EEG/MEG 3:
Time-frequency and Functional Connectivity Analysis

Workshop 5 April 2017

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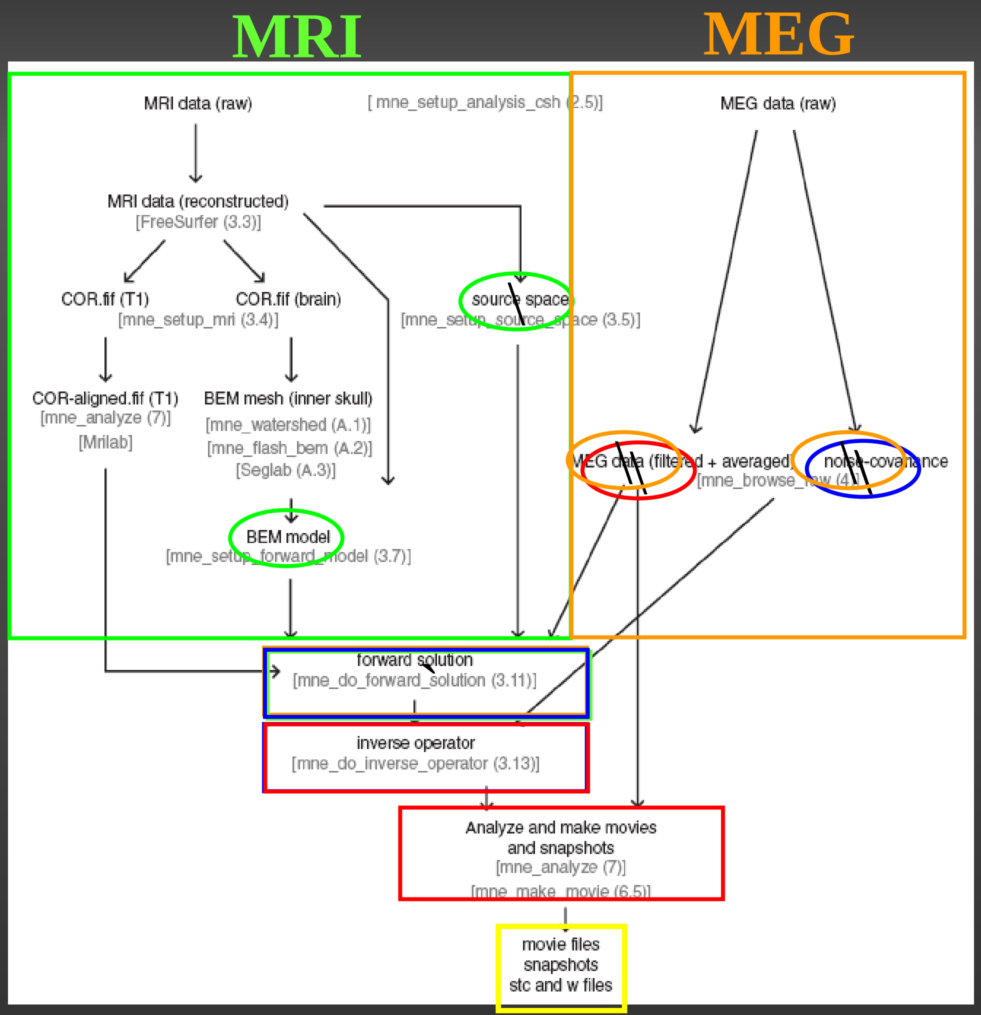
The Path to the Source

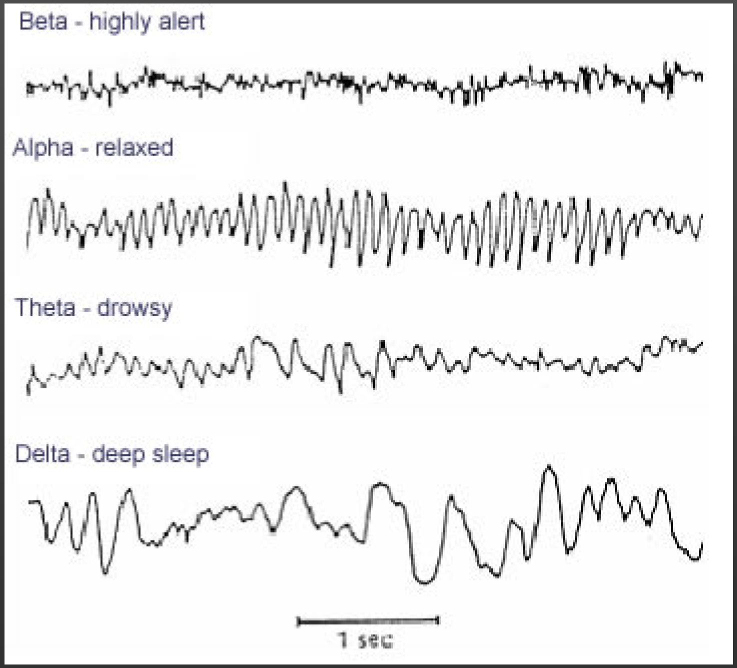


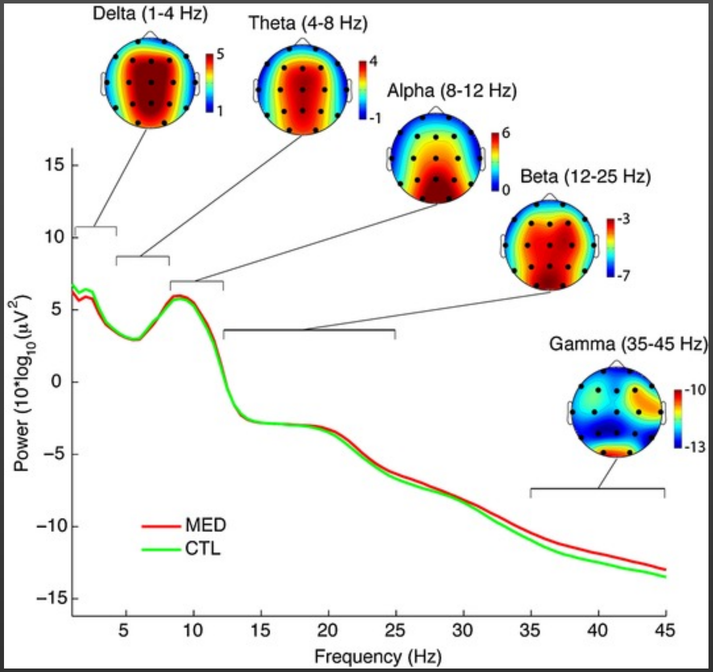
Cohen, MX. Analyzing Neural Time Series Data. MIT Press.
Hansen et al. MEG: An Introduction to Methods. Oxford U Press.
Picton et al. Guidelines for using human ERPs to study cognition. Psychophysiology 2000.
Gross et al. Good practice for conducting and reporting MEG research. Neuroimage 2013.
http://www.mrc-cbu.cam.ac.uk/methods-and-resources/imaginganalysis/
http://imaging.mrc-cbu.cam.ac.uk/meg/MEGpapers

“Brain Rhythms” and “Oscillations”

Time course and topography may differ among different frequency bands

(and may depend on task, environment, subject group etc.)





http://link.springer.com/article/10.1007%2Fs10339-009-0352-1/

Periodic Signals

A periodic signal repeats itself with a period T.

This is the case, for example, for sine and cosine functions:

In radians ($\mathbf{2\pi}$ ~ 360 degrees):

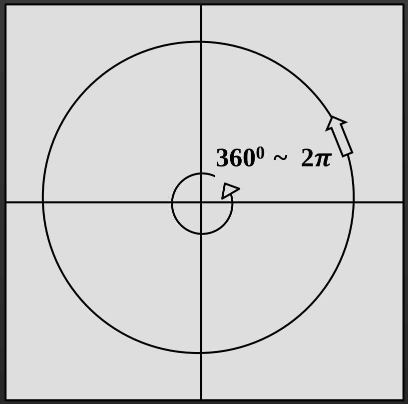
$$\boldsymbol{cos(x + 2\pi) = cos(x)}$$

$$\boldsymbol{sin(x + 2\pi) = sin(x)}$$

In degrees :

$$\boldsymbol{cos(x + 360) = cos(x)}$$

$$\boldsymbol{sin(x + 360) = sin(x)}$$



On a unit circle, a 360^0 angle corresponds to a circumference of 2*pi

Sine and Cosine

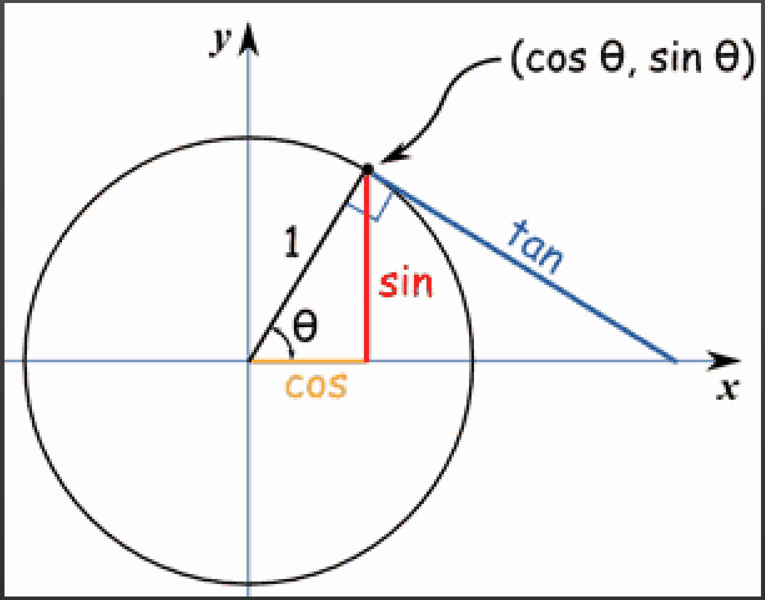
$$s(t) = a * sin(2\pi f * t + \theta)$$

a: amplitude

f: frequency

θ : phase

$$\cos(x) = \sin(x + \frac{\pi}{2}) \text{ or } \cos(x) = \sin(x + 90)$$



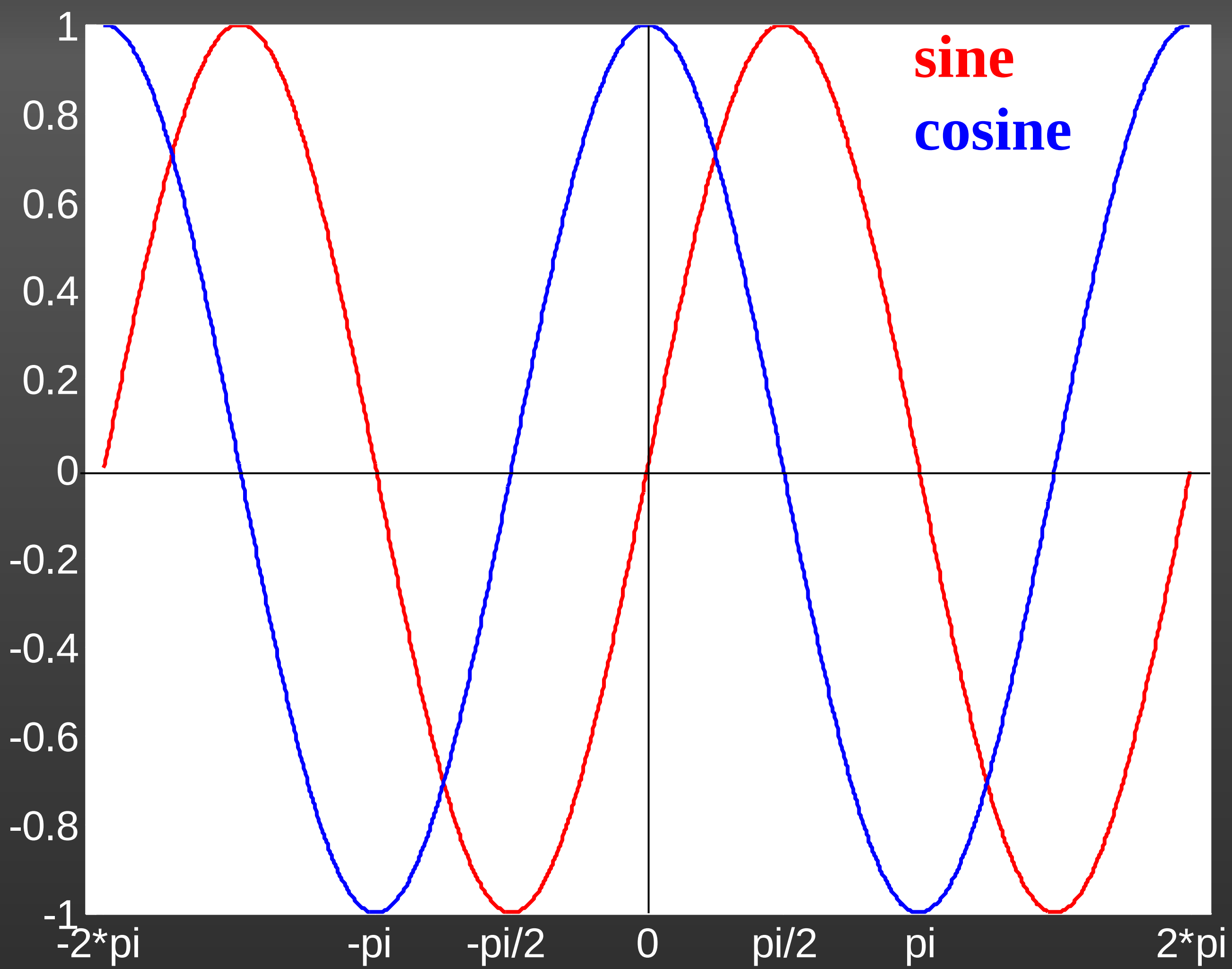
Inverse of sine and cosine: arcsine and arccosine

Given the sine/cosine values, they will yield the angle.

