Estimating transient phase-amplitude coupling using local mutual information

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Outline

Intro to theory
- Intro to Phase-Amplitude Coupling (PAC)
- Local (pointwise) Information Theory Measures
- Estimating PAC with Local Mutual Information

Results
- Simulations
- ECoG data analysis

Demo
Brain oscillations

<table>
<thead>
<tr>
<th>Frequency Range</th>
<th>Waveform</th>
</tr>
</thead>
<tbody>
<tr>
<td>gamma 32 - 100 Hz</td>
<td><img src="image" alt="Gamma Oscillations" /></td>
</tr>
<tr>
<td>beta 13 - 32 Hz</td>
<td><img src="image" alt="Beta Oscillations" /></td>
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<tr>
<td>alpha 8 - 13 Hz</td>
<td><img src="image" alt="Alpha Oscillations" /></td>
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<tr>
<td>theta 4 - 8 Hz</td>
<td><img src="image" alt="Theta Oscillations" /></td>
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<tr>
<td>delta 0.5 - 4 Hz</td>
<td><img src="image" alt="Delta Oscillations" /></td>
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</tbody>
</table>
Cross-Frequency Coupling

Found both in animals and humans

Associated to epilepsy, Parkinson’s disease, Alzheimer’s disease, schizophrenia, obsessive-compulsive disorder and mild cognitive impairment.

(Mormann et al., 2005; Cohen, 2008; Osipova et al., 2008; Tort et al., 2008, 2009, 2010; Cohen et al., 2009a,b; Colgin et al., 2009; Axmacher et al., 2010a,b; Voytek et al., 2010)

Jirsa and Muller, 2013
Amplitude Modulation Fundamentals

**Modulator**

\[ v_{\text{mod}} = V_{\text{mod}} \sin(2\pi f_{\text{mod}} t) \]

**Carrier**

\[ v_{\text{carr}} = V_{\text{carr}} \sin(2\pi f_{\text{carr}} t) \]

**AM Signal**

\[ v_{\text{AM}} = v_{\text{carr}} \sin(2\pi f_{\text{carr}} t) + \left[ V_{\text{mod}} \sin(2\pi f_{\text{mod}} t) \right] \sin(2\pi f_{\text{carr}} t) \]
By mean of the Hilbert transform a signal can be expressed as its analytic signal.

\[ S_t = s_{mt} e^{i\phi_t} \]

\[ s_{mt} = |S_t| \]

\[ \phi_t = \arg[S_t] \]

Instantaneous amplitude (or the envelope)

Instantaneous phase.

\( \text{abs(hilbert}(S_t)) \)

\( \text{angle(hilbert}(S_t)) \)
Computing PAC

Electrophysiological signal

- **High frequency band** $f_{\text{Amp}}$ (e.g: 30-50Hz)
- **Low frequency band** $f_{\text{Phase}}$ (e.g: 5-12Hz)

### Mean Vector Length

**Canolty et al. 2006**

- Composite vectors $z_t = A_t e^{i\phi_t}$
- Mean vector length

$$MVLmi = \left| \frac{1}{N} \sum_{t=1}^{T} z_t \right|$$

### Kullback-Leibler Modulation Index

**Tort et al. 2010**

$$P(j) = \frac{\langle A_{f_A}, \phi_r \rangle (j)}{\sum_{k=1}^{n} \langle A_{f_A}, \phi_r \rangle (k)}$$

$$MI = \frac{D_{KL}(P||U)}{\log N}$$

Compute the Kullback-Leibler with a uniform distribution

### GLM Measure

**Penny et al. 2008**

$$A_t = X\beta + e$$

$$X = \begin{bmatrix} \cos\phi_1 & \sin\phi_1 & 1 \\ \vdots & \vdots & \vdots \\ \cos\phi_{\text{max}} & \cos\phi_{\text{max}} & 1 \end{bmatrix}$$

Use the explained variance as an index of PAC

ERPAC

**Voytek et al. 2013**

Time resolved PAC by applying GLM Measure for each latency in event related data
Information Theory Definitions

Given the measurements $x$ and $y$ of the RV $X$ and $Y$

**Mutual Information**: average reduction in uncertainty about $X$ given the knowledge of the value of $Y$

\[
I(X,Y) = - \sum p(x,y) \log_2 \frac{p(x|y)}{p(x)}
\]

\[
I(X,Y) = H(X) - H(X|Y)
\]

The mutual information is a measure of dependency (both linear and nonlinear) between the two random variables $X$ and $Y$
KSG Mutual Information Estimator
(Kraskov, Stogbauer and Grassberger)

