Analysis of Local Field Potentials (Part I & II)

WS 2013/14 | Michael Denker – Introduction Computational Neurosci., RWTH Aachen

Outline

Understanding Local Field Potentials

What is Synchronization?

Synchronization between Local Field Potentials

- Fourier Analysis
- Coherence
- Phase Synchronization

Synchronization between Spikes and Local Field Potentials

- Spike-Triggered Averaging
- Spike-Field Coherence
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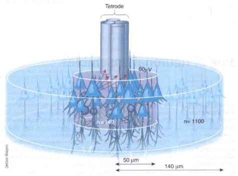

Buzsaki et al, 2004

- LFP is the low-pass filtered electrode signal

Logothetis and Wandell, 2004

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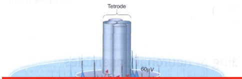

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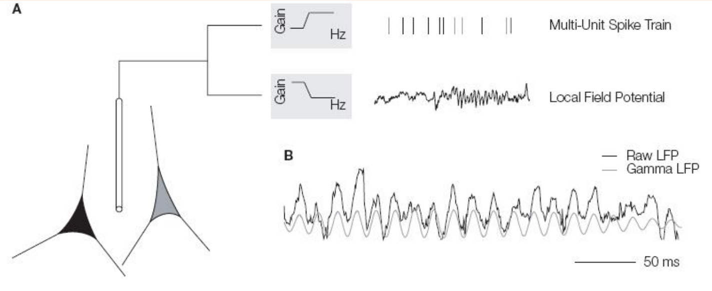
Obtaining the LFP



Berens et al, 2008

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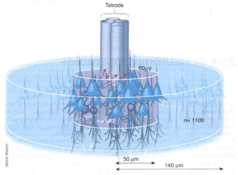

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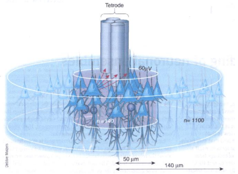

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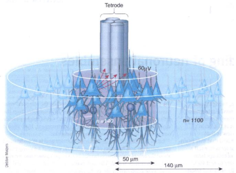

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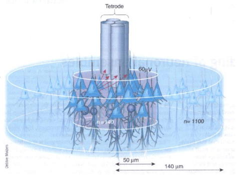

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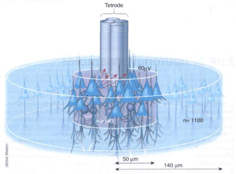

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- ...but interpretation of compound LFP is difficult
- Suggested spatial-temporal relationship between LFPs and spikes

Logothetis and Wandell, 2004

Biophysical Origin of LFP

- Under the 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)

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

ϕ: field potential I_i: current source at $\mathbf{r_i}$
(σ: conductance of extracelluler medium)

- Field potential is only dependent on the strength and the position of current sources.
- Current source/sink in extracellular space
  $\rightarrow$ transmembrane current of neurons

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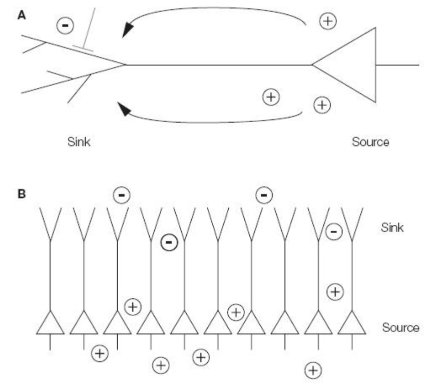

Johnston and Wu, 1995

Membrane Currents Caused by Neuronal Activities

$$I_m = \frac{V_m}{r_m} + c_m \frac{\partial V_m}{\partial t}$$

I_m: membrane current V_m: membrane potential
r_m: membrane resistance c_m: membrane capaciance

- Action potentials (somatic, axonal, dendritic)
  - Biphasic in time
  - Easily cancelled out by temporal jitter of multiple APs
- Synaptic potentials (EPSP, IPSP)
  - IPSP is much slower than EPSP
  - Ratio of EPSP- vs. IPSP-related current components = 5:1 (Mitzdorf, 1985)
- EPSPs are essentially the dominant causes of the macroscopic transmembrane current in the brain.

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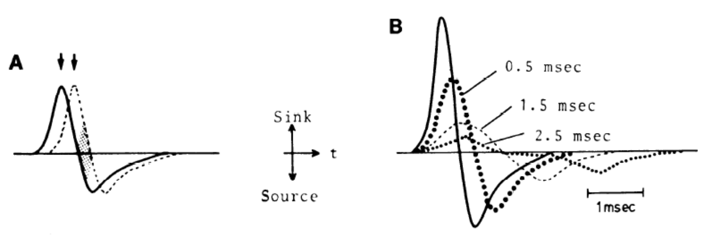
Cancellation of currents



Mitzdorf, 1985

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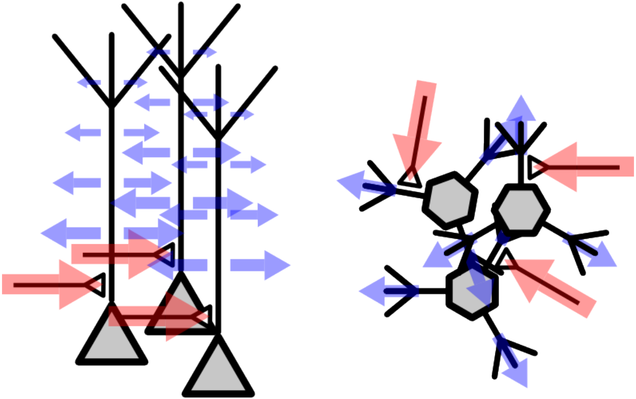
Effect of Cell Morphology

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



Further Contributions of and by LFPs

Further currents that may contribute to LFP:

- Dendritic calcium spikes
- Resonant properties of the cell, self-sustained oscillations of the membrane potential
- UP/DOWN states during anesthesia or non-REM sleep

