# Measuring synchronization: An overview of the most frequently used methods

Anoukh van Giessen (0473081)
anoukh@bic.mni.mcgill.ca

April 30, 2010

**Abstract**

From the moment gamma-band synchronization has been proposed to be a mechanism for the integration of neuronal populations in functional areas widely distributed over the brain, there has been a need for a reliable and robust method to measure this synchronization. This method could then be applied to noninvasive measurements, performed by MEG or EEG, on the human brain in order to study synchronization between different brain areas. In the past two decades several types of measures have been introduced and have been applied mainly to EEG and MEG studies on subjects performing simple tasks during the measurement and epileptic patients, with results giving an insight into some of the neuronal processes going on in the brain. Despite the interesting results, often spurious synchronizations is measured, the result is spoiled by the large amount of noise present or measures are applied to noncorresponding situations, such as stationary measures being applied in nonstationary situations. An overview of the most often used measures to detect synchronization is presented and commented here.

# Contents

# 1 Introduction

The brain is a complex dynamical system which relies on interactions between billions of neurons to produce coherent behaviours (Le van Quyen, M. et al, 2006). Cognitive acts require the integration of several functional areas widely distributed over the brain and in constant interaction with each other. This integration could be mediated by neuronal groups that oscillate in the gamma range (40-80Hz) and enter into phase-locking over a period of time; a phenomena which is called phase synchrony (Rudrauf, D. et al, 2006).
The role of synchronization of neuronal signals has been shown by results from experiments using micro-electrodes in animals. Synchronization between the activity of remote brain areas in the human brain can be studied by means of noninvasive measurements. This is possible because a group of synchronously firing neurons generate a magnetic field which can be registered outside the head by means of multichannel magnetoencephalography (MEG). Synchronization of neuronal activity between remote areas is then reflected as phase locking between MEG channels (Tass, P. et al, 1998).
Two scales of phase synchrony can be distinguished: short-range synchronies, measured from micro-electrode recordings between adjacent areas, and long-range synchronizations between widely separated brain regions (Lachaux, J. et al, 1999). Large-scale synchronization appears during integrative perceptive tasks, followed by an episode of desynchronization. Synchronization can also be a pathological phenomenon, in which the normal dynamic equilibrium of the brain is broken for a short period, which is the case with epileptic seizures (Le van Quyen, M. et al, 2006).
In order to study these phenomena of neuronal integration, several measures to detect synchronization have been proposed in the past decades. These measures all have their own characteristics: there are local and global measures, measures that can only be applied in stationary situations, measures to be used in case of nonstationarity, and measures that can be used in case of noise, or chaotic oscillations. Since synchronization measures are constantly being developed it is impossible to mention and compare all of them. In this paper an overview is given of synchronization measures that have been used most frequently in the past two decades in relevant literature. The focus is on the types of measures, the similarities and differences between them, and their advantages and limitations. The fields of research where they can be applied are sometimes mentioned but is not part of the main goal of this overview.
To give a clear overview the measures are divided in different classes; direct measures, measured applied using the concept of phase synchrony, and measures belonging to the concept of frequency flows. Within these classes there are measures for linear and nonlinear synchronization, which are applicable to stationary and/or nonstationary signals and of which some of them can also be applied in presence of noise. Finally, there are methods for measuring bivariate synchronization, i.e., synchronization between pairs of signals, and for multivariate synchronization, i.e., to measure synchrony amongst an arbitrary number of signals.

## 2 Direct measures of synchronization

This family of measures can be applied directly to the measured signals. For these direct linear and nonlinear synchronization measures there is no strict definition of synchronization, but it is seen as an interdependence or correlation between signals. Therefore no pre-processing such as band-filtering or extraction of the instantaneous phase, is necessary, which makes these measures easy and cheap in computation.

### 2.1 Linear interdependences

The measures proposed here describe to which extent different signals, bivariate or multivariate, and with or without noise, are linearly interdependent. In various articles, such as Le van Quyen, M. et al (1998) and Arnhold, J. et al (1999), convincing arguments have been given for using methods to find nonlinear interdependences. This was verified by their application on noisy and chaotic oscillators. Quian Quiroga, R. et al (2008) state that it remains open whether this is also true for real data and therefore address the use of linear synchronization measures.
Suppose there are two simultaneously measured univariate time series $x(t)$ and $y(t)$, where $t$ is the time; in this case discrete time points $t = 1, ..., T$. The cross-correlation function is then given by (Quian Quiroga, R. et al, 2001)

$$c(\tau) = \frac{1}{T-\tau} \sum_{t=1}^{T-\tau} \frac{x(t)-\bar{x}}{\sigma_x} \cdot \frac{y(t+\tau)-\bar{x}_m}{\sigma_y}, \tag{1}$$

where $\bar{x}$ and $\sigma_x$ denote the mean and variance of the series $x(t)$, and $\tau$ is a time lag. This cross-correlation is a measure of the linear synchronization between $x$ and $y$. Its absolute value ranges from zero, no synchronization, to one, perfect synchronization, and is symmetric.
The sample cross-spectrum is defined by the Fourier transform of the cross-correlation (Quian Quiroga, R. et al, 2001):

$$C_{xy}(f) = (FT(x))(f) \cdot (FT(y)) * (f), \tag{2}$$

where $FT(x))$ denotes the Fourier transform of $x$ and $f \in [-T/2, T/2]$ is the frequency and the $*$ indicates the complex conjugate is taken.
Given this, the cross-spectrum has a normalized amplitude, called the coherence function, defined by (Quian Quiroga, R. et al, 2001)

$$\Gamma_{xy}(f) = \frac{|C_{x,y}(f)|}{\sqrt{C_{x,x}(f)} \cdot \sqrt{C_{y,y}(f)}}. \tag{3}$$

This function gives a measure of the linear synchronization between $x$ and $y$ as a function of the frequency $f$. It is mainly useful when synchronization is limited to a particular frequency band, which is usually the case in EEG (Quian Quiroga, R. et al, 2001).

### 2.2 Nonlinear interdependences

In Rudrauf, D. et al (2006) it is stated that "'the brain is a complex, nonlinear, nonstationary, massively interconnected dynamical system"'. Methods

for measuring the synchronization in a nonlinear system thus seem to be very important when analyzing brain signals. Several direct nonlinear measures have been proposed of which the measures of correlation and coherence and information theoretic measures are most often used and explained here.
A nonlinear extension of the correlation coefficient is the correlation-entropy coefficient $r_E$, recently proposed by Gunduz, A. and Principe, J.C. (2009):

$$r_E = \frac{\frac{1}{T}\sum_{t=1}^{T}\kappa(x(t),y(t)) - \frac{1}{T^2}\sum_{t,u=1}^{T}\kappa(x(t),y(u))}{\sqrt{K_X - \frac{1}{T^2}\sum_{t,u=1}^{T}\kappa(x(t),x(u))}\sqrt{K_Y - \frac{1}{T^2}\sum_{t,u=1}^{T}\kappa(y(t),y(u))}}, \quad (4)$$

where

$$K_X = \frac{1}{T}\sum_{t=1}^{T}\kappa(x(t),x(t)) \quad (5)$$

and where $\kappa$ is a symmetric positive definite kernel function, for example a Gaussian, sigmoidal or polynomial kernel. The signals $x(t)$ and $y(t)$ have to be normalized here before calculating the correlation-entropy coefficient, since $x$ and $y$ may have different dynamic ranges. If $x$ and $y$ are independent $r_E$ is close to zero; if both signals are equal, then $r_E = 1$.
Similarly to the linear case, a nonlinear magnitude square coherence function, which is again a normalized measure, can be defined. This coherence-entropy coefficient $c_E(f)$ is defined as (Dauwels, J. et al, 2010)

$$c_E(f) = \frac{\langle\kappa(FT(x)(f), FT(y)(f))\rangle}{\sqrt{\langle\kappa(FT(x)(f), FT(x)(f))\rangle}\sqrt{\langle\kappa(FT(y)(f), FT(y)(f))\rangle}}, \quad (6)$$

where the averages $\langle\cdot\rangle$ are computed over $M$ segments of equal length $L$. Before $c_E(f)$ can be computed, the Fourier transforms $FT(x)(f)$ and $FT(y)(f)$ need to be normalized.

# 3 Phase synchronization

Another type of measures for synchronization that is often used is the one exploiting the concept of phase synchronization. The quantification of phase synchronization requires methods other than the direct methods described above. In order to apply measures for phase synchronization the effects of amplitude and phase, in the interrelations between two signals, have to be separated, something the direct methods do not do. The phase component has to be obtained separately from the amplitude component for a given frequency (Lachaux, J. et al, 1999).

## 3.1 Extracting the instantaneous phase

Two methods are used to separate the phase and amplitude components from the signal and compute the instantaneous phase: convolution of the signals with a Gabor or Morlet wavelet or applying the Hilbert transform to the signals (figure 1). Both methods, and their similarities and differences, will be explained here.