- Extension of Kozachenko-Leonenko estimator of Entropy
- Non-parametric estimator
- Data efficient
- Minimal bias

Assume the joint space $Z = (X, Y)$

**Determining $k$-nearest neighbors for each $z_i$**

$$||z - z'|| = \max\{||x - x'||, ||y - y'||\}$$

- Find $K$-nearest neighbor of $z_i$ (a distance $\frac{\varepsilon}{2}$)
- Count the number of points $n_x(i)$ and $n_y(i)$ in the marginal space within a row (and column) of width $\varepsilon$

**Estimate Mutual Information**

$$I(X,Y) = \psi(k) - \left\{ \psi(n_x + 1) + \psi(n_y + 1) \right\} + \psi(N)$$

*Kraskov et al. 2004*
Estimating local Mutual Information

Lizier et al. 2008, considered the estimation of Local MI from the KSG estimator.

**Estimate Mutual Information**

\[ I(X, Y) = \psi(k) - \psi(n_x + 1) + \psi(n_y + 1) + \psi(N) \]

**Estimating Local Mutual Information**

\[ i(x, y) = \psi(k) - \psi(n_x + 1) - \psi(n_y + 1) + \psi(N) \]

*Kraskov et al. 2004*

Unrolling expectation

Goal:
Estimating PAC using local Mutual Information
Instantaneous MIPAC

Data model: Continuous data \((1 \times N_{lat})\)

\[ \Delta v = \infty; \] % Initialize Percentage variance reduction
\[ c = 1; \]

\[ \text{while} \quad \Delta v_{\text{var,threshold}} < \Delta v \]
\[ \text{Estimate } i(A_t, \phi_t) \text{ for } k = c; \]
\[ \text{Compute } \Delta v_{\text{var}}; \]
\[ c = c + 1; \]

End

\[ \text{MIPAC = Low-pass filter } i(A_t, \phi_t) \text{ at } f_{\text{phase}}; \]

Assume the joint space \(Z = (A_t, \phi_t)\)

\[ \|Z - Z'\| = \max(\|\phi - \phi'\|, \|A - A'\|) \]
Circular norm (Berens, 2009) Euclidean norm

\[ i(x, y) = \psi(k) - \psi(n_x + 1) - \psi(n_y + 1) + \psi(N) \]

\[ \text{High frequency band } f_{\text{Amp}} \text{ (e.g: 30-50Hz)} \]
\[ A_t = \text{abs(hilbert}(S_A)) \]
\[ \text{Low frequency band } f_{\text{phase}} \text{ (e.g: 5-12Hz)} \]
\[ A_t = \text{angle(hilbert}(S_{\phi})) \]

Martinez-Cancino et al 2018 (under review in Neuroimage)
Event-related MIPAC

Data model:

Low frequency band ($f_{phase}$)

$A_t = \text{angle}(\text{hilbert}(S_{\phi}))$

Full cycle of $f_{phase}$

High frequency band ($f_{amp}$)

$A_t = \text{abs}(\text{hilbert}(S_{\phi}))$

Event Related MIPAC (cyclostationary)

% Epoched data

$$\text{for } t = 1: N_{lat}$$

$\Delta_{var} = \text{Inf};$ % Initialize Percentage variance reduction

$c = 1;$

$\text{while } \Delta_{var, threshold} < \Delta_{var}$

Estimate $i(A_{trl,t}(::,t), \phi_{trl,t}(::,t))$ for $k=c;$

(Neighbors are count in a latency window)

Compute $\Delta_{var}$;

$c = c+1;$

end

end

MIPAC = Low-pass filter $i(A_{trl,t}, \phi_{trl,t})$ at $f_{phase}.$

Martinez-Cancino et al 2018 (under review in Neuroimage)
Inst. MIPAC and Event-related MIPAC

MIPAC

Inst. Amplitude

Inst. Phase

MIPAC estimate

Latency

Event-related MIPAC

Inst. Amplitude

Latency windows to compute neighbors

Inst. Phase

Latency

Trials

MIPAC estimate

Latency

Trials

Event Related MIPAC

Latency

Latency
MIPAC Simulations
Simulation 1.1: Instantaneous MIPAC

\[ f_{\text{mod}} = 5Hz \]
\[ f_{\text{carr}} = 40Hz \]
\[ S_{\text{rate}} = 500Hz \]

(A) Block-shaped waveform modulation strength.
(B) Simulated signal
(C) Estimated MIPAC (red), and local MI (light red)