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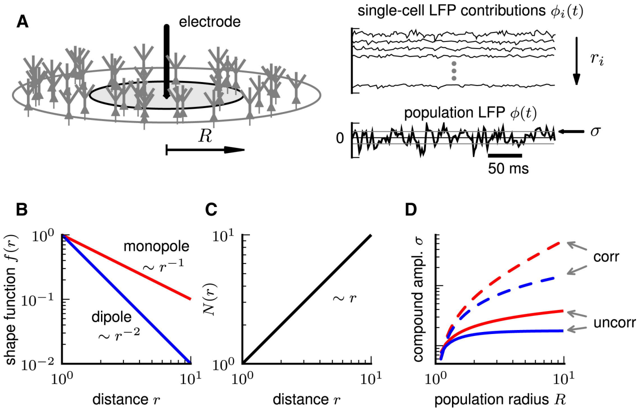
Ephaptic effects of the local field:

- In how far can the field potential influence the membrane potential of neurons?
- Evidence that constant potentials of realistic magnitude may influence spike timing e.g., Radman et al, 2007; Anastassiou et al, 2011
- Is the LFP an observable of brain dynamics or part of a feedback cycle?

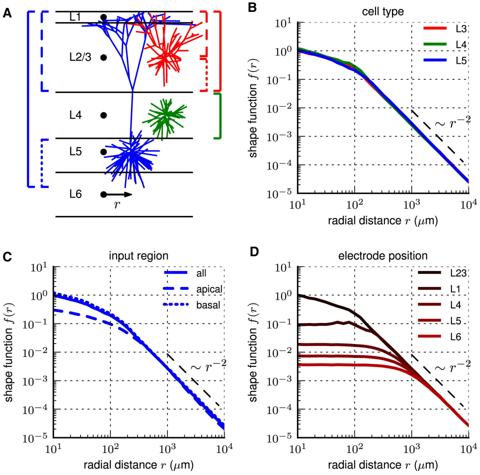
Reach of the LFP



Lindén et al, 2011

Dependence of LFP reach on cell morphology, synaptic-input distribution, and input correlations

Dependencies of the Reach



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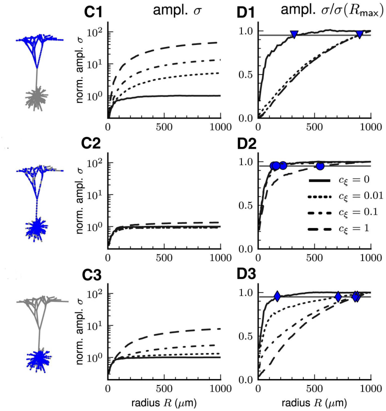

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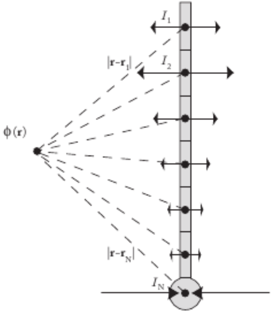
Dependencies of the Reach

- Uncorrelated activity OR symmetric cell morphology OR symmetric input distribution:

  reach $\approx 100, \ldots, 300\,\mu$m (soma layer)
- Correlated activity AND asymmetric cell morphologies (pyramidal cells) AND
  asymmetric distribution of synaptic inputs (e.g. apical input):

  reach $\approx$ spatial extent of correlated activity
- Small correlations (e.g. shared-input correlations) sufficient to boost LFP reach (≈ 1 mm)

Current Source Densities



Pettersen et al, 2010

- Forward problem straight-forward (linear sup.):

$$\phi(\mathbf{r}) = \frac{1}{4\pi\sigma} \iiint_V \frac{C(\mathbf{r}', \mathbf{t})}{|\mathbf{r} - \mathbf{r}'|} \mathrm{d}^3 r'$$

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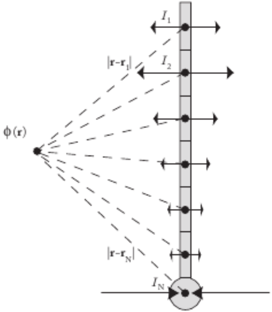

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- $C(\mathbf{r}', \mathbf{t}) = \sum_i I_i \delta^3(\mathbf{r} - \mathbf{r_i})$ is the current source density $[A/m^3]$

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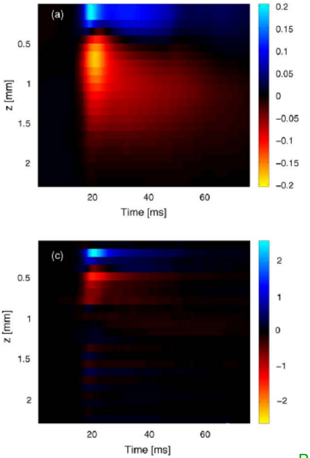
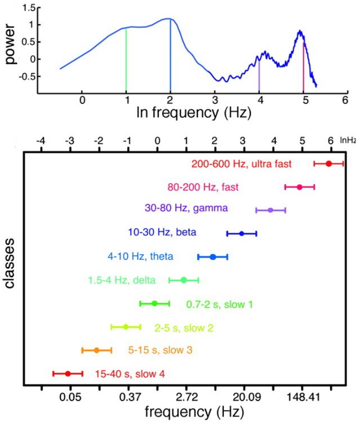
- More advanced methods available (e.g., iCSD using a direct inversion of the forward problem (Pettersen et al., 2006)).

Example: Current Source Density in Response to Whisker Deflection in Rat Barrel Cortex



Pettersen et al, 2006

LFP Features: Oscillations



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- How are such measures related to the system and/or its coupling?