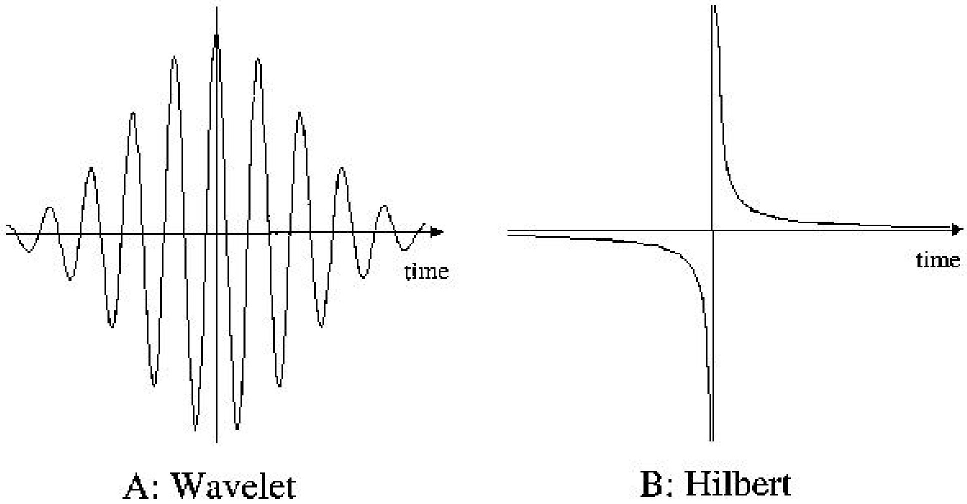


Figure 1: Two definitions of instantaneous phase: convolution of the signal with a Gabor wavelet (left) or with the function $1/\pi$t, i.e., using the Hilbert transform. (right) (Le van Quyen, M. et al, 2001)

### 3.1.1 The wavelet transform

The phase of the signals are extracted from the coefficients of their wavelet transform at the target frequency. The choice is based on a previous detailed timefrequency analysis of the signals (Lachaux, J. et al., 2000). Thus a frequency range is defined around this chosen value (+/- 2 Hz) and the subsequent analysis is done on the frequency components of the signals in this frequency range. The procedure is usually iterated in other frequency ranges to cover the whole meaningful part of the spectrum (Le van Quyen, M. et al, 2001). Let an electrode record a signal $x(t)$. Then the wavelet coefficients of the signal $x(t)$ at time $\tau$ and frequency $f$ are defined as (Lachaux, J. et al, 2000)

$$W_x(\tau, f) = \int_{-\infty}^{\infty} x(t) \cdot \Psi^*_{\tau,f}(t)dt \tag{7}$$

In this definition $\Psi^*_{\tau,f}(t)$ is the complex conjugate of the Morlet wavelet defined by (Lachaux, J. et al, 2000)

$$\Psi_{\tau,f}(t) = \sqrt{f} \cdot \exp[i2\pi f(t-\tau)] \cdot \exp[-\frac{(t-\tau)^2}{2\sigma^2}] \tag{8}$$

where $\Psi_{\tau,f}(t)$ is the product of a sinusoidal wave at frequency $f$ and a Gaussian function centered at time $\tau$ and a standard deviation $\sigma$ proportional to the inverse of $f$ (Lachaux, J. et al, 2000).

Lachaux, J. et al (1999) remark that this phase could also be obtained directly by a convolution of the data with the unfiltered signal, but this occasionally gives different results. Therefore they relied on the other method without any further verification. Lachaux et al (2000) do not mention bandpass filtering which might imply that here the convolution is performed using

the raw signal.
The Morlet wavelet depends only on $\sigma$ which sets the number of cycles of the wavelet: $n_{co} = 6f\sigma$. This value $n_{co}$ determines the frequency resolution by setting the width of the frequency interval for which the phase is measured. This width is roughly equal to $4f/n_{co}$ so that the frequency range being studied is approximately $[f - \frac{4f}{n_{co}}, f + \frac{4f}{n_co}]$.
Now the phase difference between the signals at frequency $f$ and time $\tau$ can be derived from the angles of their wavelet coefficients (Lachaux, J. et al, 2000)

$$\exp[i(\phi_y(f,\tau) - \phi_x(f,\tau))] = \frac{W_x(\tau,f)W_y^*(\tau,f)}{|W_x(\tau,f)|\,|W_y(\tau,f)|}. \tag{9}$$

Both PLS and S-PLS evaluate the variability of this phase difference across successive measurements and evaluate the statistical variability of this phase difference. PLS does this across trials by averaging over the trials and S-PLS does this within each trial. Both measures will be explained below.

### 3.1.2 The Hilbert transform

Another technique, widely used in the signal processing, to obtain the phase difference for arbitrary signals uses the Hilbert transform. This approach gives the instantaneous phase and amplitude for a signal $x(t)$ at time $t$ via construction of the analytic signal $\xi(t)$ defined as (Rosenblum, M.G. et al, 1998)

$$\xi(t) = x(t) + i\tilde{x}(t) = A(t)\exp[i\phi(t)], \tag{10}$$

where the function $\tilde{x}(t)$ is the Hilbert transform of $x(t)$

$$\tilde{x}(t) = \frac{1}{\pi}\text{P.V.}\int_{-\infty}^{\infty} \frac{x(\tau)}{t-\tau}d\tau \tag{11}$$

and P.V. indicates that the integral is taken in the sense of the Cauchy principal value. The instantaneous amplitude $A(t)$ and the instantaneous phase $\phi(t)$ of the signal $x(t)$ are uniquely defined by this function.
The Hilbert transform $\tilde{x}(t)$ of $x(t)$ can be considered as the convolution of the functions $x(t)$ and $1/\pi t$ which implies that the Fourier transform $FT(\tilde{x})$ of $\tilde{x}(t)$ is the product of the Fourier transforms of $x(t)$ and $1/\pi t$. "'For physically relevant frequencies, $f > 0$, $FT(\tilde{x}) = -jFT(x)$, this means that the Hilbert transform can be realized by an ideal filter whose amplitude response is unity, and phase response is a constant $\pi/2$ lag at all frequencies (Panter, P. 1965).
An advantage of the analytic signal approach is that the phase can easily be obtained from experimentally measured time series. This can be done by convoluting the experimental data with a pre-computed characteristics of the filter; a Hilbert transformer (Rabiner, R. and Gold, B. 1975). An important limitation of this method is that applying the Hilbert transform requires computation on the infinite time scale. Still, a precision of about 1% can be obtained. Another drawback is that the sampling rate must be such that at least 20 points per average period of oscillation and during

computation of the convolution $L/2$ points are lost at both ends of the time series, where $L$ is the length of the transformer (Rosenblum, M.G. et al, 1998).
The main goal in studying phase synchronization is to introduce a condition of phase synchronization for chaotic or noisy systems. Therefore the instantaneous phase has to be obtained which is "‘nontrivial for many nonlinear model systems and even more difficult when dealing with noisy time series of unknown origin"’ (Mormann, F. et al, 2000). Following the analytic signal approach, the instantaneous phase of an arbitrary signal $x(t)$ is given by (Mormann, F. et al, 2000)

$$\phi(t) = \arctan(\tilde{x}(t))/x(t)), \tag{12}$$

where $\tilde{x}(t)$ is the Hilbert transform of the signal $x(t)$ as defined above.

## 3.2 Phase and frequency locking

Phase synchronization of two periodic nonidentical oscillators is understood as locking of the phases, or the adjustment of their rhythms, within a limited time window $\Delta t$ due to interaction. The phase locking condition is described by (Le Van Quyen, M. et al, 2001)

$$\psi_{n,m}(t) = \text{const}, \quad \text{where } \psi_{n,m}(t) = n\phi_x(t) - m\phi_y(t), \tag{13}$$

where $n$ and $m$ are integers indicating the possible ratios of phase locking, $\phi_{x,y}$ are the phases of the two oscillators, and $\psi_{n,m}(t)$ is the relative phase or phase difference. All phases are divided by $2\pi$ for normalization and $\phi_{x,y}$ as well as $\psi_{n,m}(t)$ are defined not on the circle [0,1] but on the whole real line. In Rosenblum, M.G. et al (2000) in the definition of phase locking an average phase shift $\delta$ is also subtracted from $n\phi_x(t)$ and it is emphasized that the relative phase is generally not constant, but oscillates around this $\delta$.
The condition of phase locking is equivalent to the condition of frequency locking (Rudrauf, D. et al, 2006)

$$\psi_{n,m}(t) = n\phi_x(t) - m\phi_y(t) = \Delta\phi_{x,y}(t) \approx \text{constant} \qquad \Longleftrightarrow \tag{14}$$

$$\frac{\mathrm{d}\Delta\phi_{x,y}(t)}{\mathrm{d}t} = n\frac{\mathrm{d}\Delta\phi_x(t)}{\mathrm{d}t} - m\frac{\mathrm{d}\Delta\phi_y(t)}{\mathrm{d}t}(t) = n\omega_x(t) - m\omega_y(t) \approx 0, \tag{15}$$

with $\omega_i(t) = \frac{\mathrm{d}\phi_i(t)}{\mathrm{d}t}(t) > 0$, the angular speed.

