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Physica D 163 (2002) 236–251

PHYSICA D

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Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets

C.J. Stam [a,*], B.W. van Dijk [b]

[a] Department of Clinical Neurophysiology, University Hospital, Vrije Universiteit, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands
[b] MEG Centre, University Hospital, Vrije Universiteit, Amsterdam, The Netherlands

Received 12 June 2001; received in revised form 22 October 2001; accepted 3 November 2001
Communicated by A. Doelman

Abstract

The study of complex systems consisting of many interacting subsystems requires the use of analytical tools which can detect statistical dependencies between time series recorded from these subsystems. Typical examples are the electroencephalogram (EEG) and magnetoencephalogram (MEG) which may involve the simultaneous recording of 150 or more time series. Coherency, which is often used to study such data, is only sensitive to linear and symmetric interdependencies and cannot deal with non-stationarity. Recently, several algorithms based upon the concept of generalized synchronization have been introduced to overcome some of the limitations of coherency estimates (e.g. [Physica D 134 (1999) 419; Brain Res. 792 (1998) 24]). However, these methods are biased by the degrees of freedom of the interacting subsystems [Physica D 134 (1999) 419; Physica D 148 (2001) 147]. We propose a novel measure for generalized synchronization in multivariate data sets which avoids this bias and can deal with non-stationary dynamics.

PACS: 05.45.+b; 87.10.+e; 87.22.−q; 87.22.Jb

Keywords: Non-linear systems; Interdependent systems; Electroencephalogram; Magnetoencephalogram; Epilepsy; Alzheimer

1. Introduction

A central problem in the study of normal and disturbed brain function is the question how functional interactions take place between different specialized networks. Understanding the coordination between brain regions is important in the context of information processing in the healthy brain [4–6] but also in the case of neurological disease. Loss of neurons and connecting fibre systems may lead to diminished interactions and cognitive dysfunction such as in Alzheimer's disease [7], whereas pathologically increased synchronization is the hallmark of epileptic seizures [2,8]. Usually, functional interactions are studied by considering time series of electrical potentials (electroencephalogram (EEG)) or magnetic field strengths (magnetoencephalogram (MEG)) recorded from different brain areas. Similarities between these time series are taken to reflect functional influences between the neuronal networks generating the time series. Similarities between time series are commonly quantified with linear techniques, in particular estimates of the coherency, which is a normalized measure of linear correlation as a function of frequency (e.g. [9,10]).

* Corresponding author. Fax: +31-20-444-4816.
E-mail address: cj.stam@vumc.nl (C.J. Stam).

PII: S0167-2789(01)00386-4

While this approach has produced a large body of knowledge on normal and pathological brain function, it has a number of limitations. First coherency estimates are not suitable to characterize non-stationary data with rapidly changing interdependencies. Possibly, modifications such as event-related coherence can overcome this limitation [11]. A more important limitation is that methods such as coherency only capture linear relations between time series, and may fail to detect non-linear interdependencies between the underlying dynamical systems. Recently a variety of methods have been proposed to detect more general types of interactions between dynamical systems. One line of research is based on the analytical signal concept [12]. Here, the instantaneous phase of both time series is computed, and interactions are quantified in terms of time-dependent n:m phase locking (n and m being integers). This approach has been successful in the study of EEG seizure data [13] and in the study of synchronization between muscle and cortical activity. However, this approach is only valid when the time series are approximately oscillatory. A more general approach is based upon the theory of non-linear dynamical systems. It was demonstrated in the 1980s and early 1990s that, contrary to intuition, two interacting chaotic systems can also display synchronization phenomena [14–17]. Initially synchronization was understood as identical synchronization, implying equality of the variables of the coupled systems. In the context of unidirectionally coupled driver response systems Rulkov et al. [18] introduced the wider concept of generalized synchronization. Generalized synchronization exists between two dynamical systems X and Y when the state of the response system Y is a function of the state of the driving system $X : Y = F(X)$. When F is continuous, and x_i, x_j are two points on the attractor of X which are very close together, then the corresponding points y_i, y_j on Y will also be close together. An important feature of generalized synchronization is that the corresponding time series need not resemble each other.

