HARMOnic miNImization (Harmoni): a Novel Method for Discrimination of Genuine vs Spurious Neuronal Interactions in M/EEG Recordings

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Introduction

- Phase-phase synchronization (PPS) has been hypothesized to represent a mechanism through which spatially distributed information can be integrated in the brain.
- PPS underlies not only spatially but also spectrally distributed interactions through cross-frequency coupling (Fig. 1).

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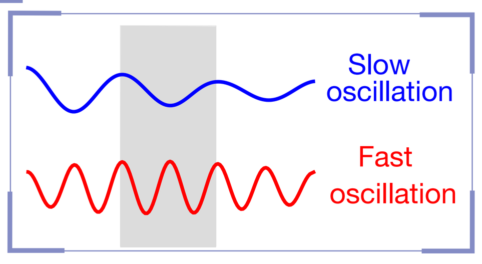

Cross-frequency synchronization(CFS)

- Connecitvity analysis of MEEG data suffers from observeation of spurious interactions.
- The non-sinusoidal shape of brain oscillatory activities is one of the main reasons of the obseervation of spurious within- and cross-frequency interactions (Fig. 2).

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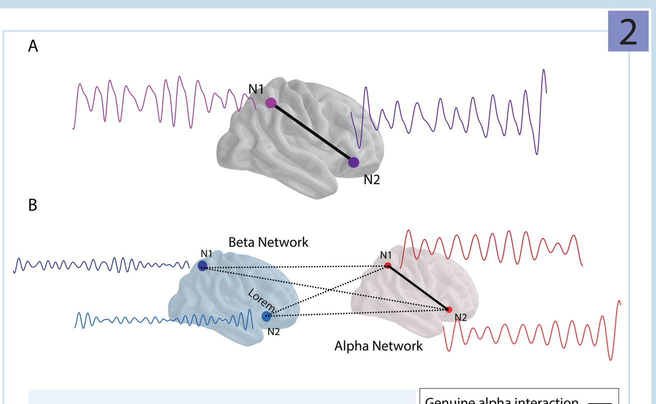

The spurious interactions (in panel B) resulted from coupling of two non-sinusoidal shaped source signals.

Signals with Nonsinusoidal waveforms

- The Fourier analysis decomposes a periodic, non-sinusoidal signal into its harmonic components (Fig. 3-A).
- The central frequencies of the higher harmonics are integer multiples of the fundamental frequency (Fig. 3-B).
- These harmonic components are – by construction – CF phase-synchronized to the fundamental component (Scheffer-Texeira and Tort, 2016) (Fig. 3-C).

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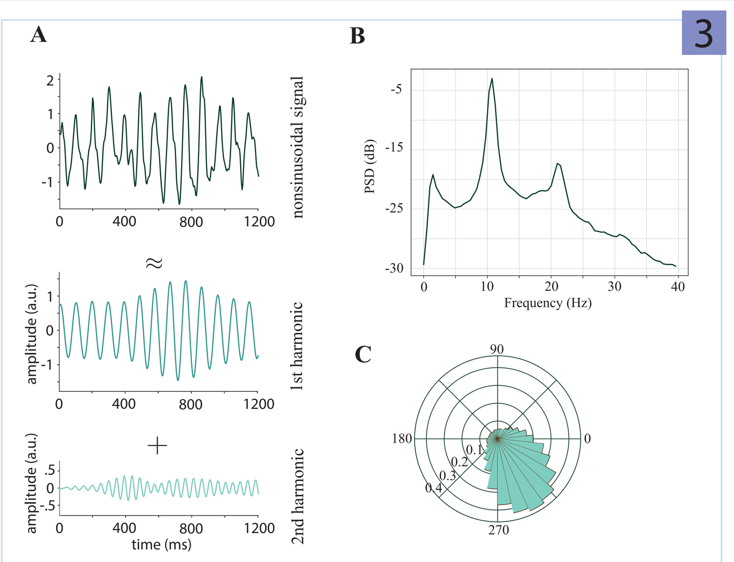

(A) a non-sinusoidal shaped signal with its harmonics. (B) The PSD of the signal in A, with two peaks at the first and second harmonics. (C) The distribution of the weighted phase difference of the two harmonics.

