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Day 2: Characterization of the local field potential and its relation to spiking activity

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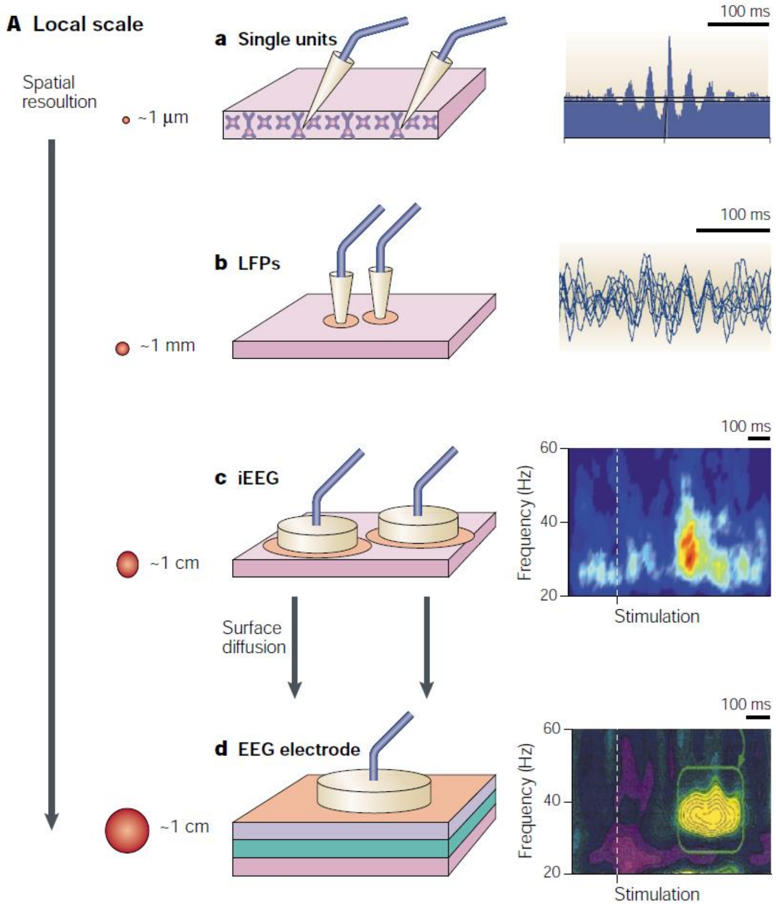
Forschungszentrum Jülich, Jülich, Germany (Nov. 24-27, 2014)

Outline

- **Introduction**
  - What is LFP? | LFP origin | oscillations in LFP
- **Spectral Analysis**
  - Fourier transform | power spectrum | coherency
- **Phase Locking Analysis**
  - Hilbert transform | wavelet transform | phase locking value
- **Spike-LFP Relation**
  - spike triggered average | spike field coherence | period histogram | vector strength

Introduction | what is local field potential?

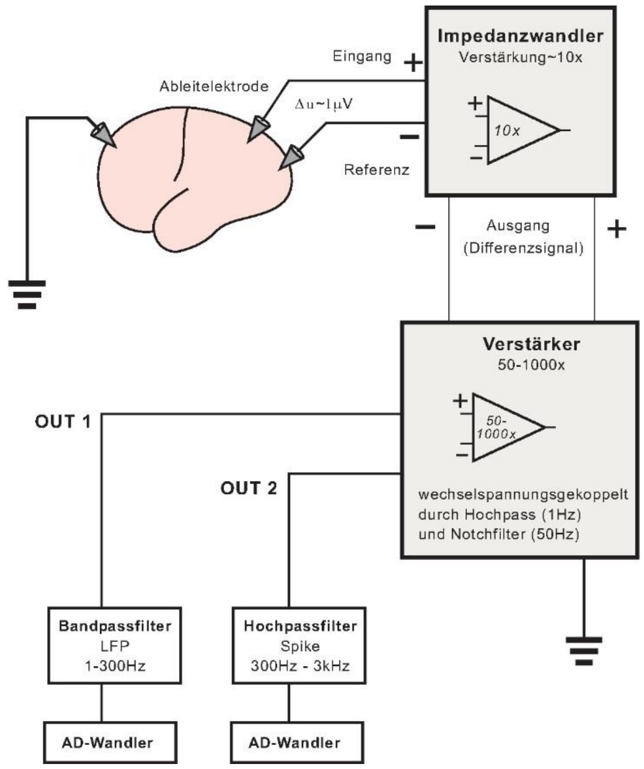
- Local field potential (LFP) is…
  - electric potential
    → high temporal resolution
  - measured within the brain using microelectrodes
    → high spatial resolution
  - caused (primarily) by excitatory synaptic currents of nearby neurons
    → reflection of inputs to the local neuronal circuit

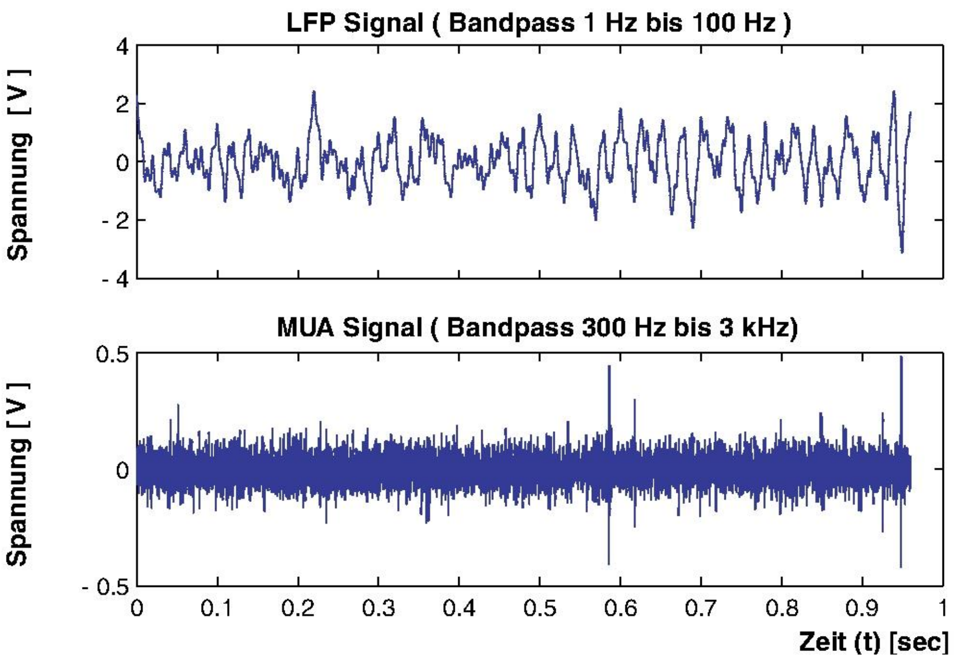


Varela et al. (2001) *Nat. Rev. Neurosci. 2*:229–39

Introduction | how to obtain the LFP?

- LFP is the low-pass filtered voltage signal





Introduction | what is the origin of the LFP?

- Under assumptions of...
  - Quasi-static (< 1 kHz) electric field (= capacitive and inductive effects are negligible)
  - Isotropic extracellular medium (= conductance is a constant scalar, instead of a tensor)

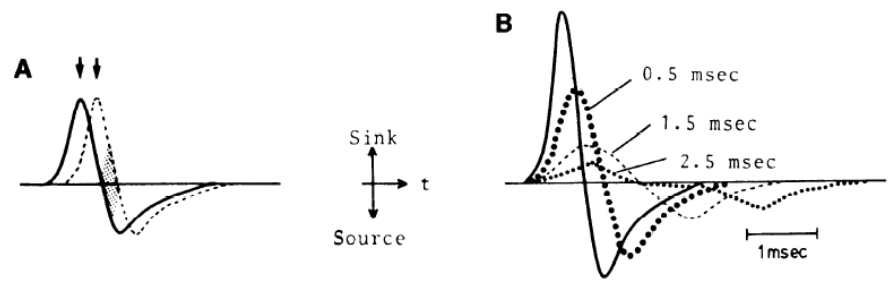
$$\phi(\vec{r}) = \sum_i \frac{I_i}{4\pi\sigma|\vec{r} - \vec{r_i}|}$$

$\phi(\vec{r})$: field potential at $\vec{r}$ I_i: current source at $\vec{r_i}$ σ: conductance of extracellular medium

  - Field potential $\phi(\vec{r})$ is dependent only on the magnitudes and positions of current sources I_i
- What causes current sources in the extracellular space?
  → transmembrane currents of neurons

Introduction | cause of transmembrane current

- Action potentials (APs)
  - Biphasic in time, easily cancelled out by temporal jitter of multiple APs



Mitzdorf (1985) *Physiol. Rev.* 65:37-100

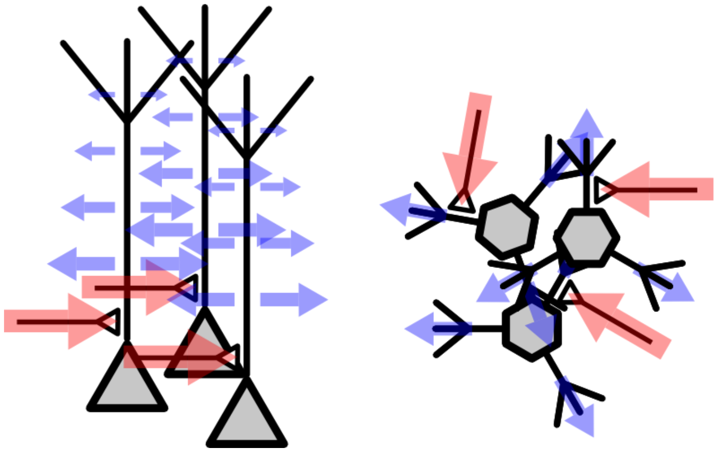
- Excitatory and inhibitory post-synaptic potentials (EPSP, IPSP)
  - Ratio of EPSP- vs. IPSP-related current components = 5:1 (Mitzdorf, 1985)

- EPSP is the dominant cause of the macroscopic transmembrane current (and therefore the LFPs) in the brain.

Introduction | cell morphology and LFP

- A cell is always electrically neutral
  → current sink is cell-wise counter-balanced by current source

- Spatial distribution of sinks and sources depends on cell shapes
  - Overlapping current sinks and sources cancel each other
  - Only localized current sinks and sources contribute to macroscopic LFP



- Excitatory synaptic inputs to pyramidal neurons contribute most to the cortical LFP

Introduction | an example LFP recording

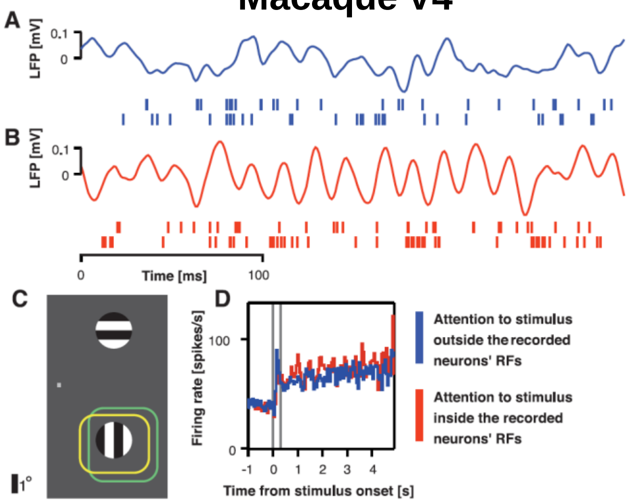
- Laminar LFP recording from the area IT of an anesthetized macaque (data by courtesy of Prof. Tamura, Osaka Univ.)

LFP movie

Introduction | oscillations in LFP

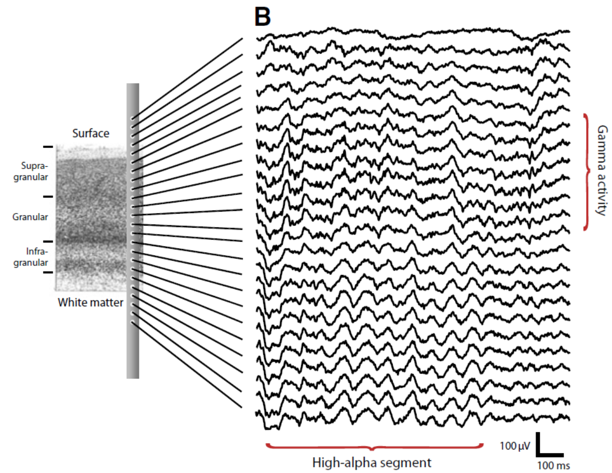
- Ubiquitous oscillations in LFP
  - in both response and ongoing activity
  - in a wide range of frequency

Macaque V4



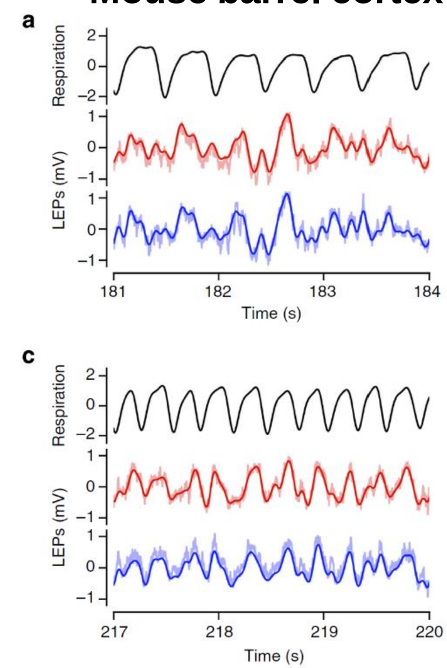
Fries et al. (2001). *Science* 291:1560–3

Macaque V1



Spaak et al. (2012) *Curr. Biol.* 2:2313–8

Mouse barrel cortex



Ito et al. (2014) *Nat. Commun.* 5:3572

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- **Spectral Analysis**
  - Fourier transform | power spectrum | coherency
- **Phase Locking Analysis**
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  - spike triggered average | spike field coherence | period histogram | vector strength

