

# Tensorpac: an open-source Python toolbox for tensor-based Phase-Amplitude Coupling measurement

Etienne Combrisson<sup>1, 2</sup>, Juan LP Soto, Aymeric Guillot, Karim Jerbi<sup>1, 2, 3</sup>

<sup>1</sup> Psychology department, Université de Montréal, Canada

<sup>2</sup> Lyon 1 University, Lyon, France

<sup>3</sup> DYCOG Lab, Lyon Neuroscience Research Center, Lyon, France

**Corresponding authors:**

Etienne Combrisson ([e.combrisson@gmail.com](mailto:e.combrisson@gmail.com))

# Abstract

We present [Tensorpac](https://github.com/EtienneCmb/tensorpac)<sup>1</sup>, a Python open-source toolbox dedicated to the calculation of Phase-Amplitude Coupling (PAC). We designed a flexible modular implementation of existing PAC methods, chance distribution evaluation and normalization types in a way that it is much easier to compare those methods. In addition, all of those methods are implemented using tensors and parallel computing and hence, perform much better on multidimensional datasets.

**Keywords:** phase-amplitude coupling, pac, tensor, python, parallel computing

## Declarations

**Funding:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**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.

---

<sup>1</sup> <https://github.com/EtienneCmb/tensorpac>

# Introduction

For decades, neuroscientists try isolate task-related changes in brain oscillations by extracting spectral features such as power, amplitude or phase. Those changes are then used to understand brain behaviors and physiological involvements or in a Brain-computer Interface (BCI) to train the machine to recognized micro-events and then, associate a command to it. For example, hand motions imply a beta power desynchronization and a gamma synchronization in the sensorimotor cortex (Crone, 1998; Crone et al., 1998). Those rhythms in specific frequency bands can also interact together (Jensen and Colgin, 2007) and this is called Cross-Frequency Coupling (CFC). Publications report cross-frequency phase-phase coupling or phase synchronization (Belluscio et al., 2012; Darvas et al., 2009; Voytek, 2010), amplitude-amplitude coupling (Friston, 1997; Shirvalkar et al., 2010; Siegel et al., 2009) and Phase-Amplitude Coupling (PAC). The latter involves the synchronization between the phase of low-frequency oscillations and the amplitude of high-frequency oscillations. Over the last decade, the PAC receive a growing interest in a large variety of task (Bruns and Eckhorn, 2004; Cohen et al., 2008; Hemptinne et al., 2013; Lee and Jeong, 2013; Lega et al., 2016; Maris et al., 2011; Newman et al., 2013; Soto and Jerbi, 2012; van der Meij et al., 2012; Watrous et al., 2015; Weaver et al., 2016; Yanagisawa et al., 2012). While the role and the mechanism of the PAC remain elusive (Canolty and Knight, 2010), a relatively large number of methodologies have been proposed (Canolty et al., 2006; Cohen, 2008; Dvorak and Fenton, 2014; Lakatos, 2005; Nakhnikian et al., 2016; Ozkurt, 2012; Penny et al., 2008; Tort et al., 2010; Watrous et al., 2015) and compared (Penny et al., 2008; Tort et al., 2010). There is still no gold standard for the choice of the method as their performances in coupling detection depends on signal processing tools and data properties such as length, noise and amount of coupling. Furthermore, CFC can also be detected in absence of coupling (Aru et al., 2015). Assessing the PAC can be done in four steps : extract the phase and the amplitude, measure the degree of coupling between them, then generate a chance distribution and finally, correct the PAC with this chance distribution to minimize non-related PAC events. For those three steps, each publication provide a particular method which decrease the potential reproducibility. There is a few number of existing toolbox to compute PAC such as [Fieldtrip](http://www.fieldtriptoolbox.org/example/cross_frequency_analysis)<sup>2</sup> (Oostenveld et al., 2011) and [PACT](https://sccn.ucsd.edu/wiki/PACT)<sup>3</sup> for EEGLAB (Delorme and Makeig, 2004) in Matlab or [pacpy](https://github.com/voytekresearch/pacpy)<sup>4</sup> developed by for Voytek's research team in Python. Those toolbox re-implement existing methods but the implementation could be improved for large datasets as computing PAC can be very long, especially for the correction part. In this context, we developed an Python open-source toolbox called [Tensorpac](https://github.com/EtienneCmb/tensorpac)<sup>5</sup>, **distributed under a BSD licence, for computing Phase-Amplitude Coupling using tensors and parallel computing. In addition, each step for assessing this coupling measure has been splitted so that the user can pick methods of his choice and then, have the most adapted combination considering data properties.**

---

<sup>2</sup> [http://www.fieldtriptoolbox.org/example/cross\\_frequency\\_analysis](http://www.fieldtriptoolbox.org/example/cross_frequency_analysis)

<sup>3</sup> <https://sccn.ucsd.edu/wiki/PACT>

<sup>4</sup> <https://github.com/voytekresearch/pacpy>

<sup>5</sup> <https://github.com/EtienneCmb/tensorpac>

# Materials and Methods

As the PAC name suggest, it consist of measuring how the phase of slow waves are coupled with the amplitude higher frequency signal. This coupling measure is bidirectional i.e. is not possible to say if it is slow waves which lead amplitude rhythms or the opposite. That said, we denote by  $f1 \leftrightarrow f2$  the PAC between a phase centered in  $f1$  and the amplitude centered in  $f2$ .

At this point it is important to note that the PAC is usually computed using the phase and amplitude coming respectively from the same signal but it is also possible to compute distant PAC.

## Synthetic signals

First of all, for the implementation and validation of coupling methods, we needed a signal with a controllable coupling frequencies. To this end, we included in the toolbox a *PacSignals* function that reproduce synthetic signals proposed by **Tort et al. 2010**.

- The coupling frequency pair of (phase, amplitude)
- The amount of coupling
- The amount of noise
- Data length and sampling frequency

To those controls, we add the possibility to generate multidimensional datasets and add an inter-trial variability variable. An example of such signals is shown in **Figure 1** and we also provide the code in the **Code snippet 1**.