https://www.youtube.com/watch?v=z82I6u4DFTo

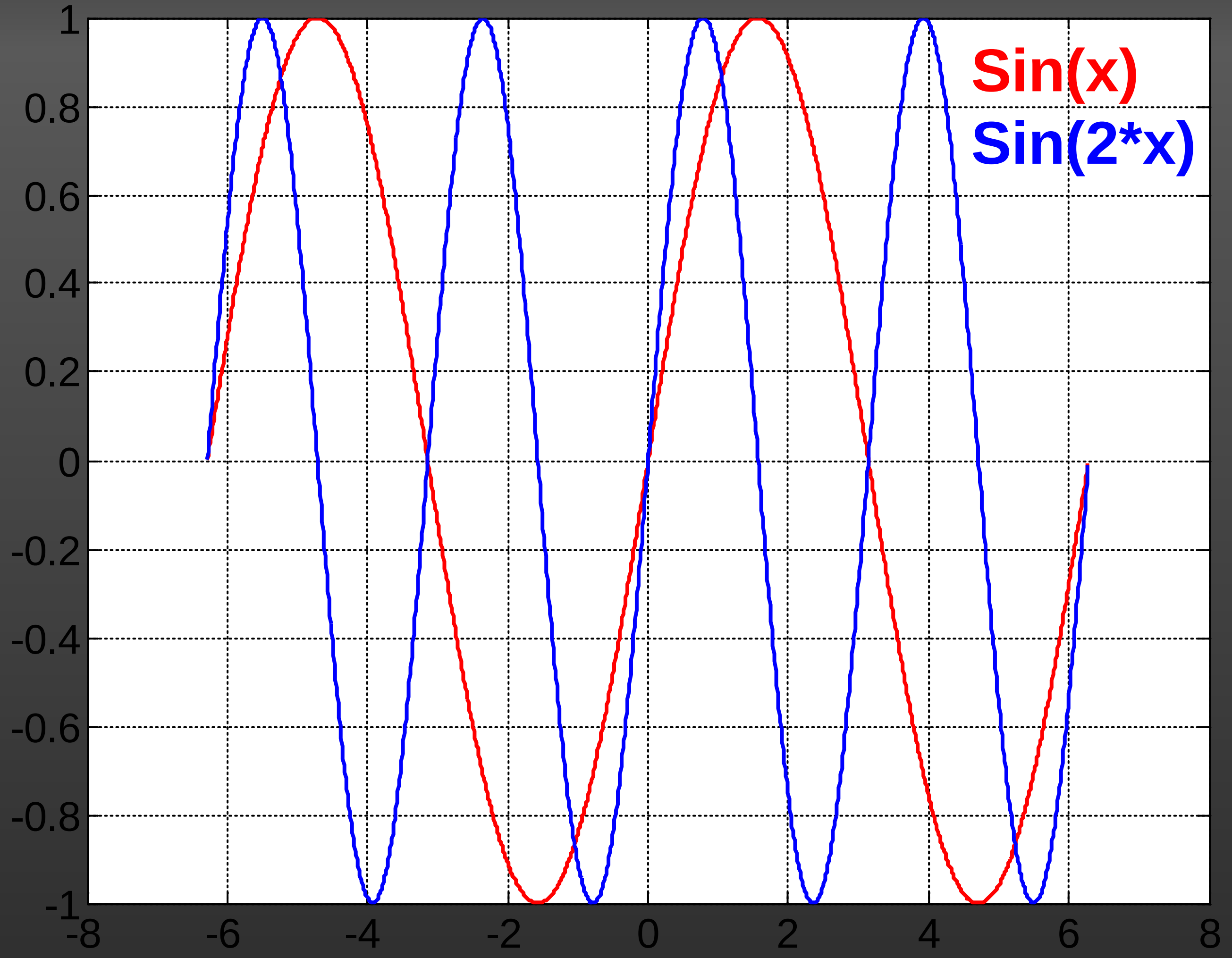
Sine and Cosine Are Orthogonal to Each Other

(at a given frequency)



$$\int \sin(f * x)\, cos(f * x)dx = 0$$

Sine/Cosine At Integer Frequency Intervals Are Orthogonal



$$\int \sin(m * f * x)\, sin(n * f * x) dx = 0 \text{ for integer m, n}$$

More “Complex” Than Necessary? Euler’s Formula

$$e^{-i\theta} = \boldsymbol{cos}(\theta) + \boldsymbol{i} * \boldsymbol{sin}(\theta) \quad \boldsymbol{i}=\sqrt{-1}$$

Therefore:

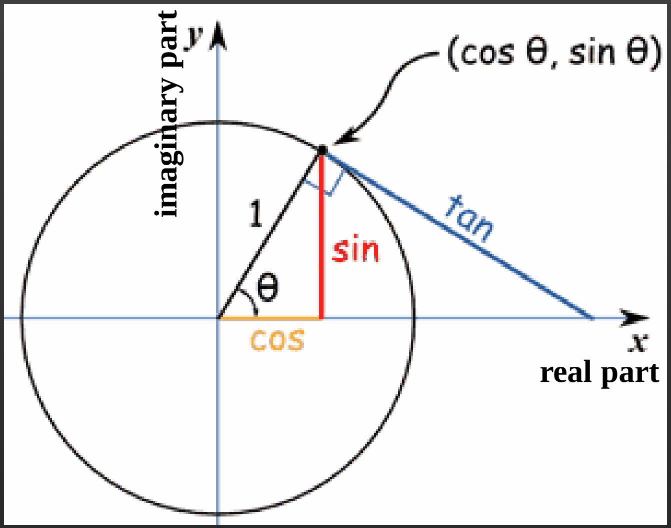
$$cos(\theta) \ = \ real(e^{-i\theta})$$

$$sin(\theta) \ = imag(e^{-i\theta})$$

This is mathematically very convenient, but not very intuitive…

Important to remember:

An oscillation at a particular frequency can be described in a “polar representation”:



Entering the Frequency Domain: Fourier Transform in Words

What you want:

You've got a signal consisting of N sample points (equidistant).
You want to know which frequencies contribute to the signal, and how much.

In other words:
You want to describe your signal as a linear combination of sines and cosines,
ideally of orthogonal basis functions made up of sines and cosines.

What you've got:

With N samples, you can estimate at most N independent parameters.

You cannot estimate frequencies above half of the sampling frequency SF (Nyquist).

For a given frequency, sine and cosine are orthogonal,
i.e. 2 basis functions per frequency.

Entering the Frequency Domain: Fourier Transform in Words

Divide the frequency range 0 to SF/2 evenly into N/2 frequencies.

For every frequency, create a sine and a cosine.

Use these (orthogonal) sines and cosines as your basis functions.

Project these basis functions onto your data, get the amplitudes for individual basis functions.

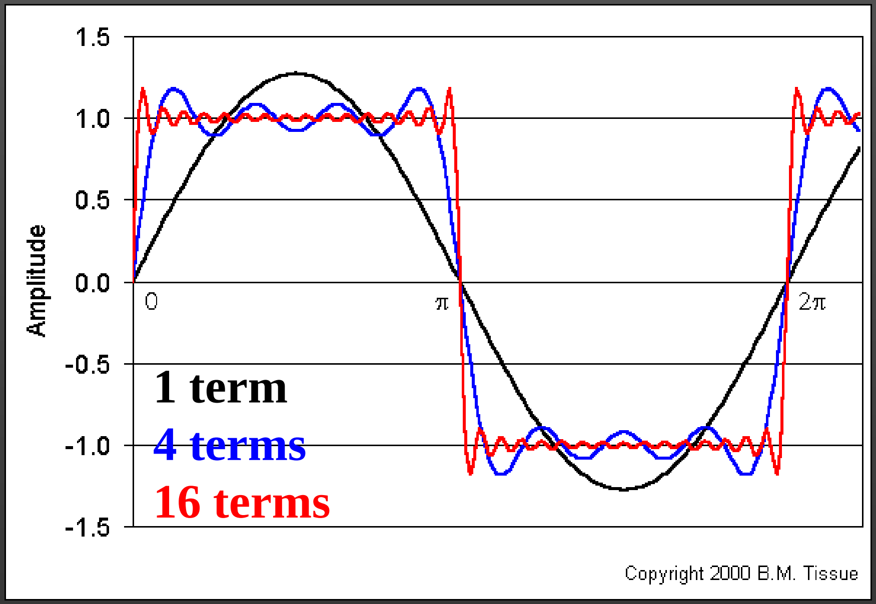
Be happy about the result!

Fast Fourier Transform (FFT): A fast algorithm to do this.

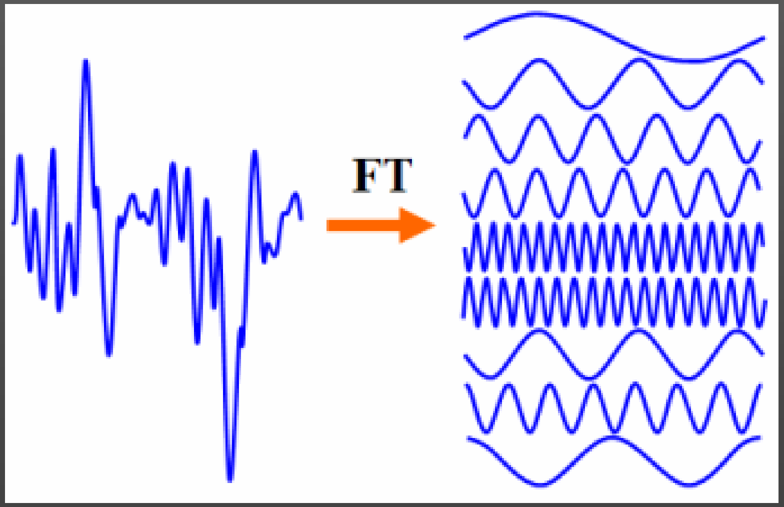
(I'm cheating a bit, assuming an appropriate N and ignoring the mean. But the principle is ok.)

Thinking About The Fourier Transform

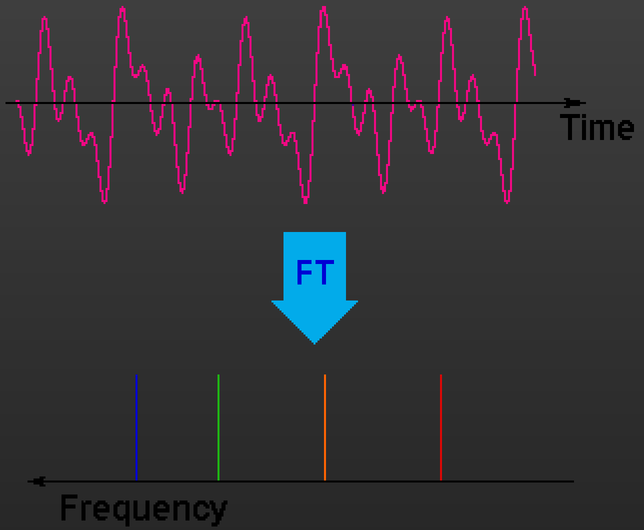
Approximating a function with Fourier terms



Decomposing signals into sine/cosine terms



Frequency Spectrum

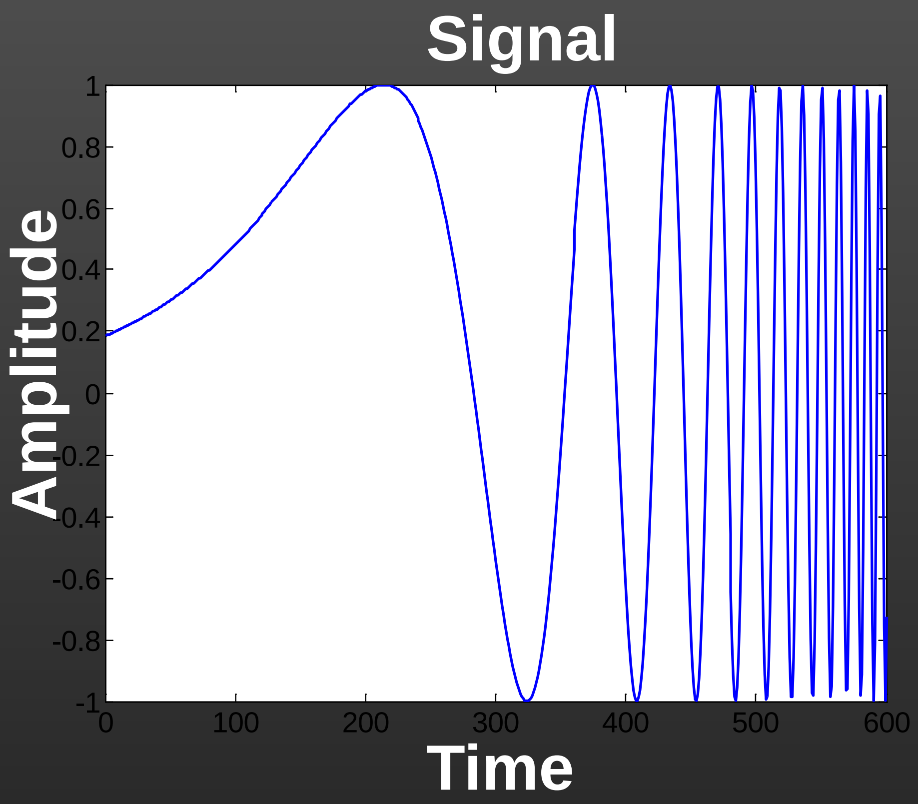


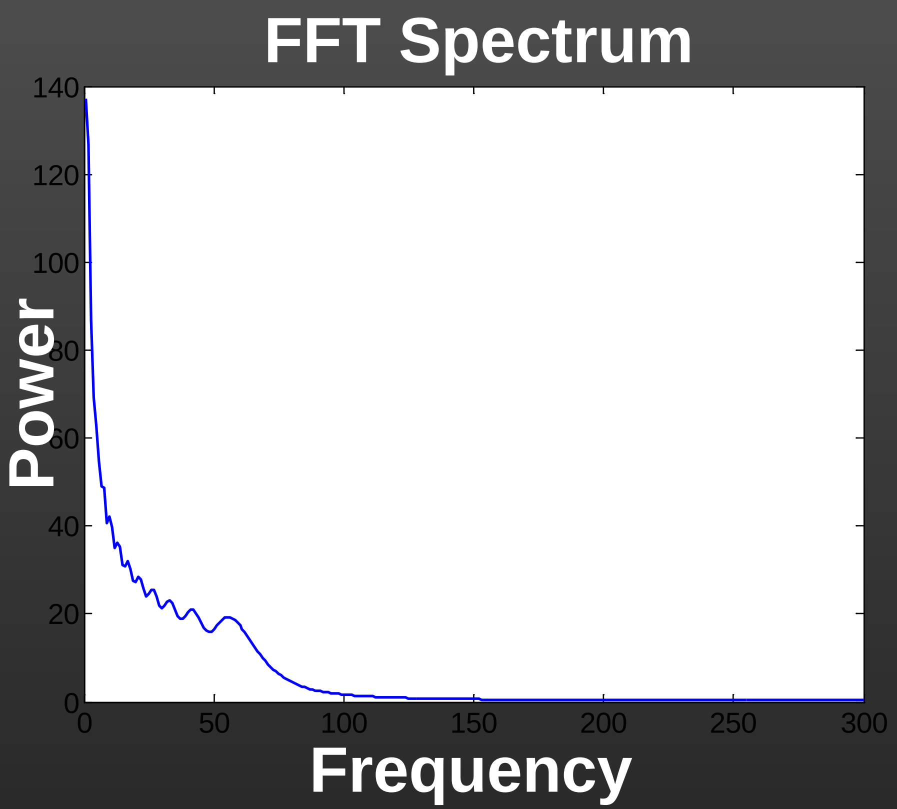
Practical Example: Band-pass filtering

Motivation for Time-Frequency Analysis

Fourier Transform assumes sines and cosines with constant amplitudes across the whole time series ("stationarity").