A well-known example: The Millenium Bridge

Start Millenium Bridge Movie

adapted from: Pikovsky, Rosenblum, Kurths

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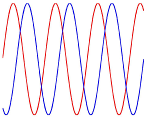
- Critical number of people on the bridge leads to strong vibrations.
- Differs from Soldiers-crossing-a-bridge explanation: no external drive!
- Instead: Coupling between walking pedestrians mediated by bridge leads to synchronization

adapted from: Pikovsky, Rosenblum, Kurths

Simplest System: Two Harmonic Waves



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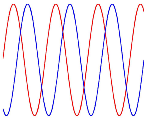

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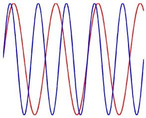

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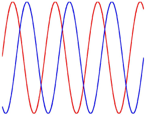
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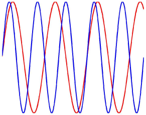
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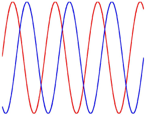

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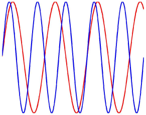

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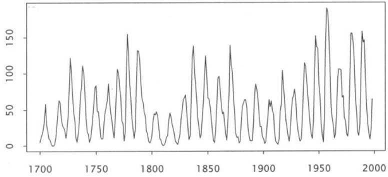
Harmonic waves $\sin(\phi_1(t))$ and $\sin(\phi_2(t))$ are $N : M$-locked for fixed differences of their phase ϕ

$$\Delta\phi = (N\phi_1(t) - M\phi_2(t)) \bmod 2\pi = \text{const}$$

Real Signals Are Not Harmonic

How to determine synchrony for complicated time series?



Rosenblum et al, 1997; Kurths and Pikovski, 2001

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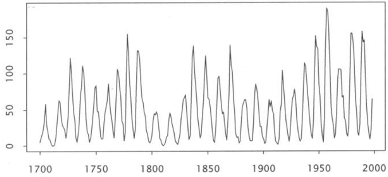

Different types of synchrony:

- Complete Synchronization
- Lag Synchronization
- General Synchronization
- Frequency Synchronization
- Phase Synchronization

Rosenblum et al, 1997; Kurths and Pikovski, 2001

How to Measure Synchronicity?

In the following, we will look at two common methods to quantify synchronized time series:

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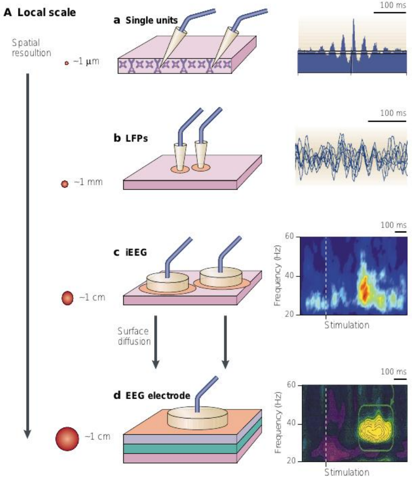
Why Study Synchrony in the Brain?



Varela et al, 2001

- Measure coorperate activity across brain areas → functional connectivity
- Relationship between signals at various mesoscopic and microscopic scales
- Coding of information in the phase information between signals

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$$x(t) = a_0 + \sum_{n=1}^{\infty} (a_n \cos(2\pi f_n t) + b_n \sin(2\pi f_n t))$$

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- The magnitude $|S(f)|$ corresponds to the amplitude of the harmonic at frequency f, the phase θ determines its offset from a cosine

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- The real-valued, squared Fourier spectrum is known as the power spectrum

$$P(f) = S(f)S^*(f) = |S(f)|^2 \exp(i(\phi - \phi)) = |S(f)|^2$$

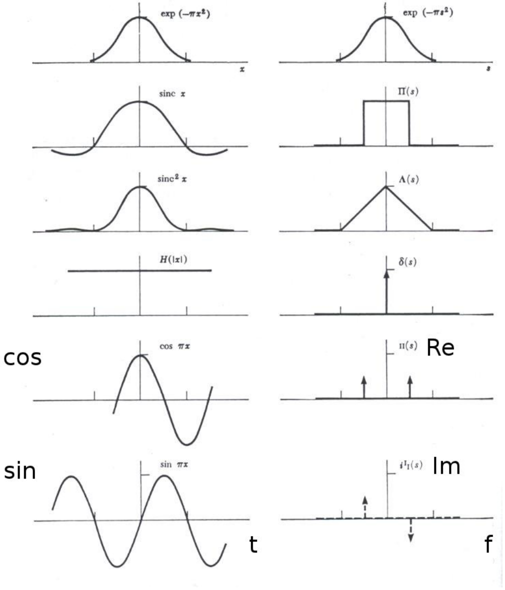
Decomposing a Signal - Fourier Analysis

- For measured time series, we obtain an estimate of the spectrum consisting of a finite number of N sample points
- Discrete Fourier Transform (DFT) yields discrete, complex-valued Fourier spectrum $S(f)$ for $N/2$ evenly-spaced frequencies from 0 to the Nyquist frequency (half the sample frequency)
- The real-valued, squared Fourier spectrum is known as the power spectrum

$$P(f) = S(f)S^*(f) = |S(f)|^2 \exp(i(\phi - \phi)) = |S(f)|^2$$

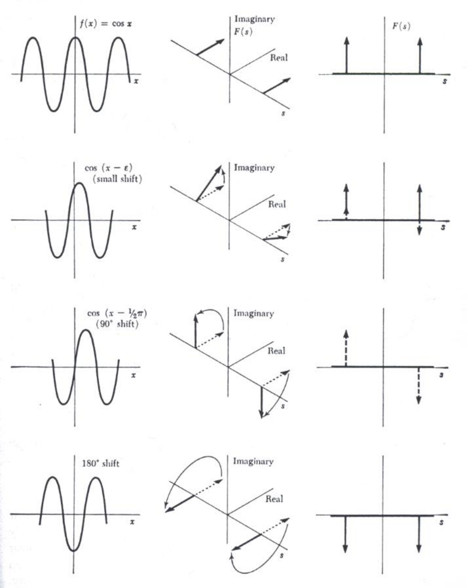
- In short: Measure of how dominiant individual frequencies are present in the signal

Examples of Simple Fourier Transforms



Bracewell, 1986

The Phase of the Fourier Transform



Bracewell, 1986

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Coherence

(Cross-)coherence measures whether a spectral component in signals $x(t)$ and $y(t)$ correlates

