Title:

Tensorpac : an open-source Python toolbox for tensor-based Phase-Amplitude Coupling measurement in electrophysiological brain signals

Short title:

Tensorpac : a Python toolbox for Phase-Amplitude Coupling measurement

Authors and Affiliations

Etienne Combrisson[1, 2,*], Timothy Nest[1,3], Andrea Brovelli[2], Robin A.A. Ince[4], Juan LP Soto[5], Aymeric Guillot[6], Karim Jerbi[1,7,8,*]

[1] Psychology Department, University of Montréal, QC, Canada

[2] Institut de Neurosciences de la Timone, UMR 7289, Aix Marseille Université, CNRS, 13385 Marseille, France

[3] Département d'informatique et de recherche opérationnelle, University of Montréal, QC, Canada

[4] Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK

[5] Telecommunications and Control Engineering Department, University of Sao Paulo, Sao Paulo, Brazil

[6] Inter-University Laboratory of Human Movement Biology, 27-29 Boulevard du 11 Novembre 1918, F-69622, Villeurbanne cedex, France

[7] MEG Center, University of Montréal, QC, Canada

[8] Mila - Quebec Artificial Intelligence Institute, QC, Canada

* Corresponding authors:

Dr Etienne Combrisson (e.combrisson@gmail.com)
Dr Karim Jerbi (karim.jerbi@umontreal.ca)

Abstract

Despite being the focus of a thriving field of research, the biological mechanisms that underlie information integration in the brain are not yet fully understood. A theory that has gained a lot of traction in recent years suggests that multi-scale integration is regulated by a hierarchy of mutually interacting neural oscillations. In particular, there is accumulating evidence that phase-amplitude coupling (PAC), a specific form of cross-frequency interaction, plays a key role in numerous cognitive processes. Current research in the field is not only hampered by the absence of a gold standard for PAC analysis, but also by the computational costs of running exhaustive computations on large and high-dimensional electrophysiological brain signals. In addition, various signal properties and analyses parameters can lead to spurious PAC. Here, we present Tensorpac, an open-source Python toolbox dedicated to PAC analysis of neurophysiological data. The advantages of Tensorpac include (1) higher computational efficiency thanks to software design that combines tensor computations and parallel computing, (2) the implementation of all most widely used PAC methods in one package, (3) the statistical analysis of PAC measures, and (4) extended PAC visualization capabilities. Tensorpac is distributed under a BSD-3-Clause license and can be launched on any operating system (Linux, OSX and Windows). It can be installed directly via pip or downloaded from Github (https://github.com/EtienneCmb/tensorpac). By making Tensorpac available, we aim to enhance the reproducibility and quality of PAC research, and provide open tools that will accelerate future method development in neuroscience.

Keywords: phase-amplitude coupling, PAC, cross-frequency coupling, open-source software, tensor, python, parallel computing, electrophysiology

Introduction

The study of electrophysiology is innately challenging due to the immense complexity of oscillatory phenomena organized at many distinct spatial and temporal scales. While common assays for measuring brain function like fMRI are able to considerably reduce the temporal complexity of functional brain dynamics, scientists interested in electrophysiology must grapple with a dizzying array of plausibly meaningful features in the spectral domain. For decades, neuroscientists have sought to isolate cognitive and task-related changes in brain oscillations by examining spectral features such as power, amplitude, and phase across frequencies and brain regions. However, increasing attention has been given to more complex and dynamic properties of neural oscillations [1]. A prominent example of such dynamic oscillatory phenomena is Cross-Frequency Coupling (CFC) [2] which has been observed both at the phase-level [3–5], and at the amplitude level [6–8]. A slightly more recent, and arguably less well characterised phenomenon, Phase-Amplitude Coupling (PAC), provides a metric to identify and quantify synchronization between the phase of low-frequency oscillations and the amplitude of high-frequency oscillations.

Over the last decade, PAC has been shown to mediate a variety of task-related and cognitive functions including attention and decision making [9,10], learning and memory [11–18], motor and visuomotor tasks [5,19–25], as well as mental disorders such as Parkinson disease and schizophrenia [26–33]. It has been proposed that PAC reflects the regulation of high frequency local computations by a larger network, oscillating at lower frequencies [34]. PAC might therefore contribute to coordinate neural activity by using a "hold and release" mechanism of gamma oscillations [25].

In order to quantify PAC, a number of methodologies and implementations have been proposed [35–44] and compared [43,44]. Until now, there is still no gold standard on which method is the best alternative, even though the Kullback-Leibler Distance [44] is probably the most widely adopted due to its noise tolerance and amplitude independence. In addition, it has been shown that PAC can be computed in an event-related manner [45]. Nevertheless, there is still no consensus on the minimal data length (i.e. the number of cycles) that is required or the most appropriate filtering methods [46,47]. It has also recently been shown that spurious PAC can occur for a variety of reasons that may be difficult to systematically control [48–51]. Among them we can mention the absence of a clear peak in the power spectrum density (PSD) of the phase, the choice of the filter bandwidth or the nonstationarity.

To date, a handful of established brain data analysis toolboxes provide built-in functionalities to compute PAC, these include Matlab-based packages such as Fieldtrip [52], Brainstorm [53] and EEGLAB [54]. The open-science Python research community has also proposed a few PAC tools, including pacpy (https://github.com/voytekresearch/pacpy/) or pactools [38], with the latter supporting MNE-Python inputs [55]. While extremely valuable, each of the

available tools covers a limited choice of PAC computations and visualization options. In addition, computational time remains a challenge that can severely limit PAC analyses at a time where data dimensionality is drastically increasing in neuroscience research.