Since the concept of generalized synchronization was introduced, several algorithms have been proposed to detect this type of interdependencies in experimental time series. Rulkov et al. [18] proposed a mutual false nearest neighbours (MFNNs) parameter and another measure based upon the predictability of the response dynamics by the driver dynamics. The idea of using mutual predictions between driver and response systems was further elaborated by Schiff et al. [19] and later applied to seizure EEG data in [2,8]. Arnhold et al. [1] proposed a very simple measure for non-linear interdependencies, which is based upon a ratio of average distances between index points, their nearest neighbours and their mutual nearest neighbours (the mutual nearest neighbours of x_i have the time indices of the nearest neighbours of y_i). All of these methods claim to be able to detect non-linear dependencies between systems as well as asymmetry due to driver response interactions. However, it has been shown that identifying the driver and the response system in the case of asymmetric interactions is not always straightforward [1,20,21]. Rather, the asymmetries in interdependence measures may reflect the different degrees of freedom of the two systems [1,20]. Pereda et al. [3] have also shown that these measures do not only reflect interdependencies between the time series but are also influenced by the properties of the individual dynamical systems, in particular their dimensionality. Pereda et al. [3] propose to overcome this problem with appropriately constructed surrogate data. While this may be valid it is also somewhat cumbersome and difficult to use with non-stationary data.

In this paper we propose a synchronization likelihood measure S which avoids the bias pointed out by Pereda et al. and gives a straightforward normalized estimate of the dynamical interdependencies between two or more simultaneously recorded time series. The measure is closely related to the concept of generalized mutual information as introduced by Pawelzik and co-workers [22,23] and this measure can also be computed in a time-dependent way, making it suitable for the analysis of non-stationary data.

This paper is organized as follows. In Section 2 we describe the synchronization likelihood S. In Section 3 we study the properties of S by applying it to a test system of two non-linearly coupled Hénon systems. The performance of S in the case of real EEG and MEG data is studied in Section 4. Finally, we discuss the main results, in particular the strengths and weaknesses of the proposed method in relation to other available algorithms, and propose some directions for future research in Section 5.

2. The synchronization likelihood

We consider M simultaneously recorded time series $x_{k,i}$, where k denotes channel number ($k = 1, \dots, M$) and i denotes discrete time ($i = 1, \dots, N$). From each of the M time series embedded vectors $X_{k,i}$ are reconstructed with time-delay embedding [24]:

$$X_{k,i} = (x_{k,i}, x_{k,i+l}, x_{k,i+2l}, \dots, x_{k,i+(m-1)l}) \tag{1}$$

where l is the lag and m is the embedding dimension.

For each time series k and each time i we define the probability $P^{\varepsilon}_{k,i}$ that embedded vectors are closer to each other than a distance ε:

$$P^{\varepsilon}_{k,i} = \frac{1}{2(w_2 - w_1)} \sum_{\substack{j=1 \\ w_1 < |i-j| < w_2}}^{N} \theta(\varepsilon - |X_{k,i} - X_{k,j}|) \tag{2}$$

Here the $|\cdot|$ is the Euclidean distance and θ is the Heaviside step function, $\theta(x) = 0$ if $x \le 0$ and $\theta(x) = 1$ for $x > 0$. Here w_1 and w_2 are two windows; w_1 is the Theiler correction for autocorrelation effects and should be at least of the order of the autocorrelation time [25]; w_2 is a window that sharpens the time resolution of the synchronization measure and is chosen such that $w_1 \ll w_2 \ll N$ (note that by averaging over all i Eq. (2) becomes the correlation integral).

Now for each k and each i the critical distance $\varepsilon_{k,i}$ is determined for which $P^{\varepsilon_{k,1}}_{k,i} = p_{\text{ref}}$, where $p_{\text{ref}} \ll 1$. Now we can determine for each discrete time pair (i, j) within our considered window ($w_1 < |i - j| < w_2$) the number of channels $H_{i,j}$ where the embedded vectors $X_{k,i}$ and $X_{k,j}$ will be closer together than this critical distance $\varepsilon_{k,i}$:

$$H_{i,j} = \sum_{k=1}^{M} \theta(\varepsilon_{k,i} - |X_{k,i} - X_{k,j}|) \tag{3}$$

This number of course lies in a range between 0 and M, and reflects how many of the embedded signals "resemble" each other.

We can now define a synchronization likelihood $S_{k,i,j}$ for each channel k and each discrete time pair (i, j) as

$$\text{if } |X_{k,i} - X_{k,j}| < \varepsilon_{k,i} : S_{k,i,j} = \frac{H_{i,j} - 1}{M - 1} \tag{4}$$

$$\text{if } |X_{k,i} - X_{k,j}| \ge \varepsilon_{k,i} : S_{k,i,j} = 0 \tag{5}$$

By averaging over all j we finally obtain the synchronization likelihood $S_{k,i}$:

$$S_{k,i} = \frac{1}{2(w_2 - w_1)} \sum_{\substack{j=1 \\ w_1 < |j-i| < w_2}}^{N} S_{k,i,j} \tag{6}$$

The synchronization likelihood $S_{k,i}$ is a measure which describes how strongly channel k at time i is synchronized to all the other $M - 1$ channels. The synchronization likelihood takes on values between p_{ref} and 1. $S_{k,i} = p_{\text{ref}}$ corresponds with the case where all M time series are uncorrelated and $S_{k,i} = 1$ corresponds with maximal synchronization of all M time series. The value of p_{ref} can be set at an arbitrarily low level, and does not depend on the properties of the time series, nor is it influenced by the embedding parameters.

