The Journal of Open Source Software

PyBispectra: A toolbox for advanced electrophysiological signal processing using the bispectrum

Thomas S. Binns [1,2,3¶], **Franziska Pellegrini** [3,4], **Tin Jurhar** [5,6], **Tien D. Nguyen** [3,4], **Richard M. Köhler** [1], **and Stefan Haufe** [2,3,4,5,7]

1 Movement Disorders Unit, Charité - Universitätsmedizin Berlin, Germany **2** Einstein Center for Neurosciences Berlin, Charité - Universitätsmedizin Berlin, Germany **3** Bernstein Center for Computational Neuroscience Berlin, Germany **4** Berlin Center for Advanced Neuroimaging, Charité - Universitätsmedizin Berlin, Germany **5** Electrical Engineering and Computer Science Department, Technische Universität Berlin, Germany **6** Donders Institute for Brain, Cognition and Behaviour, Radboud Universiteit, The Netherlands **7** Physikalisch-Technische Bundesanstalt Braunschweig und Berlin, Germany ¶ Corresponding author

DOI: 10.21105/joss.08504

Software

- Review
- Repository
- Archive

Editor: Bonan Zhu

Reviewers:

- @ntolley
- @richrobe

Submitted: 03 February 2025
Published: 20 August 2025

Summary

Various forms of information can be extracted from electrophysiology data. Of this, phase-amplitude coupling, time delays, and non-sinusoidal waveshape characteristics are of great interest, providing mechanistic insights into physiology and pathology. However, methods commonly used for these analyses possess notable limitations. Recent work has revealed the bispectrum - the Fourier transform of the third order moment - to be a powerful tool for the analysis of electrophysiology data, overcoming many such limitations. Here we present `PyBispectra`, a package for bispectral analyses including phase-amplitude coupling, time delays, and non-sinusoidal waveshape.

Statement of need

Analysis of phase-amplitude coupling, time delays, and non-sinusoidal waveshape can be applied to various forms of electrophysiology data, including: electroencephalography; magnetoencephalography; local field potentials; electromyography; and electrocardiograhy. These analyses provide important mechanistic insights into bodily functions (Canolty & Knight, 2010; Sherman et al., 2016; Silchenko et al., 2010), for instance to investigate core nervous system roles like movement and memory, including their perturbation in disease (Bazzigaluppi et al., 2018; Binns et al., 2025; Cole et al., 2017; De Hemptinne et al., 2013). However, traditional analysis methods have critical limitations in terms of robustness, interpretability, and computational demand that hinder their utility. In contrast, the bispectrum measures non-linear signal interactions in a frequency-resolved manner (Nikias & Raghuveer, 1987), overcoming traditional limitations for the analysis of phase-amplitude coupling (Zandvoort & Nolte, 2021), non-sinusoidal waveshape (Bartz et al., 2019), and time delays (Nikias & Pan, 1988).

Despite these benefits, the bispectrum has seen little use in electrophysiology research, in part due to the lack of an accessible toolbox tailored to electrophysiology data. Code written in MATLAB exists for some analyses (see e.g., github.com/sccn/roiconnect, github.com/Zuse-Dre1/AnalyzingWaveshapeWithBicoherence), however it is spread across multiple repositories and often not as toolboxes. Furthermore, this requires a paid MATLAB license, limiting accessibility. Code for computing the bispectrum exists in the free-to-use Python language

The Journal of Open Source Software

(Bachetti et al., 2024), however these implementations are not tailored for electrophysiology data, and while other Python packages perform some of these analyses on electrophysiology data (Cole et al., 2019; Denker et al., 2024), they do not make use of the bispectrum. The `PyBispectra` package addresses this by providing a comprehensive toolbox for bispectral analysis of electrophysiology data (Figure 1), including tutorials to facilitate an understanding of these analyses.