As Rudrauf, D. et al (2006) explain; when imagining two rotating vectors, the equivalence between phase and frequency locking is quite intuitive. Picture the instantaneous phases $\phi_x(t)$ and $\phi_y(t)$ as vectors rotating counterclockwise in the unit circle (figure 3A) and consider the case where $m = n = 1$ in equation (15). In order to keep the same phase difference $\Delta\phi_{x,y}$ over a period of time $\Delta t$, the vectors should rotate at the same angular speed $\omega = \mathrm{d}\phi/\mathrm{dt}$ $(rad/s)$. Conversely, if the angular speeds of two oscillators are equal during a time interval $\Delta t$, their phase difference $\Delta\phi_{x,y}$ will be constant. Dividing the angular speed by $2\pi$ gives a measure expressed in

Hertz which is usually called the instantaneous frequency, denoted here by $\tilde{\omega}$.

If two oscillators have a common instantaneous frequency $\omega(i,j)$, during a period of time $\Delta t$, they are phase synchronous during that period. This time stability of the frequency locking during a minimal $\Delta t$ period is a necessary condition, because if the instantaneous frequencies just coincide at one time point, this does not imply true phase locking. "'To be synchronous, the instantaneous frequencies should coincide in terms higher than zeroth order and thus show stability over a period of time"' (Rudrauf, D. et al, 2006). Small windows of time can be used to detect transient phenomena.

In Tass, P. et al (1998), instead of requiring a common instantaneous frequency over a time period $\Delta t$, a ratio of the average angular speed of the two oscillators should be equal. The condition of frequency locking is thus defined as

$$n\Omega_x = m\Omega_y, \quad \text{where } \Omega_{x,y} = \left\langle \dot{\phi}_{x,y} \right\rangle. \tag{16}$$

where the brackets indicate the time averaging. It is further noted that to determine states of synchronization in a system it is thus irrelevant whether the amplitudes of both oscillators are different or not or as Paluš, M. (1997) remarks: "'the amplitudes of the two systems may be completely uncorrelated, i.e. linearly independent"'.

### 3.2.1 Volume conduction, chaotic systems, and noise

In brain tissue the presence of volume conduction, overlapping volumes causing signals to be recorded by two electrodes, can cause spurious synchronization [1]. Also, the true signals are surrounded by background noise and in chaotic systems the amplitudes of synchronized systems remain chaotic and effect the phase dynamics in the same way as external noise. Therefore, when measuring synchronization in the brain, the condition of phase locking needs to be redefined. Tass, P. et al (1998) suggest to consider noisy and chaotic cases within a common framework, i.e., by the term "'noise"' both random and purely deterministic perturbations to phases are denoted. Phase synchronization is then defined as (Le Van Quyen, M. et al, 2006)

$$|n\phi_x(t) - m\phi_y(t)| \approx \text{constant} \tag{17}$$

or as (Paluš, M., 1997)

$$|n\phi_x(t) - m\phi_y(t)| < \text{constant} \tag{18}$$

A division between the cases of weak and bounded noise and strong noise can be made (Tass, P. et al, 1998). In the first scenario the relative phase fluctuates around a constant value in the synchronous state, and the condition of frequency locking is fulfilled, while in the second scenario strong noise can cause phase slips, i.e., rapid unit jumps of the relative phase by $\pm 2\pi$. These phase slips cause the phase difference to become unbounded and therefore the condition of phase locking is no longer valid (Rosenblum,

[1] Extended information on volume conduction can be found in Lachaux, J. et al (1999)

M.G. et al, 2000).
Nevertheless, synchronization of such noisy systems can be detected by the appearance of peaks in the distribution of the cyclic relative phase (Rosenblum, M.G. et al, 2000)

$$\Psi_{n,m} = \psi_{n,m} \text{ mod}1, \quad \text{where } \psi_{n,m} = n\phi_x(t) - m\phi_y(t). \tag{19}$$

Note that here the normalized phases are used, i.e. the phases have been divided by $2\pi$, otherwise use mod$2\pi$. The presence of this peak is what is meant by phase locking in a statistical sense.
In case of strong noise phase slips occur frequently in both directions. The probability of these upward or downward jumps may be equal or different, so the relative phase performs either a symmetric or nonsymmetric random walk. In the first case the averaged frequencies $\Omega_{x,y} = \left\langle \dot{\phi}_{x,y} \right\rangle$ coincide, whereas in the second case they are different. "However, in a statistical sense synchronization is characterized by the existence of one or a few preferred values of $\Phi_{n,m}$, no matter whether the oscillators' averaged frequencies are equal or different" (Tass, P. et al, 1998).

### 3.3 Measures of phase-locking

In ideal cases, where noise is absent, the $n$:$m$ locking can be detected by computing the instantaneous phase $\phi_j$ of each observed signal, picking $n$ and $m$ by trial and error, plotting the relative phase $\phi_{n,m}$ versus time, and looking for horizontal plateaus in this presentation (Rosenblum, M.G. et al, 2000). By doing this the relative frequency itself can be used as a measure to detect periods of phase-synchrony. Using this method, Rosenblum, M.G. et al (1998) showed for the Rössler system that coupled chaotic oscillators can exhibit periods of phase synchronization just as periodic oscillators do. However, as mentioned above, in the presence of considerable noise, the relative frequency can be disturbed by random rapid phase jumps, which makes it an inadequate measure for synchronization (Mormann, F. et al, 2000).
To overcome this problem, Mormann et al (2000) proposed a more statistical point of view by analyzing the distribution of the relative phase angles on the unit circle: "'if the phases are locked during most of the time, a prominent peak will result in the phase histogram, and the effect of $2\pi$-phase-jumps will no longer be pre-dominant"'. Then for instance for $m$=$n$=1 the phase difference between two signals $x(t)$ and $y(t)$ is (Rosenblum, M.G. et al, 1998)

$$\phi_x(t) - \phi_y(t) = \arctan \frac{\tilde{x}(t)y(t) - x(t)\tilde{y}(t)}{x(t)y(t) + \tilde{x}(t)\tilde{y}(t)}. \tag{20}$$

Again Rosenblum, M.G. et al (1998) show that, using this projection of the relative phases, for the Rössler system it is relatively easy to distinguish time intervals where the phases are locked, i.e., the phase difference is constant. However, according to Palûs, M. (1997) the evaluation of the phase difference $\delta\phi(t)$ alone can be insufficient to draw the conclusion on whether phase synchrony is present. "'In an experimental situation it could be hard, even for an expert, to decide from plots of the phase difference whether analyzed systems are phase synchronized but noisy, or no synchronization is present.”’(Paluš, M., 1997) Therefore, more sophisticated measures to detect phase synchronization, based on statistics and information theory, are introduced below.

### 3.3.1 Measures using the wavelet transform

After extracting the phase from the signal a certain measure is necessary to quantify synchronization. This quantification can be done across different trials, by calculating the phase locking value, or within a trial by computing the single-trial phase locking value.

#### Phase locking statistics

Once the phase differences between the signals are obtained, the phase locking value (PLV) at time $t$ can be computed. The PLV measures the variability of the phase difference at time $t$ and frequency $f$ between trials $k$ and is defined by (Lachaux, J. et al, 2000)

$$PLV(f,t) = \frac{1}{K}\left|\sum_{k=1}^{K} \exp[j(\phi_{y,k}(f,\tau) - \phi_{x,k}(f,\tau))]\right|, \tag{21}$$

The PLV is a normalized index, i.e., if the phase difference varies little across the trials, the PLV will be close to one, otherwise it will be close to zero (Lachaux, J. et al, 1999).
To differentiate significant PLVs from background fluctuations a statistical test should be performed. The hypothesis $H_0$ that the two series of phase values $\phi_{x,k}$ and $\phi_{y,k}$ are independent can be tested by calculating the degree of significance of each phase locking value by comparing it to surrogate values $y'(k) = y(perm(k))$ (Lachaux, J. et al, 1999). These surrogate values are a set of variables that are created from the signals $x$ and $y$, using (21), but first the order of trials for $y$ is permuted. Thereby the surrogate data still have the same characteristics as the original signal, but the phase differences are no longer computed between signals during the same trial, but during different trials. The PLV for the surrogate data is defined as (Lachaux, J. et al, 2000)

$$PLV_{surrogate}(f,t) = \frac{1}{P}\sum_{p=1}^{P}\left|\frac{1}{K}\sum_{k=1}^{K} \exp[i(\phi_{y,perm_p(k)}(f,\tau) - \phi_{x,k}(f,\tau))]\right| \tag{22}$$