Harmoni

- Assume two time series x(t) and y(t) in frequency bands f_0 and nf_0 respectively. We propose HARMOnic miNImization (HARMONI) as an algorithm which regresses y(t) on x(t) by minimizing the 1:n synchronization of the residuals of y(t) and x(t).
- The idea of Harmoni is that if there are components at frequency nf_0 that are harmonics of a signal with non-sinusoidal waveform, the phase information of the harmonics should be present at f_0.
- Harmoni is based on accelerating x(t) for making its frequency content n times faster (called phase-warping in Fig. 4), and hen regressing y(t) on it.

4 Grid-search Algorithm for Harmoni

Input : Signal $x(t) \in \mathbb{C}$ centered at f_0
Signal $y(t) \in \mathbb{C}$ centered at nf_0
Output: $y_{corr}(t) \in \mathbb{C}$

$x_n(t) = |x(t)| e^{jn\angle x(t)}$ // phase-warping of x
$x_n(t) = x_n(t)/std(Re(\mathbf{x}_n))$ // normalize the power
$\tilde{y}(t) = y(t)/std(Re(\mathbf{y}))$

for $c = -1$ **to** 1 *with steps* δc **do**
  for $\phi = -\pi/2$ **to** $\pi/2$ *with steps* $\delta\phi$ **do**
    $y_{res}(t) = \tilde{y}(t) - c x_n(t) e^{j\phi}$
    $plv_{c,\phi} = PLV(\mathbf{y}_{res}, \mathbf{x}_n)$

$c_{opt}, \phi_{opt} = \underset{c,\phi}{argmin}\; plv_{c,\phi}$ // find the minimum
$\tilde{y}_{corr}(t) = \tilde{y}(t) - c_{opt} x_n(t) e^{j\phi_{opt}}$
$y_{corr}(t) = \tilde{y}_{corr}(t).std(Re(\mathbf{y}))$ // set the power of y

Results

- We extensively tested Harmoni with realistic EEG simulations using forward and inverse modelling.
- Sinusoidal and non-sinusoidal source signals were simulated in the range of alpha dn beta frequency bands. The non-sinusoidal signals are simulated as superposition ofsynchronized alpha and beta signals.
- The sources were simulated coupled to each other, producing genuine and spurious interactions. The simulation scenarios are depicted in Fig. 5.
- Using an ROC analysis, the within- and cross-frequency connectivity matrices were compared before and after applying Harmoni on beta-band source-space data.

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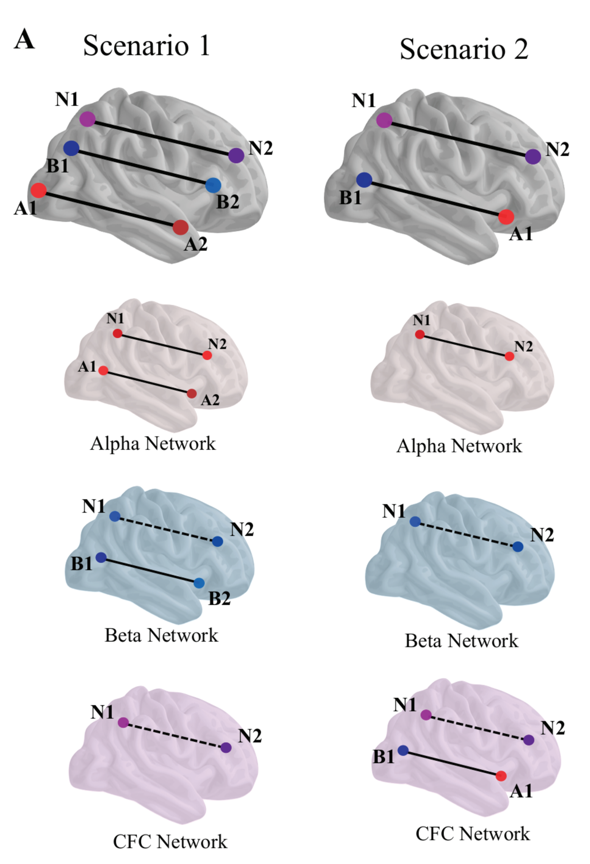