Modifications of $S_{k,i}$ can be obtained by averaging over the time index i, averaging over the channel index k, or both.

The concept of synchronization likelihood described here is closely related to the definition of the mutual information based upon the correlation integral [22]. In the special case of two time series the time-dependent mutual information M_i of [22] is related to the synchronization likelihood as follows:

$$M_i = \log_2 \frac{S_{k,i}}{p_{\text{ref}}} \tag{7}$$

A difference between M_i and $S_{k,i}$ is that the latter is normalized and the former not. Also, the computation of $S_{k,i}$ is more straightforward for data sets with more then two channels.

3. Test signals

To study the properties of our proposed synchronization measure, the synchronization likelihood

$S_{k,i}$, we consider two unidirectionally coupled chaotic Hénon maps as described in [19]. One of the systems X (with state variable x_i) is the driver system and Y (with state variable y_i) is the response system. y is a function of $x : y = F(x)$. The coupled Hénon systems are described by the following difference equations:

$$x_{i+1} = 1.4 - x_i^2 + 0.3u_i, \qquad u_{i+1} = x_i,$$
$$y_{i+1} = 1.4 - (Cx_i + (1-C)y_i)y_i + Bv_i,$$
$$v_{i+1} = y_i \tag{8}$$

The strength of the coupling between the two systems is given by the coupling parameter C, which varies between 0 (uncoupled systems) and 1 (complete coupling). For $B = 0.3$ both dynamical systems are identical, and for $B \neq 0.3$ both dynamical systems are not identical. In the following we study time series x_i and y_i consisting of 4096 samples, where the first 1000 iterations of Eq. (8) have been discarded. Initial values of x, u, y, v were random between 0 and 1. In all analyses the following fixed embedding parameters were used: lag $l = 1$; embedding dimension $m = 10$; $w_1 = 100$; $w_2 = 410$. p_{ref} was set equal to 0.05.

We addressed the following five questions: (1) does synchronization likelihood increase when the coupling strength C between identical or non-identical systems increases (Section 3.1)? (2) Does synchronization likelihood detect non-linear coupling (Section 3.2)? (3) How sensitive is synchronization likelihood to time-dependent changes in the coupling strength (Section 3.3)? (4) Is synchronization likelihood insensitive to the bias which affects the measure proposed by Arnhold et al. [1] (Section 3.4)? (5) How is the synchronization likelihood affected by different choices of p_{ref} and different noise levels?

3.1. Variation of synchronization likelihood with coupling strength between identical and non-identical systems

Realizations of the dynamical system equation (8) were obtained for values of C increasing from $C = 0$ to $C = 1$ in steps of 0.1. For each value of C 10 realizations were obtained for $B = 0.3$ (identical systems) as well as 10 for $B = 0.1$ (non-identical systems). $S_{k,i}$ was computed for each of these realizations. The obtained values were averaged over both systems (index k); over all 4096 time samples (index i), and over all 10 realizations to yield the average synchronization likelihood S for identical and non-identical systems. The error bars show the standard deviation over the different realizations. The average results are shown in Fig. 1. For two identical coupled systems S starts with a value of approximately 0.05 and then increases with increasing C. A sudden increase occurs between $C = 0.6$ and $C = 0.7$. For higher values of the coupling constant C, S rapidly goes to 1.

For non-identical systems S also increases with C. However, there are two differences: first there is a local maximum in the plot of S for $C = 0.3$; second, even for $C = 1$ S never reaches a value of 1.

3.2. Ability of $S_{k,i}$ to detect non-linear coupling: multivariate surrogate data

To demonstrate that $S_{k,i}$ is sensitive to non-linear structure in the coupling between X and Y multivariate surrogate data were used. This method has been introduced by Prichard and Theiler [26] and has been applied by Rombouts et al. [27] to demonstrate the presence of non-linear coupling in multichannel EEG data. Technical details can be found in these papers as well as in [2,19]. Briefly, to obtain multivariate surrogate data for M simultaneous time series, the Fourier transform of each time series is taken, a random number is added to each of the phases obtained and then an inverse Fourier transform is applied. The resulting time series have identical power spectra as the original time series. By adding the same random number to the phases of the different channels, the cross-spectra (and thus coherencies) are preserved as well. Thus, multivariate surrogate data preserve the linear correlations between all the channels exactly, while any non-linear information is lost.