## PAC calculation procedure

### Non-corrected PAC from extracted phase and amplitude

As shown in **Figure 2**, The first step is to extract the phase and the amplitude. This can be assessed either by filtering then taking the Hilbert transform of the filtered signals or using wavelets. Tensorac offers both possibilities and provides least squared filtered with a Python adaptation of EEGLAB (**Delorme and Makeig, 2004**), Butterworth or Bessel filters and morlet's wavelets (**Tallon-Baudry et al., 1996**). The phase and the amplitude are respectively obtained by taking the angle and modulus of complex decompositions provided by Hilbert transform or wavelets. Importantly, bandpass filtering can occurs frequency dependant phase shiftings and potentially destroy coupling. From a programming perspective, this is easily solved by using a forward high-pass filter the a backward low-pass filter and compensate delays. Finally, the PAC is computed using of the existing methodologies (Mean Vector Length, Kullback-Leibler Distance...). Tensorpac use this two-ways filter such as the recommended cycle number for the phase and amplitude filtering (**Bahramisharif et al., 2013**).

## Chance distribution and PAC correction

As described by **Tort et al. 2010**, the absence of PAC in a signal could be related to several parameters. First, filtering artefacts could be observed. Then, each one of the proposed PAC methodologies present some advantages or limitations and might be not appropriate for all type of analysis. Those methods present more or less robustness to noise, to modulation width are could be not amplitude independent (**Tort et al., 2010**). In addition, PAC estimations might be biased by the length of data and longer epochs generally lead to a more trustful PAC.

Taken together, those limitations could be minimized by computing a chance distribution and then, by correcting the PAC value. To this end, several methods exist but all share this same idea as shown in **Figure 3** : introduce a small change in data such that PAC properties are conserved but this change should only reflect events that could happened by chance or, more generally, on any type of signals. Among those existing methods, **Canolty et al. 2006** introduce a time lag to the amplitude, while **Tort et al. 2010** swap amplitude and phase trials and **Bahramisharif et al., 2013** swap time blocks. Finally, the PAC estimation is corrected using the mean and sometimes the deviation of surrogates (see **Figure 4**). The code for computing the comodulogram on multidimensional data is provided in the **Code snippet 2**.

## Modular implementation of existing methods

By setting aside the extraction of the phase and the amplitude, three steps are sufficient to compute the Phase-Amplitude Coupling :

1. Compute the non-corrected PAC
2. If needed, compute the chance distribution
3. Correct the PAC by the surrogates

With Tensorpac we propose a modular implementation of existing PAC and surrogates evaluation. When defining a *Pac* instance, we provide an *idpac* variable which consist of three integers each one respectively referring to the Pac method, to the surrogate method and how to normalize the PAC. Currently supported methods are presented in **Table 1**.

First digit : <i>PAC</i> methods	Second digit : Surrogate methods	Third digit : Normalization
1 - Mean Vector Length (MVL - <i>Canolty, 2006</i> )	0 - No surrogates	0 - No normalization
2 - Kullback-Leibler Distance (KLD - <i>Tort, 2010</i> )	1 - Swap phase/amplitude trials ( <i>Tort, 2010</i> )	1 - $PAC - m$
3 - Heigh-ratio (HR - <i>Lakatos, 2005</i> )	2 - Swap amplitude time blocks ( <i>Bahramisharif, 2013</i> )	2 - $PAC / m$
4 - Normalized Direct PAC (ndPAC - <i>Ozkürt, 2012</i> )	3 - Shuffle amplitude time-series	3 - $(PAC - m) / m$
5 - Phase Synchrony (PS - <i>Cohen, 2008</i> )	4 - Time-lag ( <i>Canolty, 2006</i> )	4 - $(PAC - m) / std$

**Table1** : implemented methods in Tensorpac toolbox. The *idpac* variable is a tuple of three integers referring to (PAC method, Surrogate method, Normalization). We denote by *PAC* the non-corrected coupling, *m* and *std* being respectively the mean and deviation of the chance distribution.

Note that the ndPAC include a statistical estimation and so surrogate evaluation is systematically ignored using it. Then, the Phase Synchrony (**Cohen et al. 2008**) is an adaptation of the Phase Locking Value (PLV) where the coupling is obtained by taking the phase of a second Hilbert transform of the amplitude of fastest oscillations.

## Tensor implementation and parallel computing combination

Formulas of PAC in publications are always imply time series i.e. one dimensional signals. Hence, computing the PAC on several signals and in several frequency bands, such as a comodulogram, demand embedded loops. While C code is efficient with loops, higher-levels languages such as Python or Matlab are considerably slower and this is a huge limitation for computing coupling on a large amount of subjects/electrodes/trials.

That said, we adapted each methodologie to be computed using tensor with a contraction over the time axis. This implementation type have two major benefits:

1. Even on smaller datasets the execution time is faster using tensors. Note that this difference in execution time is then propagate when computing surrogates and the gain of time increase.
2. Using tensors, loops are avoided and there is no restriction on data shape as soon as the time axis location is provided.

In addition to this tensor implementation two steps of the PAC evaluation can be processed in parallel with a control of the number of cores to use :

1. Extracting phase/amplitude in multiple frequency bands
2. Computing surrogates

Depending on the number of cores and the available memory, the tensor implementation and parallel computing can both drastically decrease the computing time.

# Results

## Methods comparison

### Comparison of PAC methods

In order to compare PAC methods, we generated 100 signals each one containing a 10<->100 hz phase-amplitude coupling. Then, we extracted the phase and amplitude from each signal. Finally, we computed the comodulogram on each signal and for each methodology and the final picture represent the mean over generated comodulograms. The result is presented in **Figure 5**. First, MVL and ndPac shared a similar methodology with the exception that the ndPac also include a statistical test that improve coupling localisation. The PS (also called *adapted PLV*) correctly identify the coupling but seems to be sensible to noise. Finally, KLD and HR provide very similar results as expected but, for shorter epochs, might present additional noise in slower frequencies.

