Detection of n:m Phase Locking from Noisy Data: Application to Magnetoencephalography

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We use the concept of phase synchronization for the analysis of noisy nonstationary bivariate data. Phase synchronization is understood in a statistical sense as an existence of preferred values of the phase difference, and two techniques are proposed for a reliable detection of synchronous epochs. These methods are applied to magnetoencephalograms and records of muscle activity of a Parkinsonian patient. We reveal that the temporal evolution of the peripheral tremor rhythms directly reflects the time course of the synchronization of abnormal activity between cortical motor areas. [S0031-9007(98)07333-5]

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Irregular, nonstationary, and noisy bivariate data abound in many fields of research. Usually, two simultaneously registered time series are characterized by means of traditional cross-correlation (cross-spectrum) techniques or nonlinear statistical measures like mutual information or maximal correlation [1]. Only very recently a tool of nonlinear dynamics, mutual nonlinear prediction, was used for characterization of dynamical interdependence among systems [2]. In this Letter we use a synchronization approach to the analysis of such bivariate time series and introduce a new method to detect alternating epochs of phase locking from nonstationary data. By doing so we extract information on the interdependence of weakly interacting systems that cannot be obtained by traditional methods.

Our technique, based on theoretical studies of phase synchronization of chaotic oscillators [3], can be fruitfully applied, e.g., in neuroscience, where synchronization processes are of crucial importance, e.g., for visual pattern recognition [4] and motor control [5]. Recent animal experiments have led to the conclusion that the control of coordinated movements is based on a synchronization of the firing activity of groups of neurons in the primary and in secondary motor areas [5]. Synchronization is also assumed to be involved in the generation of pathological movements, e.g., resting tremor in Parkinson's disease (PD) [6]. Although experimental studies indicate which parts of the nervous system are engaged in generating tremor activity, the dynamics of this process is not yet understood [7].

Here we study synchronization between the activity of remote brain areas in humans by means of noninvasive measurements. This is possible because a group of synchronously firing neurons within a single area generates a magnetic field which can be registered outside the head by means of multichannel magnetoencephalography (MEG) [8]. Accordingly, synchronization of neuronal activity between remote areas is reflected as phase locking between MEG channels. Our analysis reveals phase synchronization (a) between the activity of certain brain areas and (b) between the activity of these areas and the muscle activity detected by electromyography (EMG).

In particular, we find that the phase locking between the activity of primary and secondary motor areas is related to the coordination of antagonistic muscles.

Our approach is based on the notion of phase synchronization. Classically synchronization of two periodic nonidentical oscillators is understood as adjustment of their rhythms, or appearance of *phase locking,* due to interaction. The locking condition reads

$$|\varphi_{n,m}(t)| < \text{const}, \quad \text{where} \quad \varphi_{n,m}(t) = n\phi_1(t) - m\phi_2(t), \tag{1}$$

n and m are some integers, $\phi_{1,2}$ are phases of two oscillators, and $\varphi_{n,m}$ is the generalized phase difference, or relative phase; all phases are divided by 2π for normalization, and $\varphi_{n,m}$, as well as $\phi_{1,2}$, are defined not on the circle $[0,1]$ but on the whole real line. In this simplest case condition (1) is equivalent to the notion of *frequency locking* $n\Omega_1 = m\Omega_2$, where $\Omega_{1,2} = \langle \dot{\phi}_{1,2} \rangle$ and brackets mean time averaging. Note that for the determination of synchronous states it is irrelevant whether the amplitudes of both oscillators are different or not.

The definition of synchronization in *noisy and/or chaotic systems* is not so trivial. Recently it has been shown [3] that the notion of phase can generally be introduced for chaotic systems as well, and phase locking in the sense of (1) can be observed. The amplitudes of synchronized systems remain chaotic and effect the phase dynamics qualitatively in the same way as external noise [3]. Therefore in the following we consider noisy and chaotic cases within a common framework, i.e., by the term "noise" we denote both random and purely deterministic perturbations to phases. If this noise is weak (and bounded) then in the synchronous state the relative phase fluctuates around some constant value, and the condition of frequency locking is fulfilled. Strong noise can cause *phase slips,* i.e., rapid unit jumps of the relative phase. In this case the question "synchronous or not synchronous" cannot be answered unambiguously, but can be treated only in a statistical sense. Following the basic work of Stratonovich [9] we understand synchronization of noisy systems as appearance of peaks in the *distribution of the*

cyclic relative phase $\Psi_{n,m} = \varphi_{n,m} \bmod 1$, that enables us to detect preferred values of the phase difference irrespective of the noise-induced phase jumps. The probability of these upward and downward jumps may either be equal or different, i.e., the relative phase performs either unbiased or biased random walks. In the first case the averaged frequencies $\Omega_{1,2} = \langle \dot{\phi}_{1,2} \rangle$ 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 $\Psi_{n,m}$, no matter whether the oscillators' averaged frequencies are equal or different.