Here, we present Tensorpac, a cross-platform open-source Python toolbox, distributed under a BSD-3-Clause license, dedicated to the measurement of phase-amplitude relationships. This includes an array of functions to compute PAC and event-related PAC (ERPAC) alongside innovative features such as the estimation of the preferred-phase with polar plotting and exhaustive exploratory analysis across the full frequency space. Tensorpac also ships with additional tools in order to assess the reliability of the estimation such as power spectral density (PSD), Phase-Locking Value [56] and statistics. Crucially, what distinguishes Tensorpac even more from other available tools, is the combination of parallel computing and tensor-based implementation of the algorithms which drastically reduces computation time and opens up the possibility to compute PAC on large multidimensional arrays.

Design, implementation and results

In principle, estimating PAC consists in quantifying the coupling between slow-wave phase with the amplitude of higher frequency signals. As a bidirectional coupling measure, however, it is impossible to say whether PAC high-amplitude rhythms are led by slow oscillations or the contrary. Accordingly, we denote by $f1 <-> f2$ the PAC between a phase centered in $f1$ and the amplitude centered in $f2$.

### 1. Estimation of a corrected phase-amplitude coupling

Estimating PAC is usually assessed in four steps, illustrated in **Figure 1**. First, the instantaneous phases of slower oscillations and amplitudes of faster oscillations are extracted. Second, the true coupling measure between those phases and amplitudes is computed. Third, a null distribution of surrogate values of the measure in the absence of coupling is estimated. This is usually assessed by swapping either amplitude or phase time-blocks, cut at a random time-point. Finally, the true coupling measure is corrected by subtracting the mean and dividing by the standard deviation of the surrogate null distribution. This step improves the robustness and the sensibility of the measure.
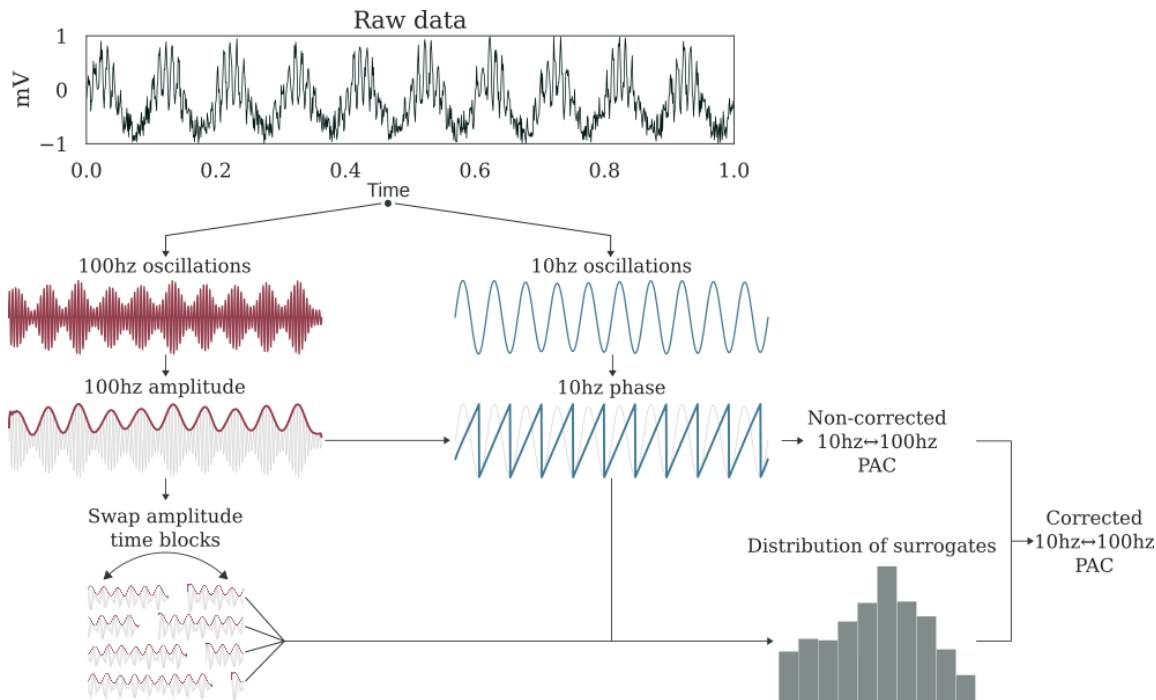
Figure 1 : Estimation process of a corrected 10<->100 hz PAC. For illustration, here simulated raw data contains a coupling between a 10 hz phase and a 100 hz amplitude. First, the raw data is respectively filtered with bandpass filters centered on 100hz and 10hz. Then, the complex analytic form of each signal is obtained using the Hilbert transform. The phase is extracted from the 10Hz signal (angle of analytic signal) and power from the 100Hz signal (amplitude of analytic signal). An uncorrected PAC measure is obtained from these two signals. To estimate the null distribution of the measure in the absence of any genuine coupling, the amplitude signal is split into two blocks at a random time point and the temporal order of those two blocks is swapped. Then, the PAC is estimated using this swapped version of amplitude and the originally extracted phase. By repeating this process and cutting at a random point, for example 200 times, we can obtain a distribution of surrogate values for which there is no genuine coupling. Finally, a corrected PAC estimate is obtained through z-score normalization of the uncorrected PAC using this distribution.