### Comparison of surrogate methods

As explained above, the PAC validity can be compromised in presence of noise or a low coupling degree, too short epochs or filtering artefacts. In **Figure 6**, we show an example of normalized PAC, using the MVL and compare how those procedure performs to retrieve the original 10 <-> 100 hz coupling among the 100 generated trials. First, all of the implemented surrogate methods enable to retrieve the coupling with approximately the same acuity. One thing should noticed, the swapping proposed by **Tort et al. 2010** requires to precise the location of the axis dimension while other methods can be performed on a single trial.

### Computing time comparison

One remaining question is how perform the tensor combine with the parallel computing implementation compare to the usual time-series one. In **Figure 7**, we show the execution time ratio of  $t_{Loop}/t_{Tensor}$  for an increasing number of datasets (A) and frequency pairs (phase, amplitude) (B). The KLD and HR PAC methods are those benefits most and for 150 signals the tensor implementation is 30 times faster (A). Other methods also performs better with tensor but the difference is smaller. The reason for such a difference is that both of the KLD and HR needs a binned amplitude according to phase values. This process slow down performances but it can be assessed with multidimensional arrays. For an increasing number of frequencies as this is the case of a comodulogram, the difference between the tensor and loop implementations follow a linear increase with a slightly different slope depending on the methods. The results for computing a non-corrected comodulogram of 100 signals using 14 phases and 13 amplitudes (182 frequency pairs in total) is presented in **Table 1**. For this particular case, tensorpac performs is in mean 38 times faster compared across methodologies compared to the basic time-series forms with a maximum for the KLD and HR which are 50 times faster.

	Execution time (loop)	Execution time (tensor)	Execution time ratio loop/tensor
Mean Vector Length	3,72	0,16	23,73
Kullback-Leibler divergence	35,83	0,65	55,03
Heights ratio	32,77	0,65	50,32
ndPac	6,60	0,17	39,19
Phase-Synchrony	5,12	0,23	22,23
Mean	16,81	0,37	38,10

**Table 1** : execution time (in seconds) comparison between the loop and tensor implementations for computing the comodulogram of 100 signals. Note that this implementation only compare non-corrected PAC and hence, does not include the calcul of surrogates.

Even on small datasets as in **Table 1**, there is an important difference in computing time. For noisy data the PAC needs to be corrected and to this end, compute surrogates. Those variations in computing time are then propagated and as expected, the difference between the tensor and loop implementation is even larger as shown in **Table 2**. Computing a corrected comodulogram with Tensorpac and with only 100 surrogates is now closed to 90 times faster with the KLD and HR around 120 faster.

	Execution time (loop)	Execution time (tensor)	Execution time ratio loop/tensor
Mean Vector Length	551,65	9,90	55,74
Kullback-Leibler divergence	3779,93	30,64	123,38
Heights ratio	3475,99	30,49	114,01
Phase-Synchrony	688,90	12,14	56,75
Mean	2124,12	20,79	87,47

**Table 2** : execution time (in seconds) comparison between the loop and tensor implementations for computing the corrected (using 100 permutations) comodulogram of 100 signals.



# Discussion

In this paper we present an open-source Python toolbox with a modular and tensor based implementation of Phase-Amplitude coupling measures. The interest of such a toolbox is 3 folds:

1. The modular implementation is not restrictive and let to the user the possibility to combine existing methods. In addition, new existing methods can easily be incorporate in the toolbox.
2. We used NumPy tensor functions that first, considerably decrease the execution time and secondly are more appropriate to multidimensional datasets.
3. The toolbox also include a documentation, examples, several filtering and complex decomposition fonctions, utility tools such as generating synthetic coupled signals. Tensorpac also includes statistics and extended plotting functions based on Matplotlib

We found a lack of existing efficient PAC softwares, and, because all neuroscientists are not methodologist, Tensorpac is an appropriate solution to the recent Phase-Amplitude Coupling demands and we also invite other laboratories to provide a source code of their methods.

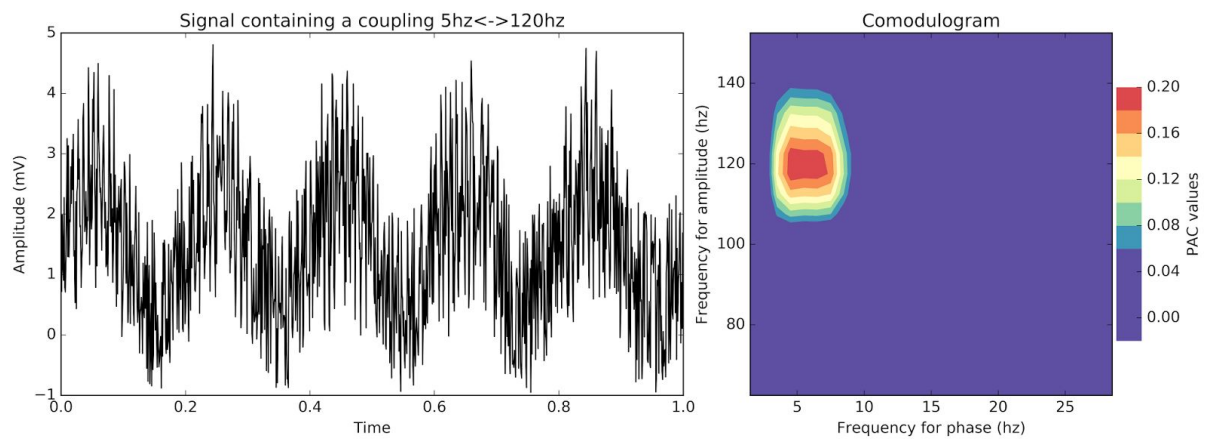
## Future directions

Currently, Tensorpac includes 5 PAC methods and it would be interesting to add old and new ones (such as Amplitude PSD (Cohen, 2008), Correlation measure (Penny et al., 2008), Generalized Linear Model (Penny et al., 2008), coherence (Colgin et al., 2009) or using generalized Morse wavelets (Nakhnikian et al., 2016)). All the presented measures are computed across time, which limit short event investigations. To this end, Voytek et al., 2013, proposed the Event Related PAC (ERPAC) which examine the consistency across trials hence, conserve the time dimension. We started to incorporate the ERPAC but the tensor conversion needs further investigations.