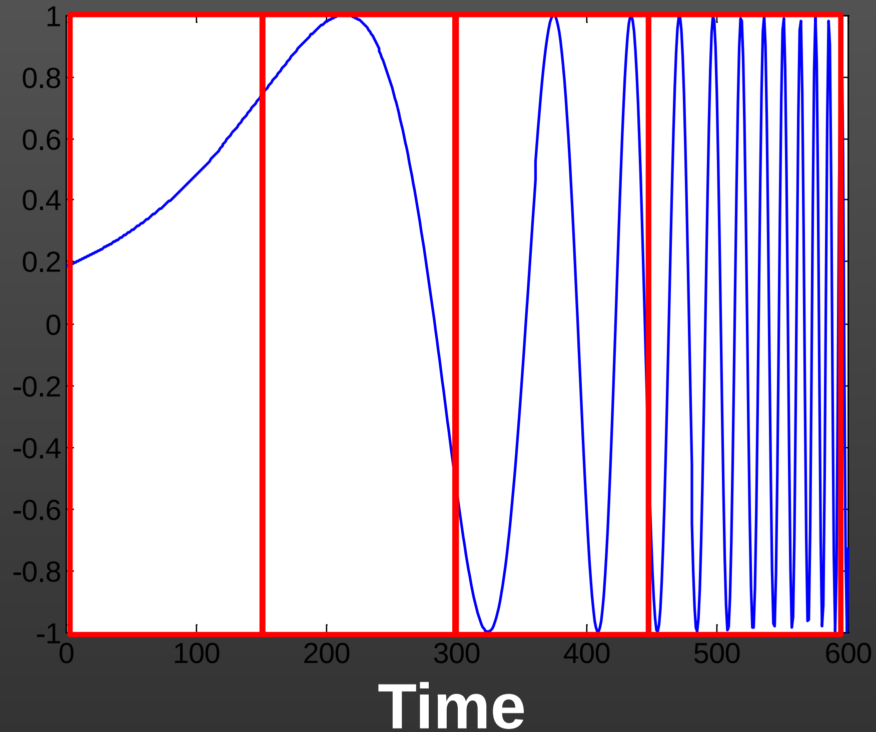
But what does an FFT mean for a signal like this?





Motivation for Time-Frequency Analysis

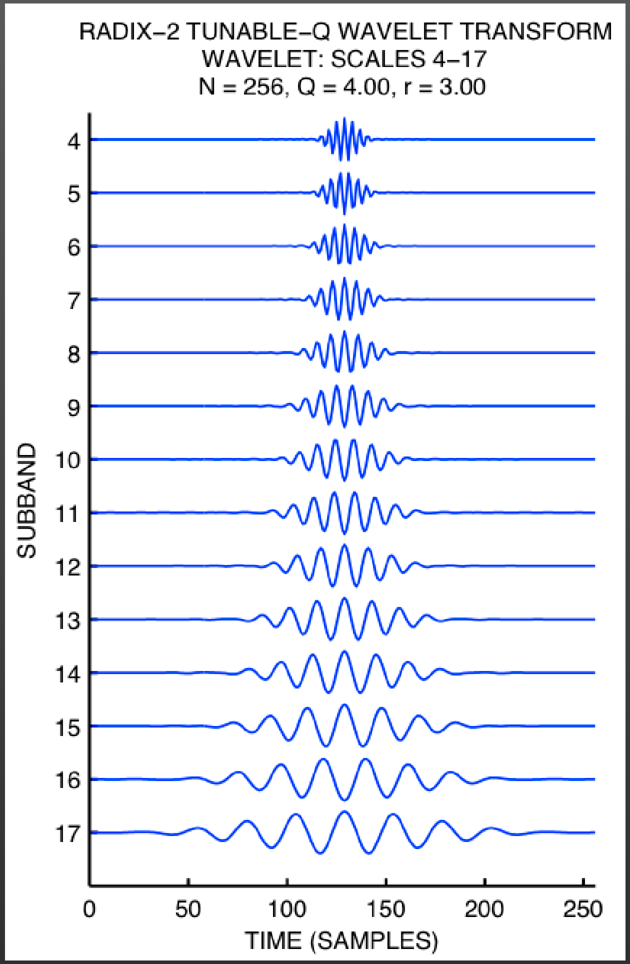
You could run separate FFTs for different (sliding) time windows:



But different window sizes are more or less optimal for different frequencies.
Run different FFTs with different window sizes for different frequency ranges? Ouff.

Time-Frequency Analysis: Wavelets

Wavelets provide an optimal trade-off between frequency and time resolution.

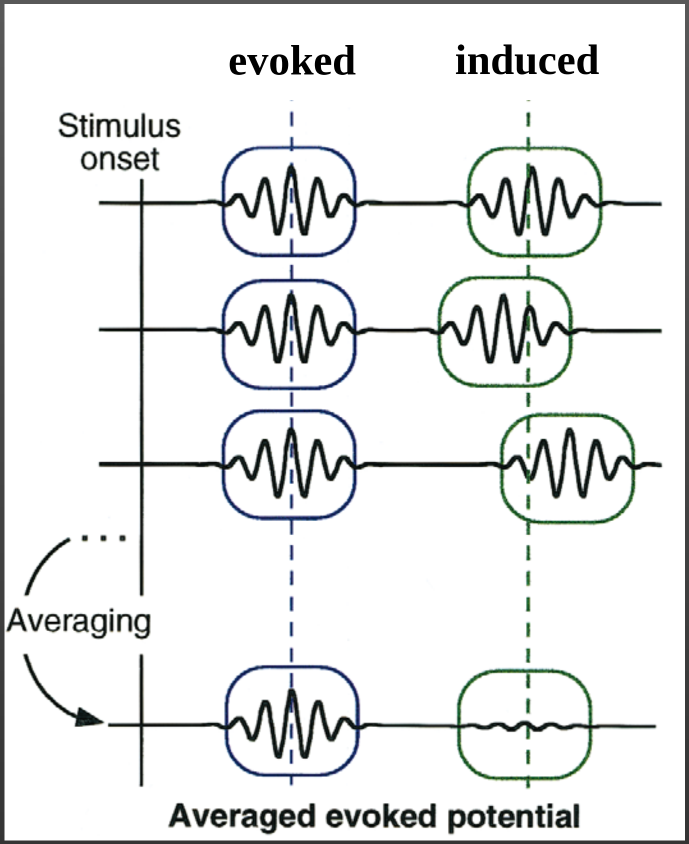


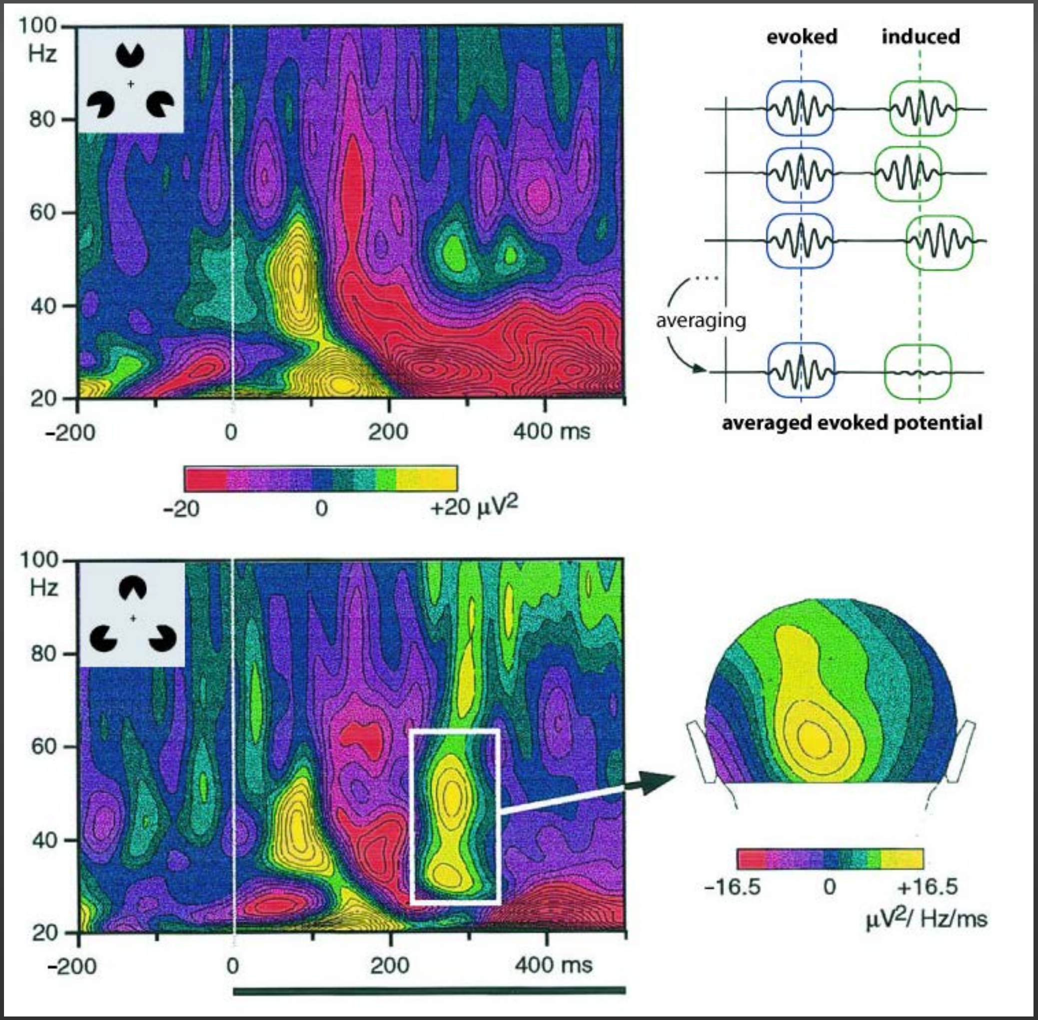
Time resolution decreases as frequency decreases

(wavelets are getting “broader”)

Wavelets are convolved with the data to give instantaneous amplitude and phase estimates for different frequency ranges.

Evoked and Induced Activity





Tallon-Baudry & Bertrand, TICS 1999

A Very Rough Rule of Thumb

One needs at least 2 cycles of a frequency to get a meaningful estimate (of amplitude, phase, etc.)