For illustration we consider two coupled nonidentical Rössler systems subject to noisy perturbations:

$$\dot{x}_{1,2} = -\omega_{1,2}y_{1,2} - z_{1,2} + \xi_{1,2} + \varepsilon(x_{2,1} - x_{1,2}),$$
$$\dot{y}_{1,2} = \omega_{1,2}x_{1,2} + 0.15y_{1,2}, \qquad (2)$$
$$\dot{z}_{1,2} = 0.2 + z_{1,2}(x_{1,2} - 10).$$

Here we introduce the parameters $\omega_{1,2} = 1 \pm 0.015$ and ε which govern the frequency mismatch and the strength of coupling, respectively; $\xi_{1,2}$ are two Gaussian delta-correlated noise terms, $\langle \xi_i(t)\xi_j(t') \rangle = 2D\delta(t - t')\delta_{i,j}$. The system is simulated by Euler's technique with the time step $\Delta t = 2\pi/1000$. If the noisy perturbations are rather weak, $D = 0.2$, the phase difference oscillates around some constant level, and its distribution obviously has a sharp peak. Therefore we can speak of frequency and phase locking here (Fig. 1a, curve 1). If the noise is stronger, $D = 1$, the relative phase performs a biased random walk, so there is obviously no frequency locking (Fig. 1a, curve 2). Nevertheless, the distribution of the phase definitely indicates locking in the statistical sense (Fig. 1b), in contrast to the nonsynchronous case (Fig. 1a, curve 3 and Fig. 1c).

It is very important to emphasize that synchronization is not equivalent to correlation. Hence, our analysis reveals different characteristics of the systems' interdependence. To illustrate this, we consider signals $u = (1 - \mu)x_1 + \mu x_2$ and $w = \mu x_1 + (1 - \mu)x_2$. By doing so we imitate the real situation: each MEG sensor measures signals originating from more than one area of neuronal activity. Nevertheless, this mixture of signals does not lead to a spurious detection of synchronization, although u and w are correlated (Fig. 1).

Now we use our approach to extract information about the underlying dynamics of the system from bivariate data at its output. With this aim in view we compute the instantaneous phase ϕ_j of each observed signal by means of the Hilbert transform (see [3], and references therein). A straightforward approach to search for *n:m* locking is to pick n and m by trial and error, plot the relative phase $\varphi_{n,m}$ vs time, and look for horizontal plateaus in this presentation [10]. Because of phase fluctuations and slips this can be misleading for noisy data (cf. Fig. 1). Thus, the above described statistical approach is needed.

To characterize the strength of synchronization, we have to quantify the deviation of the actual distribution of the
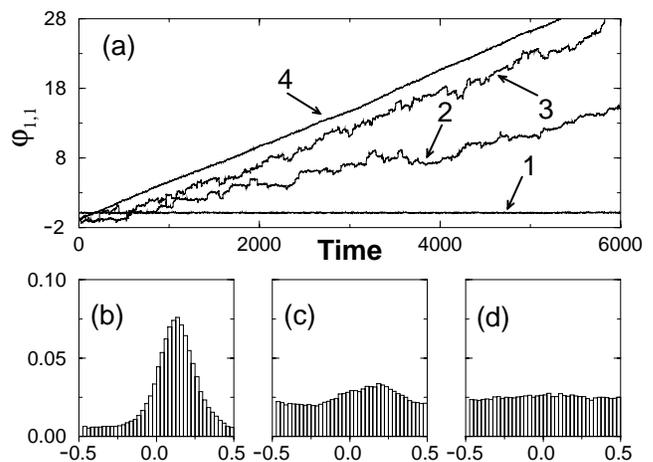