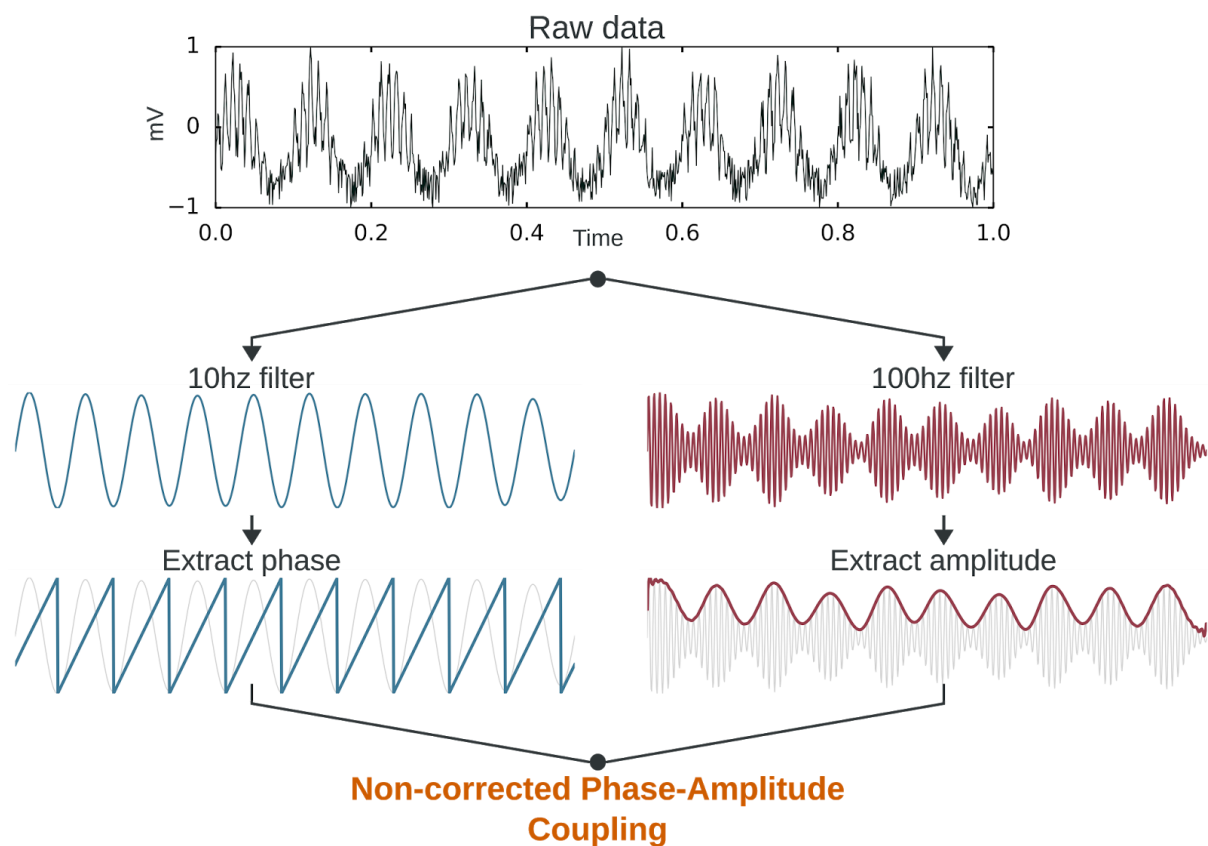
## Conclusion

Tensorpac is a promising toolbox for a fast and reliable estimation of Phase-Amplitude Coupling. The modular implementation considerably increase the number of possibilities but is also more suited to fit to the variety of data. The tensor and parallel computing combination drastically decrease the needed execution time which reinforce the probability to find the best combination, if such a combination exist.