1.1 Generating coupled signals

For the implementation and validation of coupling methods, we used synthetic signals with controllable coupling frequencies. To this end, we included in the toolbox two ways to simulate synthetic signals that can be imported from *tensorpac.signals* : *pac_signals_tort* which is a method based on pure sines summation and modulation [43] and
pac_signals_wavelet which extract the phase from a random distribution leading to more complex signals [37]. Both methods, illustrated in **Figure 2**, provide fine-grained control over the coupling frequency pair of (phase, amplitude), the amount of coupling and noise such as data length and sampling frequency.
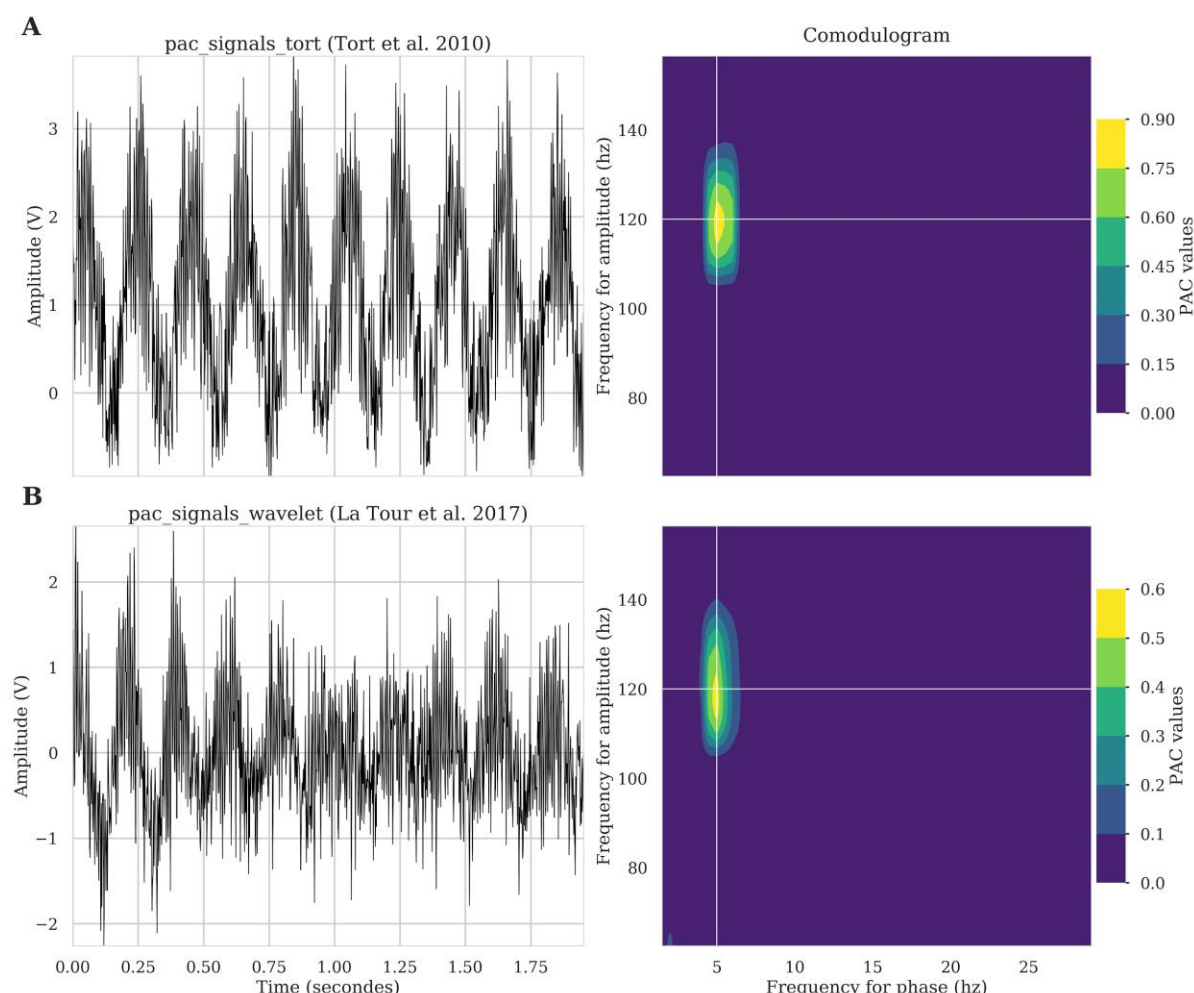
Figure 2 : Illustration of synthetic signals that can be generated to simulate phase-amplitude coupling (left column) and associated comodulogram (right column). First row shows an example of a signal that contains a 5<->120 hz coupling defined as proposed by Tort et al. [44]. Bottom signal (**B**) also contains a 5<->120 hz coupling but defined as proposed in Dupré la Tour et al. [38].

1.2 Extracting the instantaneous phase and the amplitude

Since there is no consensus about whether the Hilbert or wavelet transforms constitutes a gold standard for extracting the phase and the amplitude, Tensorpac implements both. The Hilbert transform has to be applied on pre-filtered signals. For filtering, we implemented a Python equivalent to the two-way zero-phase lag finite impulse response (FIR) Least-Squares filter implemented in the EEGLAB toolbox [54]. Filter orders are frequency dependent and are defined as a function of the number of cycles (by default 3 cycles are used for the phase and 6 cycles for the amplitude [57]). Extracting the phase and the amplitude using the absolute value and the phase of the Hilbert transform applied on these filtered signals. Both components can also be obtained by convolving with a Morlet's wavelets [58] with a default width of 7, a default value broadly used in electrophysiological data analyses.

1.3 Implemented PAC methodologies

Here, we describe the main PAC estimation methods currently available in Tensorpac, which include the Mean Vector Length, Modulation Index (KL-divergence), Height-Ratio, normalized direct-PAC and phase-synchrony (new validated methods will be continually added and documented online). In the following, we denote by $x(t)$ a time-series of length N, $f_\phi = [f_{\phi 1}, f_{\phi 2}]$ and $f_A = [f_{A1}, f_{A2}]$ the frequency bands respectively for extracting the phase $\phi(t)$ and the amplitude $a(t)$.