FIG. 1. The relative phases $\varphi_{1,1}$ (a) and distribution of $\Psi_{1,1} = \varphi_{1,1} \bmod 1$ [(b),(c)] for system (2). If the noise is weak, $D = 0.2$, the phase difference of two synchronized oscillators ($\varepsilon = 0.04$) fluctuates around some constant value (curve 1), and its distribution is obviously sharp (not shown). In the presence of strong noise, $D = 1$, the phase difference performs a biased random walk (curve 2, $\varepsilon = 0.04$), as well as in the nonsynchronous case (curve 3, $\varepsilon = 0.01$). The distributions of $\Psi_{1,1}$ [(b),(c)] clearly distinguish these states. The phase difference [(a), curve 4] computed from u and w that are linear combination (see text) of outputs from uncoupled oscillators and its distribution (d) do not lead to a spurious detection of synchronization, although cross-spectrum analysis by means of Welch technique with the Bartlett window reveals significant coherence $\gamma^2 = 0.43$ between u and w; parameters are $D = 0.2$, $\mu = 0.02$.

relative phase from a uniform one. For this purpose, we propose two measures, or *n:m synchronization indices*. (i) *Index based on the Shannon entropy* is defined as $\tilde{\rho}_{nm} = (S_{\max} - S)/S_{\max}$, where $S = -\sum_{k=1}^{N} p_k \ln p_k$ is the entropy of the distribution of $\Psi_{n,m}$ and $S_{\max} = \ln N$, where N is the number of bins. Normalized in this way, $0 \leq \tilde{\rho}_{nm} \leq 1$, where $\tilde{\rho}_{nm} = 0$ corresponds to a uniform distribution (no synchronization) and $\tilde{\rho}_{nm} = 1$ corresponds to a Dirac-like distribution (perfect synchronization). (ii) *Index based on conditional probability:* Suppose we have two phases $\phi_1(t_j)$ and $\phi_2(t_j)$ defined on the interval $[0, n]$ and $[0, m]$, respectively; index j corresponds to time. We divide each interval into N bins. Then, for each bin l, $1 \leq l \leq N$, we calculate $r_l(t_j) = M_l^{-1} \sum e^{i\phi_2(t_j)}$ for all j, such that $\phi_1(t_j)$ 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, then $|r_l(t_j)| = 1$, whereas it is zero if there is no dependence at all. Finally, we calculate the average over all bins, $\tilde{\lambda}_{nm}(t_j) = 1/N \sum_{l=1}^{N} |r_l(t_j)|$. Thus, $\tilde{\lambda}_{nm}$ measures the conditional probability for ϕ_2 to have a certain value provided ϕ_1 is in a certain bin [11]. To find n and m we try different values and pick up those that give larger indices.

Here we analyze MEG and EMG data from a PD patient who had a tremor of the right hand and forearm with a principal frequency component between 5 and 7 Hz (Fig. 2). We registered EMG from two antagonistic

muscles, namely, the right flexor digitorum superficialis muscle and the right extensor indicis muscle; standard preprocessing (cf. [7]) was used so that the resulting signal represents the time course of the muscular contraction. Next, MEG and EMG were filtered with a bandpass corresponding to the principal EMG frequency component (5–7 Hz). MEG signals were additionally filtered with a bandpass corresponding to the tremor's first harmonics (10–14 Hz). As the data are nonstationary, we perform a sliding window analysis and compute for every time point t the distribution of $\Psi_{n,m}$ within the window $[t - T/2, t + T/2]$ and synchronization indices [12].

To avoid spurious detection of locking due to noise and bandpass filtering, we derive significance levels $\rho_{n,m}^S$ and $\lambda_{n,m}^S$ for each $n{:}m$ synchronization index $\tilde{\rho}_{n,m}$ and $\tilde{\lambda}_{n,m}$ by applying our analysis to surrogate data (white noise filtered exactly 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 serves as significance level ($\rho_{n,m}^S$ or $\lambda_{n,m}^S$). Only relevant values of the $n{:}m$ synchronization indices are taken into account by introducing the significant $n{:}m$ synchronization indices $\rho_{n,m} = \max\{\tilde{\rho}_{n,m} - \rho_{n,m}^S, 0\}$ and $\lambda_{n,m} = \max\{\tilde{\lambda}_{n,m} - \tilde{\lambda}_{n,m}^s, 0\}$. For our data, computation of both indices gives consistent results.