For each surrogate series $y'$, the maximum between $x$ and $y'$ in time is measured. The proportion of surrogate values greater than the original PLV, i.e. the maximum between $x$ and $y$, is called the phase-locking statistic (PLS). It measures the probability of having false positives for a chosen level of significance (Lachaux, J. et al, 1999).
The advantage of this statistical validation method is that it doesn't require any a priori hypothesis on the distribution of the signals. A drawback is that when the phase values $\phi_x$ and $\phi_y$ remain constant across trials, the statistical method fails to detect any significant phase synchrony between the two electrodes. In that case, permuting the trials within the measures of electrode y does not change the phaselocking value, while the signals are actually synchronous. However, Lachaux, J. et al (2000) remark that

”‘these false negatives easily can be detected since they are associated with high PLV”’ or by ”‘using simpler techniques that estimate the inter trial variability of the phase of each electrode”’.
The method presented here has some important limitations. It heavily depends on the choice of a specific frequency, which is chosen to perform the wavelet transform in order to separate the amplitude and phase components of the signals. This ”‘separation is meaningless if one needs to work on a broad band”’(Lachaux, J. et al, 1999) and choosing a frequency requires filters with good resolutions in time and frequency, which do not change the phase. Frequency analysis of intracortical and scalp data shows that their spectral content is very broad and the relative amplitudes vary considerably over time during an experimental situation. Therefore, it is of interest to investigate if there are interactions between frequencies in different bands and what their functional significance is. Since PLS can only do this by repeating the analysis over several frequency bands it doesn't give a complete answer (Lachaux, J. et al, 1999).
Another limitation is that this method detects phase-locking between pairs of signals across trials and thereby synchronies that do not have a fixed time delay from trial to trial will not be detected by this method. Gamma synchronization appears to be an induced, not stimulus-locked phenomenon, which cannot be studied by averaging over trials. To detect this type of phase locking Lachaux, J. et al (2000) have also introduced a measure of phase locking within trials; single-trial phase locking statistics (S-PLS). Here averaging or smoothing over time is used to be able to work on the basis of single trials.

**Single-trial phase locking statistics**

To overcome the limitations of the PLS measuring synchrony across trials, single-trial phase locking statistics (S-PLS) was introduced. This method also exploits a complex wavelet to extract the instantaneous phase in a predefined frequency range, but S-PLS measures synchrony within single trials instead of between trials. The analysis is again done around a chosen frequency value, which indicates that S-PLS has no advantage over PLS concerning the limitation of the dependence on the chosen frequency value. The S-PLV is defined for each trial as (Lachaux, J. et al, 2000)

$$S\text{-}PLV(f,t) = \left| \frac{1}{\delta} \int_{t-\delta/2}^{t+\delta/2} \exp[(j(\phi_y(f,\tau) - \phi_x(f,\tau))]d\tau \right| \tag{23}$$

where the definition of $\delta$ is omitted, but can be assumed to define a time window, and thereby affects the temporal resolution of the measure. As for PLV, the S-PLV is a normalized value ranging from 0 to 1, where 1 indicates the strongest phase locking and 0 no phase locking.
Differentiating the synchrony from background noise and quantifying the significance of each S-PLV is again done by comparing them to surrogate values in the same way as for PLV. The proportion of surrogate values higher than the original S-PLV values is thereby computed for a time $t$ and gives the single-trial phase locking statistics (S-PLS). This S-PLS value depends on two parameters; $n_{co}$, which sets the width of the frequency interval as

explained before, and the 'size of the window of temporal integration', which can be expressed in a number of cycles at a chosen frequency $f$: $n_{cy} = f \cdot \delta$. Hence, $n_{cy}$ determines the temporal resolution of the analysis where the synchrony estimation remains stable. Small values provide a better resolution, but at the cost of statistical resolution, because short-lasting episodes of phase locking are more likely to arise by chance alone.

### 3.3.2 Measures using the Hilbert transform

When the phases are obtained from the Hilbert transform there are several statistical and information-theoretic measures that provide a distinction between synchronous and asynchronous states. One of the information-theoretic measures is suggested by Paluš, M., (1997). Let $p_x(\phi_x)$ and $p_y(\phi_y)$ be probability distributions of the phases $\phi_x$ and $\phi_y$, and $p_{x,y}(\phi_x, \phi_y)$ their joint distribution. The mutual information is defined by

$$I(\phi_x, \phi_y) = \int_{-\pi}^{\pi} \int_{-\pi}^{\pi} p_{x,y}(\phi_x, \phi_y) \times \log \frac{p_{x,y}(\phi_x, \phi_y)}{p_x(\phi_x) p_y(\phi_y)} \mathrm{d}\phi_x \mathrm{d}\phi_y \tag{24}$$

It tests the dependence between phases $\phi_x(t)$ and $\phi_y(t)$. If there is no phase synchronization the mutual information will be zero, while in case of phase synchronization, i.e. mutual dependence of the phases, it will be positive.
Applying this to experimental data detections might again lead to the detection of spurious phase synchronization. To prevent this, Paluš, M. (1997) uses surrogate data is to find the range of $I(\phi_x, \phi_y)$ values. This surrogate data can be obtained from bivariate processes having properties similar to the data, but without exhibiting any phase synchronization. Then the mutual information obtained from the experimental data is compared with the mutual information from the surrogate data, to detect a significant difference and reject the null hypothesis imposed by the surrogate data. Several types of surrogate data can be used according to the properties and quality of the experimental data: IID1 surrogates present the null hypothesis of independent white noises, i.e. neither synchronization, nor oscillations are considered. IID2 surrogates allow for a mutual dependence (cross-correlated white noises), but do not contain oscillations. The FT1 surrogates present the null hypothesis of asynchronous oscillatory processes with the same spectra as the experimental data. Rejection of the null hypotheses of all these types of surrogate data can be considered as evidence for a phase synchronization in the experimental data (Paluš, M., 1997).
Some other methods to characterize the strength of synchronization are introduced by Tass, P. et al (1998), Rosenblum et al (2000), and Mormann et al (2000). These measures, or $n : m$ synchronization indices, quantify the deviation of the actual distribution of the relative phase from a uniform one. The main different measures proposed are:

- Index based on the Shannon entropy: defined as $\tilde{\rho}_{n,m} = (S_{max} - S)/S_{max}$, where $S = -\sum_{l=1}^{L} p_l \ln p_l$ is the entropy of the distribution of the cyclic relative phase $\Psi_{n,m}$, hence $p_l$ is the probability of observing a relative frequency $\psi_{n,m}$ in time bin $l$ [2]. The maximum of

[2] $p_l$ is not defined in Tass, P. et al 1998

the entropy is given by $S_{max} = \ln L$, where $L$ is the number of bins. This gives a normalized measure where $\tilde{\rho}_{n,m} = 0$ corresponds to a uniform distribution (no synchronization) and $\tilde{\rho}_{n,m} = 1$ corresponds to a Dirac-like distribution (perfect synchronization) (Tass, P. et al, 1998).

- Intensity of the first Fourier mode of the distribution[3]: defined as $\gamma_{n,m} = \langle \cos \Psi_{n,m}(t) \rangle^2 + \langle \sin \Psi_{n,m}(t) \rangle^2$, where the brackets indicate averaging over time. This measure of synchronization also varies from 0, indicating no synchronization, to 1, indicating perfect synchronization. The advantage of this index is that it is nonparametric (Rosenblum, M.G. et al, 2000).

- Index based on conditional probability: Suppose there are two phases $\phi_x(t)$ and $\phi_y(t)$ defined on the interval $[0, n]$ and $[0, m]$ respectively and each interval is divided into $L$ bins. Then, for each bin $l$, $1 \leq l \leq L$, calculate $r_l(t) = M_l^{-1} \sum \exp[i\phi_2(t)]$ for all $t$, such that $\phi_1(t)$ belongs to this bin $l$, and $M_l$ is the number of points in this bin. If there is a complete dependence between two phases, $|r_l(t)| = 1$, while it is zero if there is no dependence at all. Finally, the average over all bins is calculated, $\tilde{\lambda}_{n,m}(t) = 1/L \sum_{l=1}^{L} |r_l(t)|$. Thereby, $\tilde{\lambda}_{n,m}$ measures the conditional probability for $\phi_y$ to have a certain value provided $\phi_x$ is in a certain bin. To find $n$ and $m$, i.e., the ratio of phase locking, try different values and pick up those that give larger indices (Tass, P. et al, 1998).