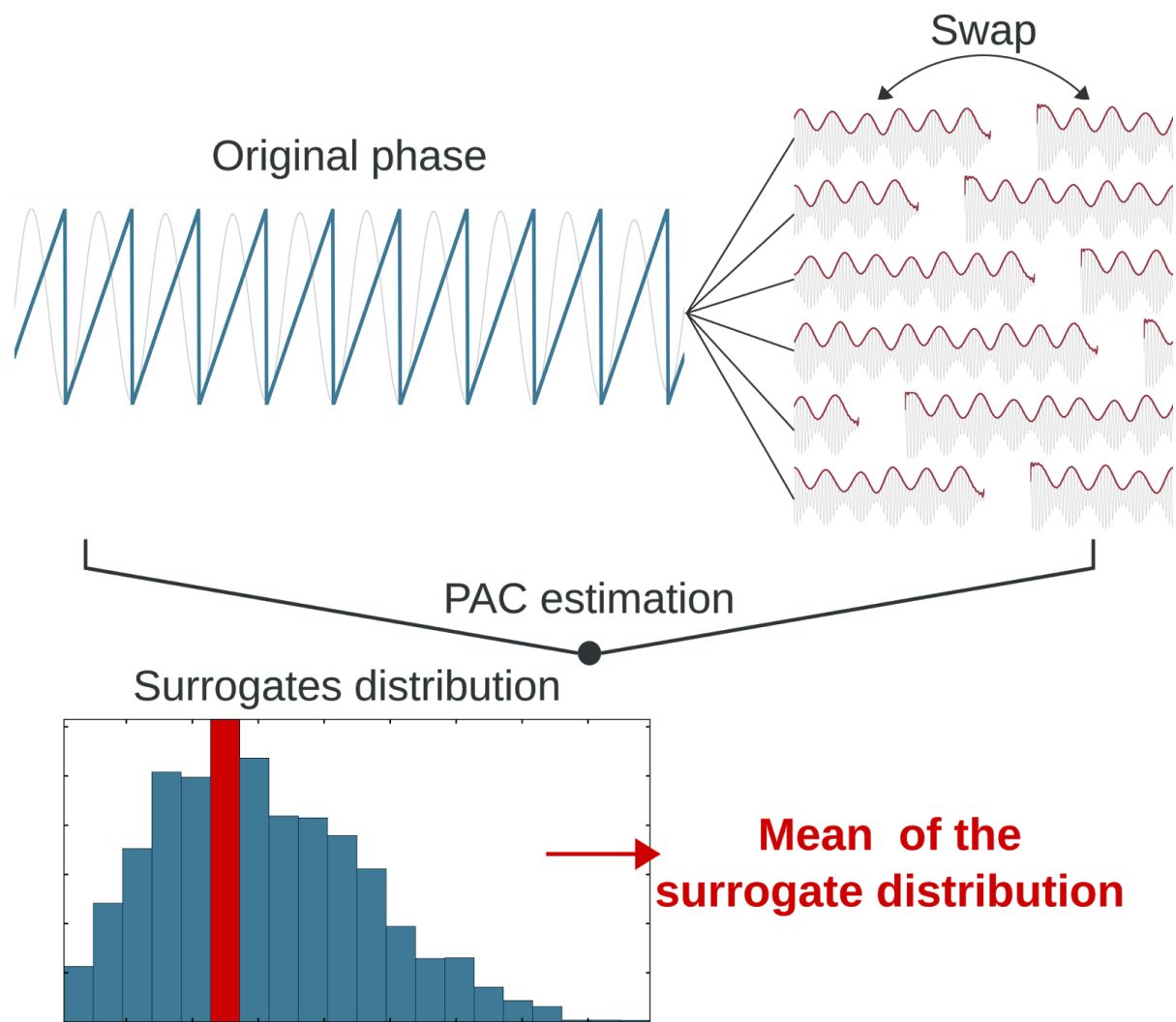
# Figures



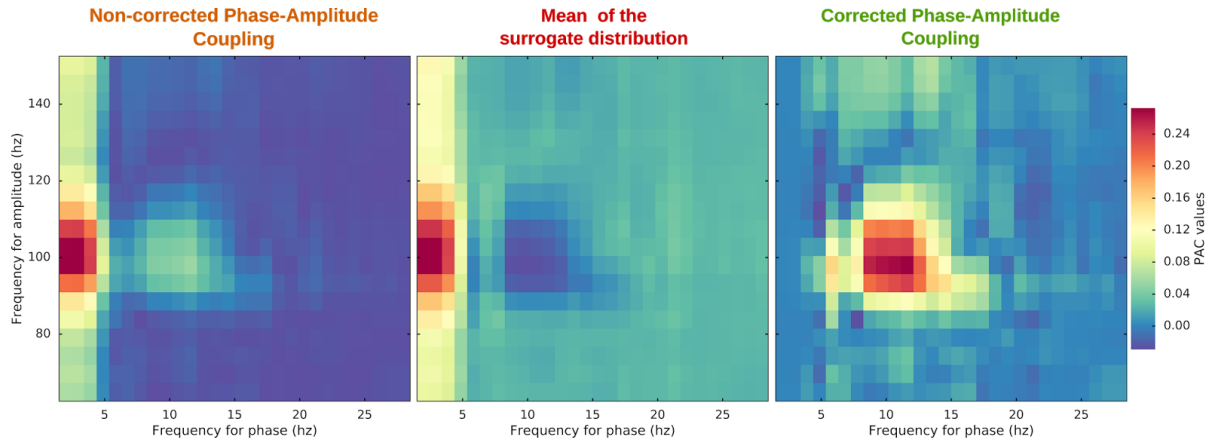
**Figure 1** : example of a signal containing a 5<->120 hz coupling and corresponding comodulogram.



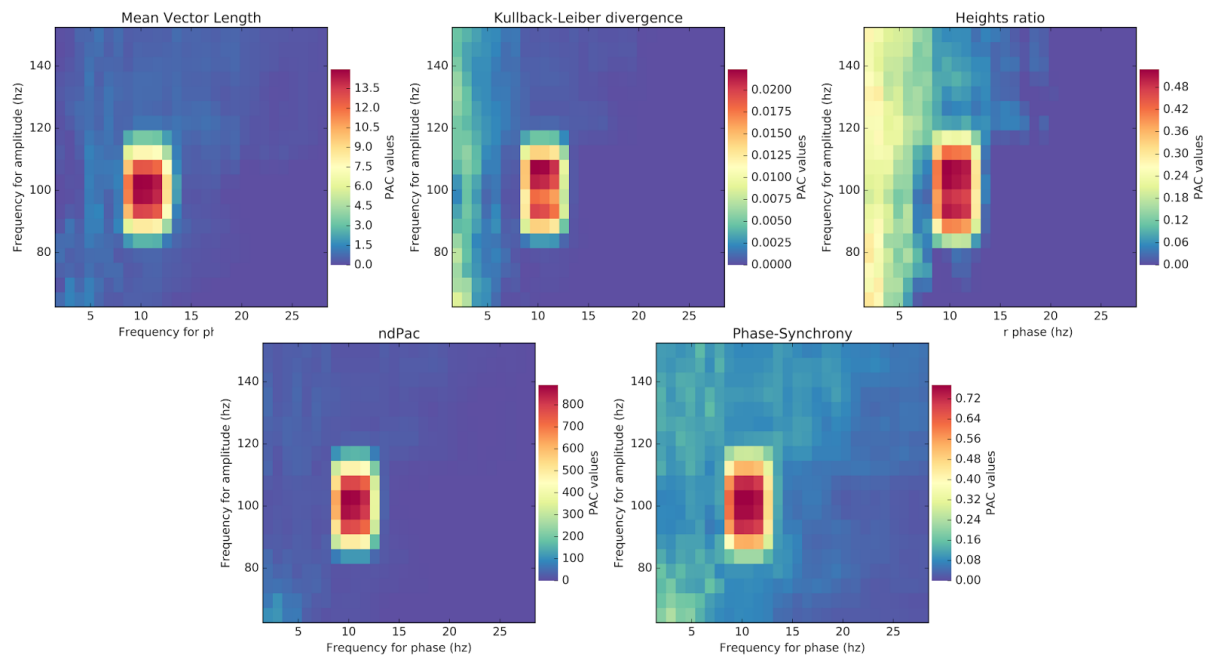
**Figure 2** : estimation process of non-corrected 5<->100 hz. For the sake of the illustration, the raw data contains a coupling between a 10 hz phase and a 100 hz amplitude. First, the raw data is respectively filtered with frequencies centered on 10 hz and 100 hz. Then, each signals are passed to the complex domain using a Hilbert transform and on the first, only the phase is kept and the amplitude and the second. Finally, the PAC is obtained, from this phase and amplitude signals using of the existing measure.