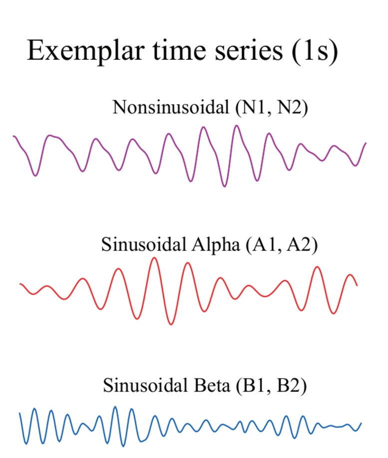

Realistic simulation scenarios. (A) The top schemes show the simulated couplings. The three smaller, colored brains show schemes of expected connectivity in each frequency band. While solid lines represent genuine coupling, the dashed lines show spurious coupling due to waveshape of the source signals. (B) examplar time series of the source signals.

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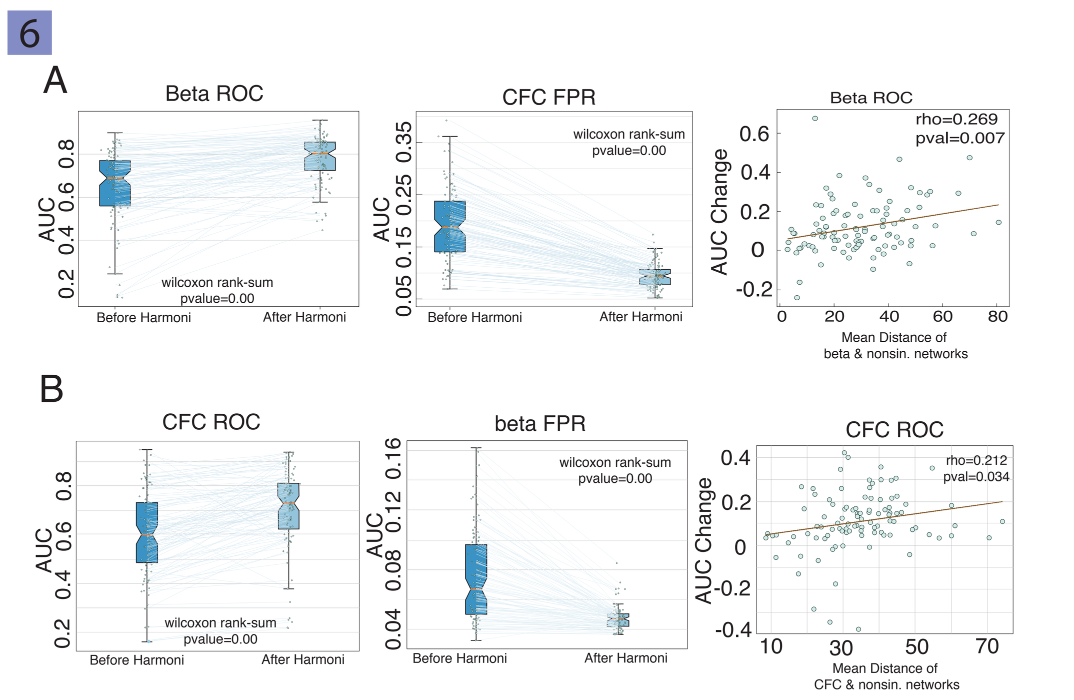
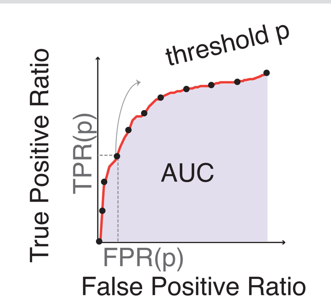


Results of the 100 realistic simulations according to scenario 1 (panel A) and 2 (panel B) of figure 5. For scenario 1, the detection of the beta network improves (A-left) and the further the distance of beta and nonsin. networks the better works Harmoni (A-right). Additionally, the spurious CFC connections are suppressed (A-middle). For scenario 2, the spurious CFC connections arealleviated (B-left) with a positive correlation between the performance of Harmoni and the distance of the CFC and nonsin. networks (B-right). Also, the spurious beta connections are removed (B-middle).