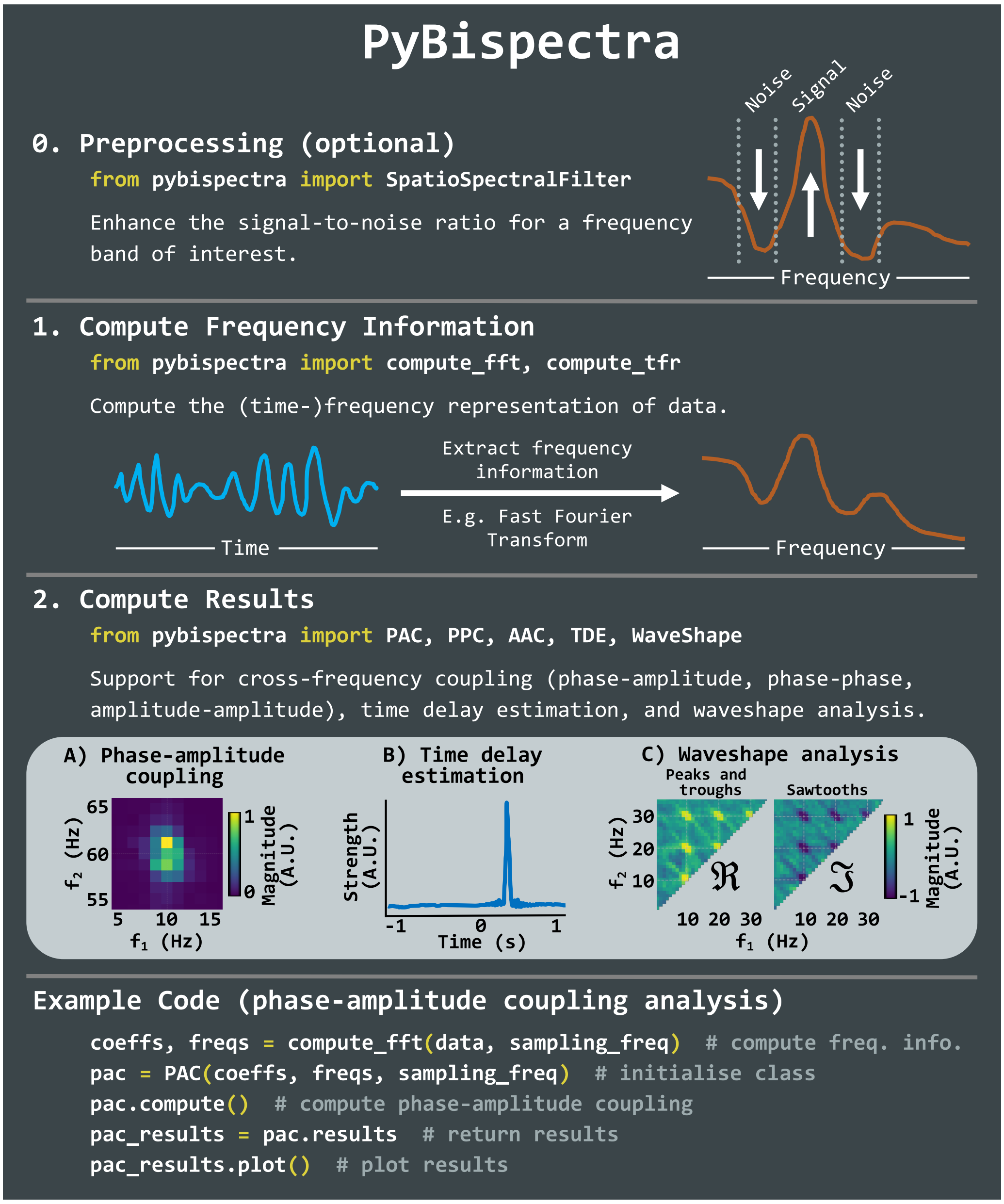

Figure 1: Overview of the `PyBispectra` toolbox. Optional preprocessing methods are supported for the multivariate analysis of waveshape. Tools are provided for computing spectral representations of time series data, as well as for computing cross-frequency coupling, time delays, and non-sinusoidal waveshape, with schematic visualisations of results shown. Also shown is an example code snippet for analysing phase-amplitude coupling.