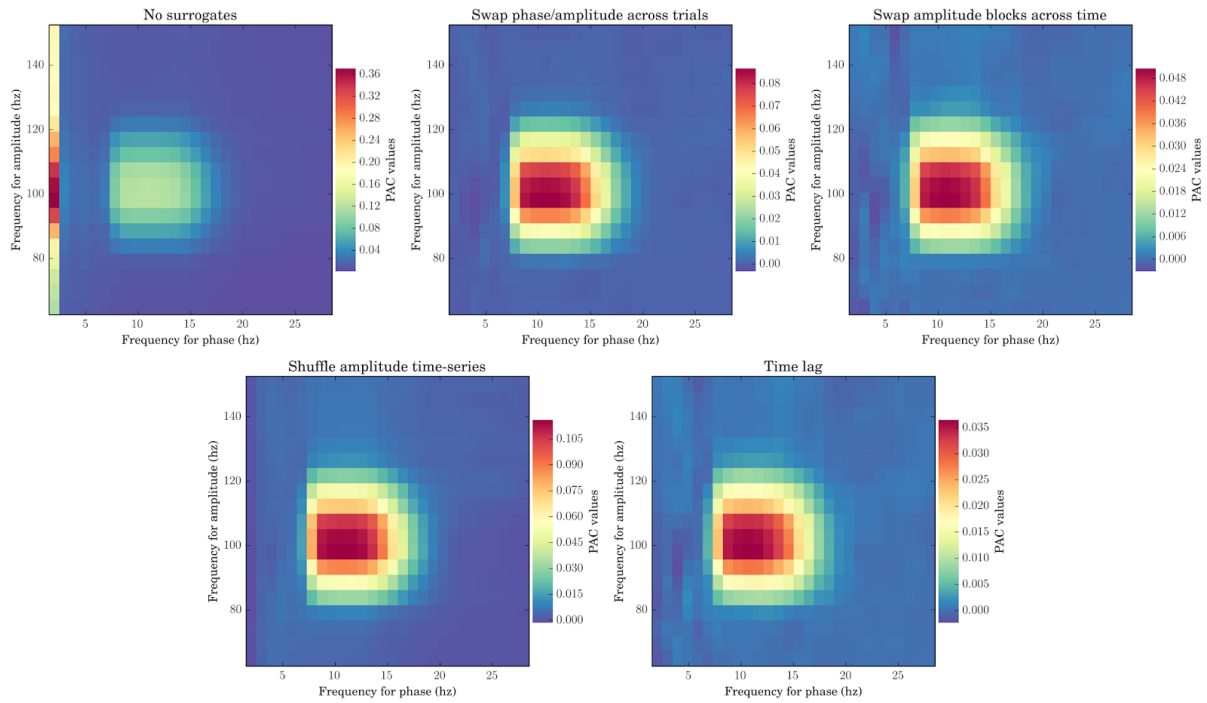
**Figure 3 :** example of surrogate distribution estimation by randomly swapping amplitude blocks. The amplitude is cut in half at a random time point and the two blocks are swapped. Then, the PAC measure is estimated using this swapped version of amplitude and the originally extracted phase. The distribution of surrogates is obtained by putting this process into a loop and varying the random cutting point.



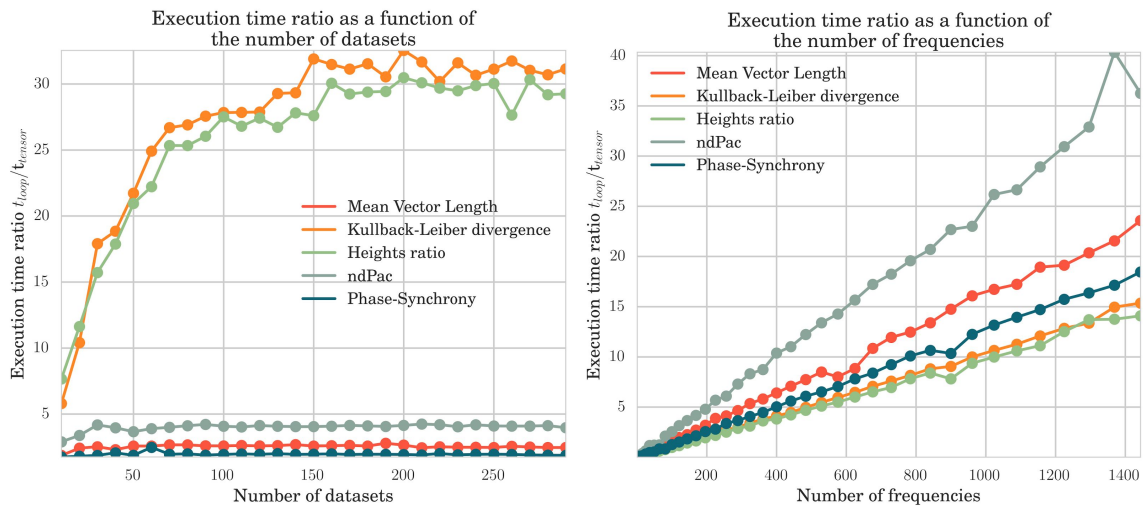
**Figure 4 :** example of PAC correction. First, the PAC is computed for several (phase, amplitude) pairs. Then, for each of those pairs, we estimate the distribution of surrogates. Both of the non-corrected PAC and surrogates shared a peak between the very low frequency phase and the 100hz amplitude. The 10 $\leftrightarrow$ 100 hz coupling is finally retrieved by subtracting the mean of the surrogate distribution to the non-corrected PAC.