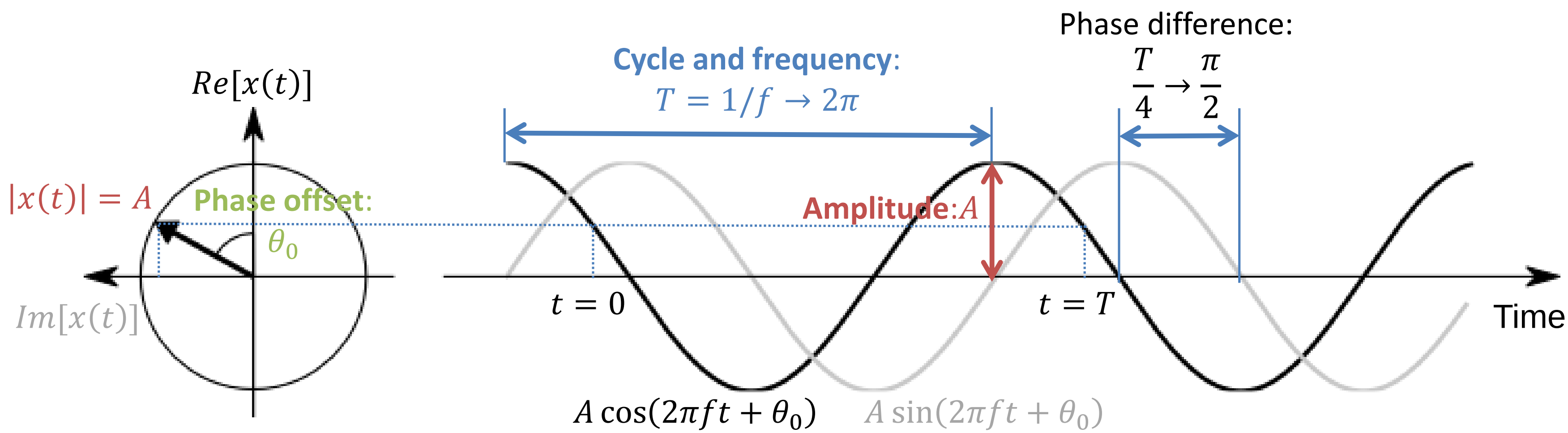
Spectral Analysis | representation of oscillation

- Sinusoid: $x(t) = A\cos(2\pi f t + \theta_0) = A\cos(2\pi(-f)t + (-\theta_0))$

$$\downarrow$$

$$x(t) = A\cos(2\pi f t + \theta_0) + i\sin(2\pi f t + \theta_0)$$

$$= A\exp[i(2\pi f t + \theta_0)]$$



Spectral Analysis | Fourier transform

- Decomposition into sinusoids

  $x(t)$: time-varying signal (real-valued scalar)

  $X(f)$: **Fourier transform** of $x(t)$

$$X(f) = \int_{-\infty}^{\infty} x(t) \exp(-i2\pi f t)\, dt \longleftrightarrow x(t) = \int_{-\infty}^{\infty} X(f) \exp(i2\pi f t)\, df$$

  $X(f)$ is a complex function of frequency : f

$$X(f) = \mathrm{Re}[X(f)] + i\mathrm{Im}[X(f)] = \boxed{A(f)}\exp[\boxed{i\theta(f)}]$$

Amplitude **Phase**

$$A(f) := \sqrt{\mathrm{Re}[X(f)]^2 + \mathrm{Im}[X(f)]^2}$$

$$\theta(f) := \mathrm{atan2}(\mathrm{Im}[X(f)], \mathrm{Re}[X(f)])$$

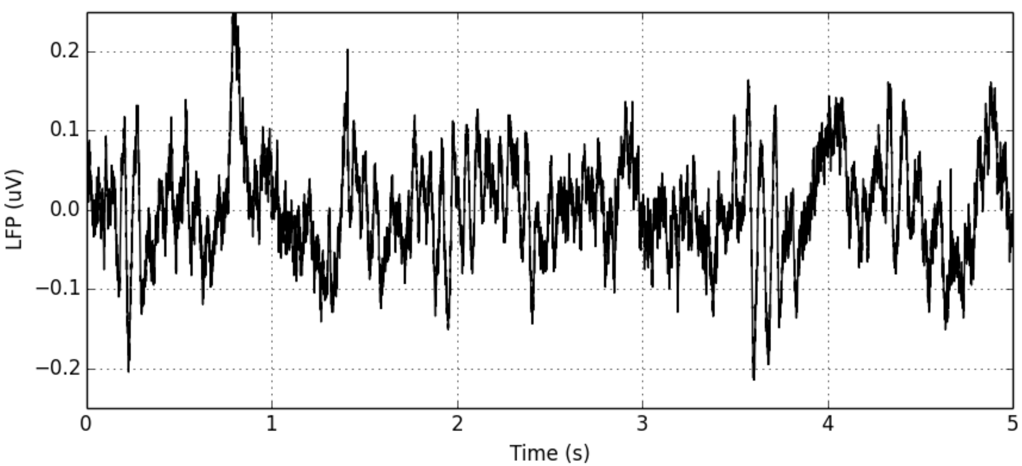
$$x(t) = \int_{-\infty}^{\infty} X(f) \exp(i2\pi f t)\, df$$ (Inverse Fourier transform)

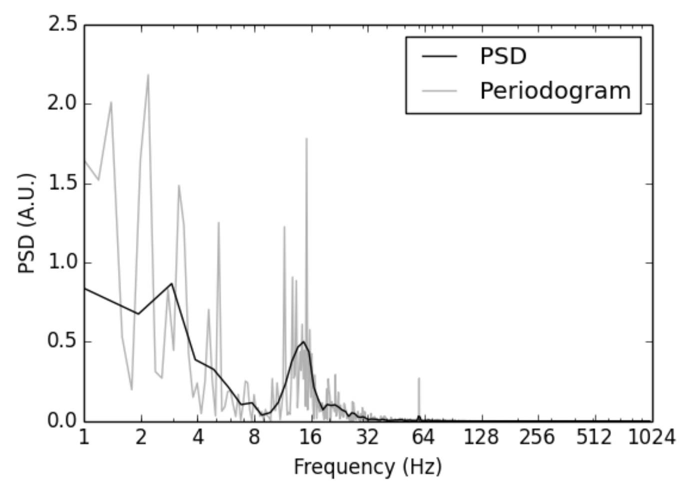
$$= \int_{-\infty}^{\infty} \boxed{A(f) \exp\left[i\left(2\pi f t + \theta(f)\right)\right]}\, df$$

f-Hz sinusoid of amplitude $A(f)$ and phase-offset $\theta(f)$

Spectral Analysis | power spectrum

- Estimation of **power spectral density (PSD)**
  - **Periodogram**:
    $$p_{xx}(f) = X(f) \cdot X^*(f) = A\exp(i\theta) \cdot A\exp(-i\theta) = A(f)^2$$
  - **Welch's method**
    - Cut a signal into segments of an identical length
    - Multiply the segments by a window function (edge smoothing)
    - Compute periodograms of the segments and average them





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Spectral Analysis | cross-spectrum

- A measure of correlation between spectral components in two signals
  - Signals: $x(t) \xrightarrow{FT} X(f); \quad y(t) \xrightarrow{FT} Y(f)$
  - **Cross-periodogram**:

$$p_{xy}(f) = X(f) \cdot Y^*(f) = A_x \exp(i\theta_x) \cdot A_y \exp\left(-i\theta_y\right)$$
$$= A_x(f) A_y(f) \exp\left[i \underbrace{\boxed{\left(\theta_x(f) - \theta_y(f)\right)}}_{\text{Phase difference}}\right]$$

  - **Cross-spectrum**
    - Estimated from the cross-periodograms of signal segments by Welch's method

$$C_{xy}(f) = \langle p_{xy}^{seg}(f) \rangle = \overbrace{\boxed{\left|C_{xy}\right|}}^{\text{Amplitude cross-spectrum}} \exp\left(i \boxed{\theta_{xy}}\right)$$

Phase cross-spectrum
(average phase difference)

$\langle \cdots \rangle$: average over segments by Welch's method

Spectral Analysis | coherency

- **Amplitude cross-spectrum**
  - $\left|C_{xy}(f)\right|$ takes values between 0 and $\left(|C_{xx}(f)|\left|C_{yy}(f)\right|\right)^{1/2}$, depending on the phase coherency between the signals x and y at frequency f
- **Coherency**
  - cross-spectrum normalized by auto-spectra (= power spectra) of the original signals

$$COH_{xy}(f) = \frac{\left|C_{xy}(f)\right|}{\sqrt{|C_{xx}(f)|\left|C_{yy}(f)\right|}}$$

$COH_{xy}(f) = 1 \longrightarrow$ perfect coherence at frequency f

$COH_{xy}(f) = 0 \longrightarrow$ independence

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Phase Locking Analysis | motivation

- Spectral analysis yields measures in *the frequency domain*
  - No direct insights into signals' behavior in *the time domain*
  - Assumption: signals are stationary in time
- In reality, neuronal signals are **highly nonstationary**
  - Stimuli are typically not constantly presented but only at specific times ("trials")
  - Even without external stimuli, spontaneous activities of neuronal systems are not stationary, but highly irregular
- Need for time-resolved spectral analysis
  - In concrete, methods to **estimate instantaneous amplitude and phase of oscillatory signals**
    → Hilbert transform, wavelet transform

Phase Locking Analysis | convolution theorem

- Convolution of $x(t)$ and $h(t)$: $(x * h)(t) = \int_{-\infty}^{\infty} x(\tau)h(t-\tau)d\tau$
- **Convolution theorem**

$$
\begin{array}{ccc}
x(t), h(t) & \overset{FT}{\longleftrightarrow} & X(f), H(f) \\
\textbf{convolution} \downarrow & & \downarrow \textbf{frequency-wise multiplication} \\
(x * h)(t) & \overset{FT}{\longleftrightarrow} & X(f) \cdot H(f)
\end{array}
$$

  - Fourier transform of the convolution of x and h is the (frequency-wise) product of Fourier transforms of x and h
  - You can compute convolution by 1) Fourier transform the functions, 2) multiply them frequency-wise, and 3) inverse Fourier transform the product

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Phase Locking Analysis | Hilbert transform

- **Hilbert transform** of $x(t)$:

$$\mathcal{H}[x(t)] = (x * h)(t), \qquad h(t) = \frac{1}{\pi t}$$

  - convolution with $h(t)$ in the time domain represents $\pm\pi/2$ radian rotation in the frequency domain

$$h(t) = \frac{1}{\pi t} \xrightarrow{FT} H(f) = \begin{cases} i & (f > 0) \\ 0 & (f = 0) \\ -i & (f < 0) \end{cases}$$

Example: multiplication by i and $-i$

$$(\cos\theta + i\sin\theta)\cdot i = -\sin\theta + i\cos\theta = \cos(\theta + \pi/2) + i\sin(\theta + \pi/2)$$
$$(\cos\theta + i\sin\theta)\cdot(-i) = \sin\theta - i\cos\theta = \cos(\theta - \pi/2) + i\sin(\theta - \pi/2)$$

  - By Hilbert transform, each and every frequency component of $x(t)$ is phase-shifted by $\pi/2$ radian

Phase Locking Analysis | analytic signal

- **Analytic signal**: complex signal of which imaginary part is Hilbert transform of its real part (i.e., $x(t) + i\,\mathcal{H}[x(t)]$)
  - Example: complex sinusoid $A(\cos 2\pi f t + i \sin 2\pi f t)$
  - Amplitude and phase of analytic signal are defined as:

$$\hat{x}(t) = x(t) + i\mathcal{H}[x(t)] = A_x(t)\exp[i\theta_x(t)]$$

$$A_x(t) = \sqrt{x(t)^2 + \mathcal{H}[x(t)]^2} \quad \theta_x(t) = \mathrm{atan2}[\mathcal{H}[x(t)], x(t)]$$

  - For *any* real-valued signal $x(t)$, a corresponding analytic signal can be constructed by Hilbert transform
  - This enables estimation of instantaneous amplitude $A_x(t)$ and phase $\theta_x(t)$ at any time t

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Phase Locking Analysis | wavelet transform

- Time- and frequency-resolved decomposition

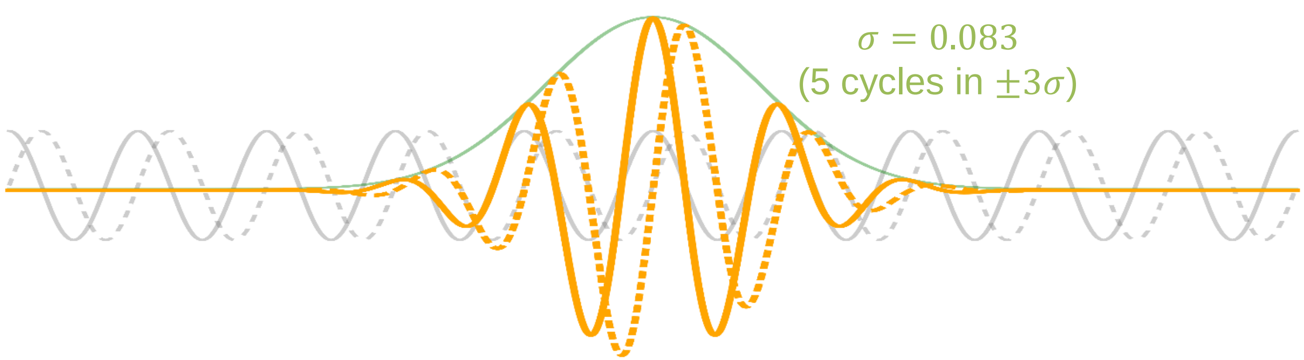
  $x(t)$: time-varying signal (real-valued scalar)