Duration (in ms) of 2 cycles at frequency f (in Hz): 2*1000/f

1 Hz: 2000 ms = 2 s

10 Hz: 200 ms = 1/5 s

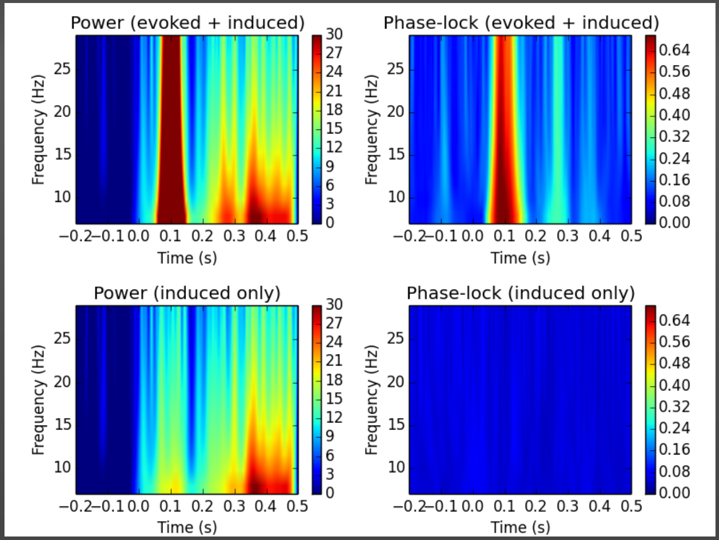
40 Hz: 50 ms = 1/20 s

100 Hz: 20 ms = 1/50 s

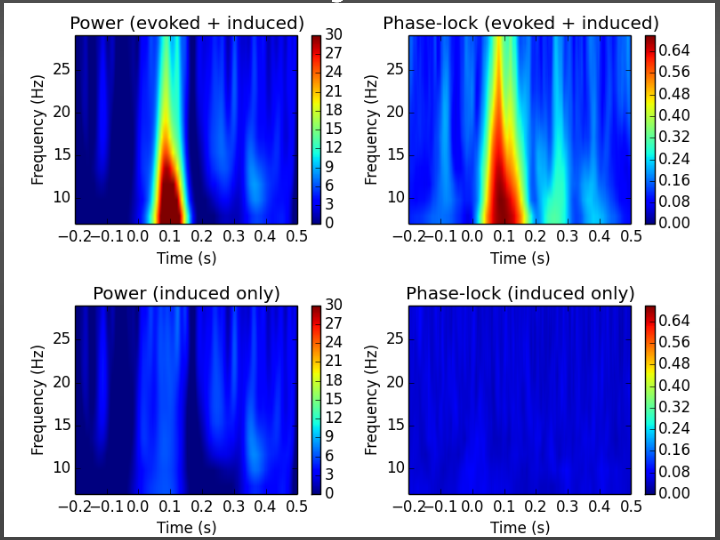
The lower the frequency, the longer the time window required to estimate the signal

Effect of Number of Cycles

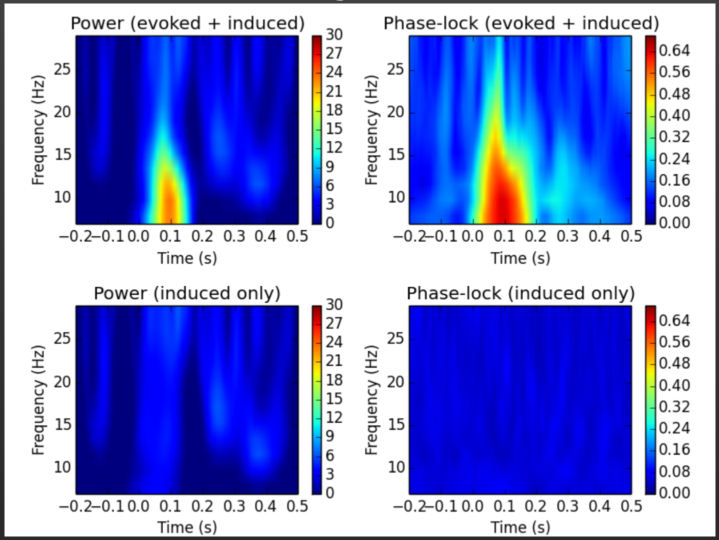
1 cycle



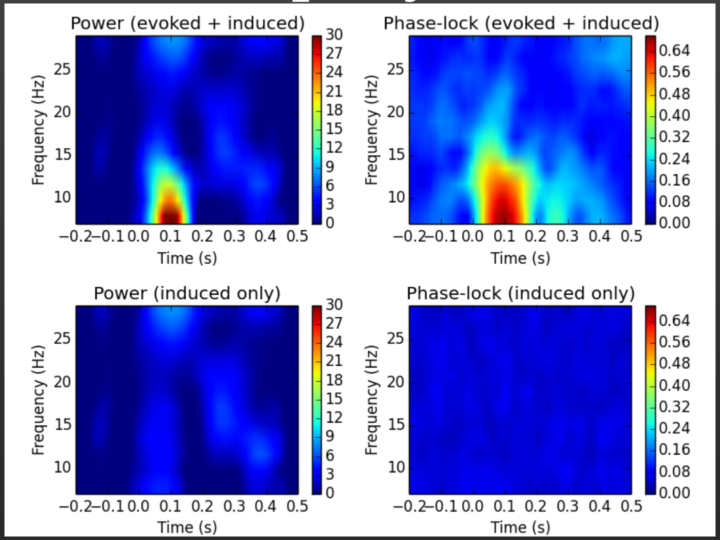
2 cycles



3 cycles



Freq/3 cycles



Single-Trial Analysis and Source Estimation

Computing the power of a signal is a non-linear transformation.

Linear transformations are associative:

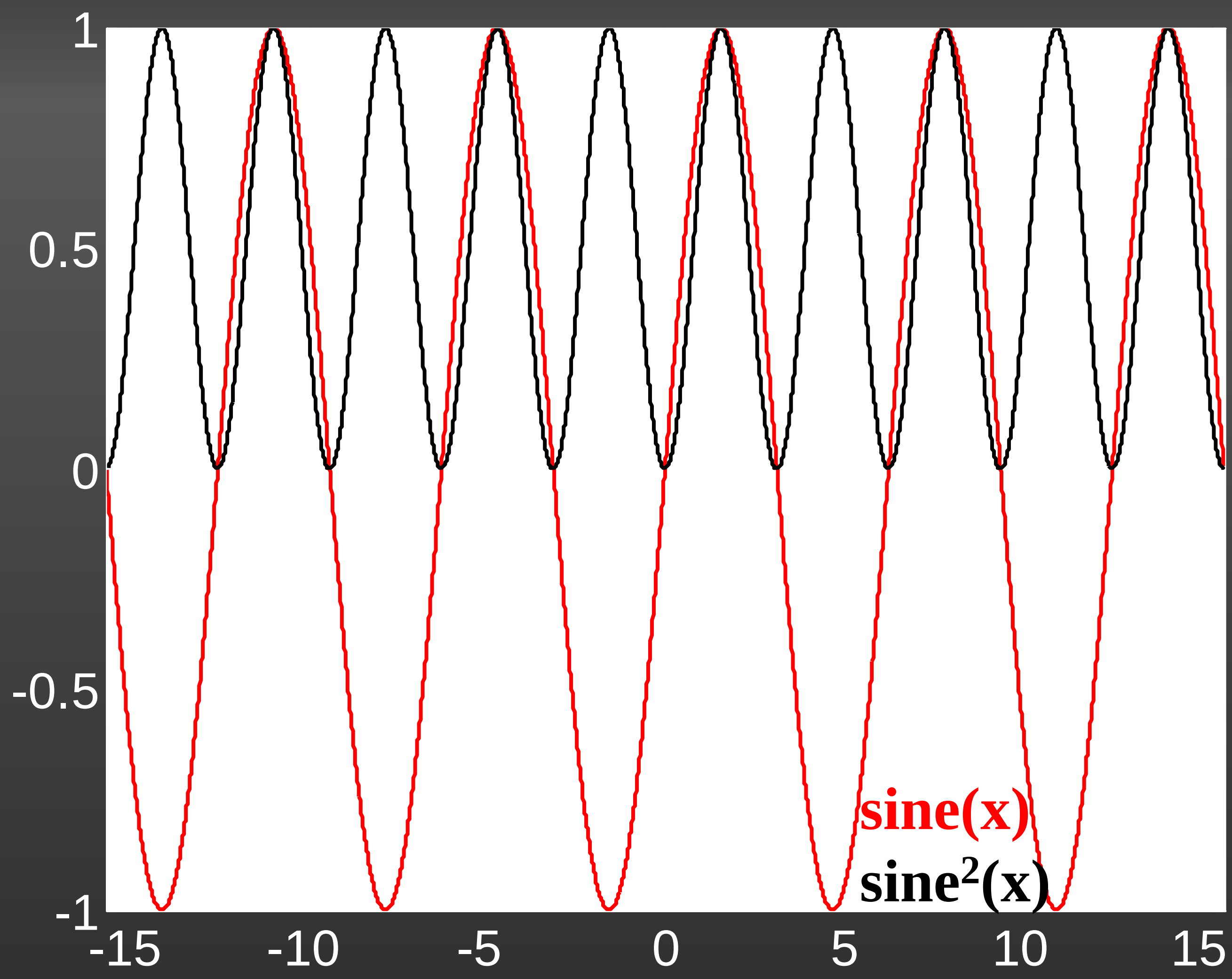
$$T(a+b) = T(a)+T(b)$$

Therefore, the result is the same whether you apply a linear transformation before or after averaging your epochs.

Spectral power is non-linear!
If you want the average power, you have to compute power for individual epochs first, then average.

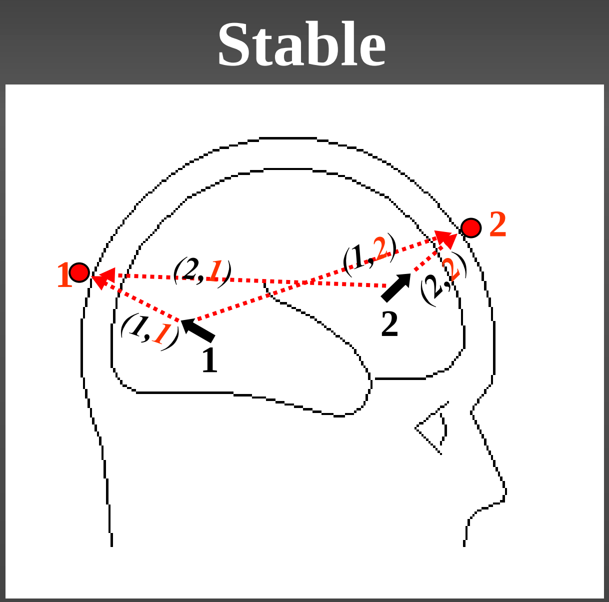
The noise level and a priori knowledge about sources will be very different for single trials compared to the average.
For example, a single/multiple dipole model may be justified for the average (e.g. auditory P1 etc.), but not for single trials.

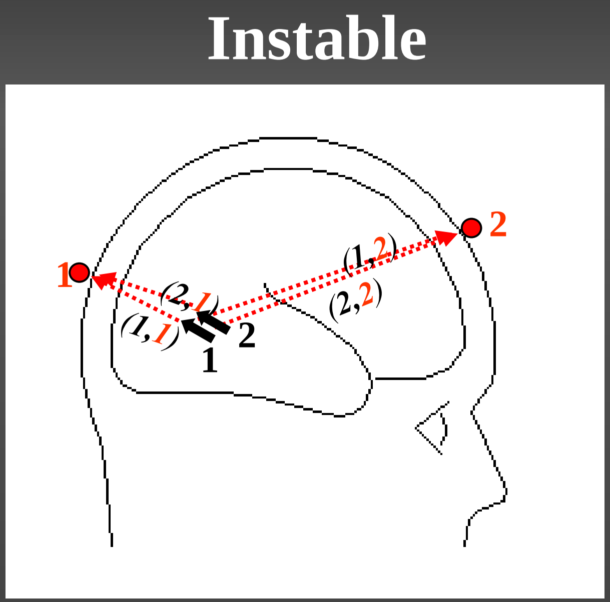
Power Estimation Changes the Time Course

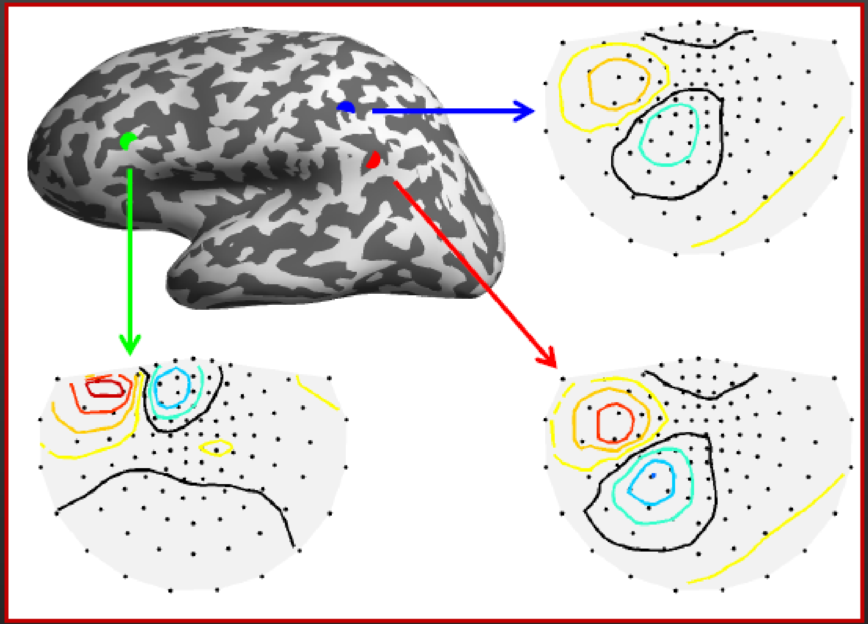


For example, the frequency spectrum for sine(x) and sine^2(x) are very different.

High Noise Levels May Mean Instable Solutions







Similar topographies are difficult to distinguish, especially in the presence of noise.