To avoid spurious detection of locking due to noise and bandpass filtering, Tass, P. et al (1998) propose to derive significance levels $\rho^S_{n,m}$ and $\lambda^S_{n,m}$ for each $n{:}m$ synchronization index $\tilde{\rho}_{n,m}$ and $\tilde{\lambda}_{n,m}$ by applying the analysis to surrogate data (white noise filtered as the original signals). The 95th percentile of the distribution of the $n{:}m$ synchronization indices ($\tilde{\rho}_{n,m}$ or $\tilde{\lambda}_{n,m}$) of the surrogates can then be used as a significance level ($\rho^S_{n,m}$ or $\lambda^S_{n,m}$). Only relevant values of the $n{:}m$ synchronization indices are taken into account by introducing significant indices $\rho_{n,m} = \max\{\tilde{\rho}_{n,m} - \rho^S_{n,m}, 0\}$ and $\lambda_{n,m} = \max\{\tilde{\lambda}_{n,m} - \lambda^S_{n,m}, 0\}$ (Tass, P. et al, 1998). The index $\lambda_{n,m}$ is also effective if the interacting oscillators are strongly nonlinear and the distribution of $\Psi_{n,m}(t)$ is nonuniform even in the absence of noise. In this case the indices $\rho_{n,m}$ and $\gamma_{n,m}$ fail (Rosenblum, M.G. et al, 2000).

## 3.4 Hilbert transform versus Wavelet methods

In order to study phase synchrony it is necessary to estimate the instantaneous phase of each signal and to provide a statistical measure to quantify the degree of phase-locking. As seen above this can be done via convolution with a complex wavelet or by applying a Hilbert transform. Le van Quyen et al (2001) compare these two methods to each other by applying both of them to three signal sets: neural models, intra cranial signals from epileptic patients and scalp EEG recordings.
The analysis was performed by first filtering the signals of overlapping consecutive windows with a bandpass corresponding to a particular frequency

[3] In Mormann, F. et al, 2000 denoted as the mean phase coherence of an angular distribution

component. Then the instantaneous phase of each filtered window was extracted by means of wavelet convolution or using the Hilbert transform and finally the stability of the phase-locking was characterized by three measures: standard deviation of the phase differences over the unit circle, the Shannon entropy of the phase differences, and the mutual information of the phases, as defined before. In order to avoid spurious detection of synchrony due to noise and bandpass filtering, a significance level is again derived by applying the analysis to surrogate data, here white noise filtered as the originals, as described before (Le van Quyen, M. et al, 2001).
Their study has shown that the differences between the two methods are minor and only manifest themselves for small windows of observation. As their computational cost is also comparable, Le van Quyen et al (2001) conclude that they are fundamentally equivalent for the study of neuro-electrical signals. This equivalence can be understood by looking at the similarities between both methods. Both methods are restricted to narrow frequency bands, the "‘signals are both convolved with a functional with decaying flanks to extract the instantaneous phase"’, and both methods use some kind of statistical measure using surrogate data to avoid the detection of spurious synchronization. This indicates that numerical problems become a decisive factor and the PLV then proved to be computationally more efficient in their study (Le van Quyen, M. et al, 2001).

# 4 Frequency Flow Analysis

While the methods mentioned above were based on estimations of the stability of the phase difference between pairs of signals over a time window, within successive frequency bands, Rudrauf et al (2006) introduce a new approach to study the dynamics of brain synchronies; frequency flow analysis (FFA). In the approaches described above, phase synchrony was measured over a window of time by means of several statistical dependence measures and by repeating this for several frequencies the relevant spectrum could be covered. However, such approaches to phase synchrony have some limitations.

First, only synchrony between pairs of signals can be directly studied. Therefore the calculation has to be done for each possible pair, which for $n$ signals means $(n^2 - n)/2$ signal pairs. Another possible limitation comes from the assumption of local frequency stationarity of the phase coupling, especially since time integration is computed within a fixed, narrow frequency band. "'This procedure can mask phenomena of phase synchronization whose frequency of synchronization varies continuously through time"' (Rudrauf, D. et al, 2006), which is the type of synchronization, with frequency nonstationarity, that can be observed in brain signals. These approaches also do not allow precise description of patterns of convergence to and divergence from periods of synchronization, which involve frequency instability within some participating oscillators. Finally, these methods may be insensitive to very brief periods of phase locking and phase scattering, because a window of time integration of significant length is used (Rudrauf, D. et al, 2006).

The FFA approach exploits the relation between phase locking and frequency locking in a nonstatistical sense and looks for continuous periods of identical instantaneous frequencies between signals, which is then equivalent to continuous periods of phase synchrony. This relation will overcome the limitations of the other approaches, but applies only in cases in which periods of phase synchrony are not affected by a high level of noise on the phases. Techniques based on this relation are not able to detect statistical phase locking, such as described before, for cases where strong noise and phase slips affect the phase difference.

Nevertheless, brain signals such as from EEG and MEG frequently show weakly chaotic behaviour, with clear time and frequency bounded oscillations. Thereby Rudrauf, D. et al (2006) justify to look at periods of phase locking with moderately low noise for which the relationship between phase locking and frequency locking can be usefully applied. "'The use of the relationship between phase and frequency locking depends on the ability to separate signal components that have a compact spectral representation, for which instantaneous phase and frequency are meaningful"' (Rudrauf, D. et al, 2006). The methods described before used band pass filtering, whereas this method employs a ridge algorithm to extract intrinsic simultaneous frequency components from the signal, with possibly time varying spectra.

## 4.1 The method

For a given signal $x_i(t)$, $n = 1, ..., N$, where $n$ indexes the recording channel, $x_n(t)$ can be transformed in its analytic form (Rudrauf, D. et al, 2006)

$$z_n(t) = a_n(t) * \exp[i\phi_n(t)], \tag{25}$$

where the amplitude $a_n(t)$ and the instantaneous phase $\exp[i\phi_n(t)]$ appear as two independent variables. Real signals which reflect a linear mixture of underlying oscillators, often include multiple spectral components so that $z_n(t) = \sum_k a_{nk}t) * \exp[i\phi_{nk}(t)]$, as well as noise. The time-frequency decomposition of $z_n(t)$ can be obtained using wavelet convolution or, after careful band pass filtering, the Hilbert transform as shown before.

A frequency flow $\Omega_n(\Delta t)$ is defined as a sequence of instantaneous frequencies continuously defined in the time-frequency plane during a time window $\Delta t$. Consider two periodic oscillators $(x, y)$ which are phase synchronous during a period $\tau \subset \Delta t$ with frequency flows defined during $\Delta t$. In the case where $n : m = 1$, a common frequency flow $\Omega_{x,y}$ will appear reflecting the $1 : 1$ phase synchronization. In the general case of $n : m$ synchronizations, $n : m$ relationships between frequency flows will be observed (figure 2B) (Rudrauf, D. et al, 2006).

In most methods proposed the possibility of having synchronization at time varying frequencies is not included. However, a constant phase difference and a constant frequency in which the phase synchrony is observed are two independent phenomena. Consider two oscillators $(x, y)$ with the same initial instantaneous frequencies. When the instantaneous frequencies vary over time with the same rate, the difference between the phases still remains constant, indicating the presence of phase-synchrony. Two oscillators with such a continuous common instantaneous frequency ${\omega_{x,y}}^4$, that changes through time according to a common continuous function $\dot{\omega}_{x,y}(t) = \ddot{\phi}_{x,y}(t) = f(t)$, exhibits phase synchrony with a nonstationary frequency (figure 2B). Phase synchrony with stationary frequency exists when the common instantaneous frequency $\omega_{x,y}$ between two oscillators is constant through time. Two oscillators with different eigenfrequencies are $n : m$ phase synchronous if during a period $\Delta t$, $\omega_x(t)/\omega_y(t)$ approximately has a ratio $n : m$ and the angular acceleration is zero (Rudrauf, D. et al, 2006).

If $k$ oscillators are mutually phase synchronous over a period of time, all the $(k^2 - k)/2$ phase differences within the ensemble will be constant. The phase differences from pair to pair can be different, but the instantaneous phases of all $k$ oscillators will have the same angular speed. Therefore the oscillators will all posses a common instantaneous frequency $\omega_{1,...,k}$ and hence will all participate in the same frequency flow $\Omega(f, t)$. By looking at the space of frequency flows, instead of the phase of phase differences, "‘a synchrony assembly is defined by a common continuous trajectory in the space of the instantaneous frequencies, i.e., a common frequency flow of minimal duration $\Delta t$"’. The size of this space is no longer $(n^2 - n)/2$, but only $n$ (Rudrauf, D. et al, 2006).

In the methods proposed above the instantaneous frequency $\omega(t)$ was defined as the positive derivative of its instantaneous phase $\phi(t)$, which was

[4] For notational convenience the instantaneous frequency, .i.e., the angular speed divided by $2\pi$ is now denoted by $\omega$

derived from the analytic form of the signal, obtained using a wavelet or Hilbert transform. However, Rudrauf, D. et al (2006) remarked that real signals such as brain signals, often contain multiple simultaneous spectral components, as well as noise. The frequency of these spectral components may vary in time and the noise is generally distributed over a broad frequency band. Therefore defining the instantaneous frequency as above is in this case meaningless.

One way to overcome the problem is to denoise and separate these multiple spectral components using a time-frequency deconvolution, such as wavelet decomposition. Le van Quyen, M. et al (2006) remark that it has been mathematically demonstrated that instantaneous frequencies can be estimated by computing the ridges, i.e. the local maxima, of the time-frequency decomposition.