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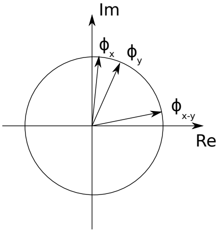
Cross-spectrum:

$$C_{xy}(f) = S_x(f)S_y^*(f) = |S_x(f)|\,|S_y(f)|\exp(i(\phi_x - \phi_y))$$



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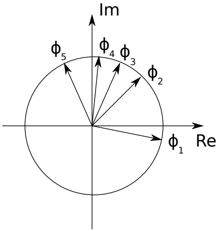

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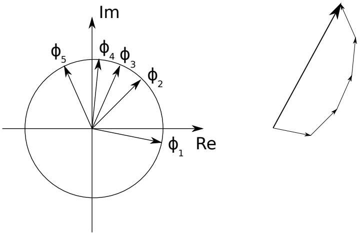

Coherence

Coherency:

$$\sigma_{xy}(f) = \left|\frac{C_{xy}(f)}{\sqrt{P_x(f)P_y(f)}}\right|$$

Absolute value of the averaged cross-spectra normalized by the average power content of signals at frequency f

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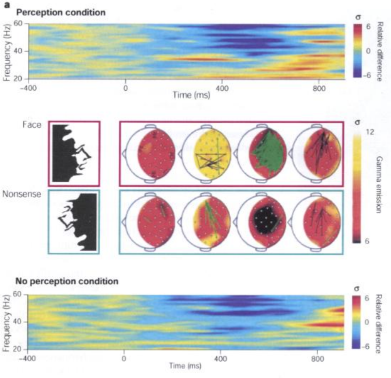
Mean-amplitude normalized coherence index

$\sigma_{xy} = 1 \ \rightarrow$ Perfect coherence

$\sigma_{xy} \rightarrow 0 \ \rightarrow$ Incoherent dynamics

Example: Long-distance Synchronization

Face-perception task in macaque EEG recordings results in long-range gamma band synchronization



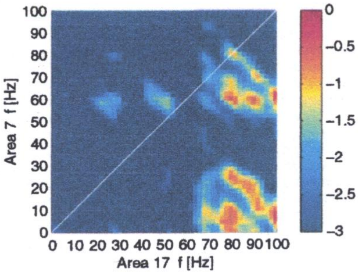
Rodriguez et al, 1999; Varela et al., 2001

Example: Dual Bi-Coherence

Cross-analyze frequencies:

$$C_{xy}(f_1, f_2) = \langle S_x(f_1) S_y(f_2) \rangle_{t,n,\Delta f}$$

$$\sigma_{xy}(f_1, f_2) = \left| \frac{C_{xy}(f_1, f_2)}{\sqrt{P_x(f_1) P_y(f_2)}} \right|$$



v. Stein et al, 2000

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Consider complicated systems that reflect oscillatory dynamics

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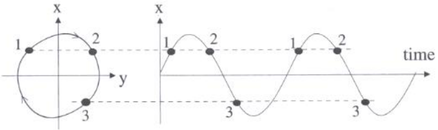

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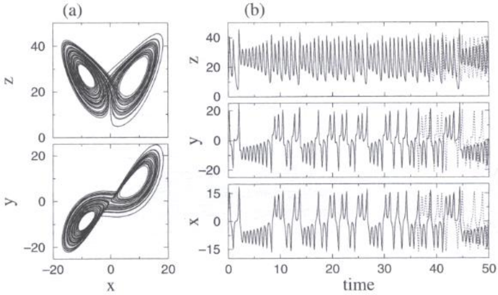

Kurths, 2001

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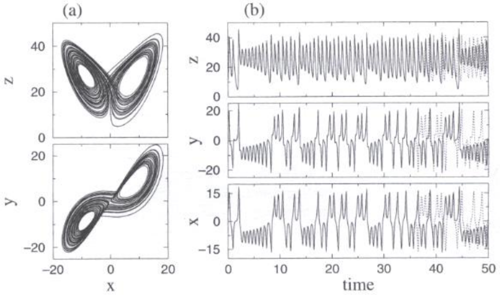

Kurths, 2001

Task 1: Assign a phase $\phi(t)$ to measured dynamics

Coupling Induces Phase Synchronization

We define $N : M$ phase synchronization between $x_1(t)$ and $x_2(t)$:

$$\Delta\phi = \mathrm{const}_t = (N\phi_1 - M\phi_2) \bmod 2\pi = \mathrm{const}.$$

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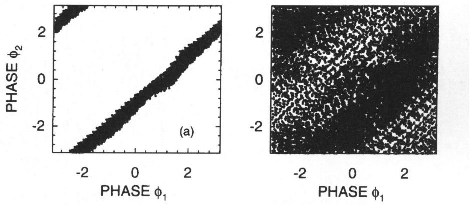

Palus, 1997

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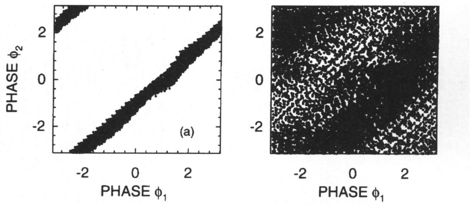

Palus, 1997

Task 1: Assign a phase $\phi(t)$ to measured dynamics
Task 2: Define index to measure degree of phase synchrony

Task 1: Obtaining Phase Estimates from Time Series

Method 1: Extract maxima of signal $x(t)$, linear interpolation between maxima from 0 to 2π
$\rightarrow$ Simple, but problematic (linearity, maxima detection)

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Second exponential is a complex rotation that detects instantaneous phase around frequency f

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Method 3: Transform into analytic signal

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Method 1: Extract maxima of signal $x(t)$, linear interpolation between maxima from 0 to 2π

→ Simple, but problematic (linearity, maxima detection)

Which method to use?

Wavelets and Hilbert yield comparable results.
Here: Use analytic signal (Hilbert) approach for simplicity.

Le van Quyen et al, 2001

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Obtaining Phase Estimates using the Analytic Signal

The Analytic Signal is defined as

$$\tilde{x}(t) = x(t) + i\mathcal{H}[x(t)]$$

via Hilbert Transform

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

Idea: $\mathcal{H}$ yields a signal phase-shifted by $\pi/2$.