Noise covariance

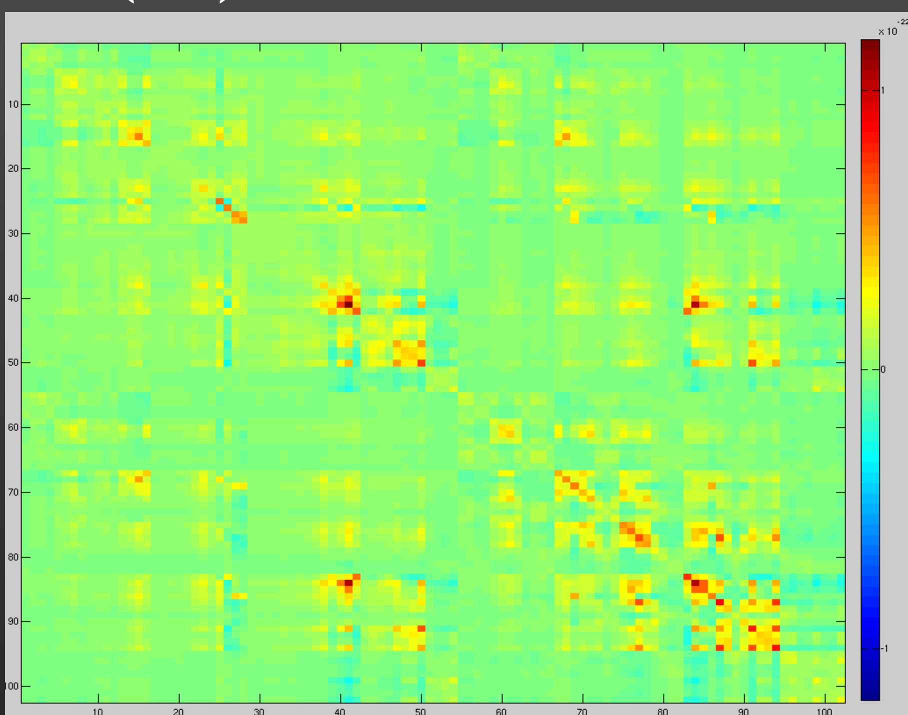
Some channels are noisier than others

⇒They should get different weights in your analysis

Sensors are not independent

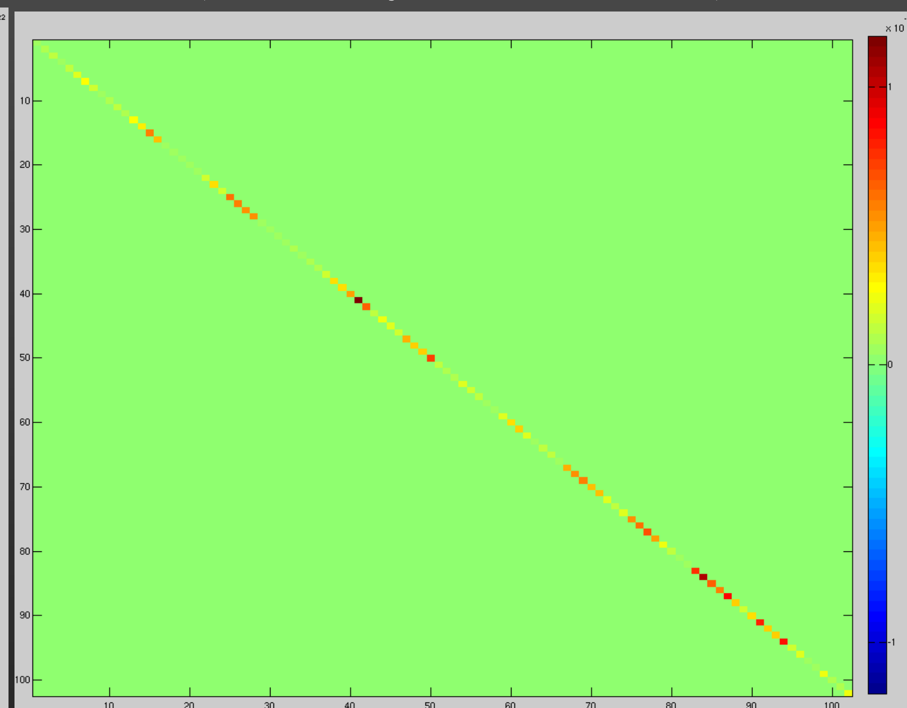
=> Sensors that carry the same information should be downweighted relative to more independent sensors

(Full) Noise Covariance Matrix

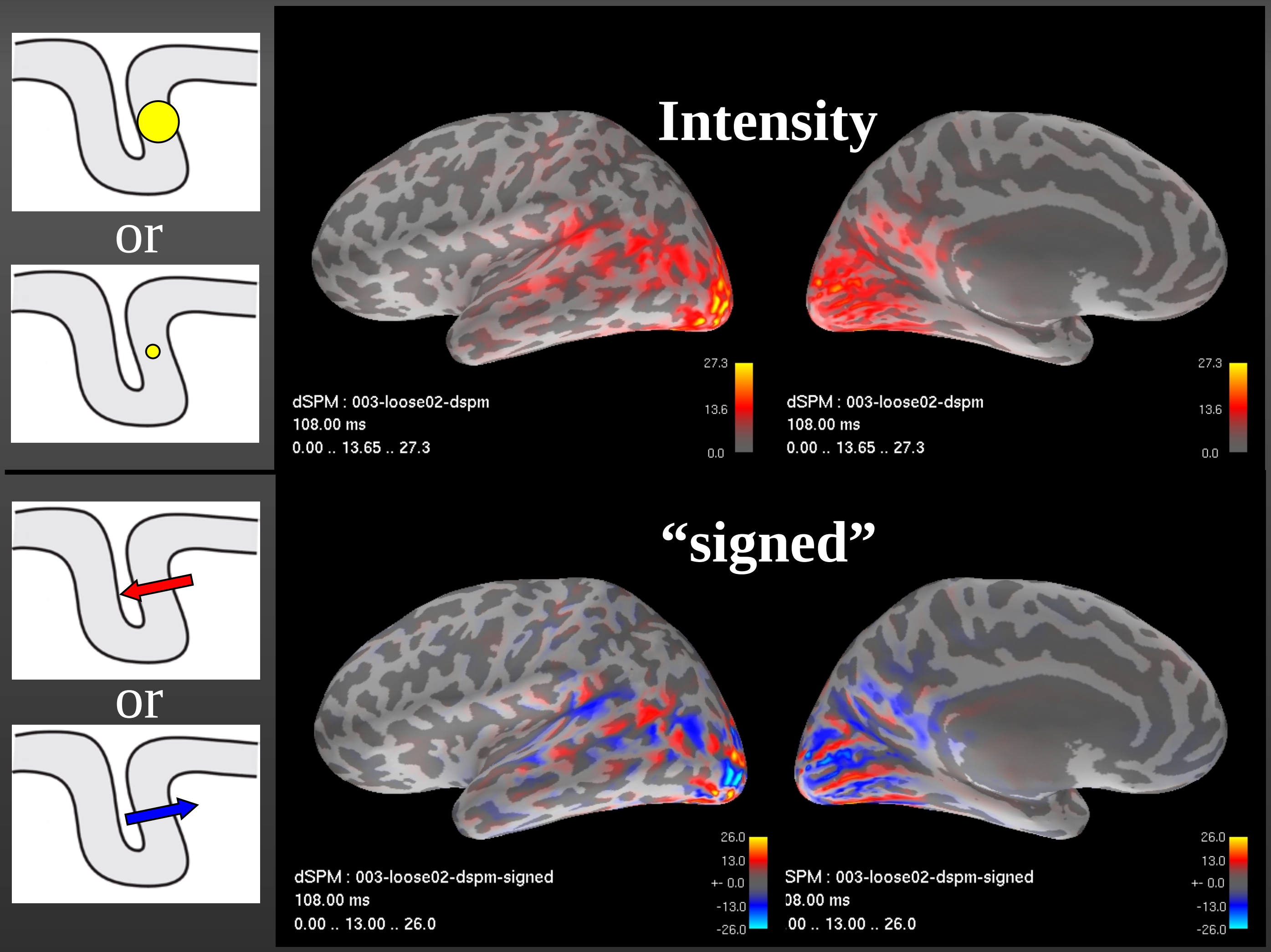


(Diagonal) Noise Covariance Matrix

(contains only variance for sensors)



Direction of Current Flow



“Brain Connectivity”

Structural/Anatomical Connectivity:
Hardware links between brain regions
(e.g. DWI/DTI)

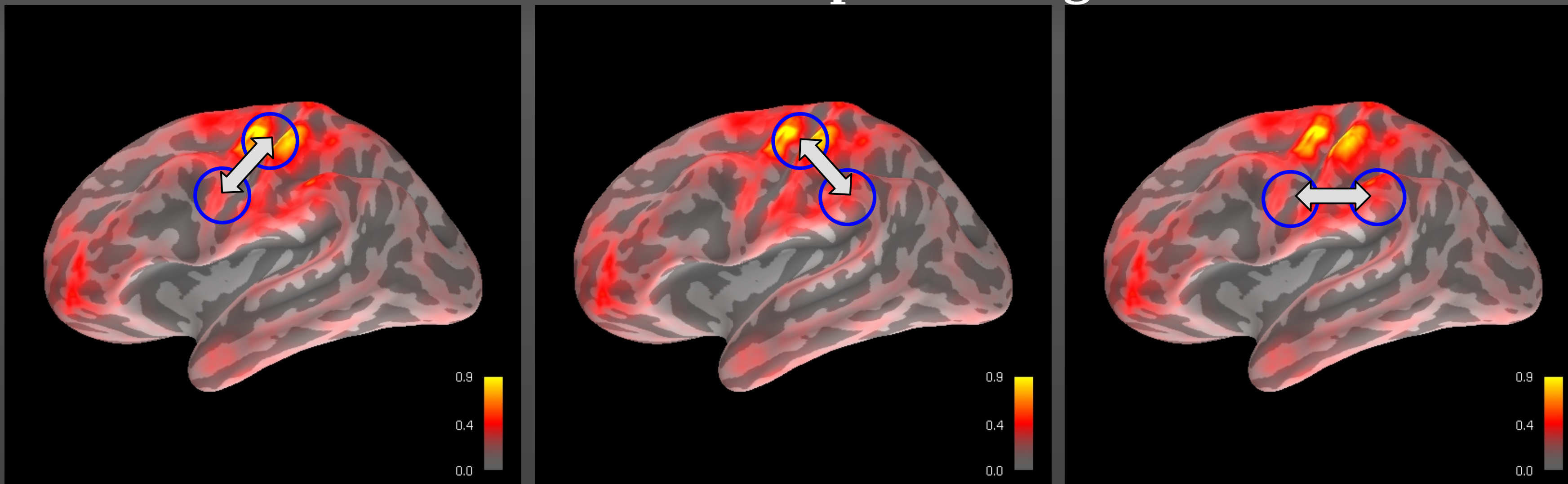
Functional Connectivity:
Statistical dependencies of activation between brain regions
(e.g. correlation, or spectral measures such as phase-locking and coherence)

Effective Connectivity
Causal interactions of activation between brain regions
(Granger Causality, Dynamic Causal Modelling)

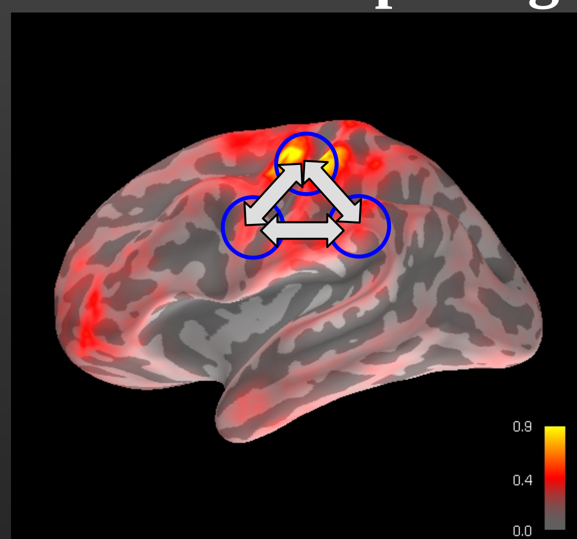
For example:
http://journal.frontiersin.org/article/10.3389/fnsys.2015.00175/full
http://www.sciencedirect.com/science/article/pii/S0165027012000817
http://www.ncbi.nlm.nih.gov/pubmed/21477655
http://online.liebertpub.com/doi/abs/10.1089/brain.2011.0008

Bivariate vs Multivariate Connectivity

Bivariate measures test one pair or regions at a time



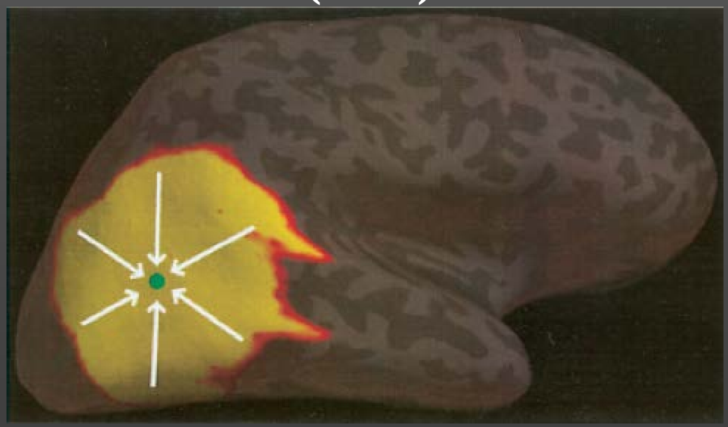
Multivariate measures test multiple regions simultaneously



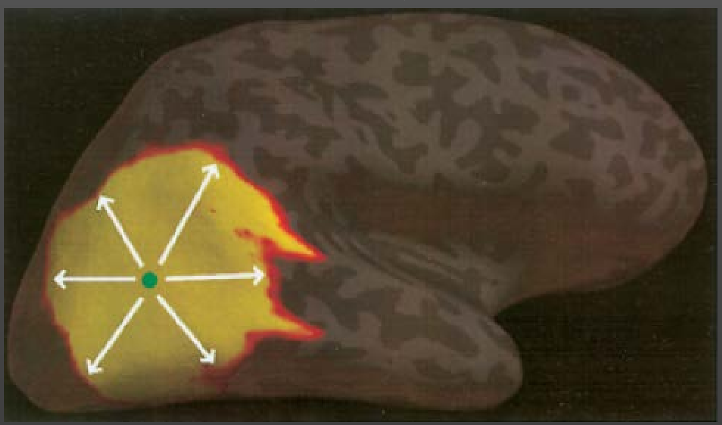
Spatial Resolution:

Point-Spread and Cross-Talk/Leakage

Cross-Talk Function
(CTF)



Point-Spread Function
(PSF)