- A Receiver Operating Characteristic (ROC) curve shows how well a detection task works with different thresholds. The ROC of an ideal detection task has an AUC equal to one, while a random detector has an AUC equal to 0.5.

  Therefore the larger the AUC, the better the detection.



An ROC curve

- Fig. 6 shows the results of the simulations, using AUC of ROC curve as the evaluation criterion.

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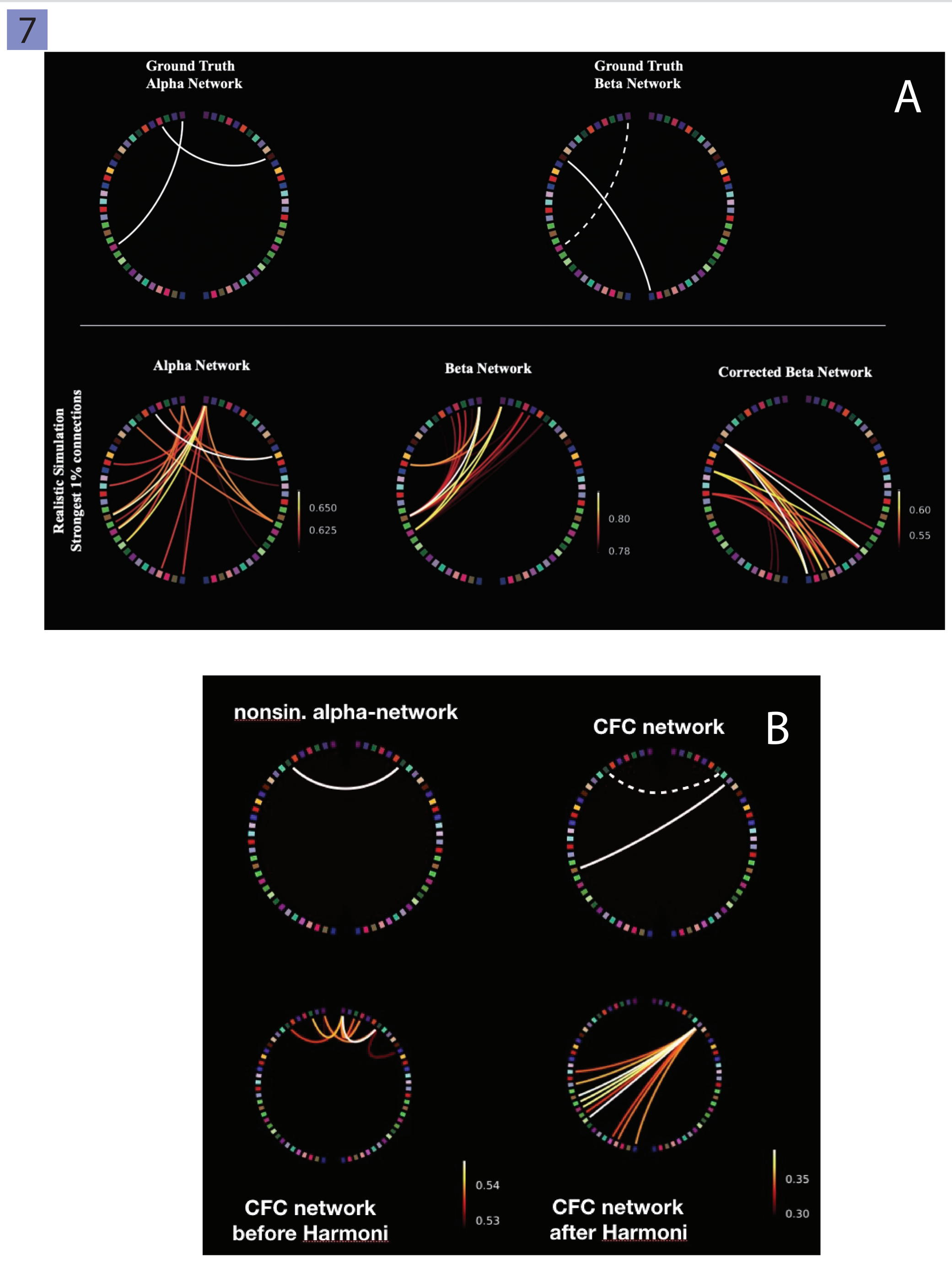

Examples of simulations from the two scenarios. Panel A and B are scenarios 1 and 2 respectively.
The dashed lines show the spurious interactions. The connectivity maps are plotted for the top 1% connections. The comparison of the networks before and after Harmoni shows that the spurious interactions are suppressed in comparison to the genuine ones.