Features

Phase-amplitude coupling

Phase-amplitude coupling is the interaction between the phase of a lower frequency oscillation and amplitude of a higher frequency oscillation. For neural signals, it has been posited as a mechanism for the integration of information across spatiotemporal scales (Canolty & Knight, 2010), with perturbations in disease (Bazzigaluppi et al., 2018; De Hemptinne et al., 2013). Common methods for quantifying phase-amplitude coupling involve bandpass filtering signals in the frequency bands of interest and using the Hilbert transform to extract phase and amplitude information (Canolty et al., 2006; Tort et al., 2010), with several limitations. First, the bandpass filters require precise properties that are not readily apparent, with poorly designed filters smearing information across a broad spectral range (Zandvoort & Nolte, 2021). Second, the Hilbert transform is a relatively demanding procedure, contributing to a high computational cost. Finally, when analysing interactions between signals, spurious coupling estimates can arise due to interactions within each signal (Pellegrini et al., 2023). In contrast, bandpass filtering is not required with the bispectrum, preserving the spectral resolution and reducing the risk of misinterpreting results (Zandvoort & Nolte, 2021). Furthermore, bispectral analysis relies on the computationally cheap Fourier transform. Finally, spurious across-signal coupling estimates can be corrected for using bispectral antisymmetrisation (Chella et al., 2014; Pellegrini et al., 2023). `PyBispectra` provides tools for performing bispectral phase-amplitude coupling, with options for antisymmetrisation and a univariate normalisation procedure that bounds coupling scores in a standardised range for improved interpretability (Shahbazi et al., 2014).

Time delays

Time delay analysis identifies latencies of information transfer between signals, providing insight into the physical connections between recording sites (Binns et al., 2025; Silchenko et al., 2010). A traditional analysis method is cross-correlation, quantifying the similarity of signals at a set of time lags. However, this approach has a limited robustness to noise (Nikias & Pan, 1988) and a vulnerability to spurious zero time lag interactions arising due to volume conduction and source mixing in the sensor space. On the other hand, the bispectrum is resilient to Gaussian noise (Nikias & Pan, 1988), and antisymmetrisation can be used to correct for spurious zero time lag interactions (Chella et al., 2014; Jurhar et al., 2025). `PyBispectra` provides tools for bispectral time delay analysis, with options for antisymmetrisation.

Non-sinusoidal waveshape

Non-sinusoidal activity can be distinguished through features such as sawtooth signals and a dominance of peaks or troughs. For neural signals, this indicates properties of interneuronal communication (Sherman et al., 2016), with perturbations seen in disease (Cole et al., 2017). Analysis can be performed on time series data using peak finding-based procedures (Cole et al., 2017), however this is computationally demanding for high sampling rate data. A further complication comes from the desire to isolate frequency-specific neural activity, with bandpass filtering suppressing non-sinusoidal information (Bartz et al., 2019). Attempts to address this remain limited by a risk of contamination from frequencies outside the band of interest (Cole et al., 2017). In contrast, the bispectrum captures frequency-resolved non-sinusoidal information directly (Bartz et al., 2019) in a computationally efficient manner. `PyBispectra` provides tools for analysing non-sinusoidal waveshape using the bispectrum, including the option of univariate normalisation to bound values in a standardised range for improved interpretability (Shahbazi et al., 2014).

Supplementary features

Two common issues faced when analysing electrophysiology data are a limited signal-to-noise ratio and interpreting high-dimensional data (Cohen, 2022). Spatio-spectral decomposition is a multivariate technique that addresses these problems, capturing key aspects of frequency-specific information in a high signal-to-noise ratio, low-dimensional space (Nikulin et al., 2011). This decomposition is supported by `PyBispectra` for the analysis of non-sinusoidal waveshape, with extensions like harmonic power maximisation targetting non-sinusoidal information (Bartz et al., 2019).

Other features of `PyBispectra` include plotting tools for the visualisation of results, low-level compilation with Numba (Lam et al., 2015), and support for parallel processing. Data formats follow conventions from popular signal processing packages like `MNE-Python` (Gramfort et al., 2013), and helper functions are provided as wrappers around `MNE-Python` and `SciPy` (Virtanen et al., 2020) tools to facilitate processing prior to bispectral analyses. Furthermore, tools for amplitude-amplitude and phase-phase coupling are also provided, following literature recommendations for identifying genuine phase-amplitude coupling (Giehl et al., 2021). Finally, analyses are accompanied by detailed tutorials, facilitating an understanding of how the bispectrum can be used to analyse electrophysiology data.