Martinez-Cancino et al 2018 (under review in Neuroimage)
Simulation 1.2: Instantaneous MIPAC

\( f_{mod} = 5\text{Hz} \)
\( f_{carr} = 40\text{Hz} \)
\( S_{rate} = 500\text{Hz} \)

(A) Saw-tooth shape waveform modulation strength.
(B) Simulated signal
(C) Estimated MIPAC (red), and local MI (light red)

Martinez-Cancino et al 2018 (under review in Neuroimage)
Simulation 1.3: Instantaneous MIPAC

\[ f_{\text{mod}} = 5\text{Hz} \]
\[ f_{\text{carr}} = 40\text{Hz} \]
\[ S_{\text{rate}} = 500\text{Hz} \]

(A) Absolute value of a sinusoid used as modulation strength.
(B) Simulated signal
(C) Estimated MIPAC (red), and local MI (light red)

Martinez-Cancino et al 2018 (under review in Neuroimage)
Simulation 2: Instantaneous MIPAC Noise Added

$$f_{\text{carr}} = 40\, \text{Hz}$$  \quad  $$S\text{rate} = 500\, \text{Hz}$$  \quad  $$f_{\text{mod}} = 5\, \text{Hz}$$  \quad  $$\text{SNR} = 10$$

MIPAC from a simulated Phase-Amplitude-Modulated signal with noise added. MIPAC was estimated from the same signals generated the previous simulations, but with a SNR= 10. Estimated MIPAC (red), and local MI (light red).
MIPAC convergence

Martinez-Cancino et al 2018 (under review in Neuroimage)
Simulation 3: Event-related MIPAC

**ER PAC data simulation**

Event related MIPAC and ERPAC (Voytek et al, 2013) were used to estimate PAC

\[ f_{mod} = 5Hz \]

\[ f_{carr} = 40Hz \]

\[ S_{rate} = 500Hz \quad SNR = 10 \]

Each trial was shifted 1-100 pts
Simulation 4: MIPAC & MImi

\[ f_{mod} = 7 \text{Hz} \]
\[ f_{carr} = 50 \text{Hz} \]
\[ S_{rate} = 500 \text{Hz} \]

Grand Mean

MI modulation index

Martinez-Cancino et al 2018 (under review in Neuroimage)
MIPAC application to real data
ECoG Data

Subject
• Clinical monitoring and localization of seizure foci
• 1 subject (mv)
• ECoG channels in: Inf. Temp. Gyrus
  Lingual Gyrus
  Fusiform Gyrus

Experimental design
• Images of Houses and Faces were presented randomly
• 3 runs 100 presentations each (50 H / 50F)

Preprocessing
Performed in EEGLAB *(Delorme and Makeig, 2004)*

1. Artifact removal
2. CAR
3. Resampling to 512Hz
4. Line noise removal ~$(60, 120)$ Hz
   Hamming-windowed FIR notch filter
5. Extract epochs time-locked to stimulus presentations  $[-400,800]$ ms

Original publication:
The physiology of perception in human temporal lobe is specialized for contextual novelty
Kai J. Miller, Dora Hermes, Nathan Witthoft, Rajesh P. N. Rao, Jeffrey G. Ojemann
ECoG Data: Mlmi in action

Martinez-Cancino et al 2018 (under review in Neuroimage)
ECoG Data: Event Related Potential Image

Channel 16
ECoG Data: Time-Frequency Decomposition

[2, 120]Hz FFTs and Hanning window tapering
Generated using EEGLAB function *newtimef.m*

Martinez-Cancino et al 2018 (under review in Neuroimage)
**ECoG Data: MIPAC vs ERPAC**

*Event-related MIPAC and ERPAC (Voytek et al. 2014) were computed*

\[ f_{phase} = 16 \text{ Hz} \]

\[ f_{amp} = 95\text{Hz} \]
**ECoG Data: MIPAC Image**

ER-MIPAC computed for *Faces* presentation

\[ f_{\text{phase}} = 16 \text{ Hz} \]

\[ f_{\text{amp}} = 95\text{Hz} \]
Conclusions

- An approach to estimating dynamical PAC in electrophysiological signals was proposed.
- The method was validated on simulated PAC signals.
- Application to human ECoG data showed positive results.
DEMO

Available from: https://bitbucket.org/ramonmc/pop_pac/
Acknowledgments

Coauthors

Joseph Heng
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Roberto Sotero
Scott Makeig

This work was supported by National Institutes of Health grant 5R01-NS047293-12 and by a gift from The Swartz Foundation (Old Field NY)