  $W_x(t, f)$: **wavelet transform** of the signal

$$W_x(\tau, f) := \int_{-\infty}^{\infty} x(t) \cdot \Psi_{\tau,f}^{*}(t) dt$$

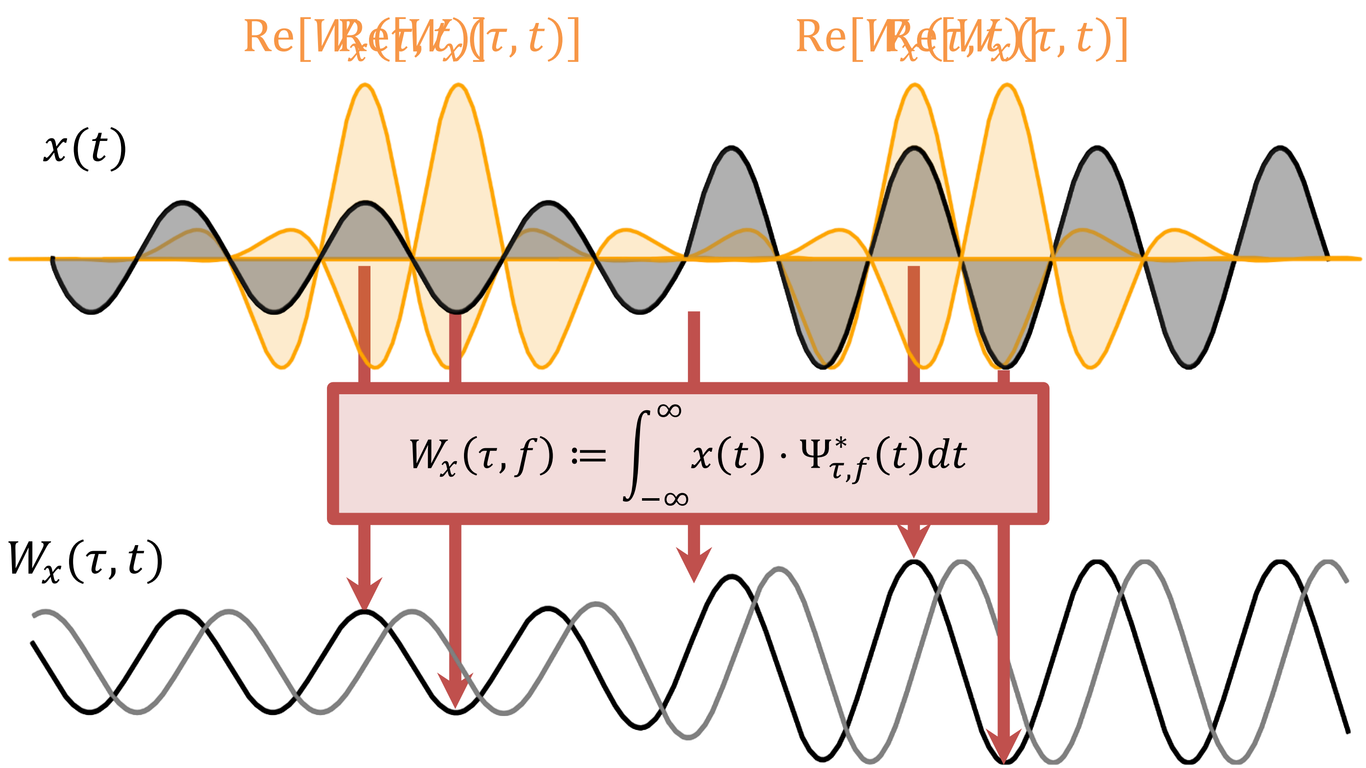
$$\underbrace{\boxed{\Psi_{\tau,f}(t)}}_{\text{Morlet wavelet}} := \sqrt{f}\, \underbrace{\boxed{\exp\big(i2\pi f(t-\tau)\big)}}_{f\text{-Hz sinusoid}}\, \underbrace{\boxed{\exp\left(-\frac{(t-\tau)^2}{2\sigma^2}\right)}}_{\text{Gaussian of width } \sigma \text{ centered at } \tau}$$

Le van Quyen et al. (2001) *J. Neurosci. Meth.* 111:83-98



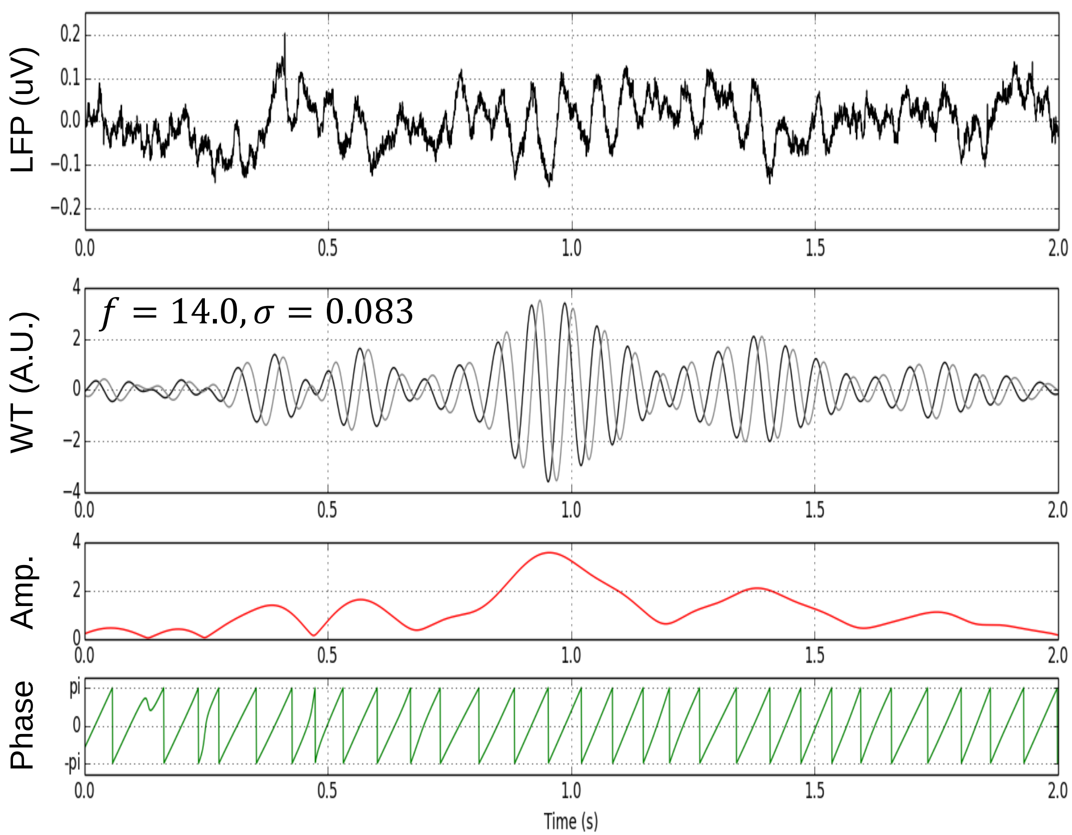
Phase Locking Analysis | wavelet transform

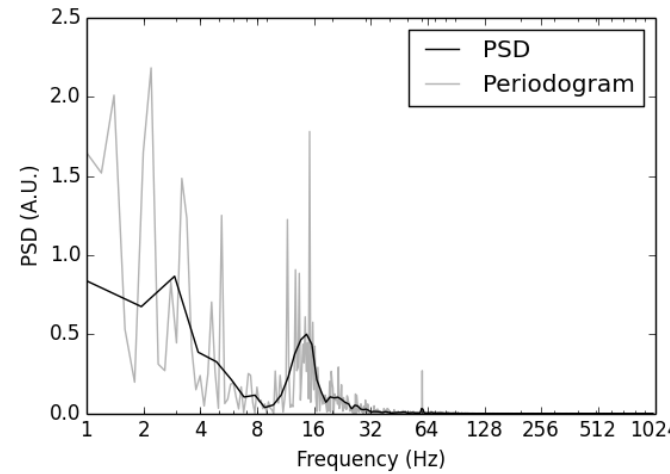
- How wavelet transform works



Phase Locking Analysis | phase estimation

- Estimation with wavelet transform





$$x(t) \xrightarrow{WT(f,\sigma)} W_x(t,f) = A_x \exp(i\theta_x)$$

$$A_x(t,f) \coloneqq \sqrt{\mathrm{Re}[W_x(t,f)]^2 + \mathrm{Im}[W_x(t,f)]^2}$$

$$\theta_x(t,f) \coloneqq \mathrm{atan2}(\mathrm{Im}[W_x(t,f)], \mathrm{Re}[W_x(t,f)])$$

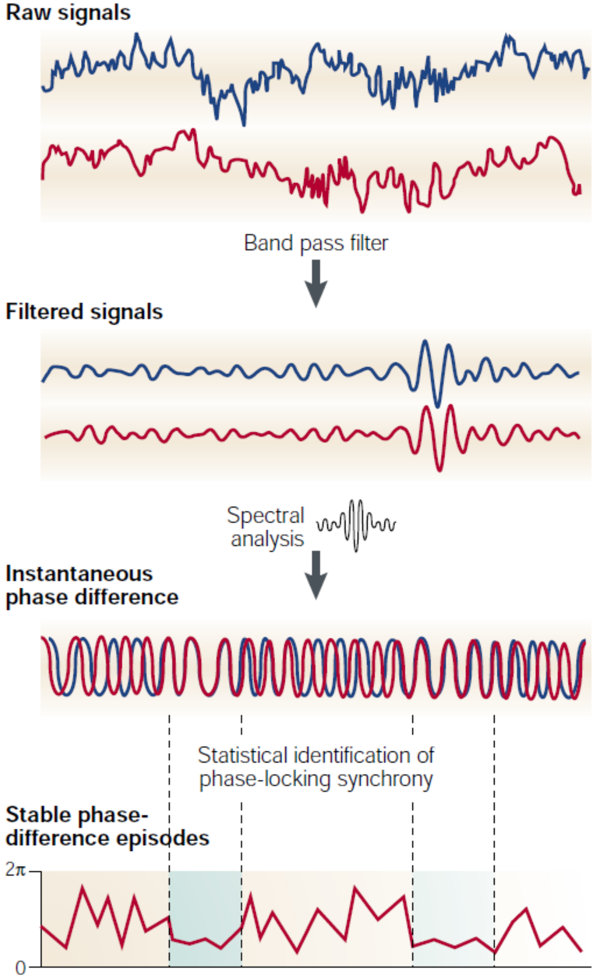
Phase Locking Analysis | phase locking value

- Instantaneous phase difference as a *time-resolved* measure of correlation between oscillatory signals

- Constant phase difference over a period of time → **phase locking**

- **Phase locking value** (PLV) for $x = A_x \exp i\theta_x$ and $y = A_y \exp i\theta_y$

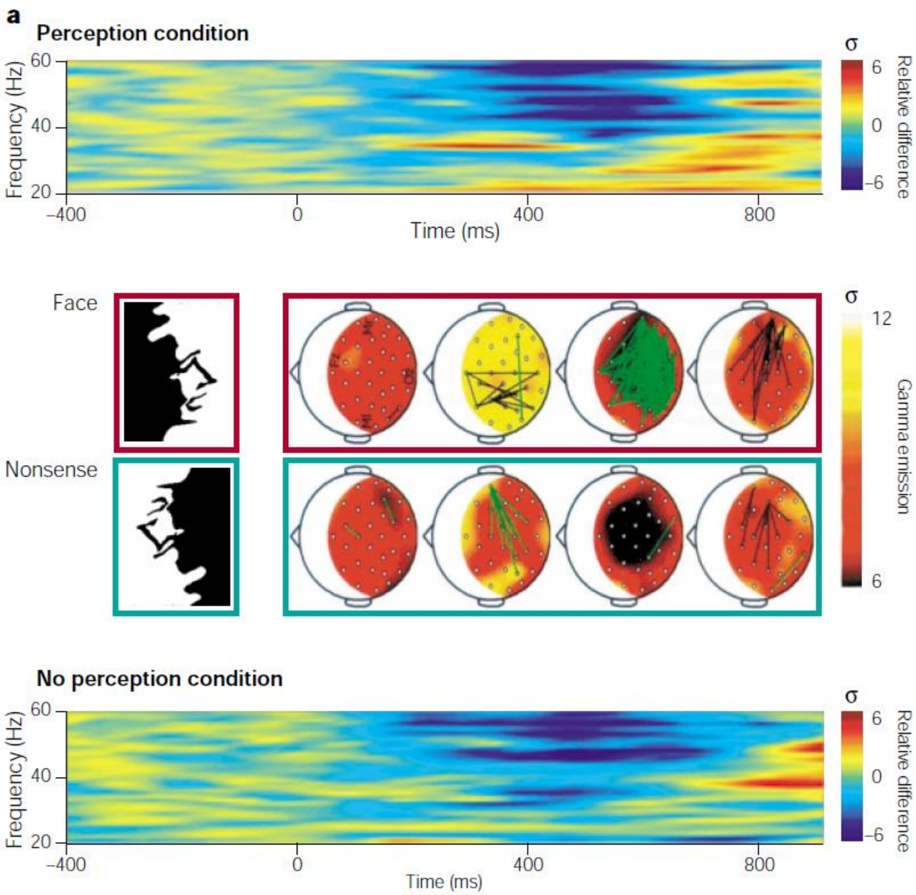
$$PLV_{xy} = \frac{1}{N}\left|\sum_{j=1}^{N} \exp\{i[\theta_x(t_j) - \theta_y(t_j)]\}\right|$$



Varela et al. (2001) *Nat. Rev. Neurosci.* 2:229–39

Phase Locking Analysis | an example application

- Rodriguez et al. (1999), EEG recording from human subjects
- Viewing of “Face” and “Nonsense” images
- Phase locking analysis over a range of frequencies (20 – 60 Hz)
- High PLVs at ~40 Hz only in Face viewing condition



