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>Oscillation Type</th>
<th>Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>gamma</td>
<td>32 - 100 Hz</td>
</tr>
<tr>
<td>beta</td>
<td>13 - 32 Hz</td>
</tr>
<tr>
<td>alpha</td>
<td>8 - 13 Hz</td>
</tr>
<tr>
<td>theta</td>
<td>4 - 8 Hz</td>
</tr>
<tr>
<td>delta</td>
<td>0.5 - 4 Hz</td>
</tr>
</tbody>
</table>

EEG
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 means of the Hilbert transform a signal can be expressed as its analytic signal.

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

Instantaneous amplitude (or the envelope)

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

Instantaneous phase.

\[
\phi_t = \text{arg}[S_t]
\]

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

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

Electrophysiological signal

\[ A_t = \text{abs}(\text{hilbert}(S_A)) \]

\[ \phi_t = \text{angle}(\text{hilbert}(S_\phi)) \]

Mean Vector Length

\[ MVLmi = \left| \frac{1}{N} \sum_{t=1}^{N} z_t \right| \]

Kullback-Leibler Modulation Index

\[ p(j) = \frac{\langle A_{f_A} \rangle \phi_{f_P}(j)}{\sum_{k=1}^{N} \langle A_{f_A} \rangle \phi_{f_P}(k)} \]

\[ MI = \frac{D_{KL}(P,U)}{\log N} \]

Compute the Kullback-Leibler with a uniform distribution

GLM Measure

\[ A_t = X\beta + e \]

Explained variance as an index of PAC

ERPAC

Time resolved ‘average’ PAC by applying

GLM Measure

for each latency in event related data
Computing PAC

Electrophysiological signal

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

$A_t = \text{abs}(\text{hilbert}(S_A))$

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

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

**Kullback-Leibler Modulation Index**

\[
P(j) = \frac{\langle A_{j}\rangle_{f_p} \phi (j)}{\sum_{k=1}^{N} \langle A_{k}\rangle_{f_p} \phi (k)}
\]

\[
MI = \frac{D_{KL}(P, U)}{\log N}
\]

Compute the Kullback-Leibler with a uniform distribution

**Mean Vector Length**

Canolty et al. 2006

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

\[
\text{MVLmi} = \left| \frac{1}{N} \sum_{t=1}^{N} z_t \right|
\]

**GLM Measure**

Tort et al. 2010

\[
A_t = X\beta + e
\]

\[
X = \begin{bmatrix}
\cos\phi_1 & \sin\phi_1 & 1 \\
\vdots & \vdots & \vdots \\
\cos\phi_N & \cos\phi_N & 1
\end{bmatrix}
\]

Explained variance as an index of PAC

**ERPAC**

Voytek et al. 2013

Time resolved ‘average’ PAC by applying GLM Measure for each latency in event related data

\[\text{GLM Measure} = 1 \times \text{lat}\]
Can we do better than this?
YES WE CAN
Goal: Estimating PAC temporal dynamics
Information Theory Definitions

**Shannon Entropy:** average amount of uncertainty associated to any measure $x$ of $X$

$$H(X) = -\sum_x p(x) \log_2 p(x)$$

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

$$I(X,Y) = H(X) - H(X|Y)$$

Non-linear form of correlation !!!!!!!
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**

$$I(X,Y) = \psi(k) - \langle \psi(n_x+1) + \psi(n_y+1) \rangle + \psi(N)$$

*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

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

Unrolling expectation

Estimating Local Mutual Information

\[ i(x,y) = \psi(k) - \psi(n_x + 1) - \psi(n_y + 1) + \psi(N) \]
Goal:
Estimating PAC using local Mutual Information
**Instantaneous MIPAC**

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

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

\[
\|Z - Z'\| = \max\left\{\left\|\phi - \phi'\right\|, \left\|A - A'\right\|\right\}
\]

Circular norm \(\quad\)

Euclidean norm

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

**Inst. MIPAC**

% Single trials or continuous

\[
\Delta_{var} = \infty; \quad % \text{Initialize Percentage variance reduction}\n\]

\[c = 1;\]

**while** \(\Delta_{var\_threshold} < \Delta_{var}\)

\[
\text{Estimate } i(A_t, \phi_t) \text{ for } k = c ;
\]

\[
\text{Compute } \Delta_{var} ;
\]

\[c = c + 1 ;\]

**End**

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

Inst. Amplitude

Inst. Phase

MIPAC estimate

Latency

Inst. MIPAC
Event-related MIPAC

Data model:

Low frequency band ($f_{\text{phase}}$)

\[
A_t = \text{angle}\left(\text{hilbert}(S_{\phi})\right)
\]

Full cycle of $f_{\text{phase}}$

\[
\phi_{t}\phantom{t}
\]

High frequency band ($f_{\text{amp}}$)

\[
A_t = \text{abs}\left(\text{hilbert}(S_A)\right)
\]

Event Related MIPAC (cyclostationary)

% Epoched data

\[
\text{for } t = 1: N_{\text{lat}}
\]

\[
\Delta_{\text{var}} = \infty; \text{ } \% \text{ Initialize Percentage variance reduction}
\]

\[
c = 1;
\]

\[
\text{while } \Delta_{\text{var.threshold}} < \Delta_{\text{var}}
\]

Estimate $i \left(A_{t_{\text{rl}},t}(\cdot,t), \phi_{t_{\text{rl}},t}(\cdot,t)\right)$ for $k=c$ ;

(Neighbors are count in a latency window)

Compute $\Delta_{\text{var}}$ ;

\[
c = c+1;
\]

end

end

\[
\text{MIPAC} = \text{Low-pass filter } i(A_{t_{\text{rl}},t}, \phi_{t_{\text{rl}},t}) \text{ at } f_{\text{phase}}.
\]
Event-related MIPAC in a nutshell
MIPAC Simulations
Simulation 1.1: Instantaneous MIPAC

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

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

(Martinez-Cancino et al., 2019)
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., 2019)
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., 2019)
Simulation 2: Event-related MIPAC

**ER PAC data simulation**

$f_{mod} = 5Hz$  
$f_{carr} = 40Hz$  
$S_{rate} = 500Hz$  $SNR = 10$

Each trial was shifted 1-100 pts

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

(Martinez-Cancino et al., 2019)
Simulation 4: MIPAC & MImi

\[ f_{\text{mod}} = 7\text{Hz} \]
\[ f_{\text{carr}} = 50\text{Hz} \]
\[ S_{\text{rate}} = 500\text{Hz} \]
Inst. MIPAC and Event-related MIPAC

MIPAC

Event-related MIPAC
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)

400 ms

**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., 2019)
ECoG Data: Event Related Potential Image

Channel 16

(Martinez-Cancino et al., 2019)
Event-related MIPAC and ERPAC (Voytek et al. 2014) were computed

\[ f_{\text{phase}} = 16 \text{ Hz} \]
\[ f_{\text{amp}} = 95 \text{Hz} \]
ECoG Data: MIPAC Image

ER-MIPAC computed for *Faces* presentation

\[ f_{\text{phase}} = 16 \, \text{Hz} \]
\[ f_{\text{amp}} = 95 \, \text{Hz} \]

(Martinez-Cancino et al., 2019)
Conclusions

• The method was validated on simulated PAC signals
• Application to human ECoG data showed positive results

Future Direction
ERPAC Tools

Available from: [https://github.com/nucleuscub/pop_pac](https://github.com/nucleuscub/pop_pac)
Acknowledgments

Coauthors

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