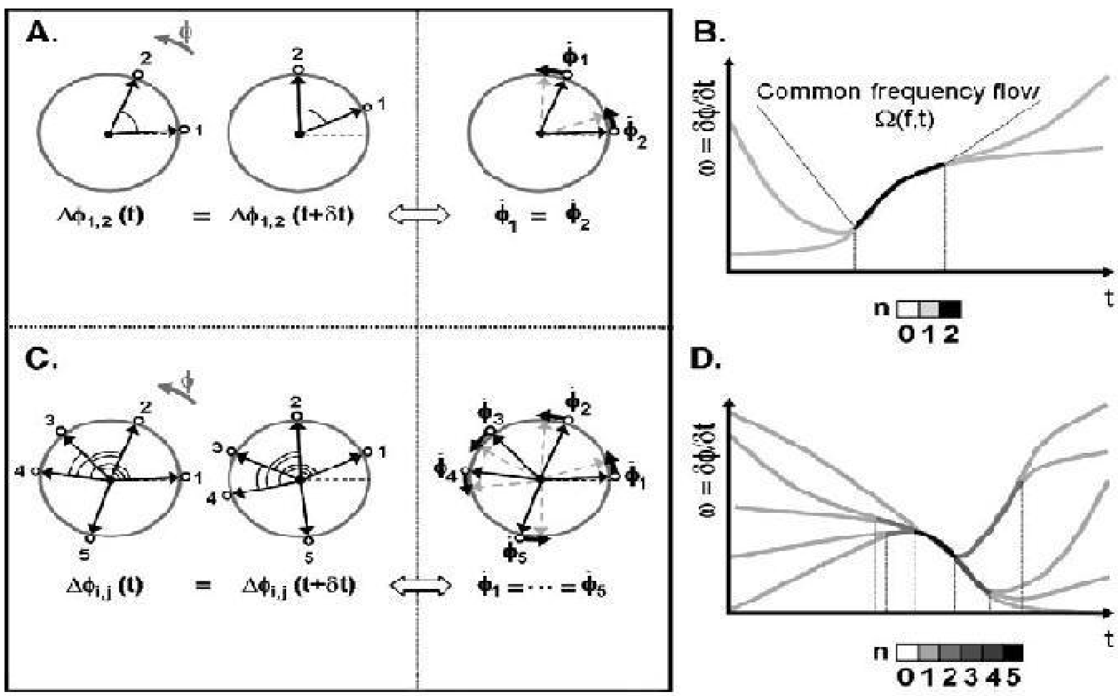


Figure 2: (Rudrauf, D. et al, 2006) "'(A) Left side: two vectors of instantaneous phases in the unitary circles. Two oscillators are phase synchronous in a given frequency band if their phase differences are conserved through time. Right side: the conservation of the phase difference during a period $\Delta t$ implies that both oscillators rotate with the same speed, i.e., that they possess the same instantaneous frequency during this period, and conversely. (B) Theoretical diagram of instantaneous frequency versus time for two oscillators. Synchronization does not need to occur at a stationary frequency. Two oscillators are synchronous if they belong to the same frequency flow during a certain amount of time. The gray scale corresponds to the number of elements with the same instantaneous frequency at a given instant. (C) Generalization to the case of an arbitrary number $k$ of oscillators constituting a phase synchronous assembly. Left side: conservation of the mutual phase differences. Right side: equivalence with the conservation of a common instantaneous frequency. An ensemble of $k$ oscillators is phase synchronous if they belong to the same frequency flow. (D) Theoretical diagram of instantaneous frequency versus time for five oscillators, illustrating the relation between frequency flows and multivariate synchronization. The gray scale corresponds to the number of elements with the same instantaneous frequency at a given instant."'

## 4.2 The ridge algorithm and Instantaneous Frequency Histograms

This algorithm, introduced by Rudrauf, D. et al (2006), estimates the distribution of instantaneous frequencies of a signal of the form $\sum_n a_n(t)\exp[i\phi_n(t)]$ by computing ridge points, or 'wavelet ridges', where the ridge points are extracted from the analytic wavelet transform (AWT) of the signal. The AWT has the characteristic that it modifies the scale of its time-frequency component so that it can follow the instantaneous frequency of rapidly varying events at high frequency.
By performing a wavelet transform $Wx(u,s)$, which uses a translated and scaled Gabor wavelet $\psi$, on the signal $x(t)$, with $u$ a time and $s$ a scale parameter, the amplitude of $x(t)$ in a time-scale neighbourhood of $(u,s)$ is measured. The AWT defines local time-frequency densities in boxes centered at $(u,\xi)$, where $\xi = \eta/s$, $\eta$ being the center frequency of the $\psi_{u,s}(t)$. The normalized energy density of the signal at $(u,\xi)$ can be calculated from this and gives the normalized scalogram of $x(t)$. This scalogram reaches its maximum at $\frac{\eta}{s(u)} = \xi(u) = \frac{\mathrm{d}\phi(u)}{\mathrm{d}t}$, which is the instantaneous frequency of the signal. The corresponding points $(u,\xi(u))$ are called wavelet ridges [5].
This result generalizes to signals of the form $x(t) = \sum_n a_n(t)\exp[i\phi_n(t)]$ including any number of time varying spectral components as long as the two spectral components are not too close [6]. If they are too close, they interfere, perturbing the ridge pattern. Thus, the set of ridge points in the scalogram at $u$ are equal to the instantaneous frequencies of the spectral components in $x(u)$ at $u$. Since the number of instantaneous frequencies is generally unknown, all the local maxima of the scalogram are detected. In practice, ridge points associated with small amplitudes $a(u,\xi)$ are removed as potential artifacts of noise variations, or shadows of other instantaneous frequencies. The ridge algorithm provides a high resolution binary map in the time-frequency plane (figure 3A), called the ridgelet transform of the signal, with ones where a significant instantaneous frequency has been found and zeroes otherwise. "'If separable oscillations exist in a multispectral noisy signal, they will appear as frequency flows on the ridgelet transform, i.e., as continuous curves in the time-frequency plane"' (Rudrauf, D. et al, 2006).
Considering an ensemble of $k$ sources of brain signals, a binary ridgelet map can be associated with each signal. Given such a set of $k$ ridgelet transforms, periods of phase synchrony between signals can be estimated by taking the summation of the binary maps. The map resulting from the summation of all the individual maps provides an instantaneous frequency histogram (IFH), which reflects the number of synchronous oscillators involved in each common frequency flow at a given time (figure 3A). The chosen frequency interval within one bin of the histogram, corresponding to the frequency bin of the ridgelet transform, defines the local synchrony resolution (Rudrauf, D. et al, 2006).

[5] technical details can be found in (Rudrauf, D. et al, 2006)
[6] a precise definition can be found in (Rudrauf, D. et al, 2006)