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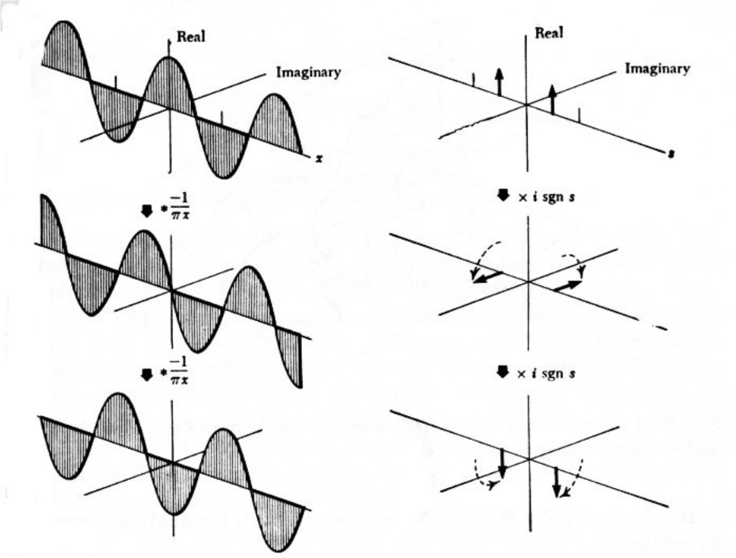
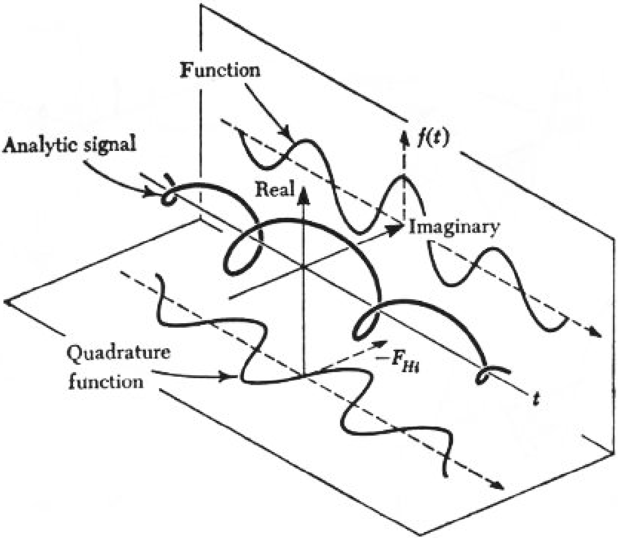
Let's look at pictures...

Hilbert Transform



Bracewell, 1986

The Analytic Signal



Bracewell, 1986

Task 2: Index for Phase Synchrony

Basis: how constant is the phase difference over time.

For a review, see Quiroga et al, 2002.

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Example: Mutual Information

Use probability distributions $p(\phi_1)$, $p(\phi_2)$ and $p(\phi_1, \phi_2)$ and calculate the mutual information

$$I = \int \int p(\phi_1, \phi_2) \log \frac{p(\phi_1, \phi_2)}{p(\phi_1)p(\phi_2)} \mathrm{d}\phi_1 \mathrm{d}\phi_2$$

Independence of phases yields $I \approx 0$

Task 2: Index for Phase Synchrony

Basis: how constant is the phase difference over time.

For a review, see Quiroga et al, 2002.

Example: Across Trials

We define the phase locking index

$$PLV(t) = N^{-1} \left| \sum_{n=1}^{N} \exp(i\, \Delta\phi(t,n)) \right|$$

where $\Delta\phi(t,n)$ is the phase difference in trial n

Lachaux et al, 1999

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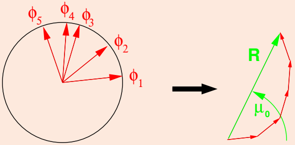
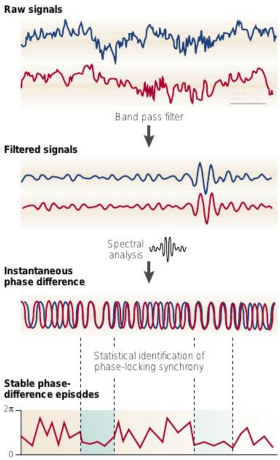


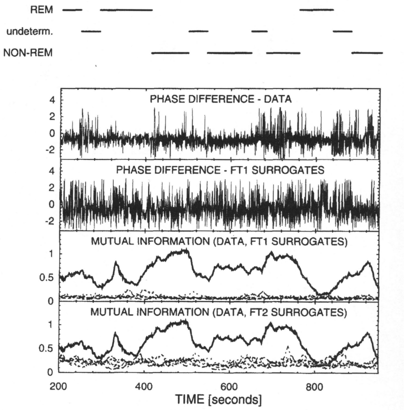
Application to Biology: Phase Synchronization



Varela et al, 2001

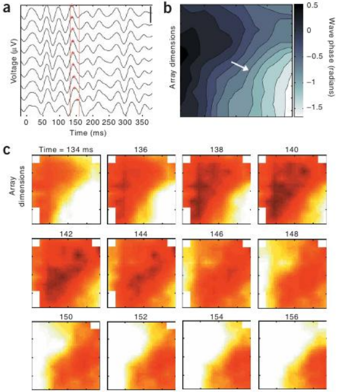
Example: Synchrony in Physiological Measurements

Measurement between respiratory and cardiac signals



Palus, 1997

Example: Measuring LFP wave propagation across cortex



Rubino et al., 2006

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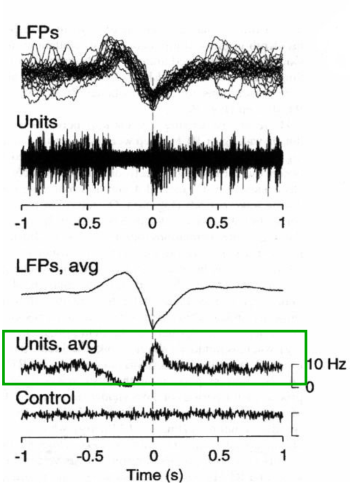
Potential Features of LFP-Spike Relationships