**Figure 5 :** comparison of implemented PAC methods. 100 10  $\leftrightarrow$  100 hz synthetic coupled signals are generated. Then, we computed the comodulogram of such signal using the MVL, KLD, HR, ndPac, PS.



**Figure 6 :** comparison of implemented surrogate methods on 100 synthetic 10  $\leftrightarrow$  100 hz coupled signals using the MVL as a primary PAC evaluation method. This figure illustrate first non-corrected PAC then corrected PAC by swapping trials, swapping time blocks, shuffling amplitude time series and finally introducing a random time lag. Finally, the mean of surrogates is subtracted to the non-corrected PAC.



**Figure 7 :** execution time comparison between the tensor and loop implementations for (A) an increasing number of signals and (B) an increasing number of frequencies.

# Code snippets

```
from tensorpac.utils import PacSignals

# Generate 100 signals with a 5<->120 hz coupling and a relatively large amount of noise :
data, time = PacSignals(ndatasets=100, fpha=5, famp=120, noise=3)
```

**Code snippet 1 : generate synthetic signals containing a 5<->120 hz PAC coupling.**

```
import matplotlib.pyplot as plt

from tensorpac.utils import PacSignals
from tensorpac import Pac

# Generate 100 signals with a 5<->120 hz coupling and a relatively large amount
# of noise. The data have a shape of (n_signals, n_points)
sf = 1024. # Sampling frequency
data, time = PacSignals(fpha=10, famp=100, noise=1, ndatasets=100, tmax=3,
                        dpha=10, damp=10, sf=sf)

# Define a Pac instance using the MVL. Then the chance distribution will be
# generated by randomly swap amplitude time blocks. Finally, the PAC is
# corrected by subtracting the mean of surrogates :
p = Pac(idpac=(1, 2, 1), fpha=(1, 30, 1, 1), famp=(60, 160, 5, 5),
        dcomplex='wavelet')

# Extract (phase, amplitude) using wavelets and compute corrected-PAC
# using 100 permutations :
pac, pvalue = p.filterfit(1024, data, data, axis=1, nperm=100)

# Finally, plot the comodulogram of the mean across trials :
p.comodulogram(pac.mean(-1), title='Comodulogram', cmap='Spectral_r')

plt.show()
```

**Code snippet 2 : compute the comodulogram of 100 signals of 3 seconds length. Phases and amplitudes are extracted using Morlet's wavelets. Then, the PAC is computed using the MVL and is then corrected by swapping amplitude time blocks 100 times and subtracting the mean of surrogates.**

## References

- Aru, J., Aru, J., Priesemann, V., Wibral, M., Lana, L., Pipa, G., et al. (2015). Untangling cross-frequency coupling in neuroscience. *Current Opinion in Neurobiology* 31, 51–61. doi:10.1016/j.conb.2014.08.002.
- Bahramisharif, A., van Gerven, M. A. J., Aarnoutse, E. J., Mercier, M. R., Schwartz, T. H., Foxe, J. J., et al. (2013). Propagating Neocortical Gamma Bursts Are Coordinated by Traveling Alpha Waves. *Journal of Neuroscience* 33, 18849–18854. doi:10.1523/JNEUROSCI.2455-13.2013.
- Belluscio, M. A., Mizuseki, K., Schmidt, R., Kempter, R., and Buzsáki, G. (2012). Cross-frequency phase–phase coupling between theta and gamma oscillations in the hippocampus. *Journal of Neuroscience* 32, 423–435.
- Bruns, A., and Eckhorn, R. (2004). Task-related coupling from high-to low-frequency signals among visual cortical areas in human subdural recordings. *International Journal of Psychophysiology* 51, 97–116.
- Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., et al. (2006). High Gamma Power Is Phase-Locked to Theta Oscillations in Human Neocortex. *Science* 313, 1626–1628. doi:10.1126/science.1128115.
- Canolty, R. T., and Knight, R. T. (2010). The functional role of cross-frequency coupling. Available at: [https://www.researchgate.net/profile/Ryan\\_Canolty/publication/47382016\\_The\\_functional\\_role\\_of\\_cross-frequency\\_coupling/links/548651f00cf2ef34478bf713.pdf](https://www.researchgate.net/profile/Ryan_Canolty/publication/47382016_The_functional_role_of_cross-frequency_coupling/links/548651f00cf2ef34478bf713.pdf) [Accessed March 18, 2016].
- Cohen, M. X. (2008). Assessing transient cross-frequency coupling in EEG data. *Journal of Neuroscience Methods* 168, 494–499. doi:10.1016/j.jneumeth.2007.10.012.
- Cohen, M. X., Elger, C. E., and Fell, J. (2008). Oscillatory activity and phase–amplitude coupling in the human medial frontal cortex during decision making. *Journal of cognitive neuroscience* 21, 390–402.
- Colgin, L. L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., et al. (2009). Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* 462, 353–357.