Let us summarize our results. Pronounced tremor activity starts after ∼50 s (Fig. 3a). During this epoch, besides the expected *peripheral coordination,* i.e., 1:1 antiphase locking of EMG's of flexor and extensor muscles, (Fig. 3b), we also find *corticomuscular* (CMS) as well as *cortico-cortical synchronization* (CCS). Namely, the activity of both sensorimotor cortex and premotor areas are 1:2 phase locked with the EMG activity of both flexor and extensor muscles (Figs. 3c and 4), whereas the activities of these two brain areas are 1:1 locked (Fig. 3d). It is important that when the strength of peripheral coordination decreases during the last ∼50 s, the strength of CMS and CCS is also reduced. We find that MEG activity in the range of 10–14 Hz is responsible for both CMS and CCS.

Our analysis reveals the brain areas with MEG activity phase locked to tremor activity (Fig. 4), while the traditional cross-spectrum technique fails here. Contralateral sensorimotor MEG signals are coherent with EMG, in accordance with the concept of Volkmann *et al.* [13] which is based on their MEG study, animal experiments, and recordings during neurosurgery in PD patients. Nevertheless, we also found tremor coherent MEG activity extended over the right hemisphere in contradiction to this concept [7]. Inefficiency of the coherence technique can additionally be seen from the fact that MEG channels overlying sensorimotor and premotor areas are coherent with practically all other MEG channels.

To conclude, we proposed a method to detect $n{:}m$ phase locking and quantify the strength of synchronization from noisy bivariate data. A very important feature of our approach is that we can avoid the hardly solvable dilemma "noise vs chaos": irrespective of the origin of the observed signals the approach and techniques of the analysis are unique. In this way we addressed a fundamental problem in neuroscience whether cortico-cortical synchronization is necessary for establishing coordinated muscle activity.
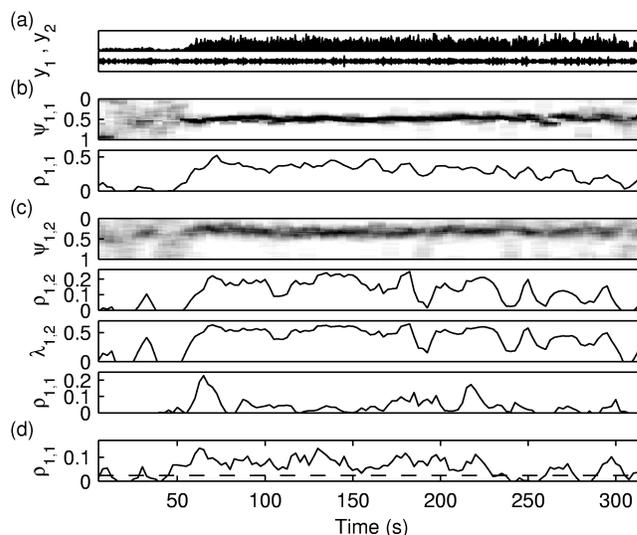
FIG. 3. (a) EMG of the right flexor muscle (RFM, upper trace) and an MEG over the left sensorimotor cortex (LSC) (lower trace). (b) 1:1 synchronization between right flexor and extensor muscles: the distribution of the cyclic phase difference $\Psi_{1,1}$ computed in the running window $[t - 5, t + 5]$ is shown as a gray-scale plot, where white and black correspond to minimal and maximal values, respectively (upper plot); the lower plot shows the corresponding significant synchronization index $\rho_{1,1}$. (c) 1:2 corticomuscular synchronization: time course of the distribution of the cyclic phase difference $\Psi_{1,2}$ between MEG signal from the LSC and EMG of the RFM (uppermost plot) and of the corresponding indices $\rho_{1,2}$ and $\lambda_{1,2}$; for comparison, 1:1 synchronization index $\rho_{1,1}$ between LSC and RFM is shown below. (d) 1:1 cortico-cortical synchronization between LSC and a premotor MEG channel. The dashed line indicates the value of $\rho_{1,1}$ corresponding to 99.9th percentile of the surrogates. Significance levels are $\rho_{1,2}^S = 0.03$, $\lambda_{1,2}^S = 0.26$, $\rho_{1,1}^S = 0.07$ [(b) and (c)], and $\rho_{1,1}^S = 0.03$ (d).
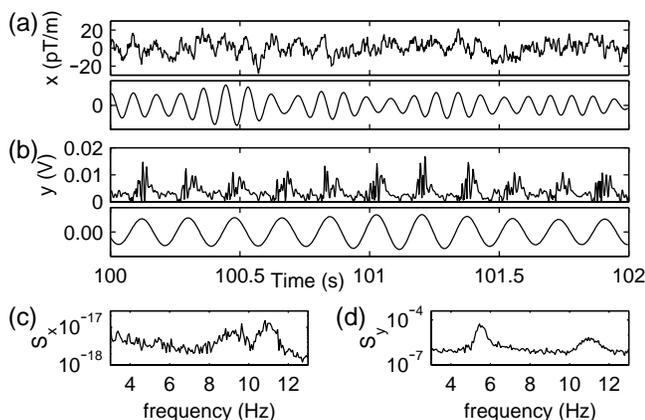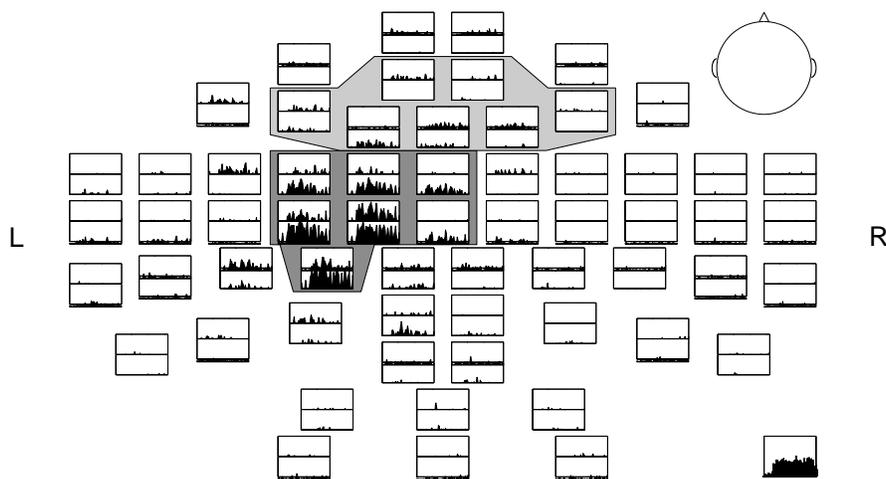