Mean Vector Length: The Mean Vector Length (MVL) was introduced by Canolty et al. [35] and is defined as the modulus of the average complex vector formed by combining the phase and amplitude signals:

$$MVL = \left| \sum_{k=1}^{N} a(k)e^{j\phi(k)} \right| \cdot \frac{1}{N}$$

Note that authors also proposed to normalize the MVL by computing surrogates using a time lag.

Kullback-Leibler distance: Originally the Kullback-Leibler distance (or divergence) (KLD) is used in information theory to measure dissimilarities between two probability distributions. Tort et al. 2010 [44] elegantly proposed an adaptation for measuring PAC which consists of defining a probability distribution of amplitudes as a function of phase and then comparing this distribution to a uniform one. To this end, the phase $\phi(t)$ is first cut into n slices. For example, if $n = 18$, the phase is binned into 18 bins of 20° each. Then, the mean of the amplitude $a(t)$ is taken inside each bin and is denoted by $< a >_\phi$. Through this binning operation, the phase and the amplitude are linked and can be said to be coupled. Finally, the probability distribution P is obtained by dividing the amplitude inside each bin by the sum over the bins,

$$P(j) = \frac{< a >_\phi (j)}{\sum_{k=1}^{n} < a >_\phi (k)}$$

where $\forall j \in [|1, n|], P(j)$ represent the normalized amplitude inside a bin. This distribution is then used to compute PAC using either the KLD.

The modulation index (MI) is obtained using the distance of Kullback-Leibler which measure how the probability distribution of amplitudes P diverges from a uniform distribution Q:
$MI = \frac{D_{KL}(P,Q)}{log(n)}$ where $D_{KL}(P, Q) = \sum_{k=1}^{n} P(k)log(\frac{P(k)}{Q(k)})$.
Note that for a uniform distribution, $\forall k[|1, n|], Q(k) = 1/n$ and therefore the MI formula can be written to :

$$MI = 1 + \frac{1}{log(n)} \sum_{k=1}^{n} P(k)log(Pk)$$

Height-Ratio: Starting from the same probability density distribution of amplitudes, the Height-Ration (HR) [39] is defined by:

$$MI = \frac{h_{max} - h_{min}}{h_{max}}$$

where h_{max} and h_{min} are respectively the maximum and the minimum of the distribution.

Normalized direct PAC: The ndPac [42] is similar to the MVL with two exceptions. First, this method uses a z-scored normalized amplitude and secondly, includes a statistical test. This test uses a closed-form statistical threshold given by:

$$x_{lim} = 2 \times (erf(1-p)^{-1})^2$$

with p the confidence level and erf^{-1} the inverse error function.

Phase synchrony

The phase synchrony (PS) [9,43] is a derivative of the Phase Locking Value (PLV) [56]. Originally, the PLV looks only at the phase consistency across trials. The PS adaptation consists of extracting the phase of the amplitude ϕ_a, subtracting it from the phase of slower oscillations, projecting the resultant time series into the complex circle and finally, calculating the mean of the length vector :

$$PS = \left| \frac{1}{N} \sum_{k=1}^{N} e^{i(\phi(k) - \phi_a(k))} \right|$$

The main PAC methods implemented in Tensorpac are presented in **Figure 3**.
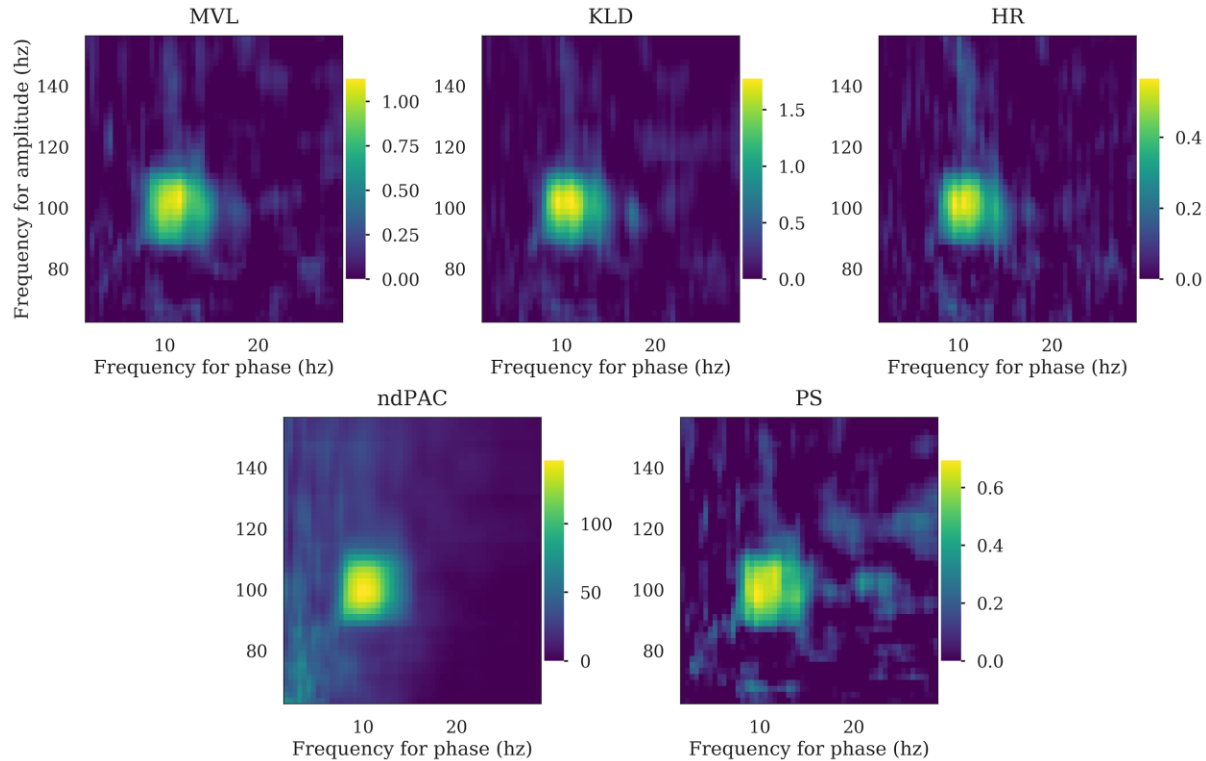