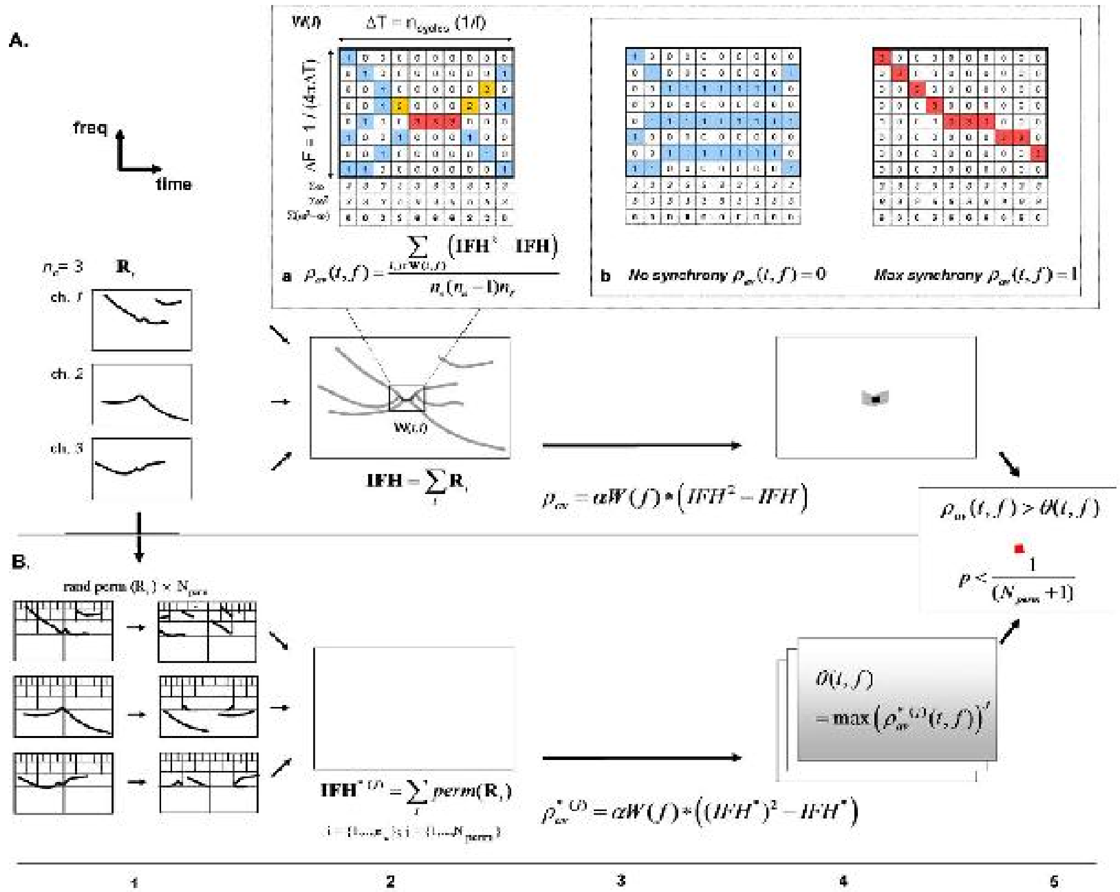

Figure 3: (Rudrauf, D. et al, 2006) "'Frequency locking and statistics. Measure of frequency locking based on the Instantaneous Frequency Histogram IFH. (A) Individual ridgelet maps $R^i$ containing frequency flows associated with $n_c$ measurement channels (step 1) are summed (step 2) in order to build an IFH map (IFH). Eq. (28) is used (step 3) in order to compute the average frequency locking map $\rho_{av}$ (step 4). In the figure, the coefficient $\alpha$ stands for $1/n_c(n_{c-1})n_T$. The upper frame describes the properties of the local frequency locking calculus within the integration box $\mathbf{W}$(f). Values from the IFH in the boxes are represented for three different configurations of frequency flows relationships (a,b,c). The numbers correspond to the number of overlapping frequency flows at (t,f); 0 and 1 corresponding to cases where no or only one frequency flow is present. The three lower rows of numbers below the boxes demonstrate the properties of the measure. (B) The $R^i$ maps are resampled using tiling and permutation, in order to generate $N_{perm}$ random IFHs (steps 12), i.e., maps $\mathbf{IFH}*^{(J)}$, and corresponding $\rho_{av}^{*J}$ (step 3), $J = 1, ..., N_{perm}$. The maxima of the set $\rho_{av}^{*J}$ are used to generate the map $\theta(t, f)$, which serves to threshold $\rho_{av}$ (step 5). Values $\rho_{av}(t, f)$ above $\theta(t, f)$ have less than $1/(N_{perm} + 1)$ chance to occur as a result of the randomization process."'

## 4.3 Measure of frequency locking

Frequency locking of signals along a certain time-frequency path will maximize the corresponding IFH within in the considered time period. But since the IFH measures coincidences of instantaneous frequencies, it does not take the stability of the coincidences between individual frequency flows through time into account, and therefore does not provide a true measure of frequency locking. Thus, a local time integration is necessary to guarantee that superimposition between frequency flows is conserved during a

relevant time period. Time integration is difficult because since frequency flows can have many different orientations in the time-frequency plane, the coincidence between frequency flows has to be integrated in 2D, through time and frequency (Rudrauf, D. et al, 2006).
The approach proposed by Rudrauf, D. et al (2006) exploits the relationship between the IFH and the average pairwise correlation among the binary vectors representing a region of the frequency flow map, which arises from the fact that a frequency flow within a sufficiently small region of the time-frequency plane can be represented as a binary vector.
Let $\mathbf{x}_i = \omega_i(W)$ and $\mathbf{x}_j = \omega_j(\mathbf{W})$ be a pair of vectors with binary elements representing the frequency flows associated with a pair of channels $(i, j)$ defined in a local time-frequency box $\mathbf{W}(\Delta F, \Delta T)$; with $\Delta F$ the frequency range for integrating the flows during time $\Delta T$. The correlation between $\mathbf{x}_i$ and $\mathbf{x}_j$ gives a measure that reflects the degree of coincidence within $\mathbf{W}$. The average correlation between all the pairs of locally defined frequency flows amongst the channels is used in order to have a measure for the whole population of signals.
The average pairwise correlation $\rho_{av}$ between the binary vectors representing the frequency flows in $\mathbf{W}$ is defined by (Rudrauf, D. et al, 2006):

$$\rho_{av} = \frac{1}{n_c(n_c - 1)}[\sum_{i,j} \frac{\mathbf{x}_i^T \mathbf{x}_j}{\mathbf{x}_i \mathbf{x}_j} - n_c] \tag{26}$$

where $n_c$ is the total number of channels and $\rho_{av}$ varies between 0 and 1. In this equation, for channels not contributing to the frequency flow $\mathbf{W}$ the correlation is undefined.
By making some simplifying assumptions [7] on this average pairwise correlation laborious pairwise computation is avoided and the calculation of the average interchannel correlation directly from the IFH is possible. The full time-frequency map of average correlation can now be computed by convolving an adaptive window $W(f)$ with the difference of the squared IFH and IFH (Rudrauf, D. et al, 2006):

$$\rho_{av} = \frac{1}{n_c(n_c - 1)n_t(f)} W(f) * (IFH^2 - IFH) \tag{27}$$

The size of $W$ is chosen to be a function of the central frequency $f$ in the region of the IFH where it is applied. The width of the time integration is defined as $\Delta T = n_{cycles}(1/f)$, and $\Delta f = 1/(4\pi\Delta t)$.
This convolution treats absence of frequency flows corresponding to channels that are not represented within the integration box as noncorrelated frequency flows. Here the average pairwise correlation is normalized by the total number of channels, and hence strong synchronization between a few channels will lead to small average correlation. A measure which is independent of the number of channels involved and which is more sensitive to synchronization between small groups of channels and less sensitive to weak synchronization among large groups of channels can also be obtained. This can be done by substituting $n_c$ by the number of channels actually represented in the integration box $\mathbf{W}$, giving a local average, which is defined only for regions of the IFH containing two or more contributing channels.

[7] technical details can be found in (Rudrauf, D. et al, 2006)

By combining the use of the average and local average pairwise correlations a differentiation can be made between conditions in which a few channels are highly synchronized and in which many channels are weakly synchronized (Rudrauf, D. et al, 2006).

## 4.4 Statistical approach

To avoid detecting spurious synchronization and take into account the presence of noise statistical resampling methods can again be used to test the significance of the observed frequency flows. It is important to preserve some of the time-dependent as well as frequency-dependent properties of the measures while performing the statistical test. Rudrauf, D. et al (2006) use a bootstrap approach in which blocks of the time-frequency plane are permuted across time. "'Within each frequency band, blocks of dimension $\Delta f \times \Delta t$, are randomly permuted across time, so that the instantaneous frequency distribution and part of the autocorrelation of the frequency flows are preserved whereas the phase relationship between the individual channels are randomized."'
Permutations are calculated for each ridgelet map associated with a given channel and randomized average frequency locking maps are computed from the IFHs of the bootstrapped data (figure 3B) The maximum of these frequency locking maps at each time-frequency point is used to build a map of maximal random synchronization, which gives a threshold of significance for the observed average interchannel correlation $\rho_{av}$. With this threshold the probability of observing a given value of $\rho_{av}$ by chance can be estimated and the statistical test can thus be performed (Rudrauf, D. et al, 2006).

# 5 Discussion

Several widely used methods to measure synchronization have been described and compared. Direct methods measuring coherence in linear and nonlinear systems, statistical and information-theoretical methods using the notion of phase synchronization, where the phase is extracted by wavelet convolution or the Hilbert transform, and frequency flow analysis. All these described methods can be used to detect bivariate synchronization, i.e., synchronization between two signals, whereas frequency flow analysis has the advantage that it can also directly detect multivariate synchronization, i.e., synchronization between an arbitrary number of signals. Examination of multivariate synchronization using bivariate synchronization measures has to be done by repeated pairwise analysis, which can become incomprehensible when the number of links increases. Also, using bivariate methods, "‘the covariance structure of the synchronous ensemble present in the data is not accounted for, and direct information about large-scale coherent integrative dynamics across space and time, as observed in spatially extended coupled nonlinear systems, is not provided"’ (Le van Quyen, M. et al, 2006).
These types of characterizations of methods might be used in order to decide which approach to use in an experimental situation. However, one should also be careful when using these measures. While Dauwels, J. et al (2010) recently discussed some synchrony measures and made a quite clear distinction between measures for stationary and nonstationary and linear and nonlinear systems, often these cases are not differentiated and limitations on the methods are not very clear.
The coherence measure for instance has several limitations. Quian Quiroga, R. et al (2008) remark that these measures can only be used to measure bivariate linear synchronization, while Lachaux, J. et al (1999) state that coherence measures also assume stationarity in time or across trials; an assumption of which nothing is mentioned in Quian Quiroga, R. et al, (2001). This assumption however implies that the coherence measure can only be applied to stationary signals. Further Lachaux, J. et al (1999) note that "‘coherence also increases with amplitude covariance, and the relative importance of amplitude and phase coherence in the coherence value is unclear"’, which makes it an inadequate measure is case of varying amplitudes since it does not quantify phase relationships. Rosenblum, M.G. et al (1998) remark that "‘as the data are practically always nonstationary, the application of traditional techniques such as cross-spectrum and cross-correlation analysis or nonlinear characteristics like generalized mutual information has its limitations"’.
The proposed methods exploiting the concept of phase synchronization, while using a wavelet convolution or Hilbert transform to extract the instantaneous phase, are able to deal with nonstationarity of couplings in the brain. Because of the separation between phase and amplitude these measures also cope with the possibly independent and varying amplitudes. The limitation of this method comes from the assumption of local frequency stationarity of the phase coupling. An integration time window $\Delta t$ is used within each frequency band as a criterion of stability of the phase synchrony. This one-dimensional integration is performed within a narrow frequency band and thereby assumes a minimal frequency stability, which limits the possibility