Conclusion

Altogether, the bispectrum is a robust and computationally efficient tool for the analysis of phase-amplitude coupling, time delays, and non-sinusoidal waveshape. Bispectral approaches overcome key limitations of traditional methods which have hindered electrophysiology research. To aid the uptake of bispectral methods, `PyBispectra` provides access to these tools in a comprehensive, easy-to-use package, tailored for use with electrophysiology data.

Acknowledgements

We acknowledge contributions from Mr. Toni M. Brotons and Dr. Timon Merk, who provided valuable feedback and suggestions for the design of the `PyBispectra` package and its documentation.

References

Bachetti, M., Huppenkothen, D., Stevens, A., Swinbank, J., Mastroserio, G., Lucchini, M., Lai, E. V., Buchner, J., Desai, A., Joshi, G., Pisanu, F., Pisupati, S. G. D., Sharma, S., Tripathi, M., & Vats, D. (2024). Stingray 2: A fast and modern Python library for spectral timing. *Journal of Open Source Software*, *9*(102), 7389. https://doi.org/10.21105/joss.07389

Bartz, S., Avarvand, F. S., Leicht, G., & Nolte, G. (2019). Analyzing the waveshape of brain oscillations with bicoherence. *NeuroImage*, *188*, 145–160. https://doi.org/10.1016/j.neuroimage.2018.11.045

Bazzigaluppi, P., Beckett, T. L., Koletar, M. M., Lai, A. Y., Joo, I. L., Brown, M. E., Carlen, P. L., McLaurin, J., & Stefanovic, B. (2018). Early-stage attenuation of phase-amplitude coupling in the hippocampus and medial prefrontal cortex in a transgenic rat model of Alzheimer's disease. *Journal of Neurochemistry*, *144*(5), 669–679. https://doi.org/10.1111/jnc.14136

Binns, T. S., Köhler, R. M., Vanhoecke, J., Chikermane, M., Gerster, M., Merk, T., Pellegrini, F., Busch, J. L., Habets, J. G. V., Cavallo, A., Beyer, J.-C., Al-Fatly, B., Li, N., Horn, A., Krause, P., Faust, K., Schneider, G.-H., Haufe, S., Kühn, A. A., & Neumann, W.-J. (2025). Shared pathway-specific network mechanisms of dopamine and deep brain stimulation for the treatment of Parkinson's disease. *Nature Communications*, *16*(1), 3587. https://doi.org/10.1038/s41467-025-58825-z

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., Berger, M. S., Barbaro, N. M., & Knight, R. T. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science*, *313*(5793), 1626–1628. https://doi.org/10.1126/science.1128115

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences*, *14*(11), 506–515. https://doi.org/10.1016/j.tics.2010.09.001

Chella, F., Marzetti, L., Pizzella, V., Zappasodi, F., & Nolte, G. (2014). Third order spectral analysis robust to mixing artifacts for mapping cross-frequency interactions in EEG/MEG. *NeuroImage*, *91*, 146–161. https://doi.org/10.1016/j.neuroimage.2013.12.064

Cohen, M. X. (2022). A tutorial on generalized eigendecomposition for denoising, contrast enhancement, and dimension reduction in multichannel electrophysiology. *NeuroImage*, *247*, 118809. https://doi.org/10.1016/j.neuroimage.2021.118809

Cole, S., Donoghue, T., Gao, R., & Voytek, B. (2019). NeuroDSP: A package for neural digital signal processing. *Journal of Open Source Software*, *4*(36), 1272. https://doi.org/10.21105/joss.01272

Cole, S., Meij, R. van der, Peterson, E. J., Hemptinne, C. de, Starr, P. A., & Voytek, B. (2017). Nonsinusoidal beta oscillations reflect cortical pathophysiology in Parkinson's disease. *Journal of Neuroscience*, *37*(18), 4830–4840. https://doi.org/10.1523/JNEUROSCI.2208-16.2017

De Hemptinne, C., Ryapolova-Webb, E. S., Air, E. L., Garcia, P. A., Miller, K. J., Ojemann, J. G., Ostrem, J. L., Galifianakis, N. B., & Starr, P. A. (2013). Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. *Proceedings of the National Academy of Sciences*, *110*(12), 4780–4785. https://doi.org/10.1073/pnas.1214546110

Denker, M., Kern, M., & Richter, F. (2024). *Elephant*. Zenodo. https://doi.org/10.5281/zenodo.13133971