Figure 3 : Comparison of the main PAC methods currently implemented in Tensorpac. The comodulograms were computed using the MVL, KLD, HR, ndPac and PS, from 100 trials of simulated data containing a 10 <-> 100 hz phase-amplitude coupling. The data is available in Tensorpac and can be used to validate and benchmark other methods.

1.4 Statistical analysis of PAC

The absence of PAC in a signal could be related to several parameters that have been previously described [43]. Each one of the proposed PAC methodologies presents some advantages or limitations and may not be appropriate for all types of analysis. These methods exhibit differences in terms of robustness to noise, as well as modulation width, neither of which are necessarily amplitude independent [44]. In addition, PAC estimations may be biased due to limited amounts of data being available.

Generally, these limitations can be taken into account by computing a surrogate null distribution and using this to correct or normalize the PAC measure. To this end, several methods exist, all based on a common idea: introducing a small change into the data such that the temporal characteristics of the time-series are preserved but the relationship between the phase and the amplitude is disrupted. Among existing methods, [35] introduced a time lag to the amplitude, while [44] swap amplitude and phase trials and [57] swap time blocks, cut at a random point. The latter method, with only two blocks, has been described as the most conservative strategy to generate the distribution of PAC that can be observed by chance [47]. Finally, this null distribution is then used to perform non-parametric inference or to correct the measure estimated from the data (usually by subtracting the mean and divide by the deviation of this distribution). An example of a corrected PAC is presented in **Figure 4**.
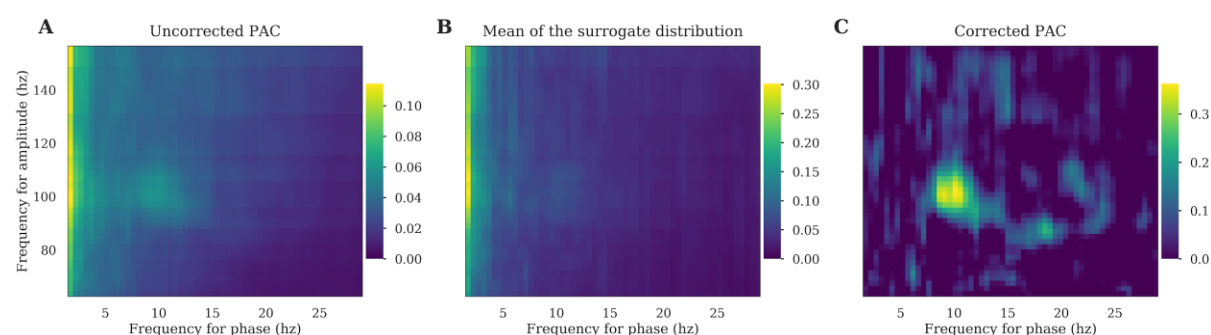
Figure 4 : Comparison between corrected and uncorrected PAC. (**A**) PAC comodulogram is computed for several (phase, amplitude) pairs. (**B**) For each of those pairs, we estimate the distribution of surrogates and plot the mean comodulogram of these permutations. Note that both uncorrected and surrogate PAC comodulograms exhibit a spurious peak in the very low frequency phase. (**C**) The true 10<->100 hz coupling is finally retrieved by subtracting the mean of the surrogate distribution (panel B) from the uncorrected PAC (panel A).
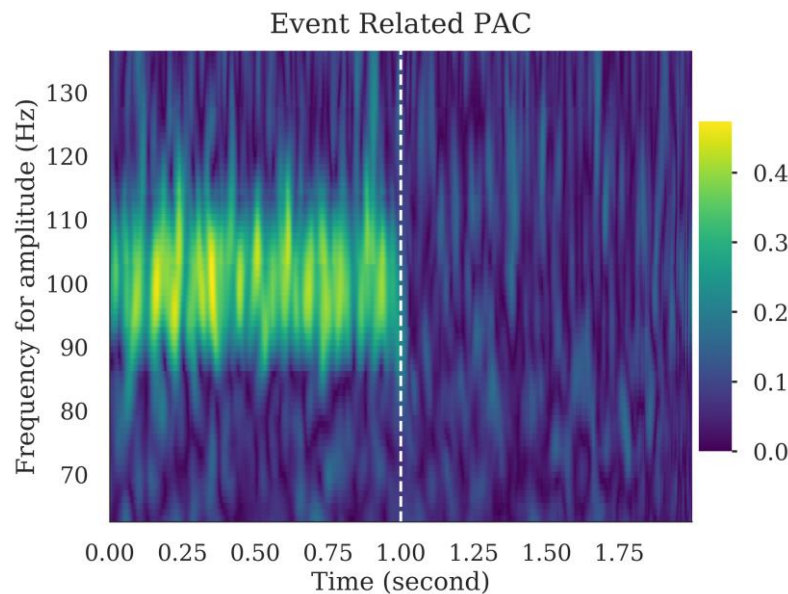
1.5 Event-related phase-amplitude coupling (ERPAC)