Varela et al. (2001) *Nat. Rev. Neurosci.* *2*:229–39

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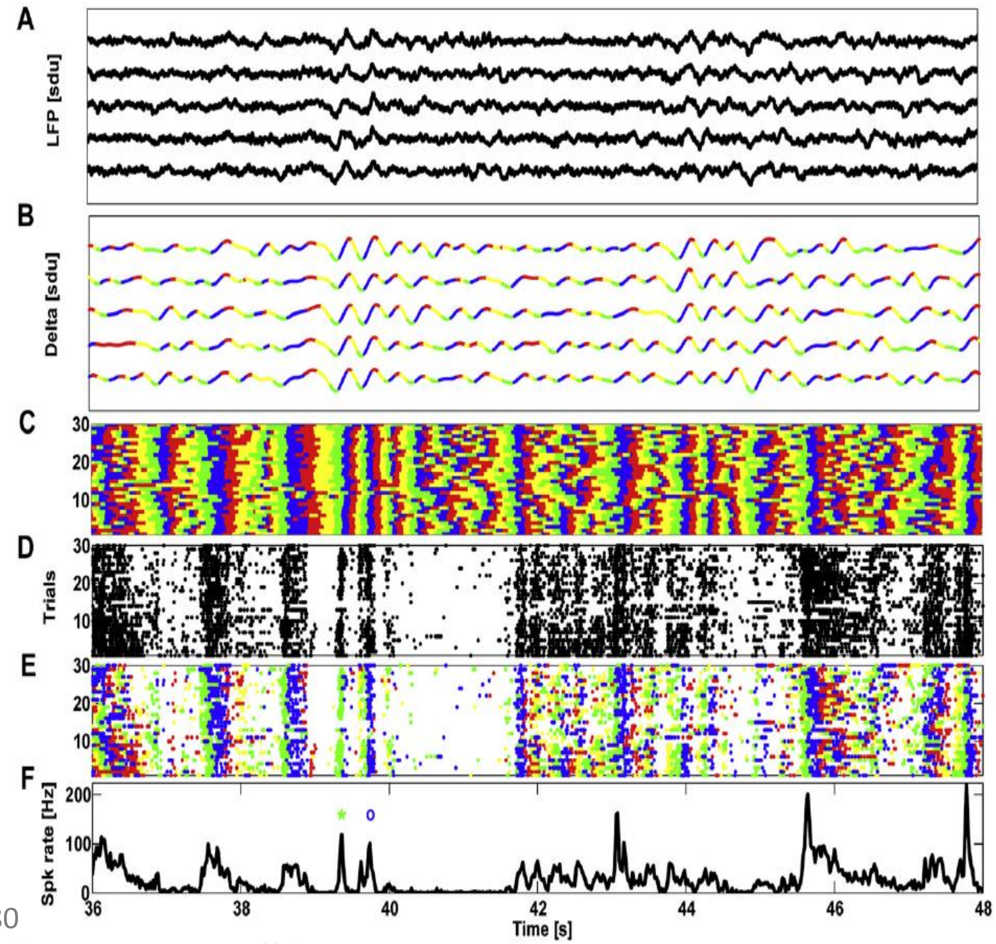
Spike-LFP Relation | spike-LFP parallel recording

- Montemurro et al. (2008), recording from V1 of anesthetized macaques
- Repeatedly stimulated with a natural movie
- Reliable oscillatory LFP responses across trials
- How are spike timings related to the phase of LFP oscillations? How to quantify the relation?



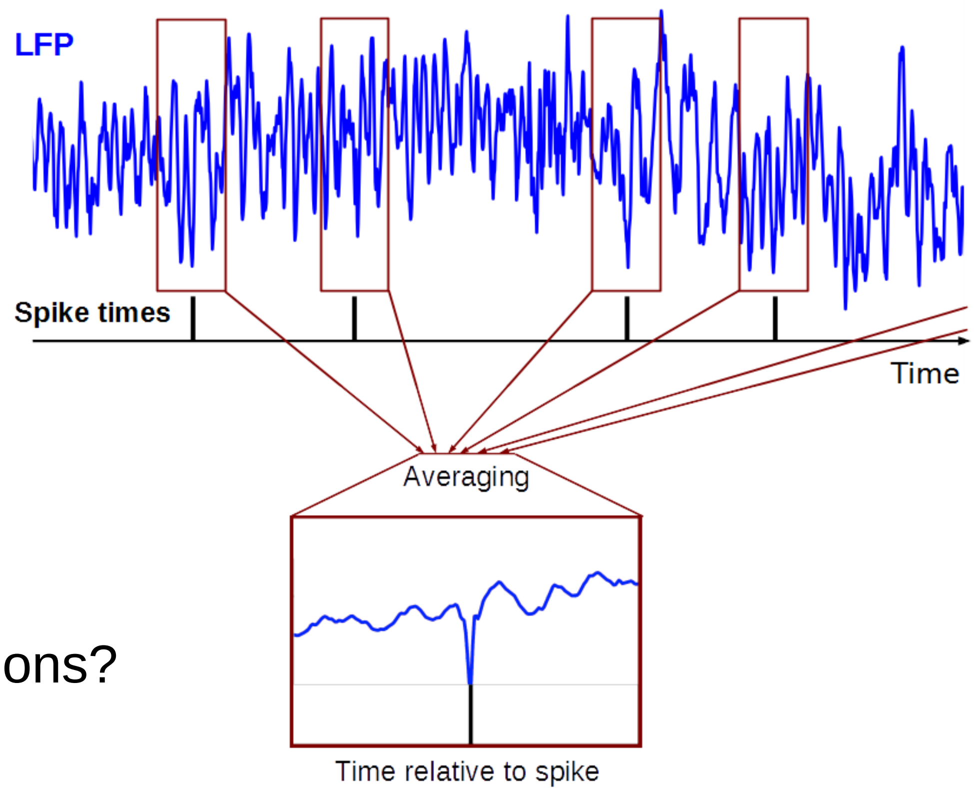
Montemurro et al. (2008) *Curr. Biol.* 18:375–80

Spike-LFP Relation | spike triggered average

- Average of LFP segments with spike times as triggers

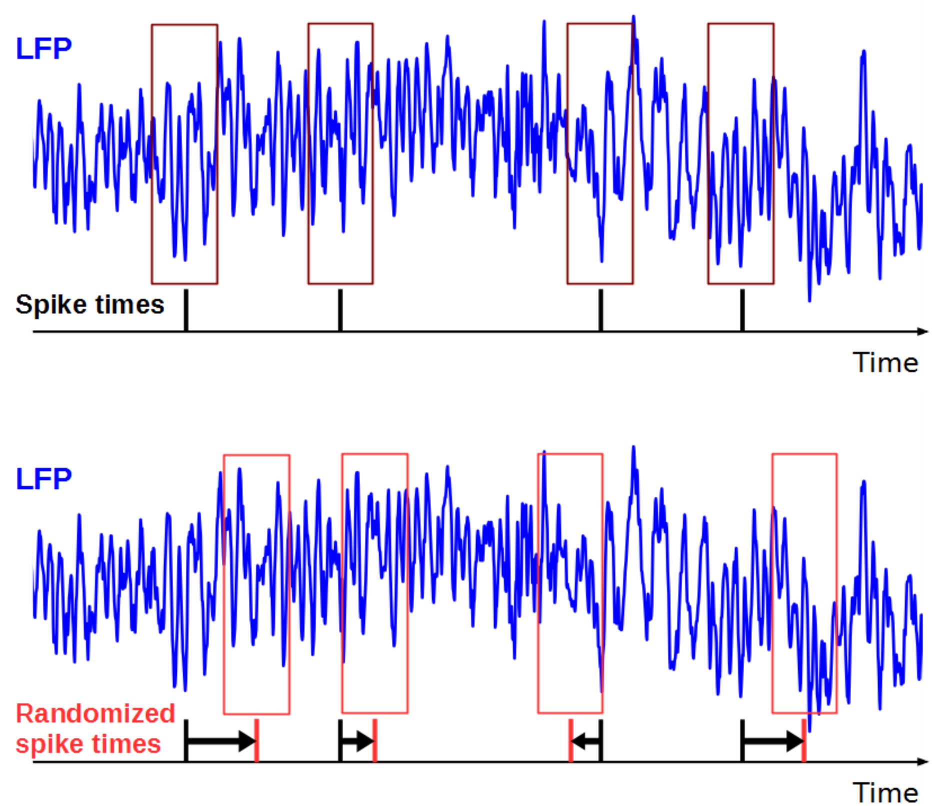
- If spikes prefer a specific phase of the LFP oscillation, its oscillatory waveform would remain in the average, while random fluctuations would be averaged out

- ...but, how can one tell if an obtained STA reflects phase locking or remaining fluctuations?
  → need for significance test



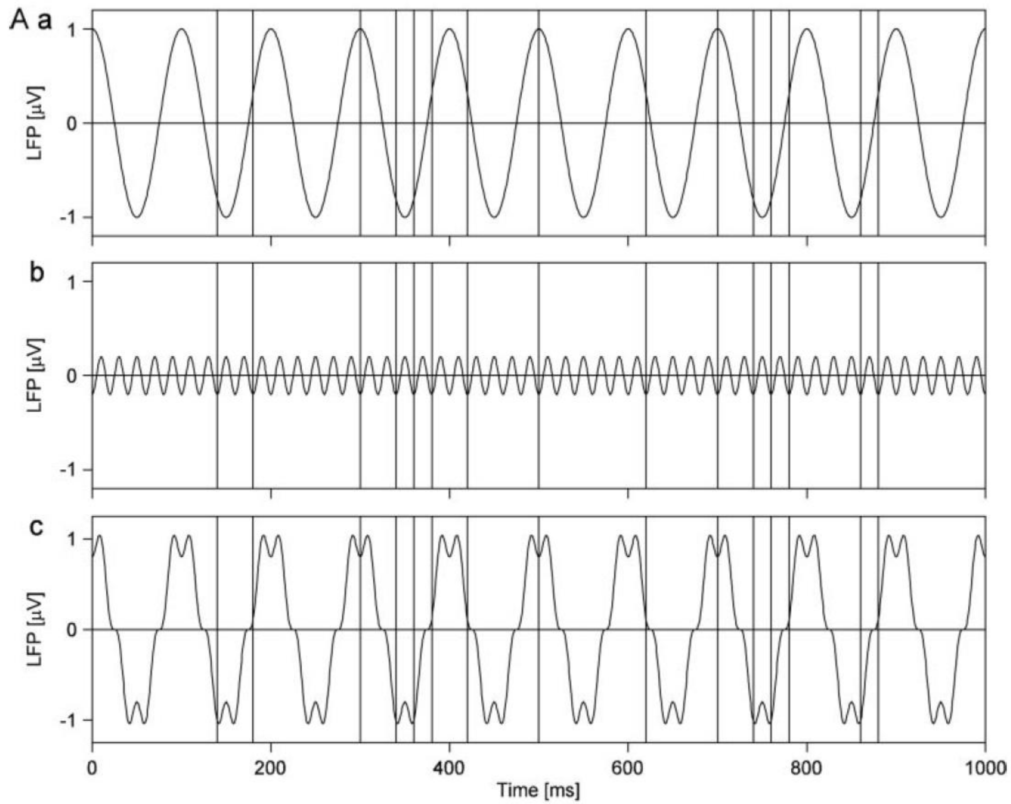
Spike-LFP Relation | significance test

- **Spike time randomization** for significance test
  1. Generate a surrogate spike data by randomly shuffling spike times
  2. Compute STA using the surrogate spike data and the original LFP data
  3. Repeat 1 and 2 many times (typically > 1,000)
  4. Compute the **distribution of surrogate STAs**, and test the significance of the original STA against it



Spike-LFP Relation | spike-field coherence

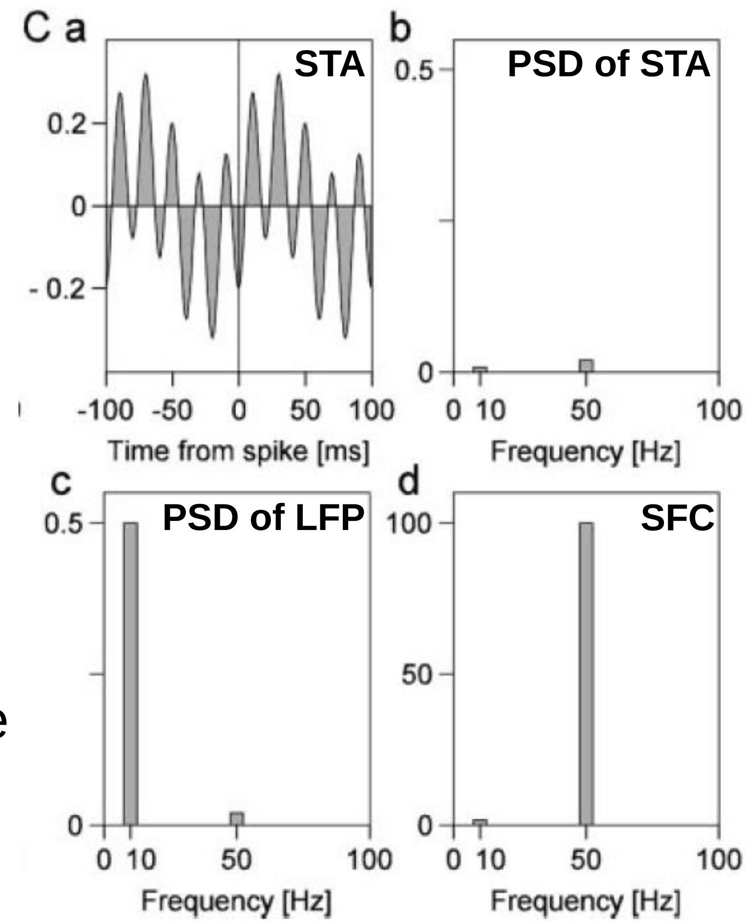
- STA can give a spurious result when the LFP has large power in other frequencies than the one that spikes are related to
- In such cases, STA needs to be “normalized” by the power in each frequency
  → Spike-field coherence (SFC)