- Locking observed in terms of a locking probability $p(\phi)$

Destexhe et al, 1999

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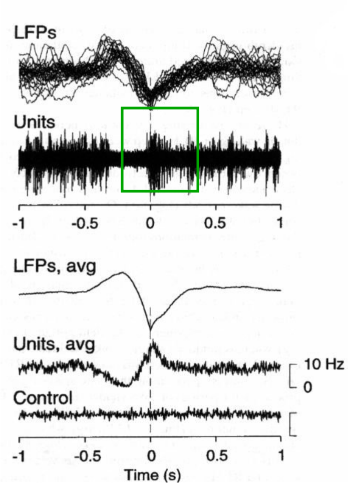

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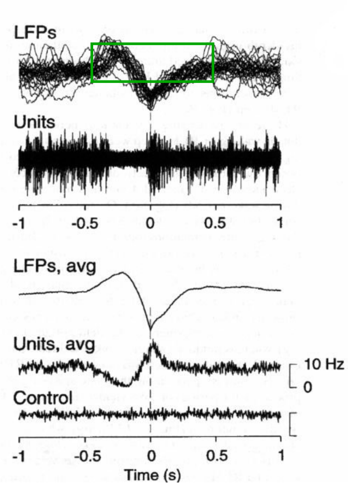

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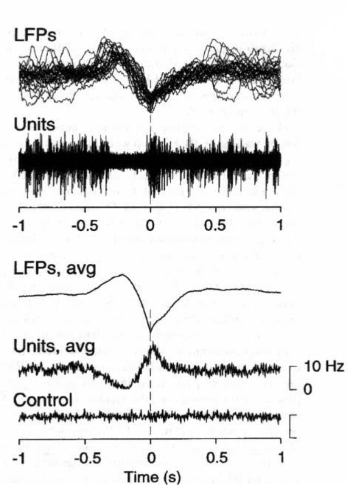

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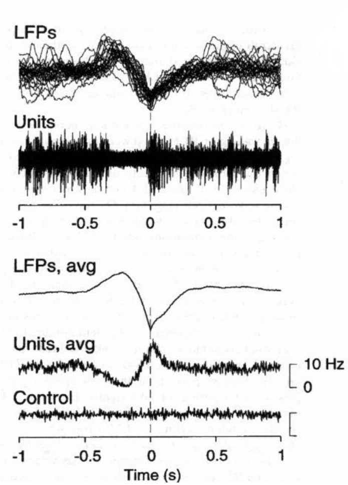

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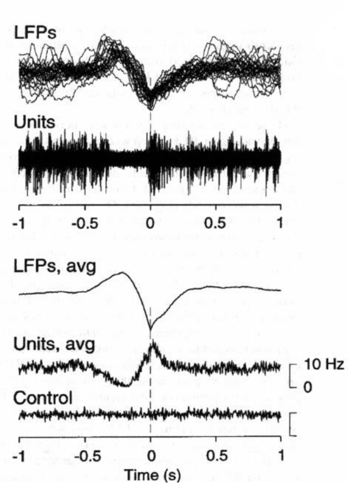

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- Multi-modal distribution of $p(\phi)$

Destexhe et al, 1999

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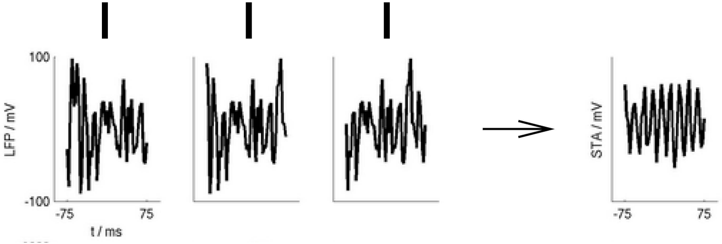
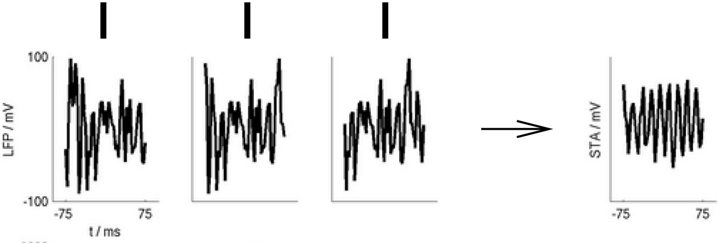
Spike-Triggered Averaging (STA)



- Cut out LFP segments around spikes…

Spike-Triggered Averaging (STA)



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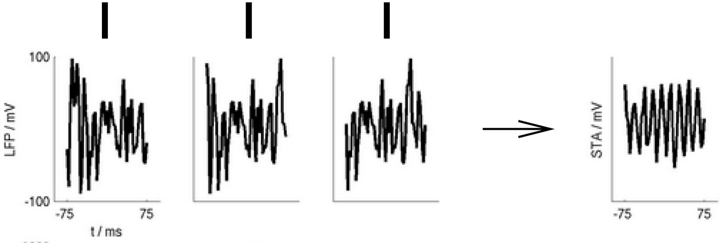

- Cut out LFP segments around spikes…
- …and average them!
- If spikes prefer a specific part of an oscillation cycle, it will not average out in the STA

Spike-Triggered Averaging as Correlation

Assume LFP signal $L(t)$ and a spike train $S(t) = \sum_i \delta(t - t_i)$, where t_i are the spike times

Then, the STA can be written as correlation (or alternatively: correlation coefficient)

$$c(\tau) = \int L(t)S(t+\tau)\,\mathrm{d}t$$

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However: Significance estimate of STA is not trivial.

Typically one uses surrogates, such as trial shuffling, shifting the LFP, or bootstrap procedures.