FIG. 2. An original and filtered MEG signal (from a channel over the left sensorimotor cortex) (a) and its power spectrum (c). The EMG signal of the right flexor digitorum muscle (b) and its power spectrum (d).

FIG. 4.   Time dependence of the significant synchronization index $\rho_{1,2}$ characterizing 1:2 locking between the EMG of the right flexor muscle (reference channel, plotted in the lower right corner) and all MEG channels. Each rectangle corresponds to an MEG sensor, time axis spans 310 s and y axis scales from 0 to 0.25. The head is viewed from above, "L" and "R" mean left and right (see the "head" in the upper right corner). The upper and lower gray regions correspond to premotor and contralateral sensorimotor areas, respectively. The results are similar for the extensor muscle. Significance level $\rho_{1,2}^{S} = 0.03$ and window length $T = 10$ s.

By means of our technique we showed for the first time that the temporal evolution of the coordinated peripheral tremor activity directly reflects the time course of the strength of the synchronization of abnormal rhythmic activity within a neural network involving cortical motor areas. Additionally, we localized areas with tremor related brain activity from noninvasive measurements.

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[11] We note that calculation of the indices in both directions, i.e., taking first or second signal as the reference one, gives coinciding results, so the information on the directionality of driving cannot be obtained in this way.

[12] We use bandpass FIRCLS filters [I. W. Selesnick, M. Lang, and C. S. Burrus, IEEE Trans. Signal Processing, **44**, 1897 (1996)]. We tested the filters between 3.5−7 and 5−6.5 Hz for the lower band and between 7−14 and 10−13 Hz for the higher band. The window length T was varied between 2 and 20 s. Our results are robust with respect to variations of T and the band edges of all filters used. Below we present the results obtained for the following parameters: bandpass of EMG signals: 5−7 Hz, bandpass of MEG signals: 5−7 and 10−14 Hz (for quantification of 1:1 and 1:2 locking, respectively). Our findings were additionally confirmed by analyzing the data filtered with two-band filters (e.g., 5−7 Hz plus 10−14 Hz).

[13] Volkmann *et al.* [7] suggested that rhythmic thalamic activity drives premotor areas (premotor cortex and supplementary motor area) which drive the primary motor cortex. The latter drives the spinal motoneuron pool which gives rise to rhythmic bursts of the muscles' action potentials detected by means of EMG. The peripheral feedback reaches the motor cortex via the thalamus.