One issue that has been raised is that, since PAC is computed across time, non-stationary signals can cause the appearance of spurious coupling [47]. An illustrative example taken from the same study explains that if there is an induced phase locking of lower frequencies and simultaneously a high frequency power increase, a coupling between them is going to be observed. Interestingly, a complementary approach to the time-averaged PAC has been proposed and consists of computing time-resolved PAC across trials [44]. Accordingly, the Event-Related PAC (ERPAC) measure is based on a circular-linear correlation [59] which evaluates the Pearson correlation, across trials, of the amplitude a_t and with the sine and cosine of the phase

ϕ_t. We denote by $c(x, y)$ the Pearson correlation between two variables x and y, $r_{sx} = c(sin(\phi_t), a_t)$, $r_{cx} = c(cos(\phi_t), a_t)$ and $r_{sc} = c(sin(\phi_t), cos(\phi_t))$ hence, the circular-linear correlation ρ_{cl} is defined as:

$$\rho_{cl} = \sqrt{\frac{r_{sx}^2 + r_{cx}^2 - 2r_{sx}r_{cx}r_{sc}}{1 - r_{sc}^2}}$$

In contrast to the original Matlab version [45], we implemented a tensor-based version of the ERPAC (*tensorpac.EventRelatedPac*) illustrated in the **Fig 5**. It is noteworthy that a measure of event-related PAC has been proposed using a mutual information framework [39]. In addition, it has also been proposed to compute PAC using the power spectrum on sliding windows [60].


Figure 5 : Example of Event-Related Phase-Amplitude Coupling (ERPAC). We first generate 300 one-second trials each containing a 10<->100hz coupling. Next, one-second of random noise is appended to these signals. The depicted ERPAC represents time-resolved PAC estimation over the two-second window, computed with a phase between [9, 11] hz and for multiple amplitudes.

2. Additional cross-frequency tools

2.1 Distribution of amplitudes and preferred phase

The preferred-phase (PP) is defined as the phase for which the distribution of amplitudes is maximum. This can be used to find out if amplitudes are aligned at a specific phase angle [24]. To compute the PP (*tensorpac.PreferredPhase*), the probability density distribution of amplitudes

is first generated according to a number of phase slices (just as KLD and HR). Then, the phase bin for which the amplitude is maximum is defined as the preferred phase. Usually, the preferred phase is reported using a histogram (see **Fig 6A**), where a specific phase and a specific amplitude band have been used. Here, we introduce a new plotting method where, still for a single phase, but now binned amplitudes in consecutive frequency bands can be observed using a polar representation (**Fig 6B**). This provides a more fine-grained representation where the preferred phase can be observed with a wide range of amplitude frequencies. Both methods and visualizations are available in Tensorpac (*tensorpac.PreferredPhase.pacplot* and *tensorpac.PreferredPhase.polar*).
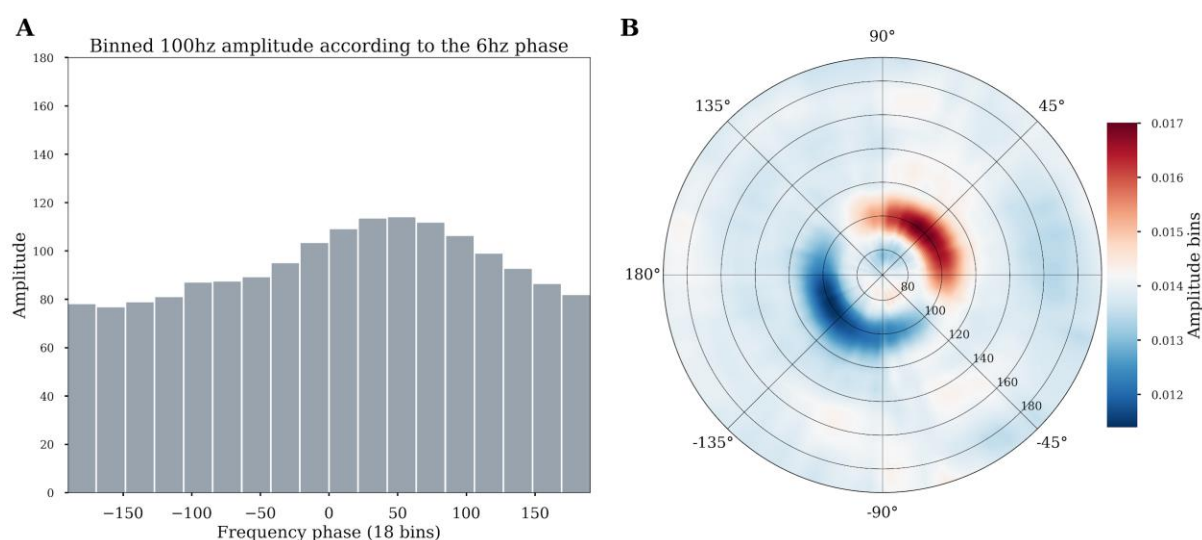

Figure 6 : Illustrative example of the preferred phase estimation based on 100 trials generated with coupling between 6hz<->100hz and where the amplitude is locked to the 6hz phase at 45° (pi/4). (**A**) The 100 hz amplitude is first binned according to the phase using 18 slices of 20° each. The sum of the amplitude inside each slice is plotted as a histogram and the preferred phase is identified as the phase for which the amplitude is maximum (45°). (**B**) An alternative polar visualisation available in Tensorpac displays the strength across multiple amplitude frequency bands. Phase is binned as before, but now multiple amplitude signals from different bands are calculated for each phase bin. In these polar plots, the angle represents the phase of the low-frequency (here 6Hz), and the radial axis represents different frequencies considered for the amplitude signal. The color depicts the average value of the amplitude of a given frequency inside the corresponding phase bin. The preferred 45° phase for the 6hz<->100hz PAC is clear in this representation.