Fries et al. (2002) *J. Neurosci* 22:3739-54

Spike-LFP Relation | spike-field coherence

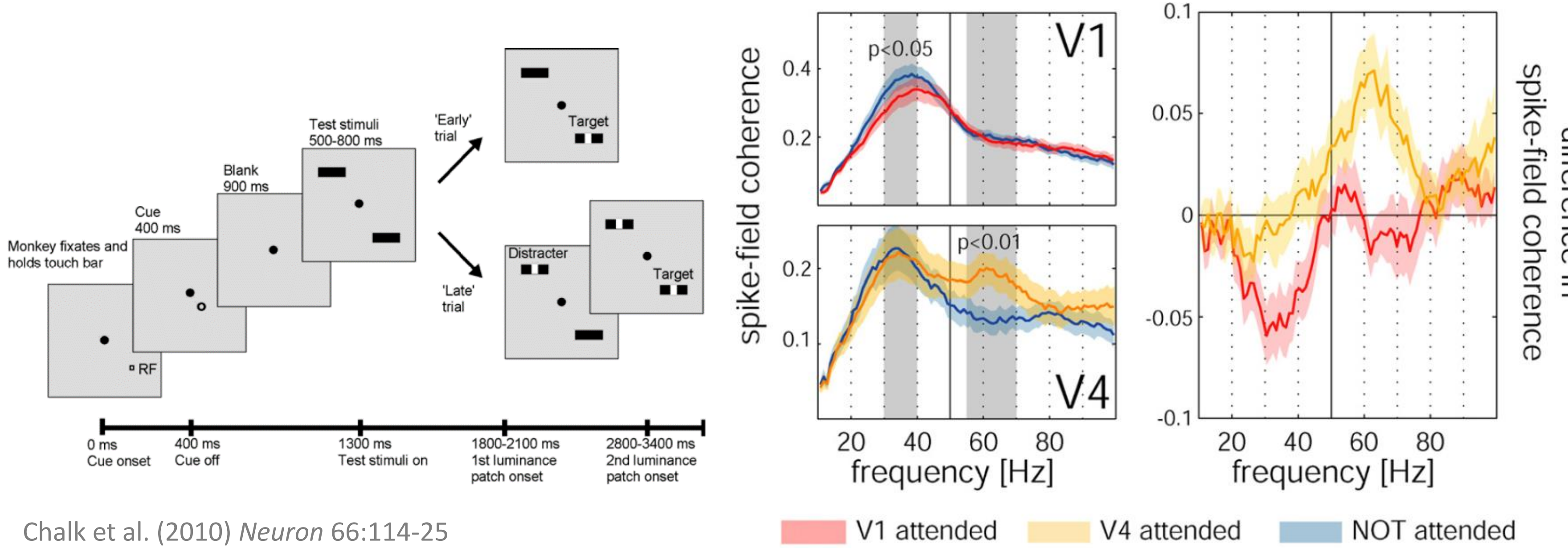
- SFC is...
  - defined as **the power spectrum of STA divided by the power spectrum of the LFP**
  - a measure in the frequency domain
  - a normalized measure taking a value between 0 and 1 for each frequency (0: independence; 1: perfect coherence)
  - actually coherency between spike train and LFP (with spike train represented as sum of delta peaks)



Fries et al. (2002) *J. Neurosci* 22:3739-54

Spike-LFP Relation | an example application

- Chalk et al. (2010), recording from V1 and V4 of awake behaving macaques
- SFC reflects attentional state of the animal

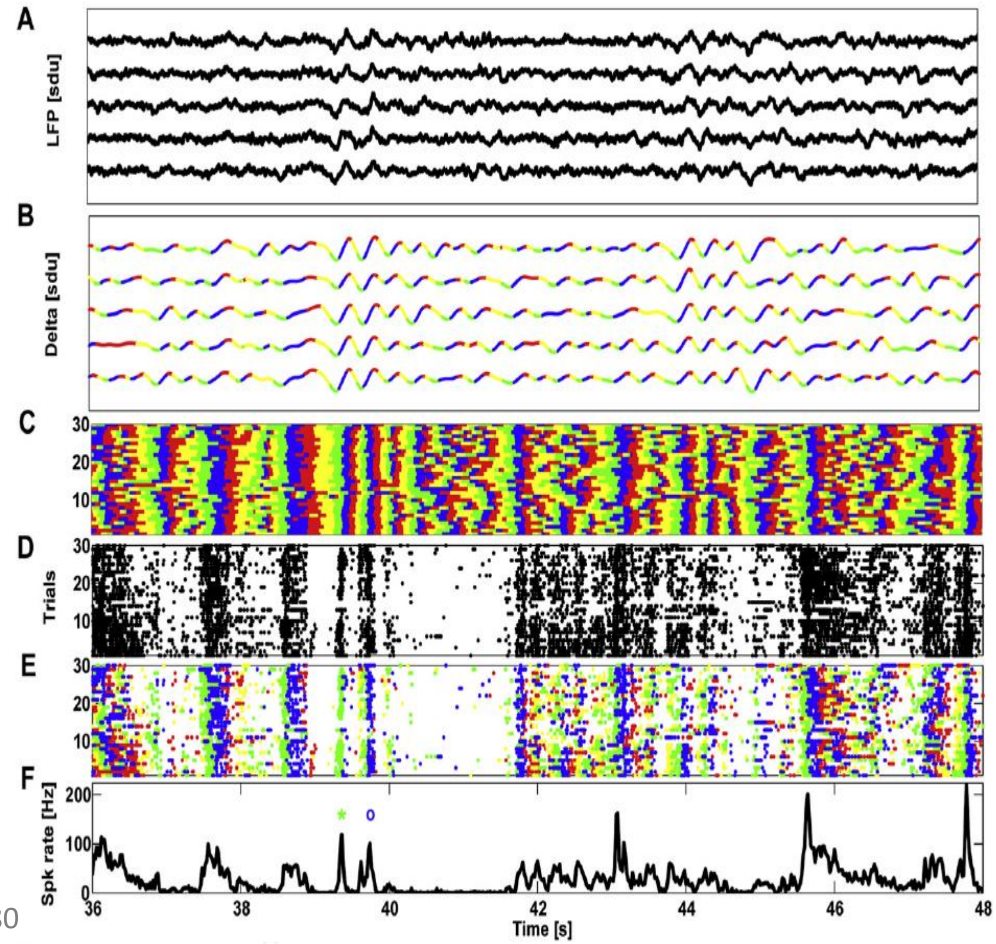


Chalk et al. (2010) *Neuron* 66:114-25

Spike-LFP Relation | phase locking analysis

- Phase extraction enables characterization of spike-LFP relation with a fine temporal resolution

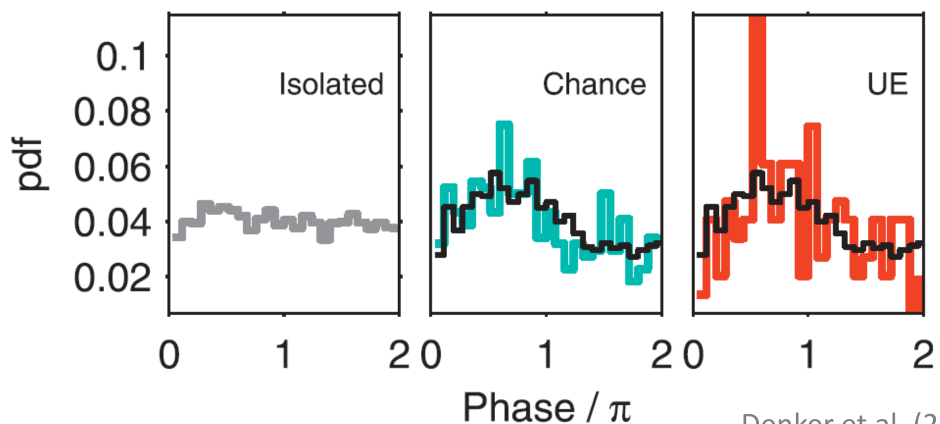
- What phase do spikes prefer?
  How are spike times distributed across phases within a cycle?
  → period histogram



Montemurro et al. (2008) *Curr. Biol.* 18:375–80

Spike-LFP Relation | period histogram

- Simultaneously recorded LFP and spikes
  - LFP: $x(t) = A_x(t)\exp[i\theta_x(t)]$
  - spike times: $S = \{\tau_1, \tau_2, \dots, \tau_N\}$
- Phases at spike times: $\phi_i = \theta_x(\tau_i) \quad (1 \le i \le N)$
- Histogram of ϕ_i is called **period histogram**



Denker et al. (2011) *Cereb. Cortex 21:2681-95*

Spike-LFP Relation | vector strength

- Vector strength (or mean vector length):

$$R = \frac{1}{N}\left|\sum_{j=1}^{N} \exp\{i[\theta_x(\tau_j)]\}\right|$$

  - c.f. (LFP-to-LFP) phase locking value

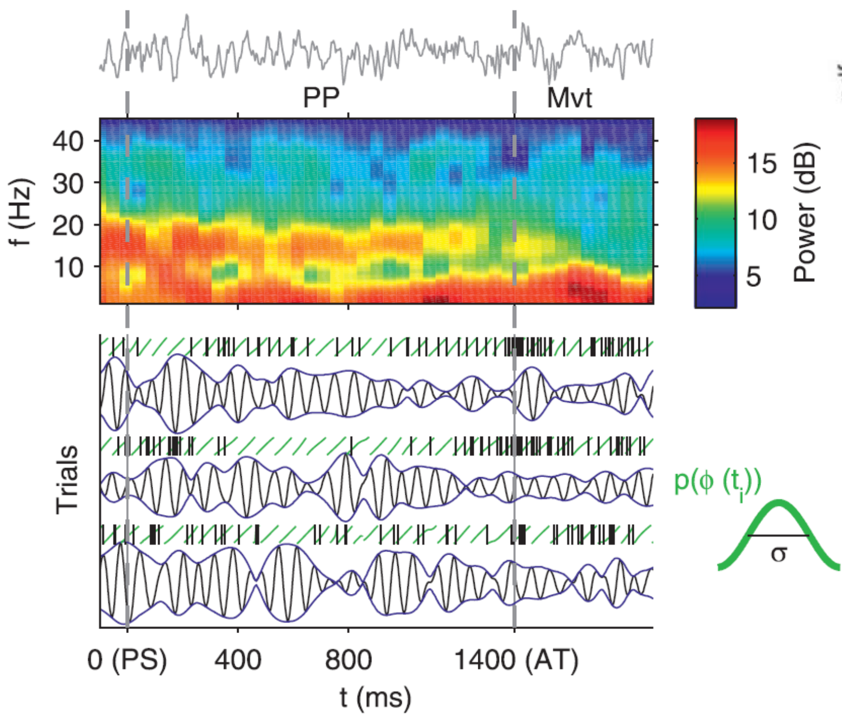
$$PLV_{xy} = \frac{1}{N}\left|\sum_{j=1}^{N} \exp\{i[\theta_x(t_j) - \theta_y(t_j)]\}\right|$$

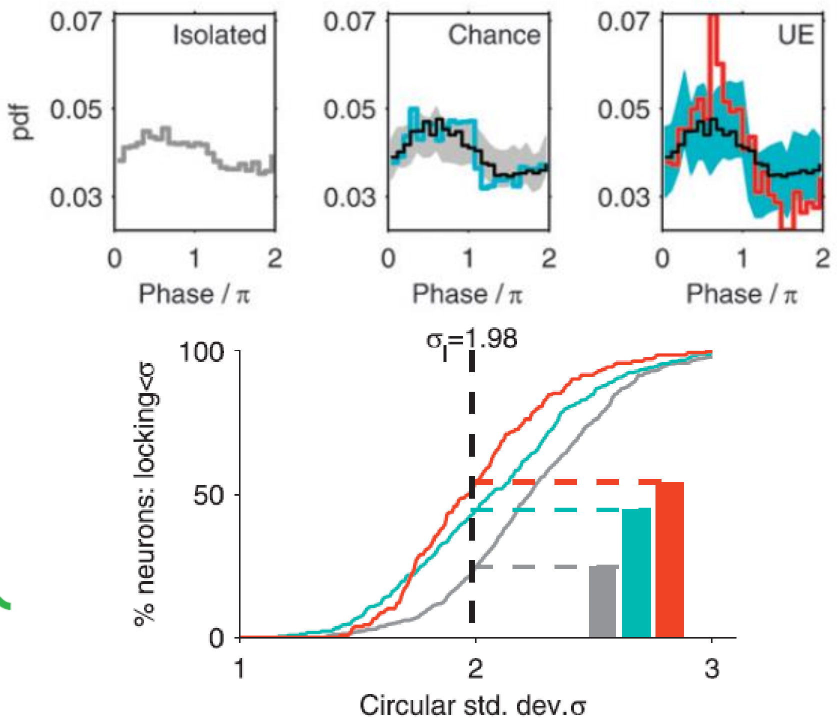
  - Quantifies the degree of spike-to-LFP phase locking

$R = 1 \longrightarrow$ perfect phase locking
$R = 0 \longrightarrow$ independence

Spike-LFP Relation | an example application

- Denker et al. (2011), recording from M1 of awake behaving macaques (note: circular std. dev. $\sigma = \sqrt{-2 \log R}$)





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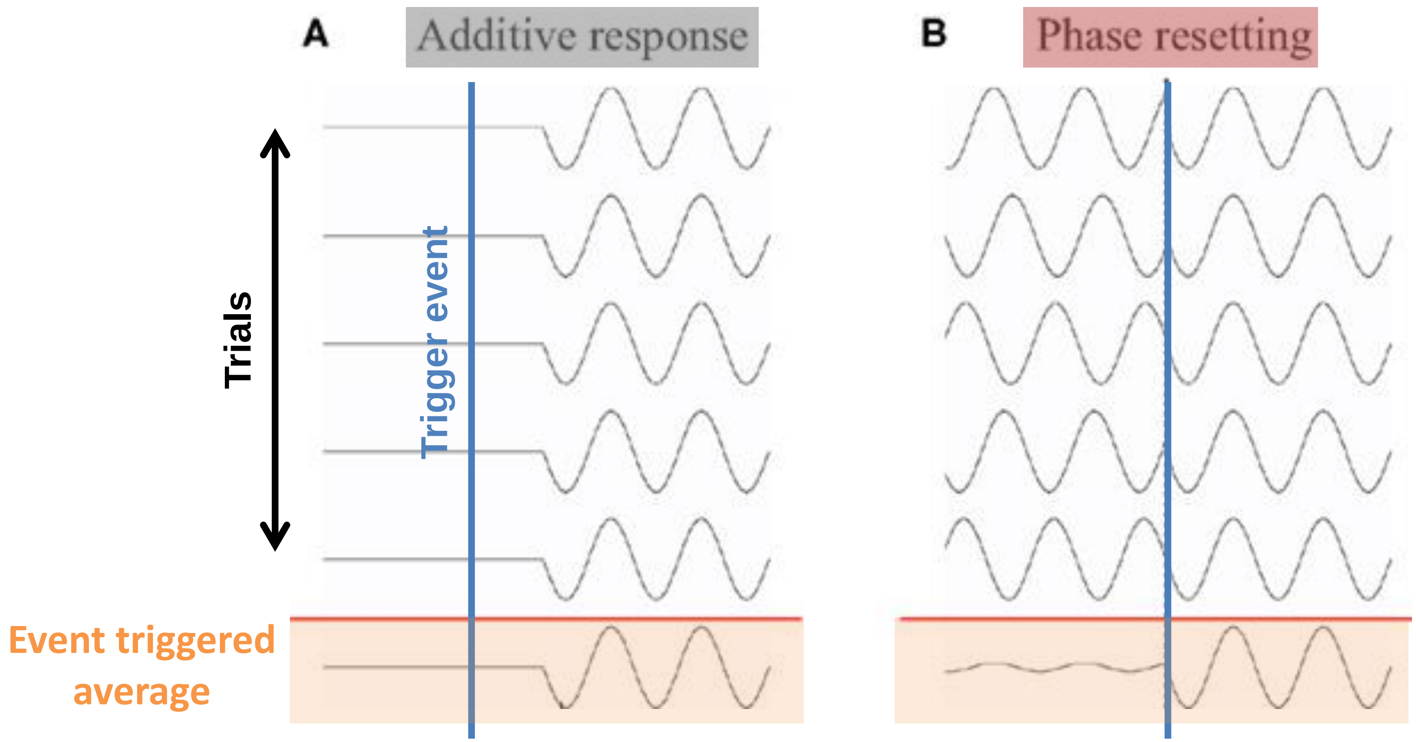
Advanced Topics