Discussion

- Using extensive realistic simulations and analysis of real data, we show that Harmoni is able to alleviate the detrimental effect of harmonics on connectivity estimation of M/EEG data significantly.
- There has been an attempt from (Siebenhuhner et al 2020) to omit the ambiguous connections from CF connectivity graphs based on the detection of ambiguous motifs in the connectivity graphs. Such an approach cannot disentangle the within-frequency spurious interactions in the harmonic frequency bands, and moreover is specific to the CF connectivity graphs and cannot be used in any other analysis pipeline.
- Harmoni is the first approach that cleans the data components that can be associated with the harmonics of the periodic neuronal activity. Such an approach can provide the opportunity of using the clean narrow-band data (in the frequency range of the harmonics) for any kind of analysis, including, but not limited to, connectivity analysis.
- Harmoni can be the first steppingstone towards the development of other methods aiming at refining within-frequency and CF PPS analysis of M/EEG.

Real Data: SSVEP BCI

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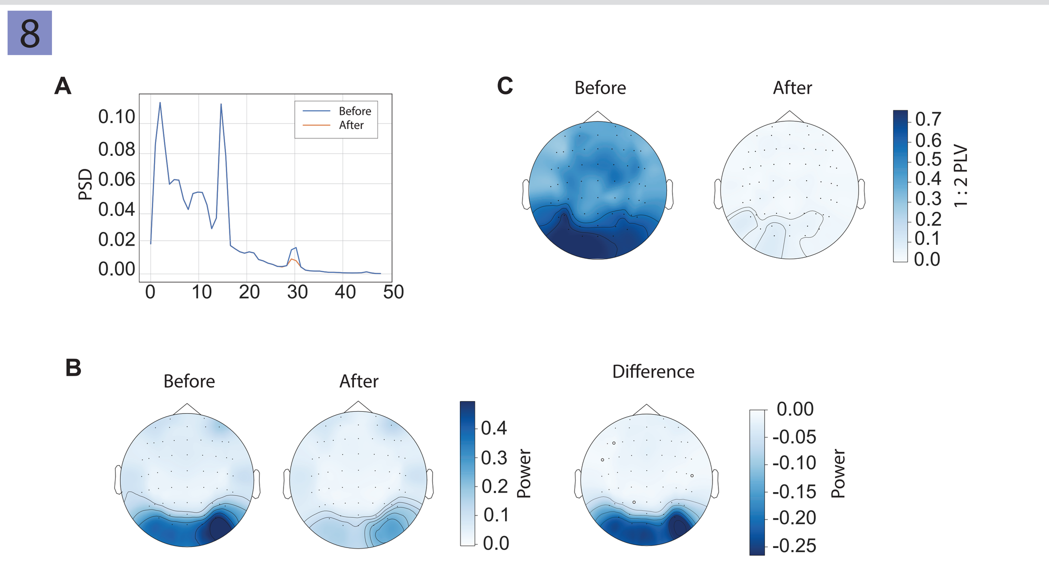

Harmoni on grand-average SSVEP data from all the trials of 24 subjects looking at a 15Hz-flickering object. Panel A shows the median PSD of all channels/subjects before and after removal of second harmonic components. This drop in power level can be also seen in panel B topographies, where the mean power of 30Hz frequency band (over all subjects) is shown before and after HarmoRemo. The mean difference of each channel is tested with wilcoxon signed-rank test with Bonferroni correction. The channels that do not survive the multiple-comparison correction are marked in the right-most topography of panel B on top of the power difference. Panel C shows the 1:2 PLV of 15Hz and 30Hz frequency band components at each channel, before and after HarmoRemo. The reduction in the PLV of the two frequency bands along with the power drop can show the successful removal of second harmonic components of the SSVEP.

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