Liu et al., HBM 2002

How other sources may affect the estimate for this source

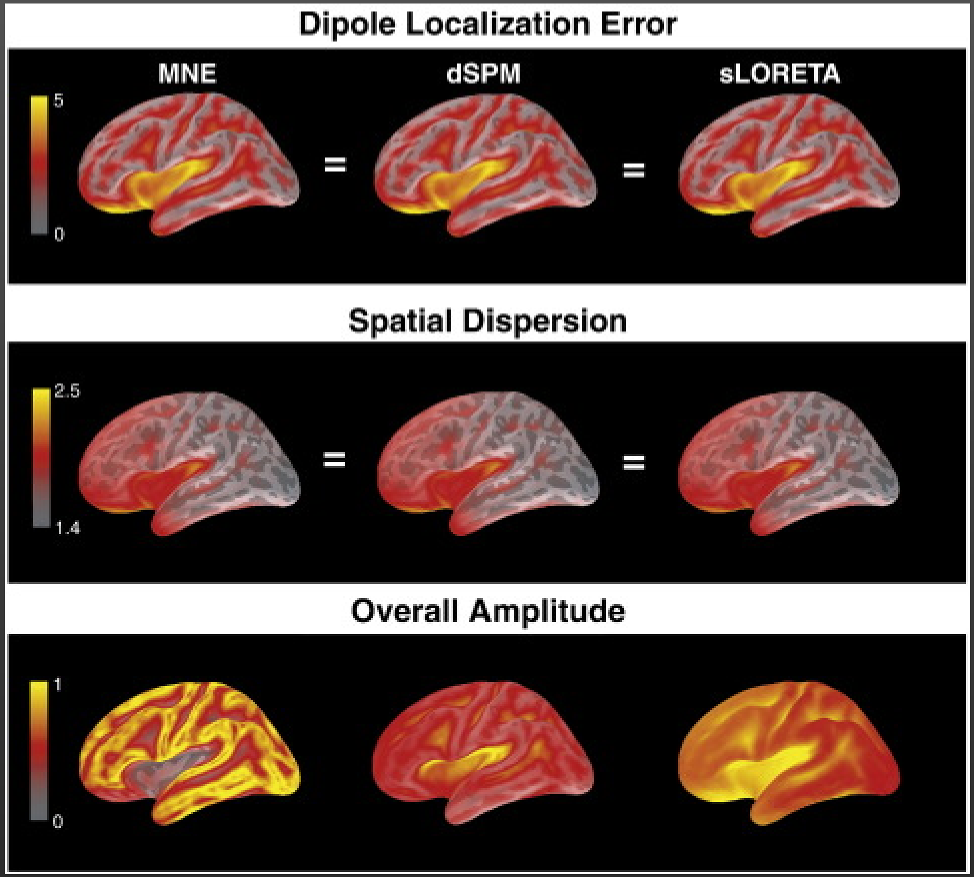
How this source affects estimates for other sources

For implications on source estimation for connectivity, see e.g.
Schöffelen & Gross, HBM 2009: http://www.ncbi.nlm.nih.gov/pubmed/19235884
Hauk & Stenroos, HBM 2014: http://www.ncbi.nlm.nih.gov/pubmed/23616402

Cross-Talk/Leakage Matters For Connectivity

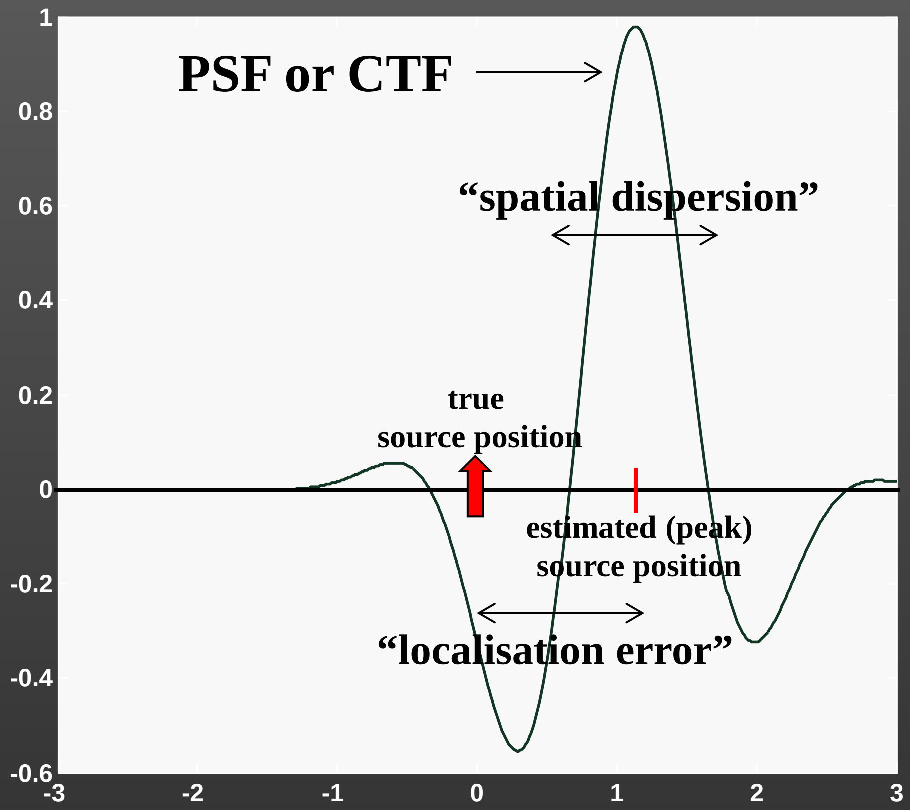
Cross-talk determines how independent source estimates for different locations are

For some methods (e.g. MNE, dSPM and sLORETA) cross-talk is the same, and connectivity results won't differ



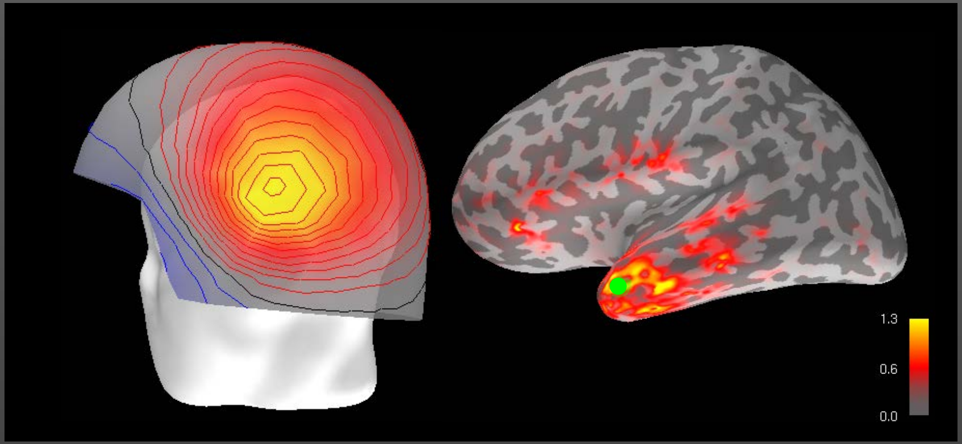
Hauk, Wakeman, Henson. Neuroimage 2011.

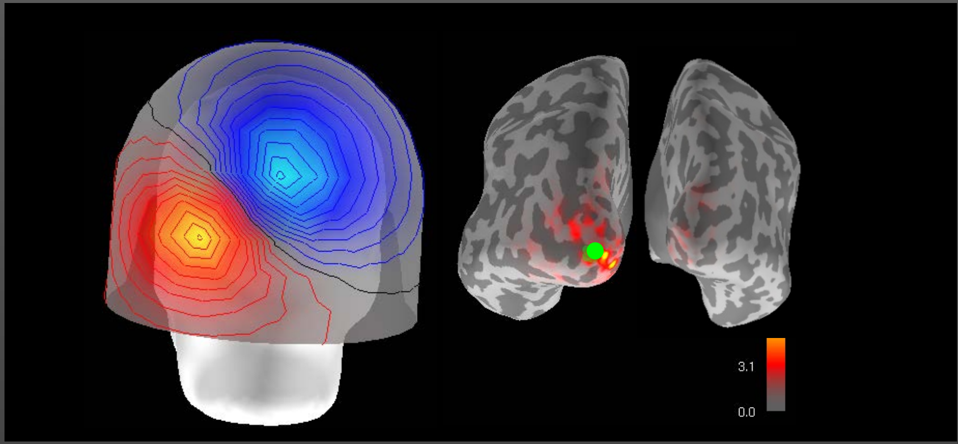
Quantifying “Resolution”



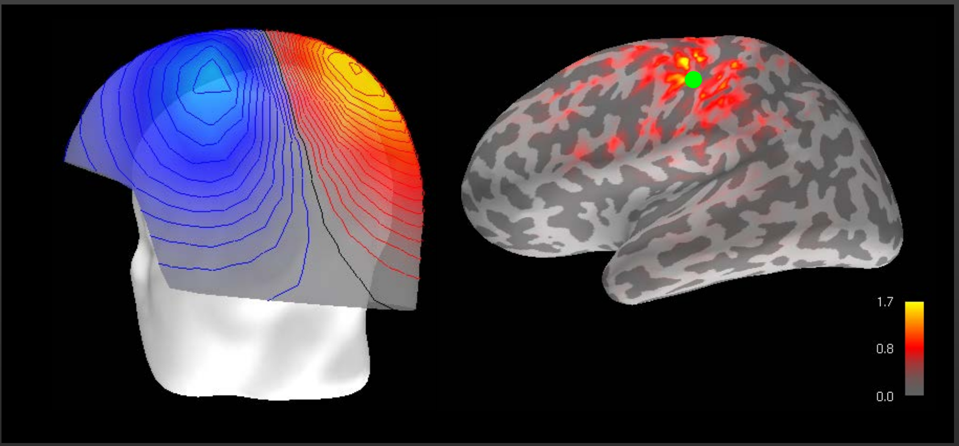
PSFs and CTFs for Some ROIs

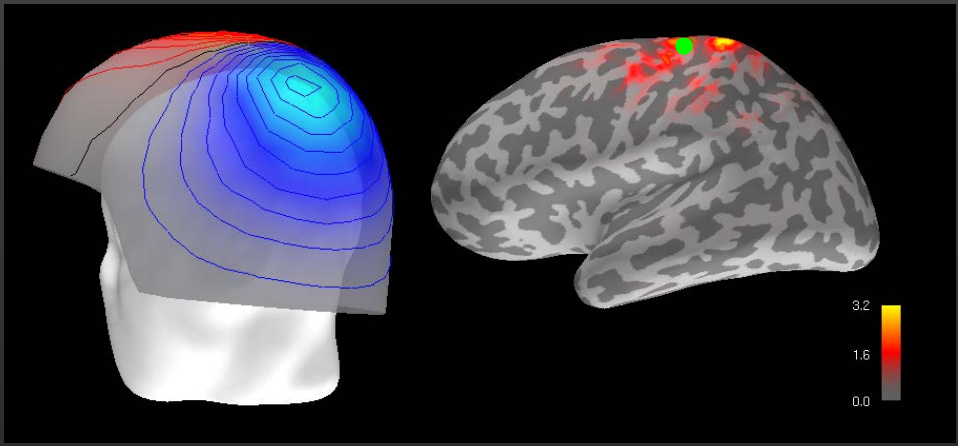
For MNE, PSFs and CTFs turn out to be the same