- **Analysis of oscillatory response activities**
- **Phase-amplitude coupling**
- **Time-resolved spike-to-LFP phase locking analysis**

Analysis of Response | response types

- **Additive response**: amplitude increase
- **Phase resetting** : no amplitude change, but phase reset

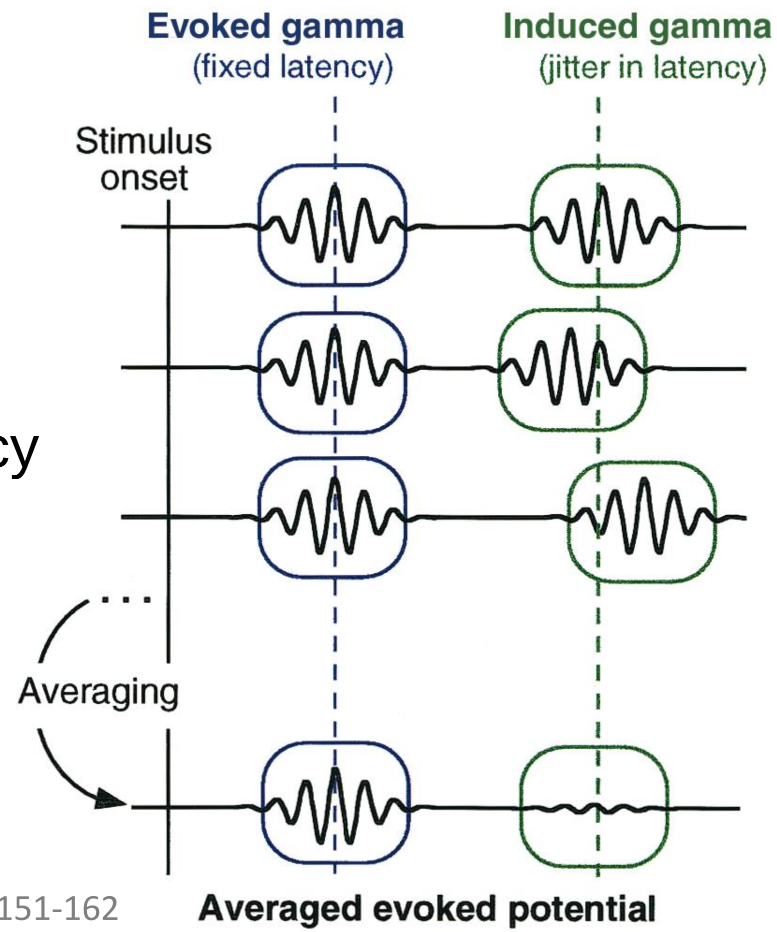


Mazaheri and Jensen (2010) *Front. Hum. Neurosci.* 4:177

Analysis of Response | response types

- **Evoked response**: fixed latency
  → phase coherence across
  trials

- **Induced response**: jitter in latency
  → no phase coherence across
  trials

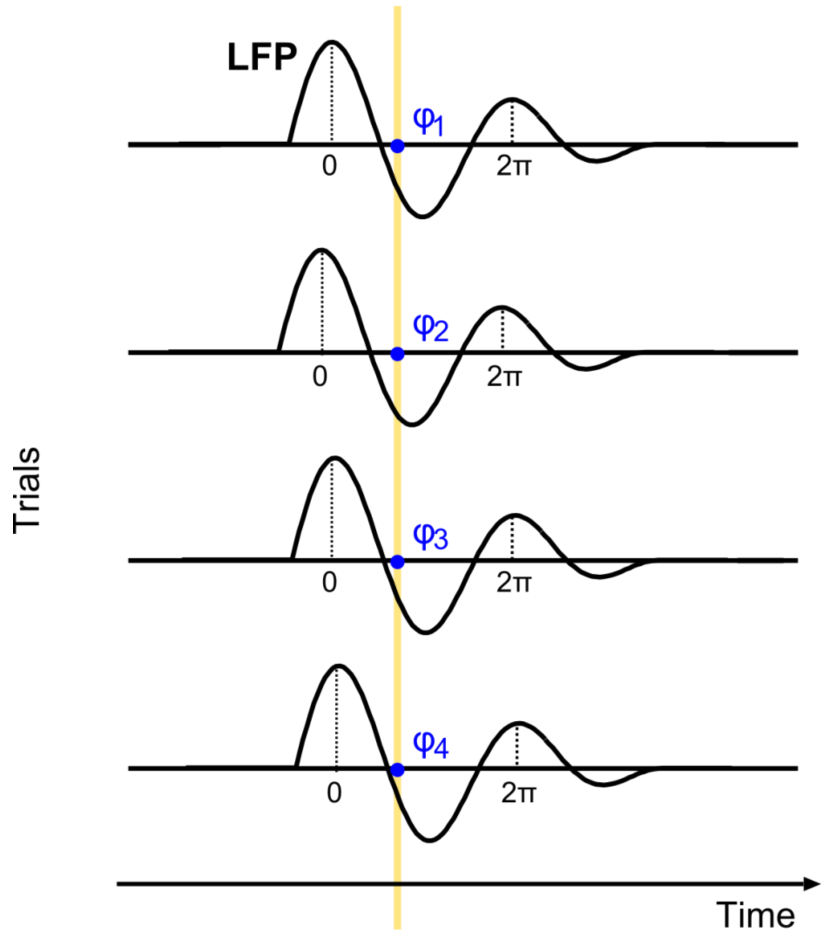


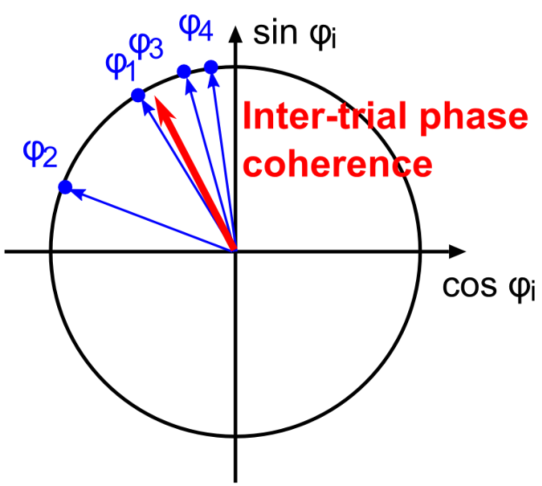
Tallon-Baudry and Bertrand (1999) *Trend Cogn Sci* 3:151-162

Analysis of Response | response types

Response type		Amplitude Increase	Phase coherence
Phase resetting		✗	✓
Additive	**Evoked**	✓	✓
	Induced	✓	✗

Analysis of Response | coherence measure

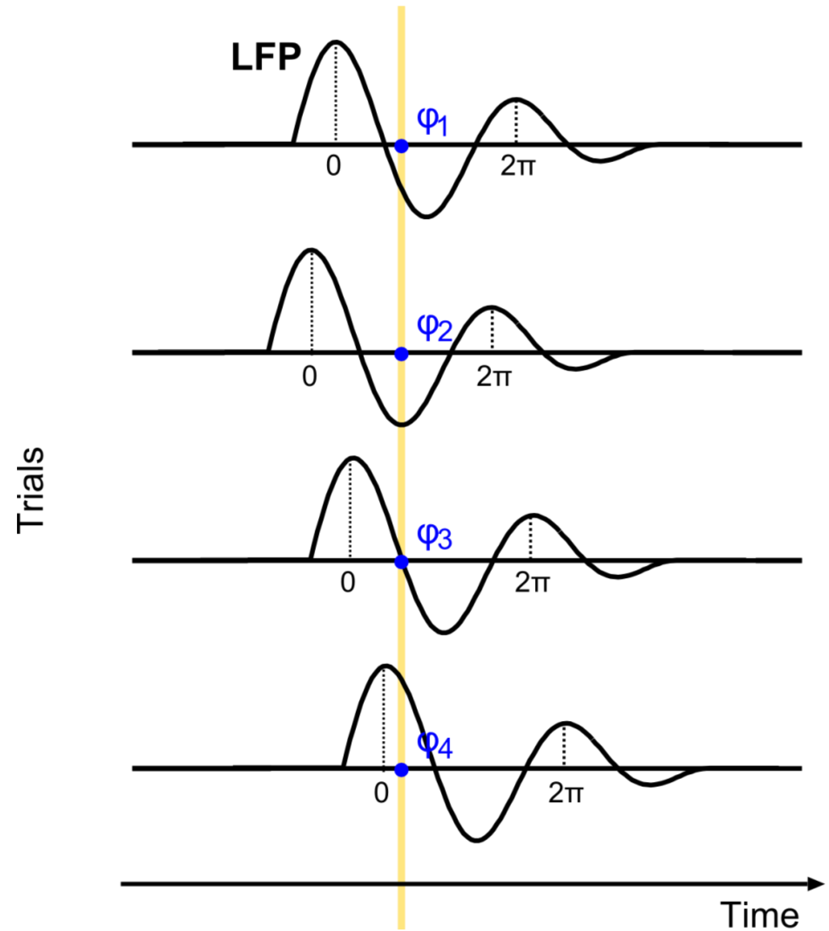


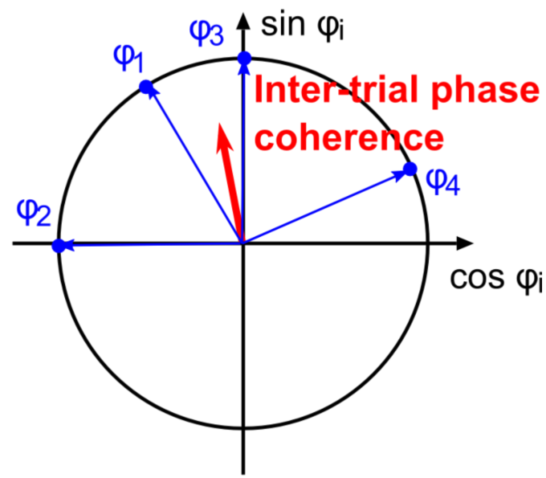


Inter-trial phase coherence (IPC)

$$\mathrm{IPC} \coloneqq \frac{1}{N}\left|\sum_{j=1}^{N} \exp\left(i\phi_j\right)\right| \quad (N: \#\ \text{trials})$$

Analysis of Response | coherence measure



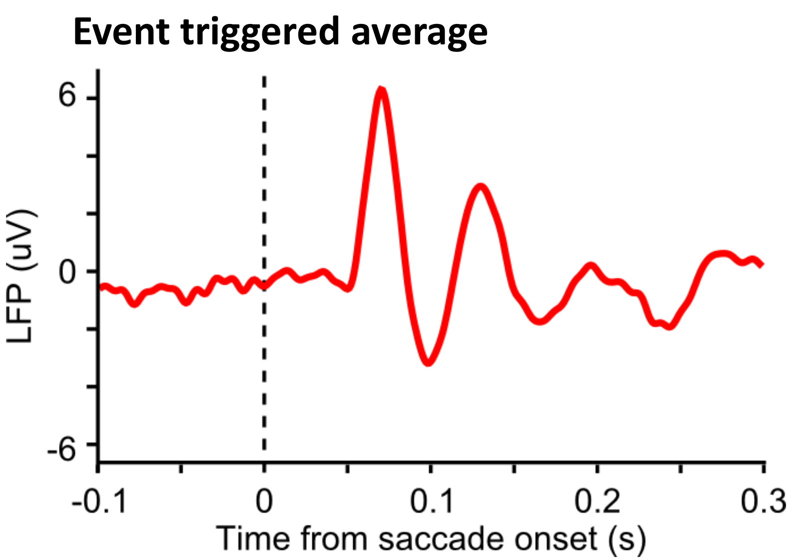


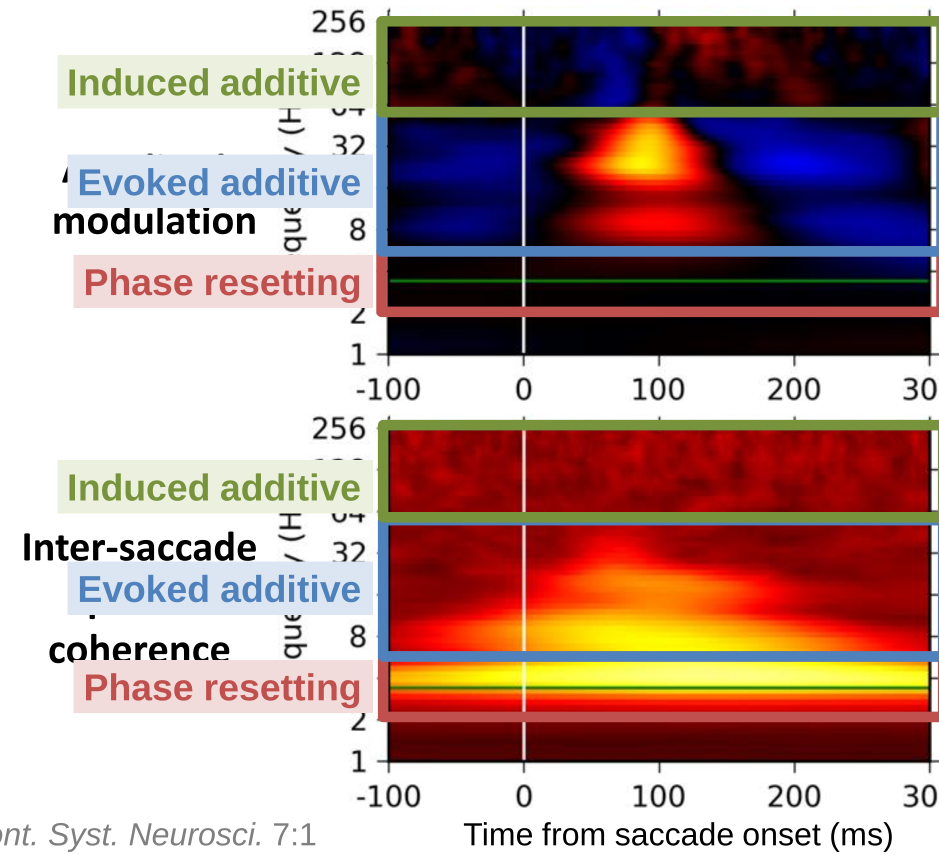
Inter-trial phase coherence (IPC)

$$\mathrm{IPC} := \frac{1}{N}\left|\sum_{j=1}^{N} \exp(i\phi_j)\right| \quad (N\text{: \# trials})$$

