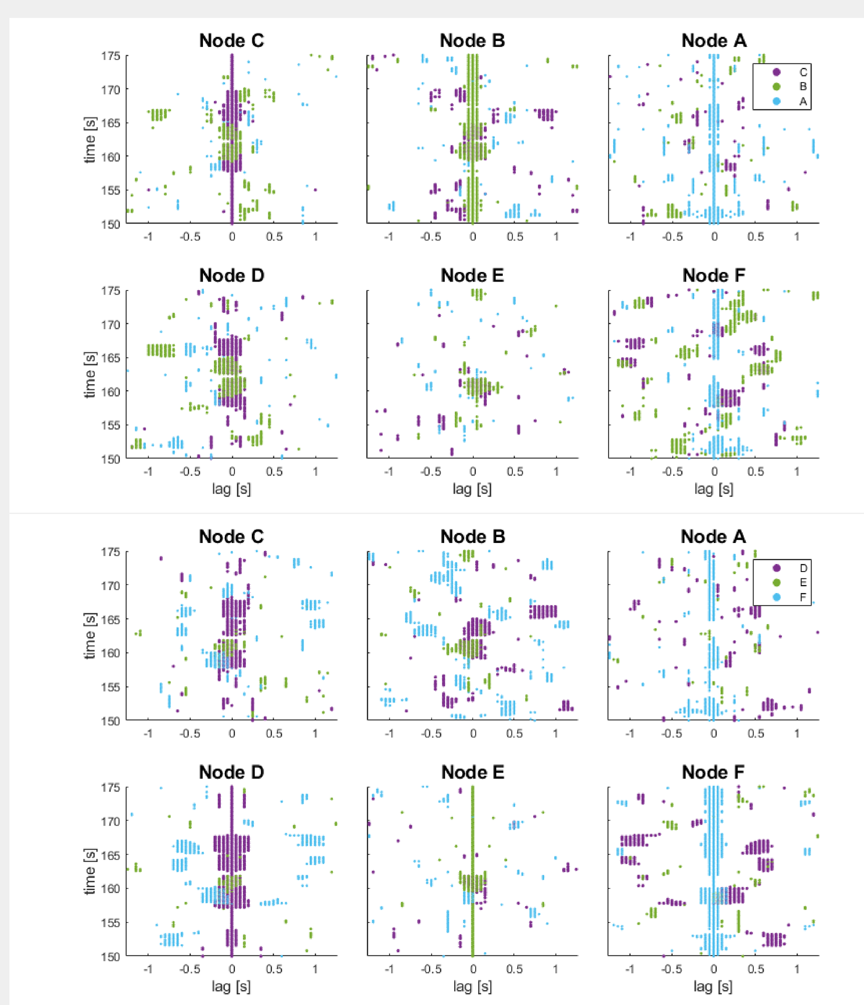

Figure 11: Merged cross-correlograms of KSts during AS for the same slice as *fig 10*, for two sets of target nodes for the same epoch.

- All the nodes exhibit sustained SO, but not all do engage equally in the UP-front propagation, nor in the same order (*fig 10*).
- A general regime of asynchrony prevails during the AS, were not for the occurrence of some UP-like bursts of activity (*fig 11*).
- Columnar connectivity (from infra- to supra-granular) seems still favoured in AS.
- Some evidences of slower long-range connectivity of integrated activity during the AS.

References

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