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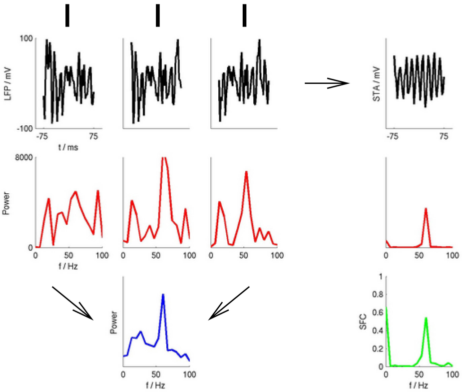
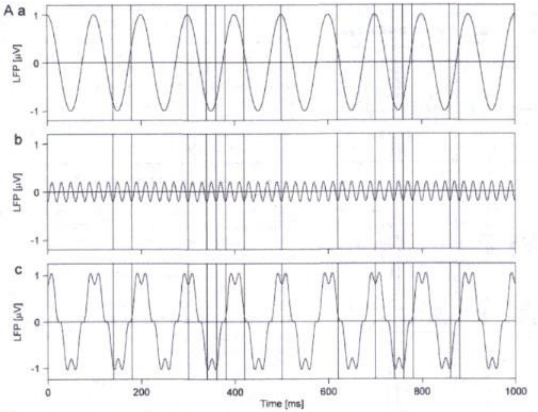
A Simple Spike-Field Coherence (SFC)



SFC is the power spectrum of the STA, normalized by average power spectrum of individual segments.

Why the normalization?

Normalization removes mean-amplitude dependence, locking to oscillations with small amplitudes becomes visible



Fries et al, 2002

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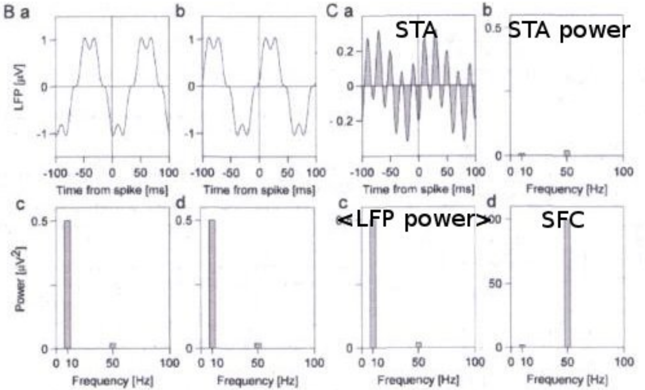

Fries et al, 2002

Insight: Relationship to Coherence

In fact, spike-field coherence is only a special case of coherence as discussed before. Why?

for derivations, confidence intervals, see e.g., Jarvis et al, 2001

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Correlation Theorem (sloppy):

$$\mathcal{F}(CCF(x(t), y(t))) = \mathcal{F}(x(t)) \cdot \mathcal{F}(y(t))$$

where $\mathcal{F}(\cdot)$ denotes the Fourier transform and CCF the cross-correlation function

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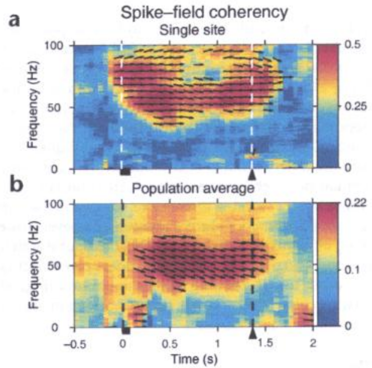
Equivalence:

$$\mathcal{F}(STA) = C_{xy}(f)$$

for derivations, confidence intervals, see e.g., Jarvis et al, 2001

Example: Memory Task in Macaque



Pesaran et al, 2002

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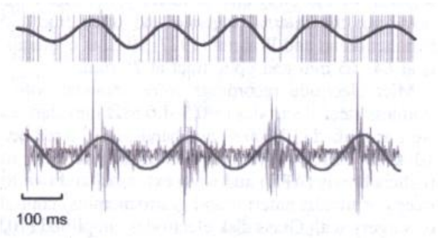
Extension to Phase Analysis

Simple Idea: Transform spike train to rate signal, and use normal phase synchronization

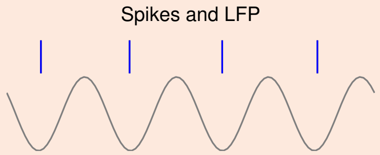


Hurtado et al, 2004

Drawback: Loose precise timing information about spikes (early average)

Alternative

Determine instantaneous phase of the LFP signal related to spike timing



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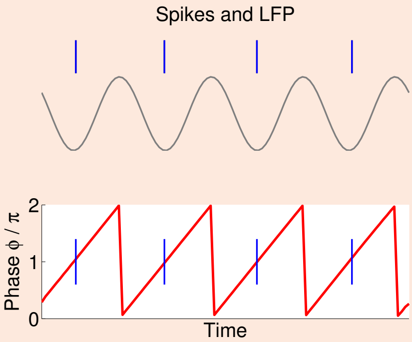
Determine instantaneous phase of the LFP signal related to spike timing



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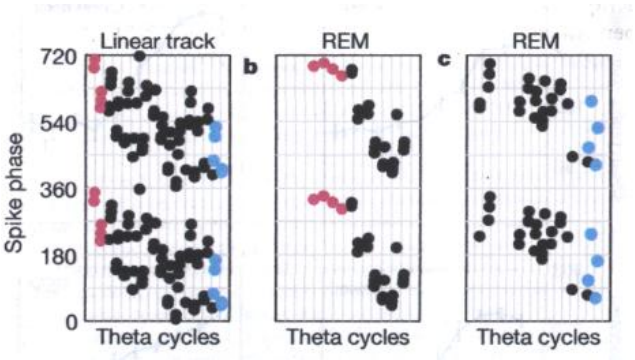
Direct Phase Estimation

Obtain phases at time instances of discrete occurances (e.g. spikes)

$\rightarrow$ Stroboscopic sampling of the system, a synchrogram



Harris et al, 2002

JÜLICH FORSCHUNGSZENTRUM

Phase Locking Statistics

Given:

Extracted phases $\phi(t_i)$ of LFP at spike times t_i, $i = 1 \ldots N$.