- Crone, N. (1998). Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. I. Alpha and beta event-related desynchronization. *Brain* 121, 2271–2299. doi:10.1093/brain/121.12.2271.
- Crone, N. E., Miglioretti, D. L., Gordon, B., and Lesser, R. P. (1998). Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. *Brain* 121, 2301–2315.
- Darvas, F., Miller, K. J., Rao, R. P., and Ojemann, J. G. (2009). Nonlinear phase–phase cross-frequency coupling mediates communication between distant sites in human neocortex. *Journal of Neuroscience* 29, 426–435.
- Delorme, A., and Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of neuroscience methods* 134, 9–21.
- Dvorak, D., and Fenton, A. A. (2014). Toward a proper estimation of phase–amplitude coupling in neural oscillations. *Journal of Neuroscience Methods* 225, 42–56. doi:10.1016/j.jneumeth.2014.01.002.
- Friston, K. J. (1997). Another neural code? *Neuroimage* 5, 213–220.
- Hemptinne, C. de, Ryapolova-Webb, E. S., Air, E. L., Garcia, P. A., Miller, K. J., Ojemann, J. G., et al. (2013). Exaggerated phase–amplitude coupling in the primary motor cortex in Parkinson disease. *PNAS*. doi:10.1073/pnas.1214546110.
- Jensen, O., and Colgin, L. L. (2007). Cross-frequency coupling between neuronal oscillations. *Trends in cognitive sciences* 11, 267–269.
- Lakatos, P. (2005). An Oscillatory Hierarchy Controlling Neuronal Excitability and Stimulus Processing in the Auditory Cortex. *Journal of Neurophysiology* 94, 1904–1911. doi:10.1152/jn.00263.2005.
- Lee, J., and Jeong, J. (2013). Correlation of risk-taking propensity with cross-frequency phase–amplitude coupling in the resting EEG. *Clinical Neurophysiology*. doi:10.1016/j.clinph.2013.05.007.
- Lega, B., Burke, J., Jacobs, J., and Kahana, M. J. (2016). Slow-Theta-to-Gamma Phase–Amplitude Coupling in Human Hippocampus Supports the Formation of New Episodic Memories. *Cerebral Cortex* 26, 268–278. doi:10.1093/cercor/bhu232.



- Maris, E., van Vugt, M., and Kahana, M. (2011). Spatially distributed patterns of oscillatory coupling between high-frequency amplitudes and low-frequency phases in human iEEG. *Neuroimage* 54, 836–850.
- Nakhnikian, A., Ito, S., Dwiel, L. L., Grasse, L. M., Rebec, G. V., Lauridsen, L. N., et al. (2016). A novel cross-frequency coupling detection method using the generalized Morse wavelets. *Journal of Neuroscience Methods* 269, 61–73. doi:10.1016/j.jneumeth.2016.04.019.
- Newman, E. L., Gillet, S. N., Climer, J. R., and Hasselmo, M. E. (2013). Cholinergic Blockade Reduces Theta-Gamma Phase Amplitude Coupling and Speed Modulation of Theta Frequency Consistent with Behavioral Effects on Encoding. *Journal of Neuroscience* 33, 19635–19646. doi:10.1523/JNEUROSCI.2586-13.2013.
- Ozkurt, T. E. (2012). Statistically Reliable and Fast Direct Estimation of Phase-Amplitude Cross-Frequency Coupling. *Biomedical Engineering, IEEE Transactions on* 59, 1943–1950.
- Penny, W. D., Duzel, E., Miller, K. J., and Ojemann, J. G. (2008). Testing for nested oscillation. *Journal of Neuroscience Methods* 174, 50–61. doi:10.1016/j.jneumeth.2008.06.035.
- Shirvalkar, P. R., Rapp, P. R., and Shapiro, M. L. (2010). Bidirectional changes to hippocampal theta–gamma comodulation predict memory for recent spatial episodes. *PNAS* 107, 7054–7059. doi:10.1073/pnas.0911184107.
- Siegel, M., Warden, M. R., and Miller, E. K. (2009). Phase-dependent neuronal coding of objects in short-term memory. *PNAS* 106, 21341–21346. doi:10.1073/pnas.0908193106.
- Soto, J. L., and Jerbi, K. (2012). Investigation of cross-frequency phase-amplitude coupling in visuomotor networks using magnetoencephalography. in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE (IEEE)*, 1550–1553. Available at: [http://ieeexplore.ieee.org/xpls/abs\\_all.jsp?arnumber=6346238](http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6346238) [Accessed March 18, 2016].
- Tallon-Baudry, C., Bertrand, O., Delpuech, C., and Pernier, J. (1996). Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. *The Journal of Neuroscience* 16, 4240–4249.

- Tort, A. B. L., Komorowski, R., Eichenbaum, H., and Kopell, N. (2010). Measuring Phase-Amplitude Coupling Between Neuronal Oscillations of Different Frequencies. *Journal of Neurophysiology* 104, 1195–1210. doi:10.1152/jn.00106.2010.
- van der Meij, R., Kahana, M., and Maris, E. (2012). Phase-Amplitude Coupling in Human Electroencephalography Is Spatially Distributed and Phase Diverse. *Journal of Neuroscience* 32, 111–123. doi:10.1523/JNEUROSCI.4816-11.2012.
- Voytek, B. (2010). Shifts in gamma phase–amplitude coupling frequency from theta to alpha over posterior cortex during visual tasks. *Frontiers in Human Neuroscience* 4. doi:10.3389/fnhum.2010.00191.
- Voytek, B., D'Esposito, M., Crone, N., and Knight, R. T. (2013). A method for event-related phase/amplitude coupling. *NeuroImage* 64, 416–424. doi:10.1016/j.neuroimage.2012.09.023.
- Watrous, A. J., Deuker, L., Fell, J., and Axmacher, N. (2015). Phase-amplitude coupling supports phase coding in human ECoG. *eLife* 4, e07886.
- Weaver, K. E., Wander, J. D., Ko, A. L., Casimo, K., Grabowski, T. J., Ojemann, J. G., et al. (2016). Directional patterns of cross frequency phase and amplitude coupling within the resting state mimic patterns of fMRI functional connectivity. *NeuroImage* 128, 238–251.
- Yanagisawa, T., Yamashita, O., Hirata, M., Kishima, H., Saitoh, Y., Goto, T., et al. (2012). Regulation of Motor Representation by Phase–Amplitude Coupling in the Sensorimotor Cortex. *J. Neurosci.* 32, 15467–15475. doi:10.1523/JNEUROSCI.2929-12.2012.