2.2 Phase / amplitude frequency interval optimization

When choosing the parameters to use in PAC analysis, researchers are often confronted with important decisions related to parameter selection. Even if the frequency bands for phase and amplitude are chosen based on a scientific hypothesis or previous reports in the literature, it is often impossible to know what the optimal frequency intervals are in the data one is analyzing. One might argue that it makes little sense to compute theta-gamma coupling in canonical

frequency bands for example using 4-7 Hz (theta phase) and 30-70 Hz (gamma amplitude) if these bands don't really capture key oscillatory modulations in the data at hand. We therefore reasoned that it would be useful to (a) be able to check for the presence of peaks in the power spectrum to potentially guide the choice of the bandwidth for filtering [48], and (b) to automatically search for the best frequency intervals in a data-driven manner. Tensorpac provides functionalities that can help address these issues. First of all, a standard tool to compute the Power Spectrum Density (PSD) is available and adapted for standard electrophysiological data formats, i.e. datasets organized as an array with the number of epochs as rows and the number of time points as columns (See example in **Fig 7A**). This can be used to identify prominents peaks either for the low or high frequency components. More importantly, in order to address the question of how to optimize the selection of the starting and ending frequencies for the intervals to use for PAC computation, Tensorpac allows *for* the possibility of defining triangular vectors and computing PAC for a range of starting and ending frequencies ($PAC(F_{min}, F_{max})$). In addition, this triangular search can be used to find the best interval for the amplitude or for the phase. The visualization of the results (*tensorpac.Pac.triplot*) can be used to determine the hotspots within a triangular representation of PAC, i.e. determining the Fmin/Fmax combination that corresponds to PAC peak (see **Fig 7B**): The x-axis determines the starting frequency (F_{min}) and the y-axis the ending frequency (F_{max}). The maximum coupling that emerges from this triangular representation can be taken a an indication for the optimal frequency interval to use $[F_{min}, F_{max}]$. Note here that the standard comodulogram often used in PAC analyses is obtained by computing PAC in successive (*phase, amplitude*) pairs of bands with pre-defined bandwidths. While useful for identifying coupling the comodulogram is not suitable for identifying the optimal starting and ending frequencies to use. Taken together, the PSD tool and this exhaustive Fmin/Fmax search for best frequency bounds are valuable tools that can guide decisions regarding parameter selection in PAC analyses.

As a side note, the choice of the filter bandwidth for the phase and amplitude is still debated. While some previous studies recommended filtering the amplitude with a bandwidth twice as large as the one used for phase (2:1 ratio) [48], a recent study suggests that a 1:1 ratio might be better as this could prevent smearing [61].
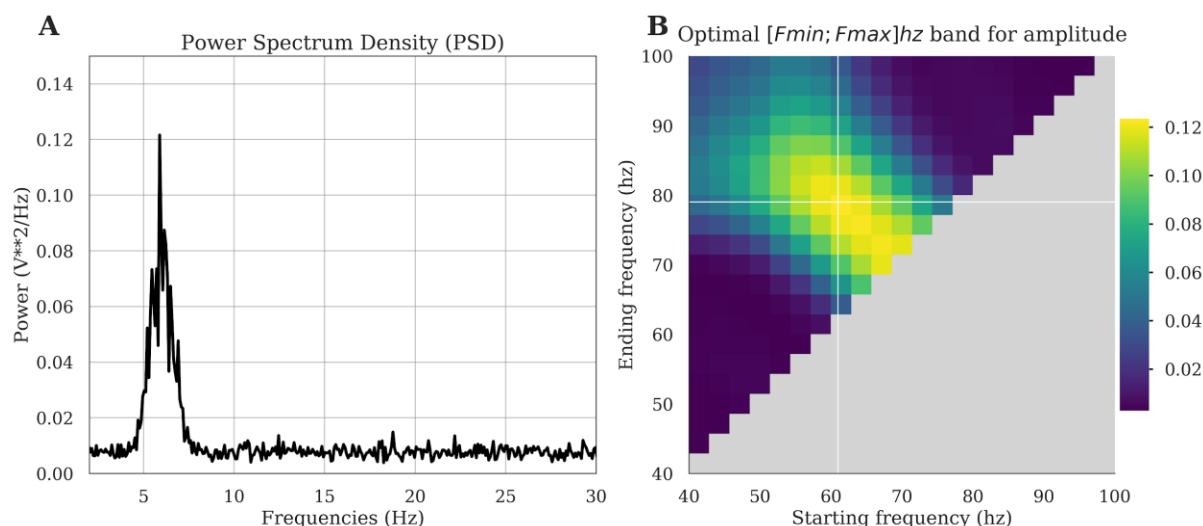
Figure 7 : Investigation of the presence of a phase peak and data-driven exploration of the optimal bandwidth. In this example, we first generated a 6 <-> 70hz phase-amplitude coupling. (**A**) The PSD retrieves the presence of the phase peak around 6hz. (**B**) For a fixed phase filtered in [5, 7] hz, we search for the optimal amplitude band, defined as the bandwidth for which the PAC is maximum. The triangular freq-freq representation depicts coupling strength across many possible combinations of amplitude frequency bounds, where the x-axis corresponds to the starting frequency and the y-axis to the ending frequency. Here, the PAC is maximum for an amplitude range of [61, 79] hz.