Analysis of Response | example

- Eye movement related LFP modulation in macaque V1

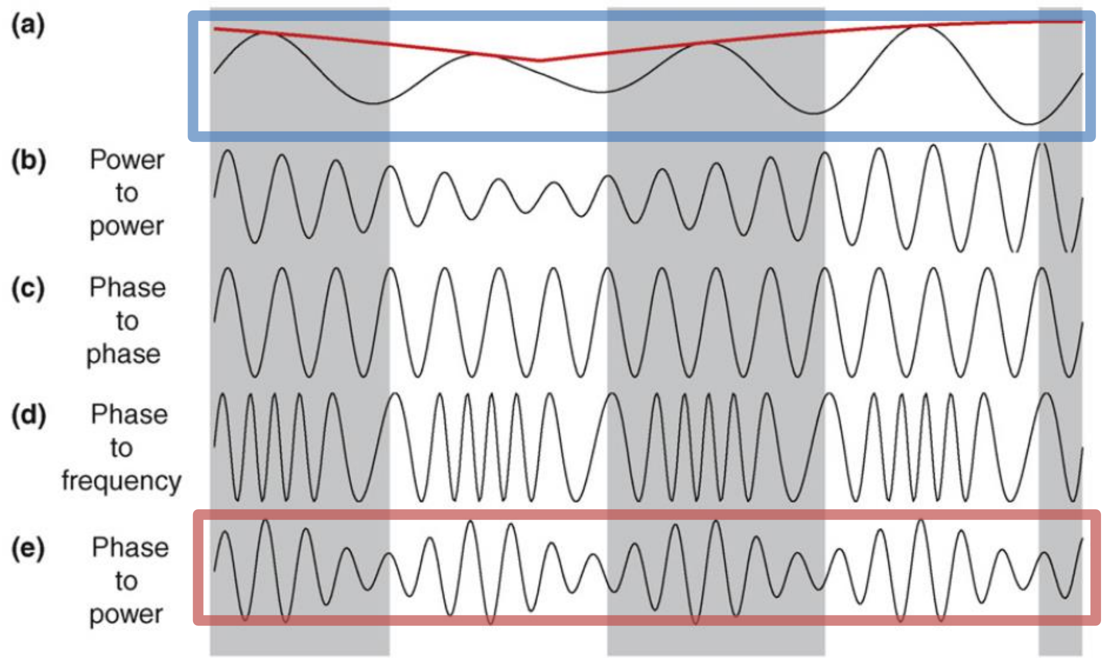




Ito et al. (2013) *Front. Syst. Neurosci.* 7:1

Phase-amplitude coupling | definition

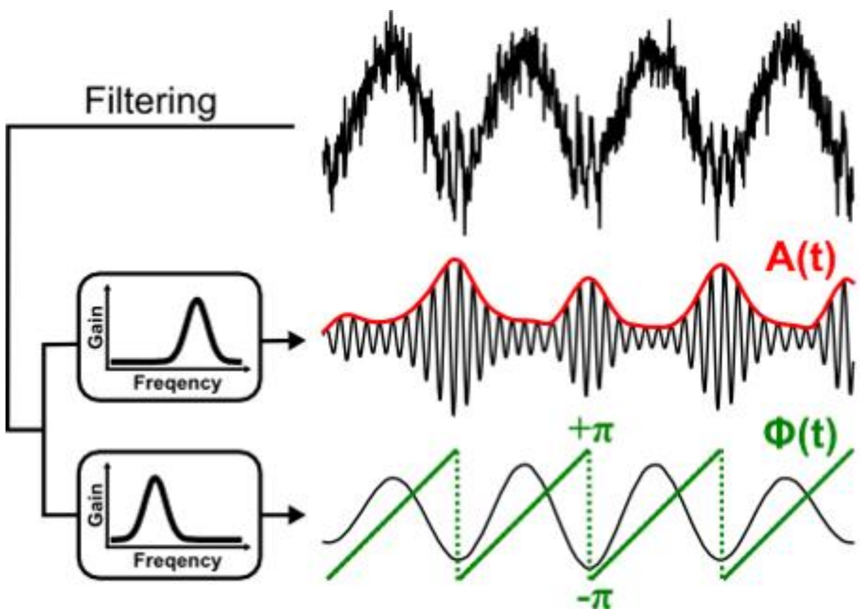
- **Phase-amplitude coupling (PAC)**
  - modulation of the amplitude of a fast frequency component coherent with the phase of a slow frequency component

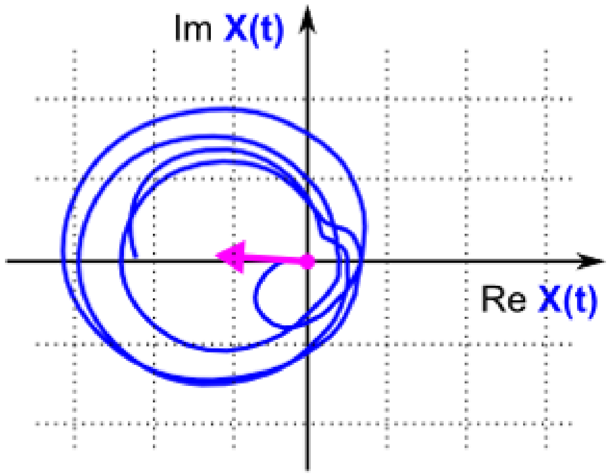


Jensen and Colgin (2007)
Trends Cogn. Sci. 11:267-9

Phase-amplitude coupling | PAC measure

- **Mean vector length (MVL)**





Composite signal:

$$X(t) \coloneqq A(t)\exp\big(i\Phi(t)\big)$$

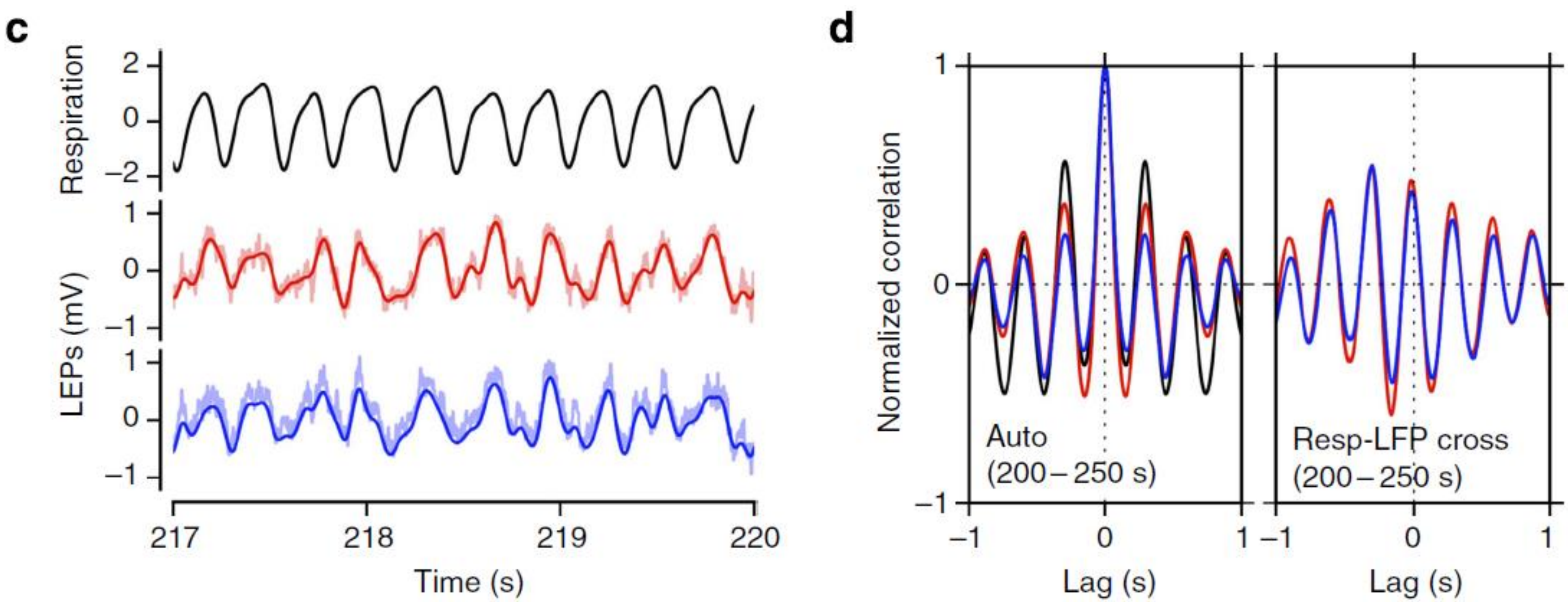
Mean vector length (MVL)

$$\mathrm{MVL} \coloneqq \sqrt{\langle \mathrm{Re}[X(t)]\rangle^2 + \langle \mathrm{Im}[X(t)]\rangle^2}$$