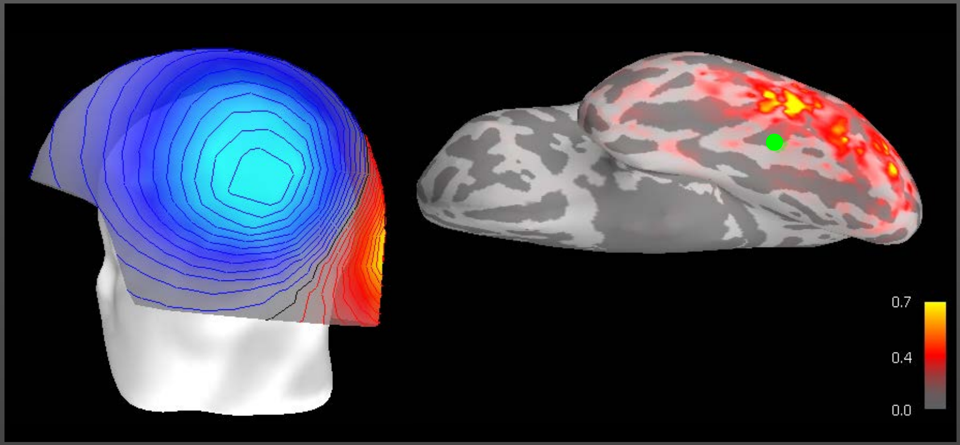


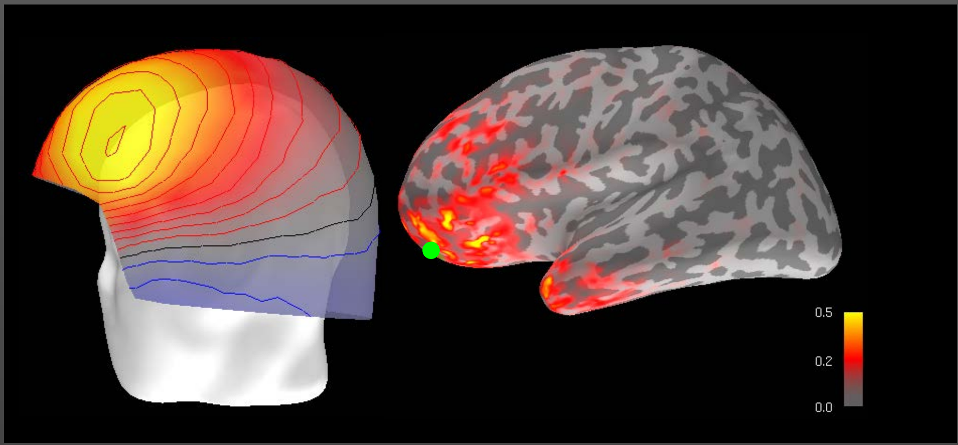
Good



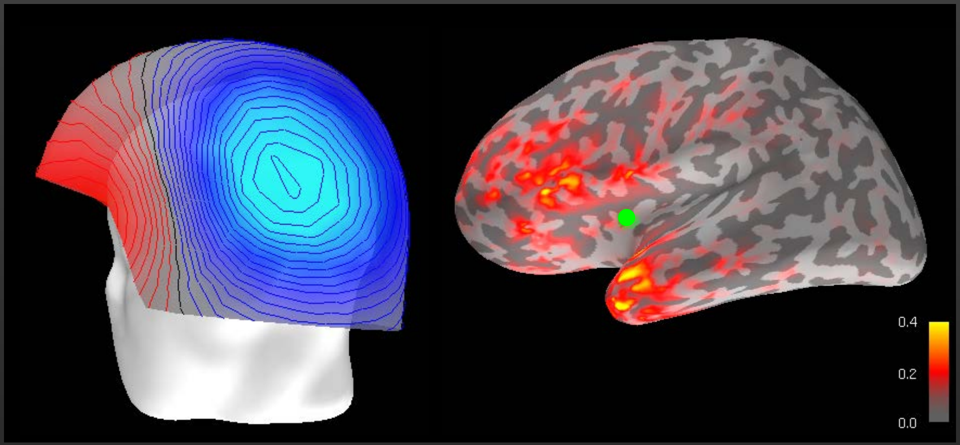


Localisation for Some ROIs





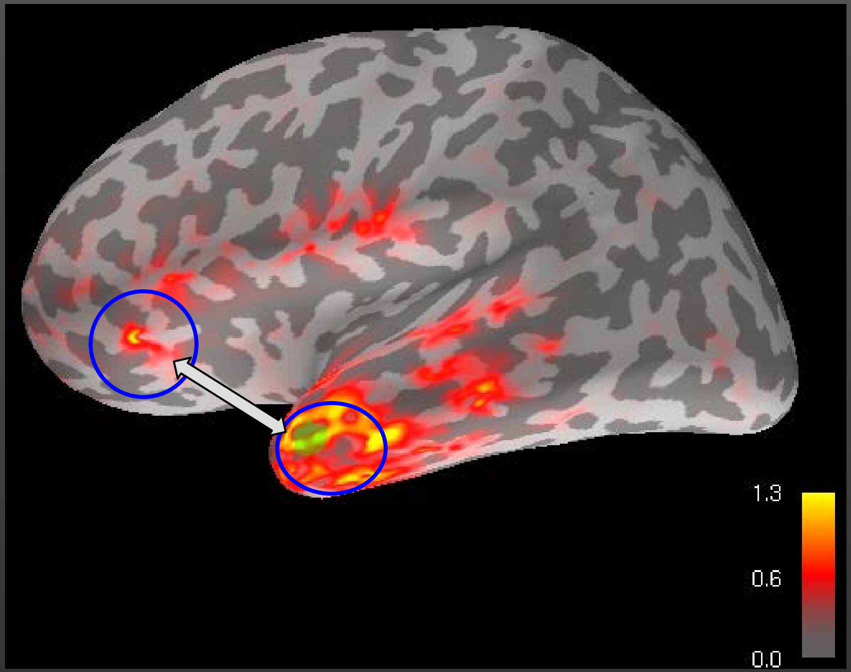
Less good

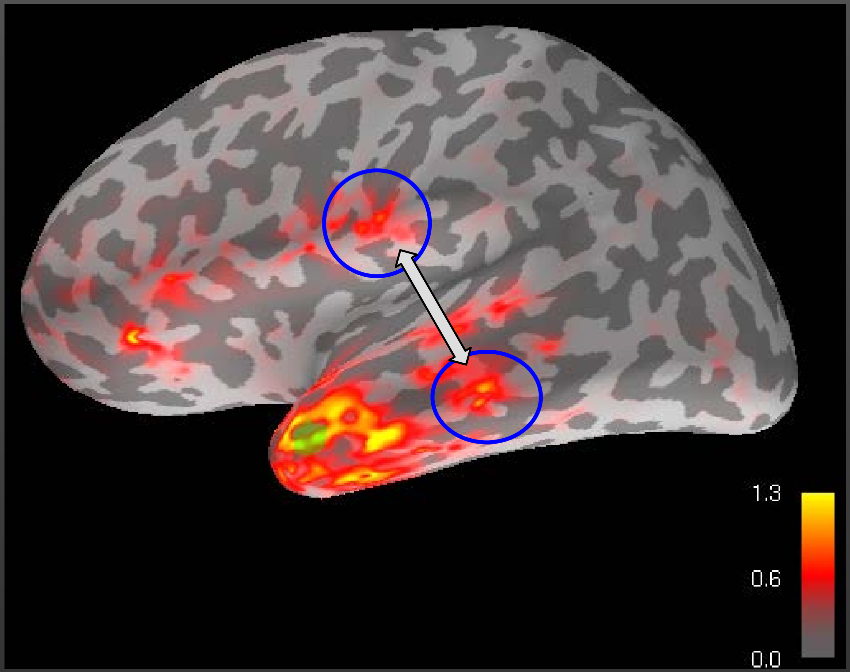


Field Spread / Point Spread

Connectivity between two regions may reflect point spread from one of the regions

Connectivity between two regions may reflect point spread from a third region



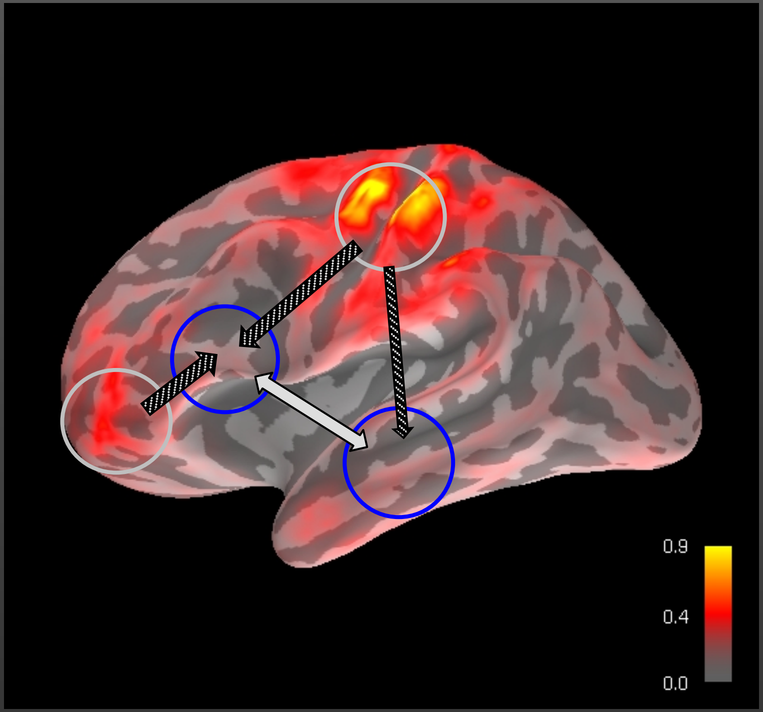


Some connectivity measures can rule out "zero-lag" connectivity

(but they are then also insensitive to real zero-lag connectivity)

Field Spread / Point Spread

Connectivity between two regions may reflect point spread from several other regions



This is bad, and there is not much you can do – except getting your model right in the first place

(Magnitude-Squared) Coherence

For two signals x(t) and y(t) at frequency f:

$$C_{xy}(\text{f}) = \frac{|G_{xy}(f)|^2}{G_{xx}(f)G_{yy}(f)}$$

$G_{xx}(f)$ *is power at f of x(t)*

$|G_{xy}(f)|^2$ *is cross − spectral density of* $x(t)$ and y(t)

$G_{xy}(f)$ is also called “Coherency” (and can be a complex number).

(MS-)Coherence yields the shared variance of two signals at a given frequency.

C_{xy}(f)=1: Signals perfectly coherent at frequency f.

C_{xy}(f)=0: Signals not coherent at all at frequency f.

This looks a bit like a correlation – but in this case it depends on amplitude and phase of the signals at frequency f

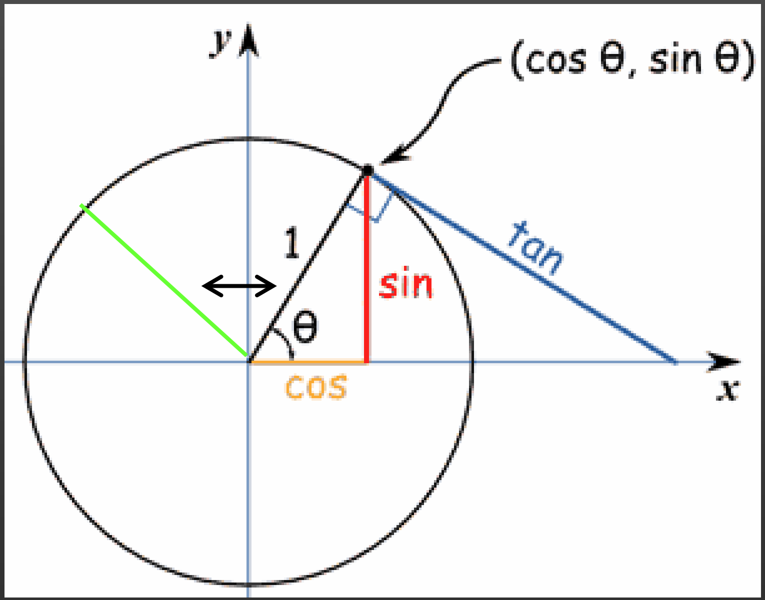
Phase-Locking

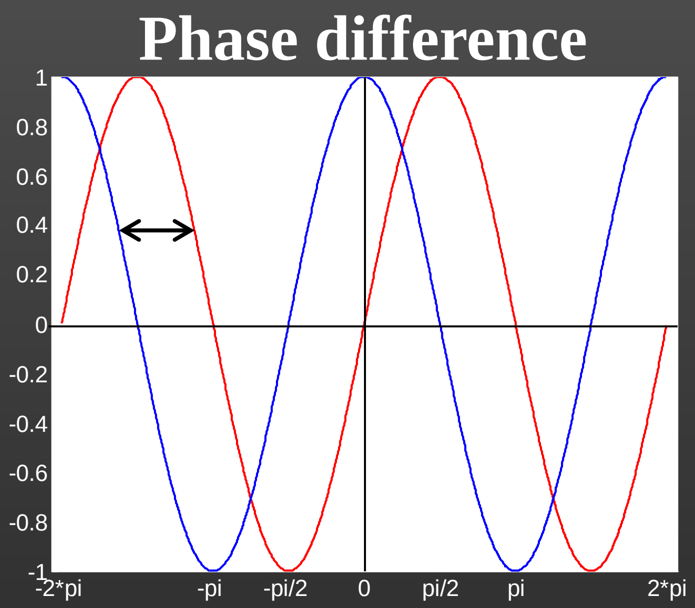
$$s(t) = a * sin(2\pi f t + \theta)$$

a: amplitude

f: frequency

θ : phase



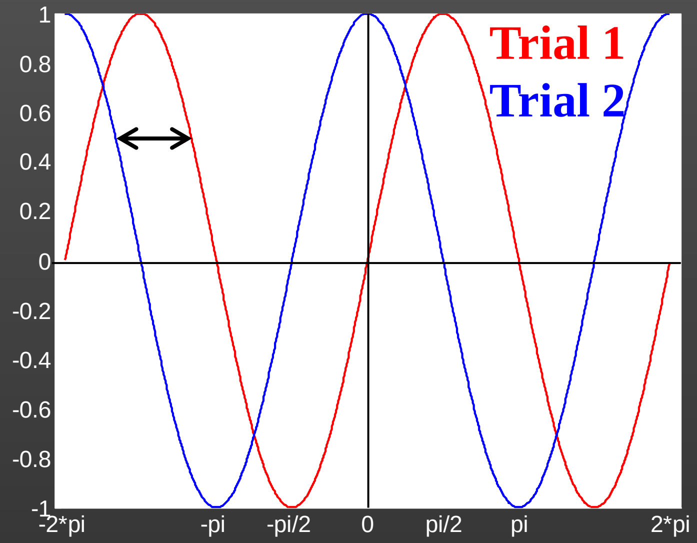


Lachaux et al., HBM 1999: http://www.ncbi.nlm.nih.gov/pubmed/10619414

Different Types of Phase-Locking

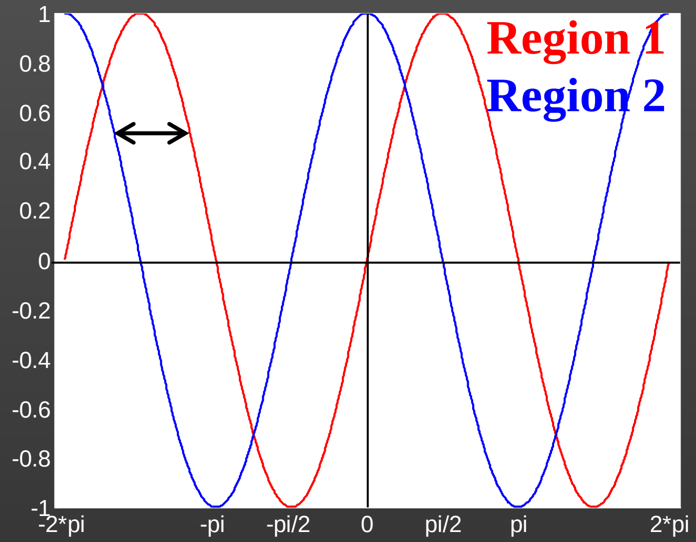
We ignore amplitudes, and are only interested in phase-relationships between two signal at a frequency f

Inter-Trial Phase-Locking



Does the phase at a particular frequency remain stable across trials with one region? (not connectivity)

Inter-Regional Phase-Locking

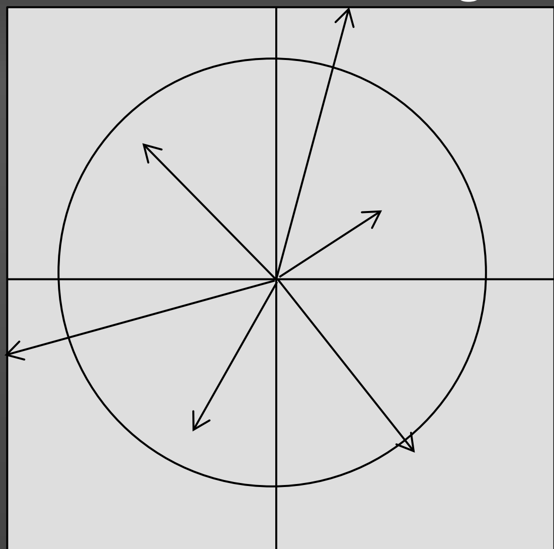


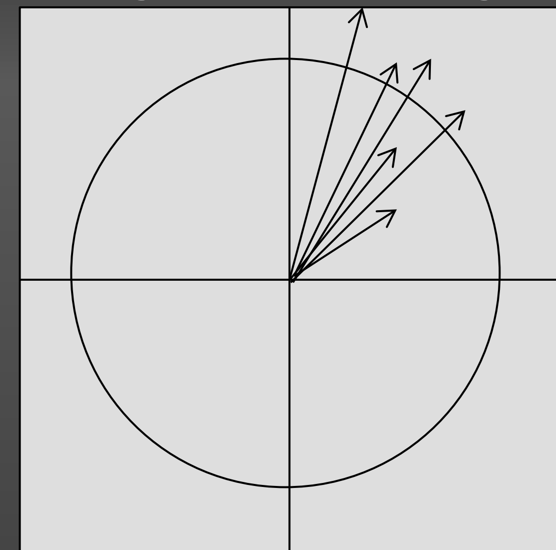
Does the phase difference between two regions at a particular frequency remain stable across trials with one region? (not connectivity)