of detecting phase synchrony with nonstationary frequency. The approach of frequency flows also uses a time integration window in order to assess a minimal stability of the coincidence between frequency flows, but since the signal here was integrated through the time-frequency plane, nonstationary frequencies are also taken into account (Rudrauf, D. et al, 2006).
The limitation in the method of frequency flows arises when noise is present, in which case one can only speak of phase synchrony in a statistical sense. Detecting phase synchrony using the criteria of frequency locking can overlook cases of statistical phase locking, since it is a deterministic approach which does not make use of the distribution of the phase differences. In Tass, P. et al (1998) a differentiation is made between weak and bounded noise, in which in the synchronous state the relative phase fluctuates around some constant value, and the condition of frequency locking is still fulfilled, and strong noise which can cause phase slips, and where synchrony can only be treated in a statistical sense. Still, Rudrauf, D. et al (2006) remark that the deterministic nature of many simple behaviours leads one to suppose that brain correlates must exist which exhibit similarly deterministic patterns. "'Such an assumption is implicit in any method relying on averaging of brain signals, in which deterministic patterns emerge through the attenuation of noise. An implicit but central goal in the study of the brain responses is the identification of signals and patterns that more directly and reliably, i.e., noiselessly, reflect cognitive and perceptual states; precisely such a correlate is sought in the study of phase-synchrony. It remains to be clearly demonstrated whether phase synchrony can or cannot be useful in this respect, and doing so awaits sufficiently advanced techniques of analysis"'(Rudrauf, D. et al, 2006).
However, also the approaches using statistical notions of phase synchronization suffer from noise. For noisy phases, difficulties arise because strong noise can cause phase slips, i.e., rapid jumps of the relative phase, and the derivative of the phase of the signal may take negative values thus misleading the interpretation of instantaneous frequency (Le van Quyen, M. et al, 2006). Therefore one has to be careful when applying these methods to experimental data with a considerable amount noise. Often the issue of noise is mentioned when introducing or describing the used methods for synchronization measurement, but there are also cases where nothing is mentioned about the issue of noise. This also accounts for the notion of nonstationarity and nonlinearity. For instance Doesburg, S.M. et al (2007) do mention the problem of volume conductivity and the influence of the reference-electrode on synchrony, while nothing is mentioned about general noise, stationarity or linearity issues. Rossberg, A.G. et al (2004) do address the issue of noise and mention nonlinearity, but do not include the issue of stationarity.
Attention should also be paid to the type of statistical validation that has been performed. Permutation and bootstrapping of signals would be a good validation since it preserves the characteristics of the original signals, but just randomizes the order. In the testing of the coherence measures and also in some of the tests using surrogate data, like IID1 and IID2 used by Paluš, M. (1997) and the surrogate data used by Le Van Quyen, M. et al (2001), the statistical test is based on comparison with white noise signals. Since neural signals are not white noise signals the $H_0$ hypothesis might be too strong and too easily rejected (Lachaux, J. et al, 1999), which is probably

why Paluš, M. (1997) remarks that all the hypotheses of the tests on several types of surrogate data should be rejected.

The issue of linearity is most often avoided when methods for synchronization measurement are proposed. Linear measures are often applied to detect synchrony in nonlinear systems without mentioning this. Rosenblum, M.G. et al (2000) do make a distinction in linear and nonlinear systems when describing the statistical analysis of the relative phase and proposing the information-theoretic measures. In most cases however, measures exploiting the Hilbert transform or wavelet convolution, which assume linearity, are easily applied to nonlinear systems without even remarking the issue, probably by assuming a general notion of phase synchrony for all systems. However, phase synchronization requires different conditions for every type of system, or as Le Van Quyen, M. et al (2001) remark: "‘a conceptually clear and applicable extension of the definition of phase synchrony to all types of nonlinear systems remains to be done"’.

# 6 References


1 Lachaux, J. et al, 1999, *Measuring phase synchrony in brain signals*, Human Brain Mapping 8, 194-208.

2 Rudrauf, D. et al, 2006, *Frequency flows and the time-frequency dynamics of multivariate phase synchronization in brain signals*, NeuroImage 31, 209-227.

3 Doesburg, S.M. et al, 2007, *Large-scale gamma-band phase synchronization and selective attention*, Cerebral Cortex 18, 386-396.

4 Le Van Quyen, M. et al, 2006, *Exploring the dynamics of collective synchronizations in large ensembles of brain signals*, Journal of Physiology, Paris 100, 194-200.

5 Kreuz, T. et al, 2007, *Measuring synchronization in coupled models: a comparison of different approaches*, Physica D 225, 29-42.

6 Paluš, M., 1997, *Detecting phase synchronization in noisy systems*, Physics letters 235, 341-351.

7 Lachaux, J. et al, 2000, *Studying single-trials of phase synchronous activity in the brain*, International Journal of Bifurcation and Chaos, Vol. 10, No. 10, 2429-2439.

8 Tass, P. et al, 1998, *Detection of n:m phase locking from noisy data*, Physical review letters, Vol. 81, No. 15, 3291-3294.

9 Rosenblum, M.G. et al, 2000, *Detection of phase synchronization from the data: application to physiology*, AIP Conference Proceedings, vol. 502, iss. 1, 154-161.

10 Rossberg, A.G. et al, 2004, *Phase synchronization from noisy univariate signals*, Physical Review Letters 93.

11 Le Van Quyen, M. et al, 2001, *Comparison of Hilbert transform and wavelet methods for the analysis of neuronal synchrony*, Journal of Neuroscience methods 111, 83-98.

12 Dauwels, J. et al, 2010, *A comparative study of synchrony measures for the early diagnosis of Alzheimer's disease based on EEG*, Neuroimage 49, 668-693.

13 Quian Quiroga, R. et al, 2001, *On the performance of different synchronization measures in real data: a case study on EEG signals*, Chaotic Dynamics, September 2001, 1-32.

14 Rosenblum, M.G. et al, 1998, *Analysing synchronization phenomena from bivariate data by means of the Hilbert transform*, Nonlinear Analysis of Physiological Data, 91-99.

15 Mormann, F. et al, 2000, *Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients*, Physica D 144, 358-369.

- Rodriguez, E. et al, 1999, *Perception's shadow: long-distance synchronization of the human brain*, Nature 397, 430-433.

- Pereda, E. et al, 2005, *Nonlinear multivariate analysis of neurophysiological signals*, Progress in Neurobiology 77, 1-37.

- Wang, Y. et al, 2006, *Phase synchrony measurement in motor cortex for classifying single-trial EEG during motor imagery*, Proceedings of the 28th IEEE EMBS Annual International Conference, New York City, USA.

- Sazonov, A.V. et al, 2009, *An investigation of the phase locking index for measuring of interdependency of cortical source signals recorded in the EEG*, Biol Cybernetics 100, 129-146.

- Panter P., 1965, *Modulation, noise, and spectral analysis*, McGraw-Hill, New York.

- Rabiner R, Gold B., 1975, *Theory and application of digital signal processing*, Prentice-Hall, Englewood Cliffs, NJ.

- Schalk, G. et al, 2008, *Real-time detection of event-related brain activity*, NeuroImage 43, 245-249.

- Bracewell, R.N., 2000, The Fourier transform and its applications, 3rd edition, Mc Graw-Hill companies, Singapore.

- Ward, L.M., Dynamical cognitive science, 2002 Massachusetts Institute of Technology.

- R. Quian Quiroga, J. Arnhold and P. Grassberger. Phys. Rev. E, 61, 5142 (2000)

- Le van Quyen, M. et al, 1998, *Nonlinear interdependencies of EEG signals in human intracranially recorded temporal lobe seizures*, Brain Research 792, 2440.

- Arnhold, J. et al, 1999, *A robust method for detecting interdependences: application to intracranially recorded EEG*, Physica D 134, 419430.

- Gunduz, A., Principe, J.C, 2009, Correntropy as a novel measure for nonlinear tests, Signal Processing 89 (1), 14-23.