$\langle\cdot\rangle$: temporal average

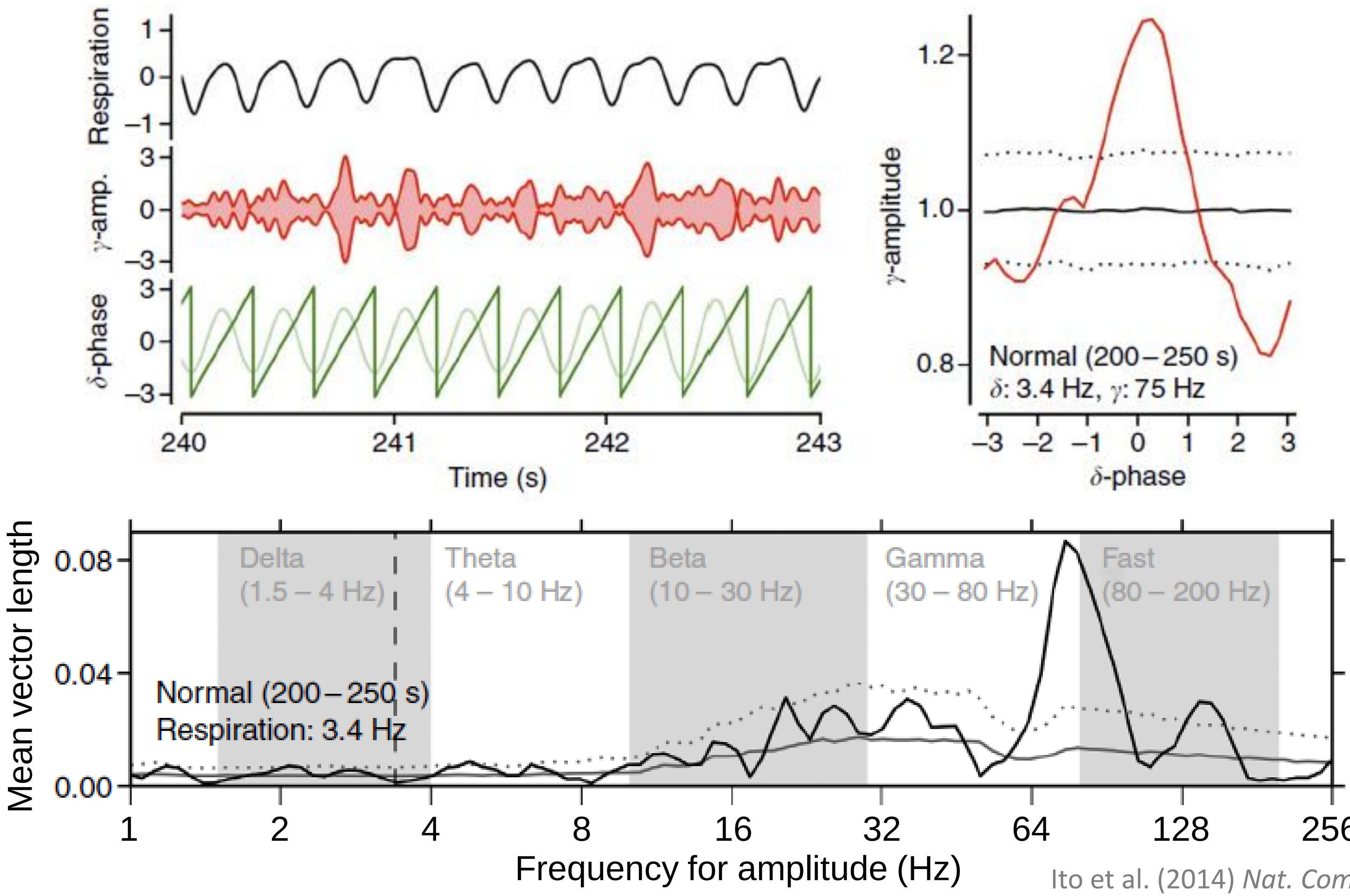
Phase-amplitude coupling | example

- Mouse barrel cortex LFP oscillations linked to respiration



Ito et al. (2014) *Nat. Commun.* 5:3572

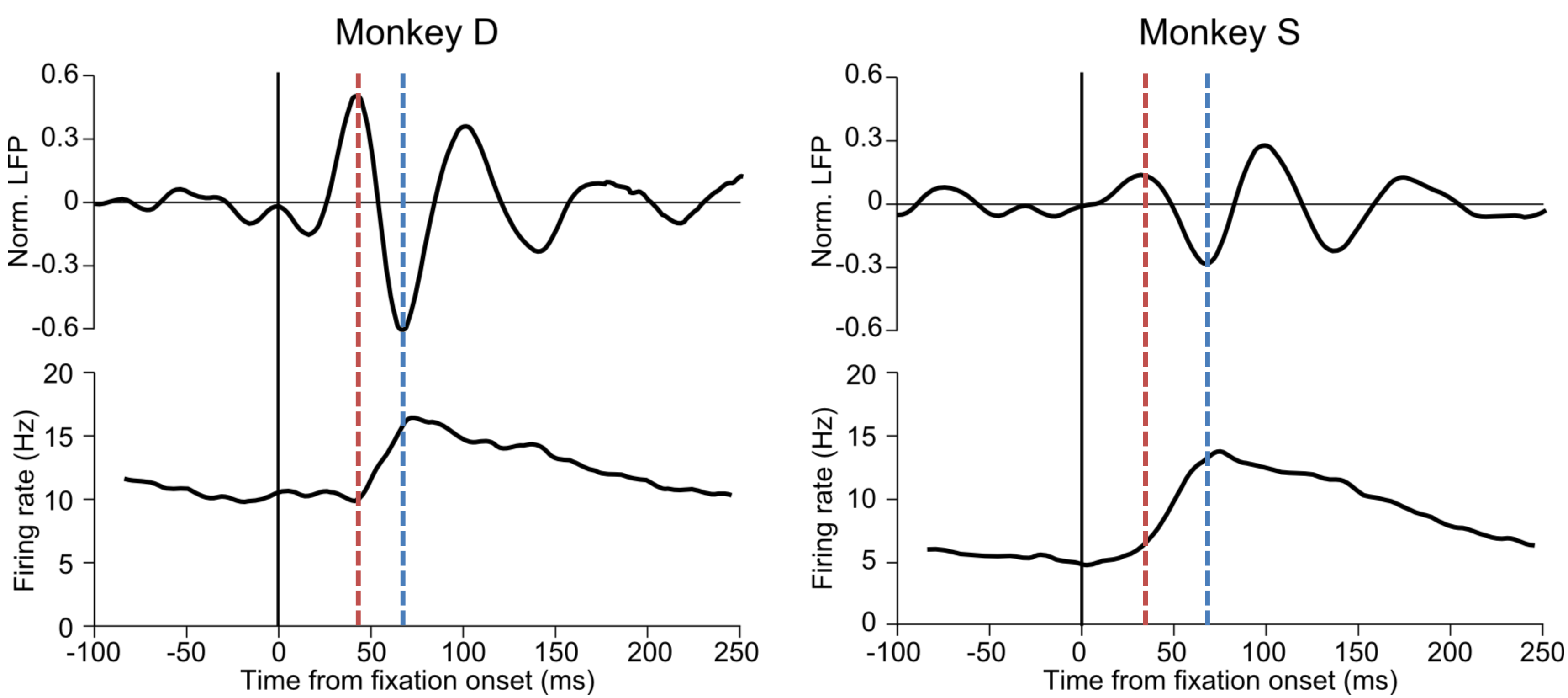
Phase-amplitude coupling | example



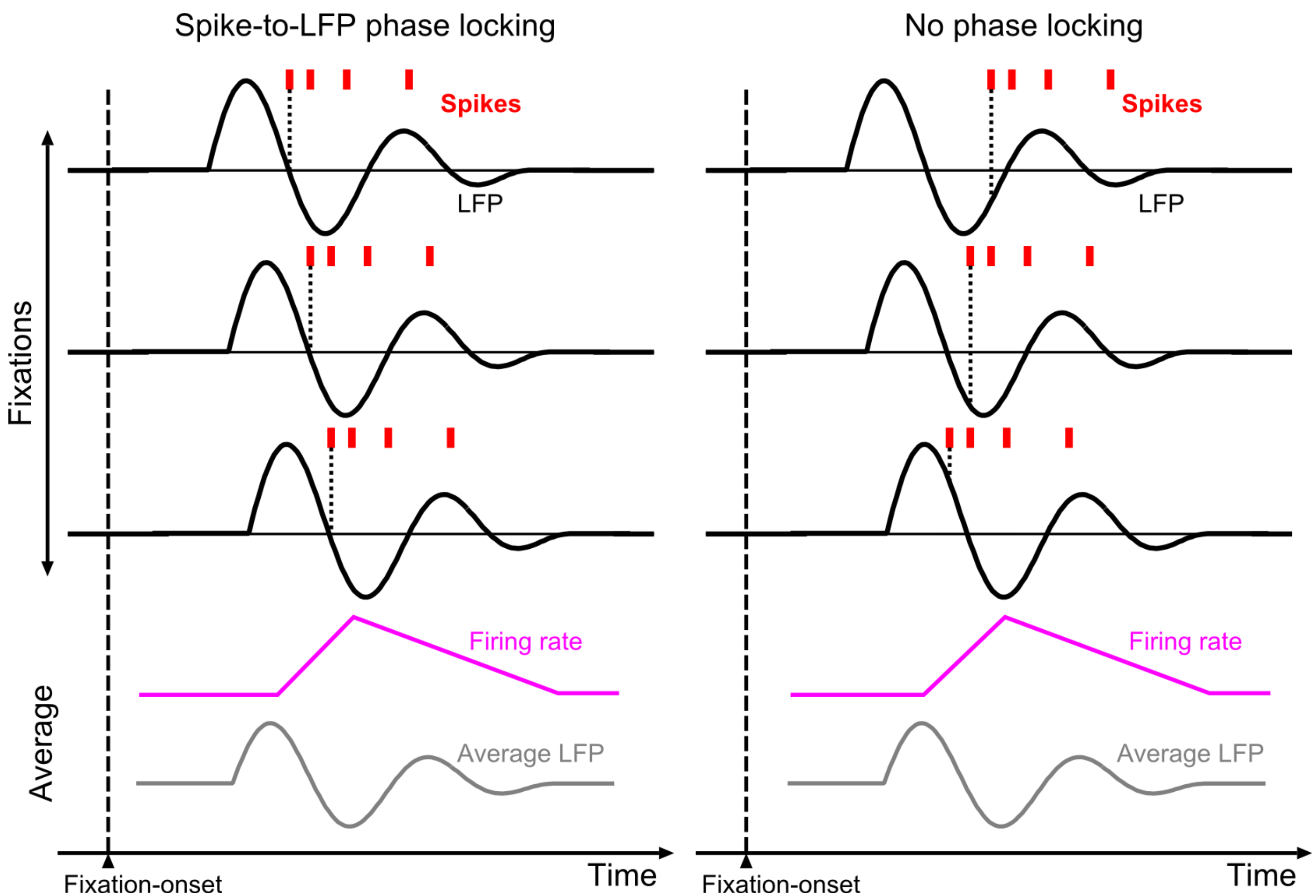
Ito et al. (2014) *Nat. Commun.* 5:3572

Phase Locking Analysis | spike-to-LFP locking

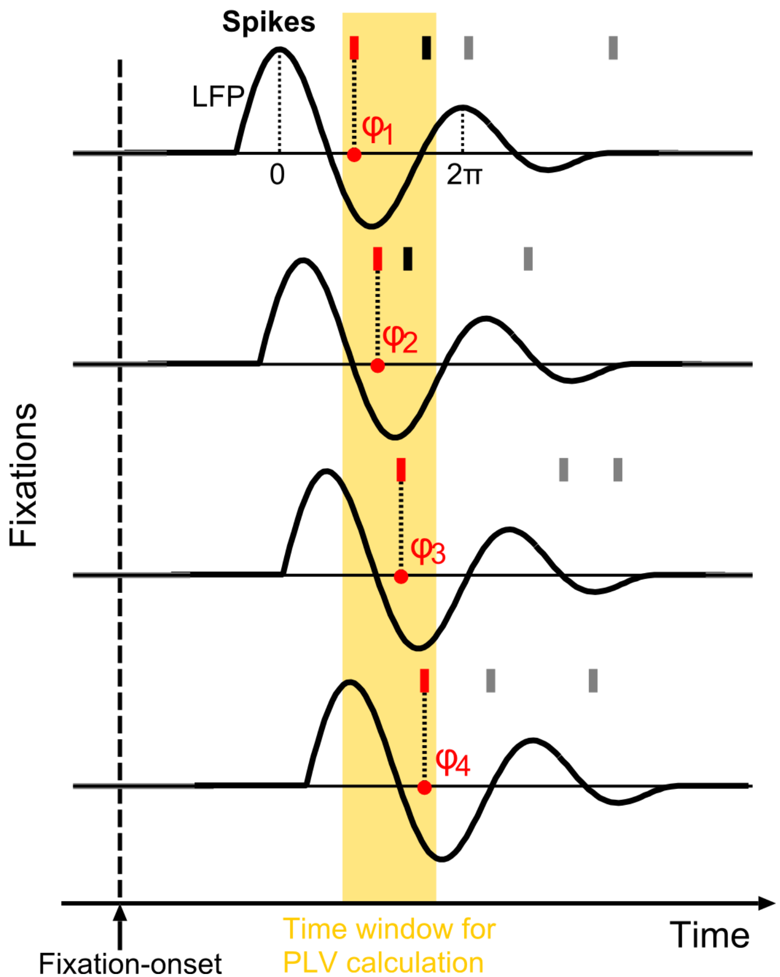
- Temporal relation between LFP and firing rate

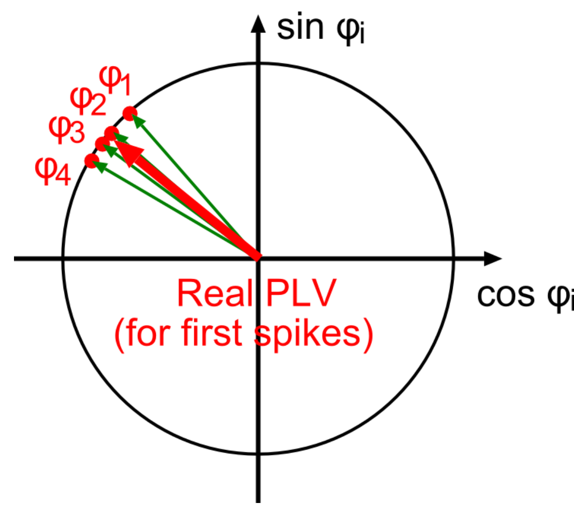


Phase Locking Analysis | spike-to-LFP locking



Phase Locking Analysis | spike-to-LFP locking



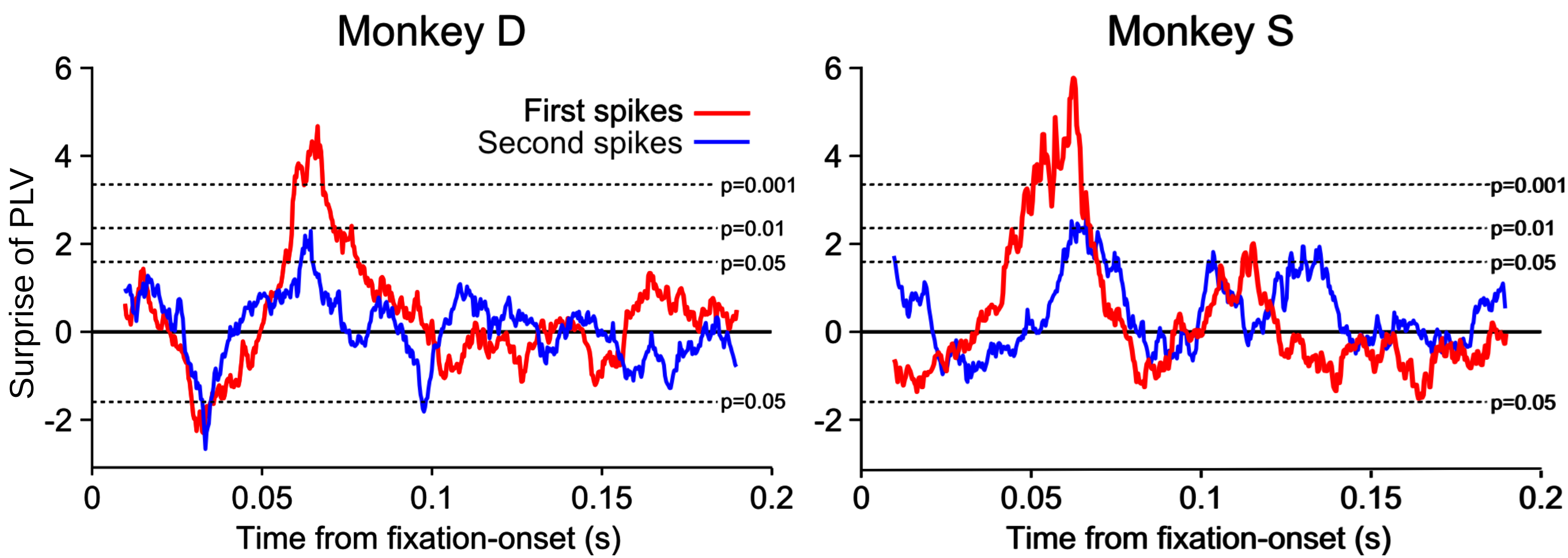


Spike-to-LFP phase locking value (PLV)

$$\mathrm{PLV} := \frac{1}{N}\left|\sum_{j=1}^{N} \exp(i\phi_j)\right| \quad (N: \#\ \text{spikes})$$

Phase Locking Analysis | example

- Time resolved spike-to-LFP phase locking analysis
  - phase locking calculated separately for first and second spikes after fixation onset



Ito et al. (2011) *Cereb. Cortex* 21:2482-97