Phase-Locking

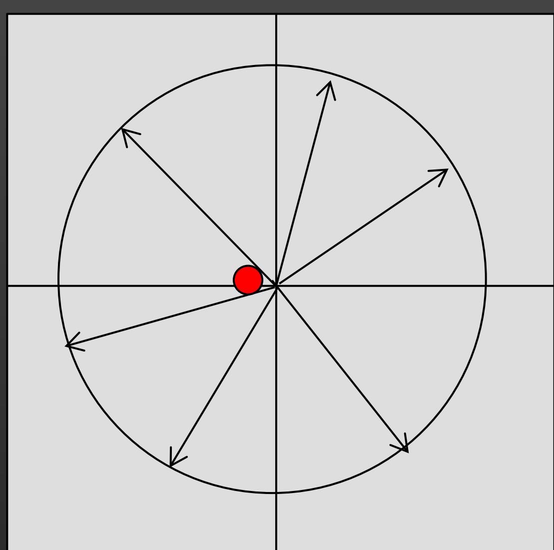
Low Phase-Locking

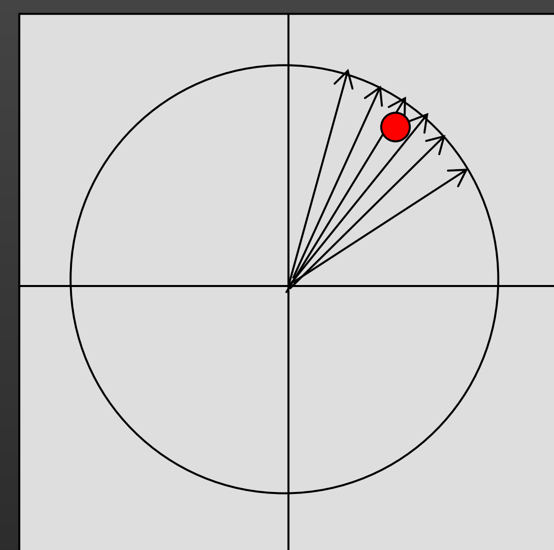
High Phase-Locking





Every vector represents the amplitude and phase of one signal
(e.g. phase difference between two regions across trials).

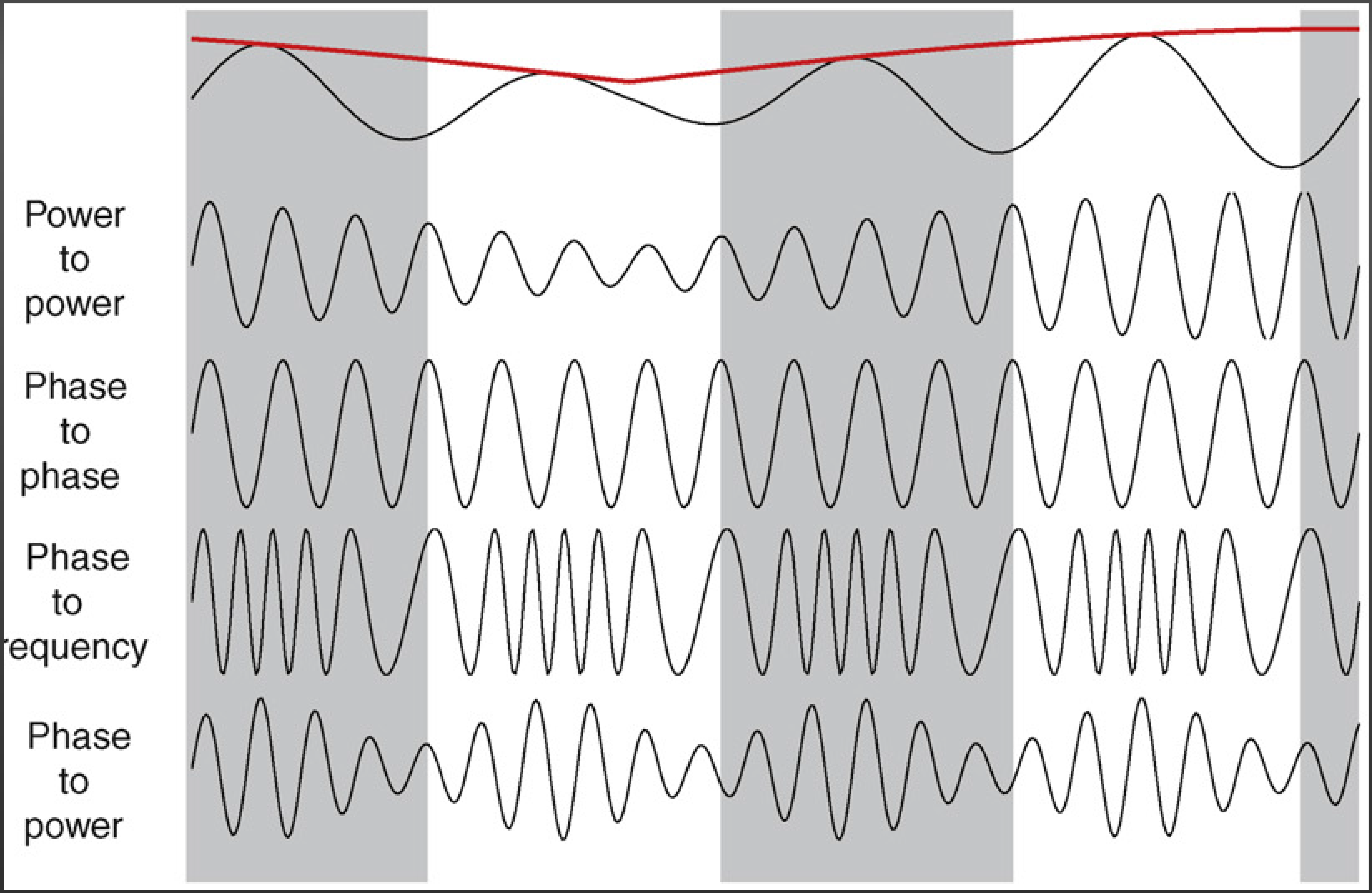




We are not interested in amplitude, and normalise all vectors to unit length.
The average vectors measure the phase-consistency across signals
(phase-locking value, PLV).

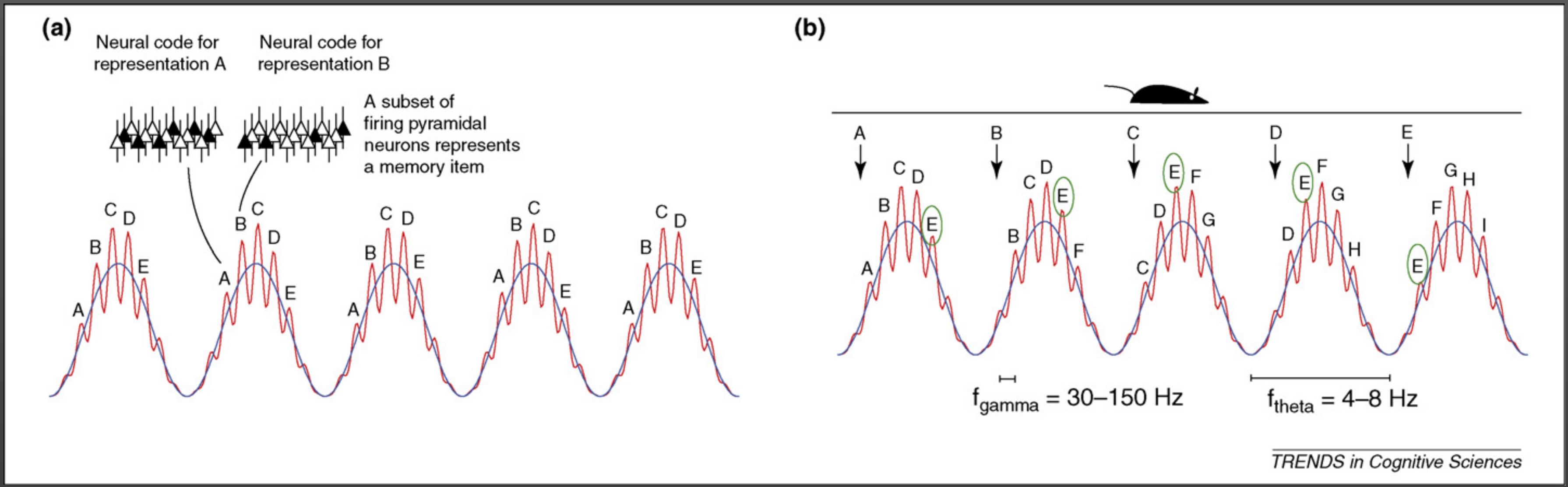
Phase-locking values (PLVs) are sensitive to the number of trials:
low number of trials => larger absolute PLVs

Cross-Frequency Coupling



Jensen & Colgin, TICS 2007

For Example: Theta-Gamma Coupling

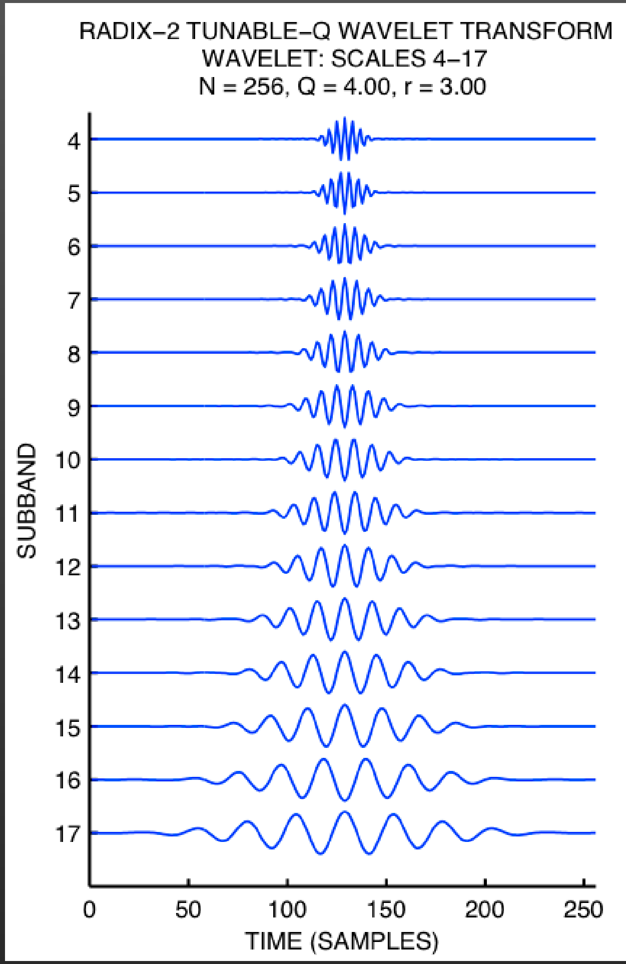


Jensen & Colgin, TICS 2007

Figure 2. Models proposing computational roles for cross-frequency interactions between theta and gamma oscillations by means of phase coding. (a) In a model for working memory, individual memory representations are activated repeatedly in every theta cycle [10] (reviewed in Ref. [11]). Each memory representation is represented by a subset of neurons in the network firing synchronously. Because different representations are activated in different gamma cycles, the gamma rhythm serves to keep the individual memories segmented in time. The number of gamma cycles per theta cycle determines the span of the working memory. (b) A model accounting for theta phase precession in rats. As a rat advances through an environment, positional information is passed to the hippocampus. This activates the respective place cell representations, which provokes the prospective recall of upcoming positions. In each theta cycle, time-compressed sequences are recalled: one representation per gamma cycle. Consider the firing of a cell participating in representation E. As the rat advances, this cell fires earlier in the theta cycle, thus accounting for phase precession. According to this scheme, the number of gamma cycles per theta cycle is related quantitatively to the phase precession [13].

Time-Resolved Connectivity

Spectral connectivity measures can be computed for separate time windows, or they can be computed continuously using wavelets or Hilbert transform (subject to general trade-off between frequency and time resolution)



Time resolution decreases as frequency decreases

(wavelets are getting "broader")

And Beyond…

**The previously introduced measures are spectral measures,
i.e. they are computed for specific frequencies (or frequency bands).**

They rely on the assumption that brain signals can meaningfully be decomposed into "oscillations" or "frequency bands".

This is a big assumption, and may not be the case for all modalities, stimuli, tasks etc., or may not even be true in general.

Therefore…

Non-Spectral and Effective Connectivity

Granger Causality: Is one time series useful to predict another?
x(t) Granger-causes y(t) if past values of x(t) add information to past values of y(t) for predicting future values of y(t).

http://www.scholarpedia.org/article/Granger_causality
Multivariate Granger Toolbox: http://www.sussex.ac.uk/sackler/mvgc/
http://journal.frontiersin.org/article/10.3389/fnsys.2015.00175/full

Structural Equation Modelling (SEM):
Models covariance structure of brain activation across brain regions (e.g. "path analysis").

Dynamic Causal Modelling (DCM):
Models brain dynamics across regions as differential equations, in combination with Bayesian parameter/model estimation.

http://www.scholarpedia.org/article/Dynamic_causal_modeling