Giehl, J., Noury, N., & Siegel, M. (2021). Dissociating harmonic and non-harmonic phase-amplitude coupling in the human brain. *NeuroImage*, *227*, 117648. https://doi.org/10.1016/j.neuroimage.2020.117648

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L., & Hämäläinen, M. (2013). MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience*, 267. https://doi.org/10.3389/fnins.2013.00267

Jurhar, T., Pellegrini, F., Toro, A. I. N. del, Stephani, T., Nolte, G., & Haufe, S. (2025). Estimating Time Delays between Signals under Mixed Noise Influence with Novel Cross- and Bispectral Methods. *arXiv*. https://doi.org/10.48550/arXiv.2502.17474

Lam, S. K., Pitrou, A., & Seibert, S. (2015). Numba: A LLVM-based Python JIT compiler. *Proceedings of the Second Workshop on the LLVM Compiler Infrastructure in HPC*, 1–6. https://doi.org/10.1145/2833157.2833162

Nikias, C. L., & Pan, R. (1988). Time delay estimation in unknown Gaussian spatially correlated noise. *IEEE Transactions on Acoustics, Speech, and Signal Processing*, *36*(11), 1706–1714. https://doi.org/10.1109/29.9008

Nikias, C. L., & Raghuveer, M. R. (1987). Bispectrum estimation: A digital signal processing framework. *Proceedings of the IEEE*, *75*(7), 869–891. https://doi.org/10.1109/PROC.1987.13824

Nikulin, V. V., Nolte, G., & Curio, G. (2011). A novel method for reliable and fast extraction of neuronal EEG/MEG oscillations on the basis of spatio-spectral decomposition. *NeuroImage*, *55*(4), 1528–1535. https://doi.org/10.1016/j.neuroimage.2011.01.057

Pellegrini, F., Nguyen, T. D., Herrera, T., Nikulin, V., Nolte, G., & Haufe, S. (2023). Distinguishing between-from within-site phase-amplitude coupling using antisymmetrized bispectra. *bioRxiv*. https://doi.org/10.1101/2023.10.26.564193

Shahbazi, F., Ewald, A., & Nolte, G. (2014). Univariate normalization of bispectrum using Hölder's inequality. *Journal of Neuroscience Methods*, *233*, 177–186. https://doi.org/10.1016/j.jneumeth.2014.05.030

Sherman, M. A., Lee, S., Law, R., Haegens, S., Thorn, C. A., Hämäläinen, M. S., Moore, C. I., & Jones, S. R. (2016). Neural mechanisms of transient neocortical beta rhythms: Converging evidence from humans, computational modeling, monkeys, and mice. *Proceedings of the National Academy of Sciences*, *113*(33), E4885–E4894. https://doi.org/10.1073/pnas.1604135113

Silchenko, A. N., Adamchic, I., Pawelczyk, N., Hauptmann, C., Maarouf, M., Sturm, V., & Tass, P. A. (2010). Data-driven approach to the estimation of connectivity and time delays in the coupling of interacting neuronal subsystems. *Journal of Neuroscience Methods*, *191*(1), 32–44. https://doi.org/10.1016/j.jneumeth.2010.06.004

Tort, A. B. L., Komorowski, R., Eichenbaum, H., & Kopell, N. (2010). Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. *Journal of Neurophysiology*, *104*(2), 1195–1210. https://doi.org/10.1152/jn.00106.2010

Virtanen, P., Gommers, R., Oliphant, T. E., Haberland, M., Reddy, T., Cournapeau, D., Burovski, E., Peterson, P., Weckesser, W., Bright, J., Walt, S. J. van der, Brett, M., Wilson, J., Millman, K. J., Mayorov, N., Nelson, A. R. J., Jones, E., Kern, R., Larson, E., … SciPy 1.0 Contributors. (2020). SciPy 1.0: Fundamental algorithms for scientific computing in Python. *Nature Methods*, *17*(3), 261–272. https://doi.org/10.1038/s41592-019-0686-2

Zandvoort, C. S., & Nolte, G. (2021). Defining the filter parameters for phase-amplitude coupling from a bispectral point of view. *Journal of Neuroscience Methods*, *350*, 109032. https://doi.org/10.1016/j.jneumeth.2020.109032