2.4 Statistically tests of stationarity

As mentioned earlier, stationary signals are a prerequisite for calculating phase-amplitude coupling. Tensorpac includes a function (*tensorpac.stats.test_stationarity*) to perform an Augmented Dickey-Fuller test (ADF) [62] to test the stationarity of time-series. The null hypothesis of the ADF test is that there is a unit root in the time-series. Said differently, H0 represents a non-stationary signal. Tensorpac uses the Statsmodels Python package [63] and returns a dataframe that contains, for each epoch, the p-values, a boolean if H0 has been accepted or rejected, the statistical test and critical values at 0.05 and 0.01.

3. Tensor-based implementation

Traditionally, phase-amplitude coupling measures are implemented in a vector fashion where only a single time-series is processed at a time. This is the most straightforward implementation and the easiest to read, however computing PAC on relatively large datasets can be dramatically slow, especially when the number of dimensions increases (i.e the number of trials, phases and amplitudes). In Tensorpac, all of the implemented PAC methods have been adapted in order to support multidimensional computations and thereby decrease computing time. This was made possible by using the NumPy function *einsum* which uses the Einstein summation convention in order to perform linear algebraic array operations. In order to illustrate the gains in terms of computing time, we compared the vector-based and the tensor-based implementations on simulated data (100 trials and 3000 time points). We then computed a comodulogram with 26 phases and 24 amplitudes. **Figure 8** presents the comparison of computing time per method (Fig 8A) and the ratio (Fig 8B). The tensor-based implementation is between 6 times to more than 12 times faster than the vector-based one depending on the PAC method that is used. This gain in terms of computation time would be obviously even larger when considering an increasing number of phases and amplitudes or if the permutations for assessing statistics have to be measured.
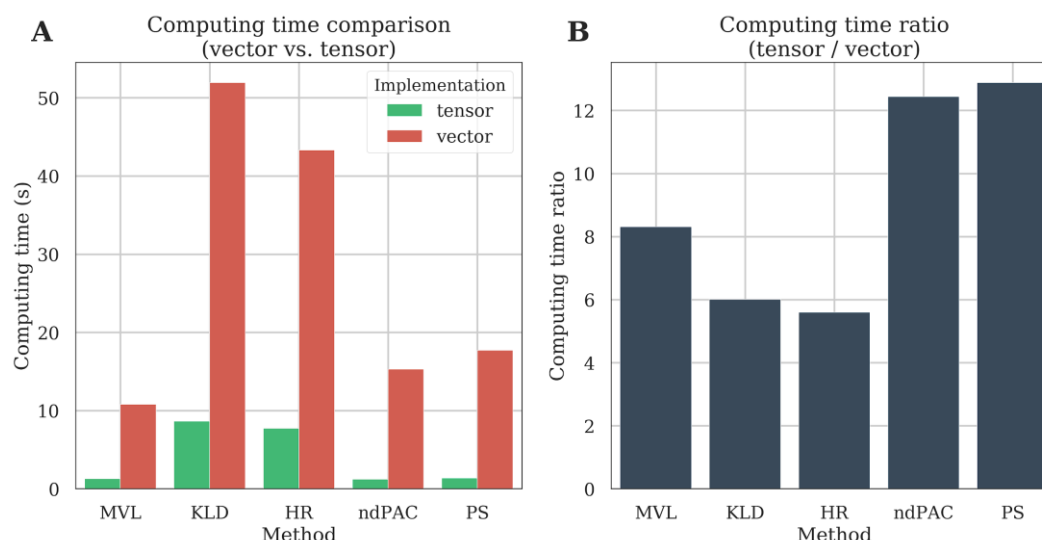
Figure 8 : Computation time of the vector and tensor-based implementations. We first generate a relatively small dataset composed of 100 trials of 3000 time points each. We then evaluated the comodulogram by extracting 26 phases and 24 amplitudes. The comodulogram is then either computed using one-dimensional time-series (vector-based) or directly using multidimensional arrays (tensor-based). Computing time is compared as a function of PAC method **(A)** or as a ratio where the computing time using tensors is divided by the one using vectors **(B)**.

4. Documentation and API provision

Tensorpac is a Python 3 package and is distributed under a BSD-3-Clause license. This package relies on NumPy [64], SciPy [65], Joblib for parallel computing and Matplotlib for plotting. In addition, Pandas [66] and Statsmodels [63] is required if the stationarity test is to be performed. We also provide full documentation for the package (https://etiennecmb.github.io/tensorpac) which is automatically built using sphinx. This documentation also explains how to install Tensorpac. An API tab is accessible from this documentation and describes the most up-to-date implemented functions and descriptions (using NumPy doc convention). It also feature a gallery of examples, built with sphinx-gallery, which illustrate all classes and functions of Tensorpac. For beginners or non-python users that want to cross the open-source bridge, we added a public Gitter chat for answering questions. Finally, the code follows PEP8 and Flake8 guidelines for code readability. We also added a suite of unit-tests that are systematically launched on Linux and Windows systems.

Availability and Future Directions

This paper introduces the workflow and functionalities of Tensorpac, a free and open-source Python toolbox with a tensor-based implementation of both time-averaged and trial-averaged phase-amplitude coupling measures. In addition to those most frequently used methods

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we also presented some unique features such as the preferred phase or an exhaustive research of frequency bounds. As spurious coupling can be observed in many scenarios, we also provide additional tools and statistics to control both the reliability of an estimation. The latest version of Tensorpac is hosted on Github (https://github.com/EtienneCmb/tensorpac) but can also be installed via the pip command from a regular terminal. Tensorpac comes with an online documentation that describes installation options, also for contributors, the functionalities and illustrative examples. We plan to continue adding new methods to the toolbox and we encourage collaborative development and contributions from the community. In particular, we welcome contributions of new methods of PAC estimation but also tools that can help control the reliability of PAC metrics and reduce spurious detections.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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