Approach 1: Period Histogram

Bin phase axis $[0; 2\pi)$

Phase Locking Statistics

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Approach 1: Period Histogram

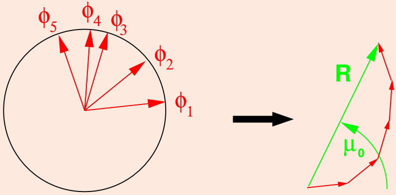
Approach 2: Circular Statistics cf., eg., Mardia and Jupp, 2000

Mean phase μ_0: $Re^{i\mu_0} = N^{-1} \sum_i e^{i\phi_i}$,
Variance: $S := 1 - R = 1 - N^{-1} |\sum_i e^{i\phi_i}|$,
Standard deviation: $\sigma = \sqrt{-2 \ln R}$,

Null hypothesis of uniform phase distribution:
$2NR^2$ is χ^2-distr. with 2 deg. of freedom.

Phase Locking Statistics

Mean and variance on the circle



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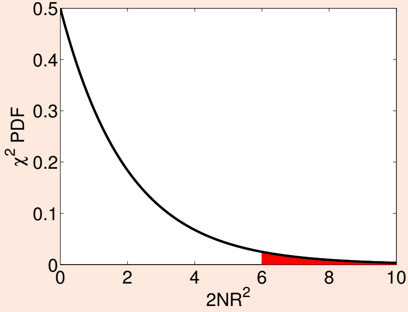
Distribution of R



Approach

Approach

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Approach 1: Period Histogram

Approach 2: Circular Statistics

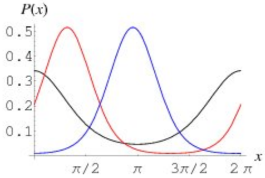
Non-stationarity / Transient Locking

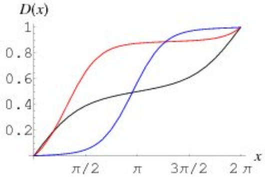
Analysis performed in sliding windows.

Circular tests and the von Mises distribution

- Several tests in circular statistics are available, equivalent to tests on the line. Batchelett, 1976; Fisher, 1995
- Use of bootstrap and resampling methods. Stark and Abeles, 2005
- Standard unimodel distribution is the von Mise distribution

$$P_{a,b}(x) = \frac{e^{b\cos(x-a)}}{2\pi I_0(b)}$$



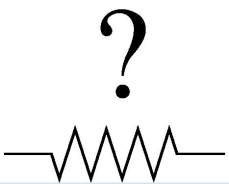


Weisstein (MathWorld)

Using Surrogates To Detect Genuine Locking

- Q: When I observe phase synchronization between two signals, is it real?

Using Surrogates To Detect Genuine Locking Synchronization?



Using Surrogates To Detect Genuine Locking

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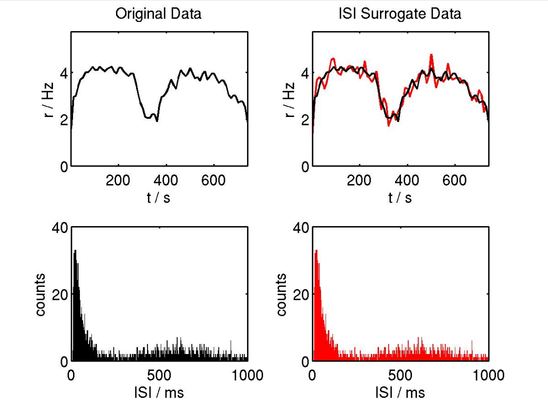
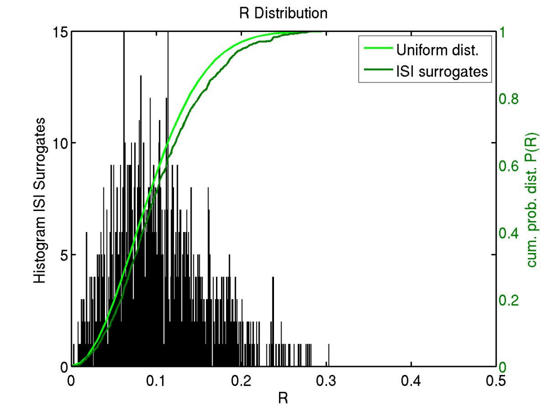
- Here: Surrogates by locally shuffling inter-spike intervals

Using Surrogates To Detect Genuine Locking

Local ISI Shuffles



Using Surrogates To Detect Genuine Looking R Distributions



The Meaning of Phase

- Instantaneous phase (IP) and Fourier phase (FP) are two distinct measures!
- Interpretation of IP is controversial.
- Commonly instantaneous frequency defined as the instantaneous change of phase angle.
- Time-average of the IP frequency is related to the average spectral frequency:

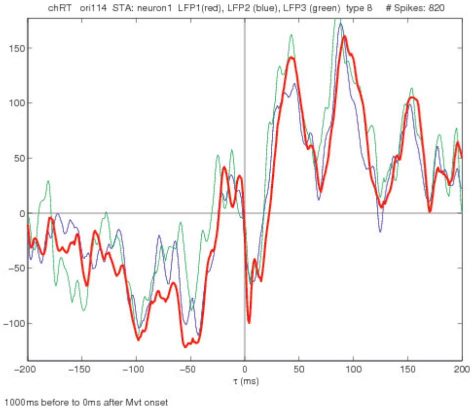
$$< f_F >_f = < f_{IP} >_t$$

- Hard to interpret IP for multi-component signals . . .
- . . . or small amplitude signals!
- IP tracks non-stationarity of signals in time.
- SFC and phase-locking are two important complementary measueres.

Boashash, 1992a,b; Lachaux et al, 2001

The Electrode Issue

Spikes recorded from the LFP electrode may contaminate high frequency LFP



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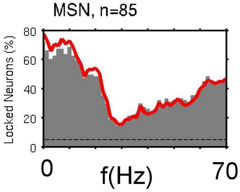

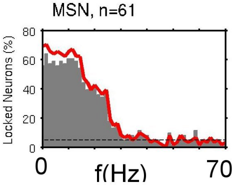

Today's Exercises

- Task 1: Implement STA and spike-triggered phases
- Task 2: Apply these measures to the data set