We computed S for non-identical ($B = 0.1$) coupled systems for C increasing from 0 to 1 in steps of 0.1. For each of these realizations 19 multivariate surrogate data sets were obtained, and S was computed for these surrogate data also. If S for the Hénon attractors is larger than the largest of all S of the

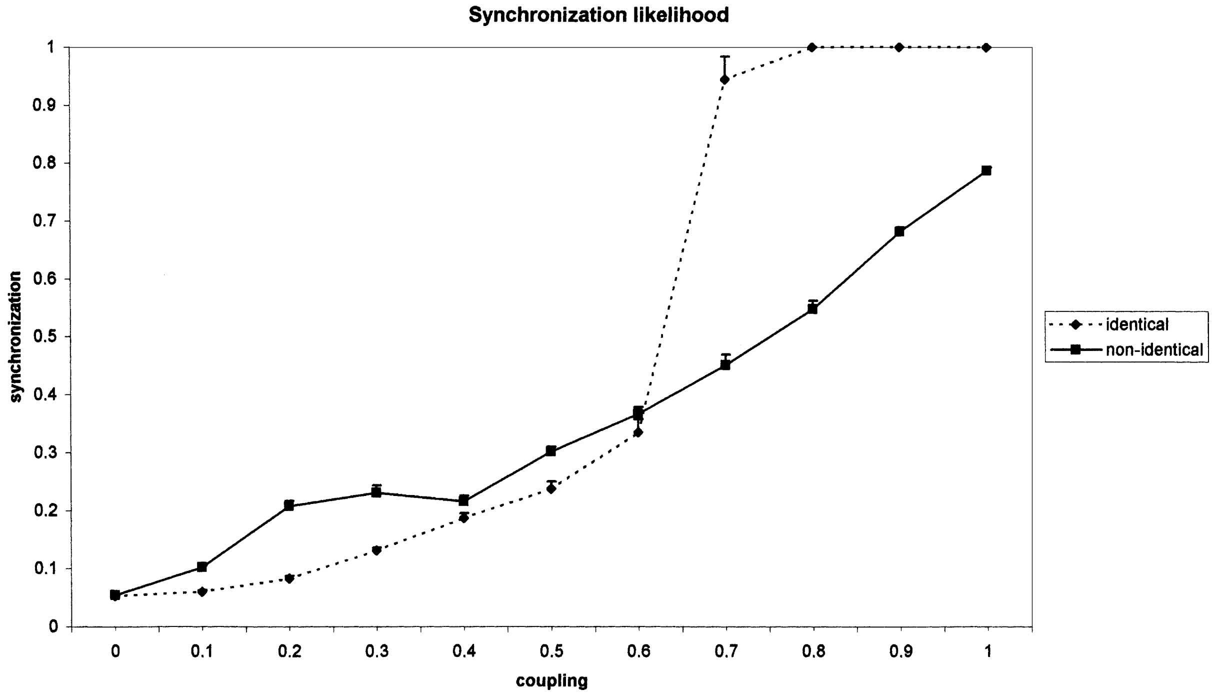


Fig. 1. Changes of S as a function of coupling strength C in identical ($B = 0.3$) and non-identical ($B = 0.1$) unidirectionally coupled Hénon systems. The small vertical bars denote the standard deviations.

surrogate systems non-linear coupling has been detected with a probability $p < 0.05$. The results are shown in Fig. 2. The synchronization likelihood S increases with increasing C for both the Hénon data and for the surrogate data; however, with the exception of $C = 0$, the synchronization likelihood of the Hénon data is always much larger than that found for any of the surrogate data. Thus, S can detect the non-linear structure in the coupling between X and Y with great significance, even for weak coupling ($C = 0.1$).

3.3. Sensitivity of synchronization likelihood to time-dependent changes in coupling

The sensitivity of $S_{k,i}$ to changes in C was studied by considering two identical dynamical systems ($B = 0.3$) that were coupled only during a single epoch and otherwise uncoupled. We choose $C = 0$ for ($i < 1500$ or $i > 2500$) and $C = 0.5$ for ($1500 \leq i \geq 2500$). The average results for 10 realizations are shown in Fig. 3. For $C = 0$ $S_{k,i}$ fluctuates around the expected value of 0.05. At $i = 1500$ there is a sharp increase in $S_{k,i}$ and at $i = 2500$ there is a sharp decrease back to the level of 0.05. So $S_{k,i}$ can detect a change in the coupling between the dynamical systems with a high time resolution; this makes the measure appropriate for application to non-stationary data sets.

3.4. Bias in estimates of dynamical interdependencies

Many of the properties of S described in Sections 3.1–3.3 are also shared by other recently proposed measures for dynamical interdependencies [1,18,19]. However, as has been shown in [3] these measures may be biased by differences in the dynamics between the two systems. Here we demonstrate this bias for the measure proposed by Arnhold et al. [1] and show that our proposed synchronization likelihood is not affected.

We consider two uncorrelated time series x_i and y_i, $i = 1$–4096 of identically distributed white noise. The time series were not normalized. The first time series

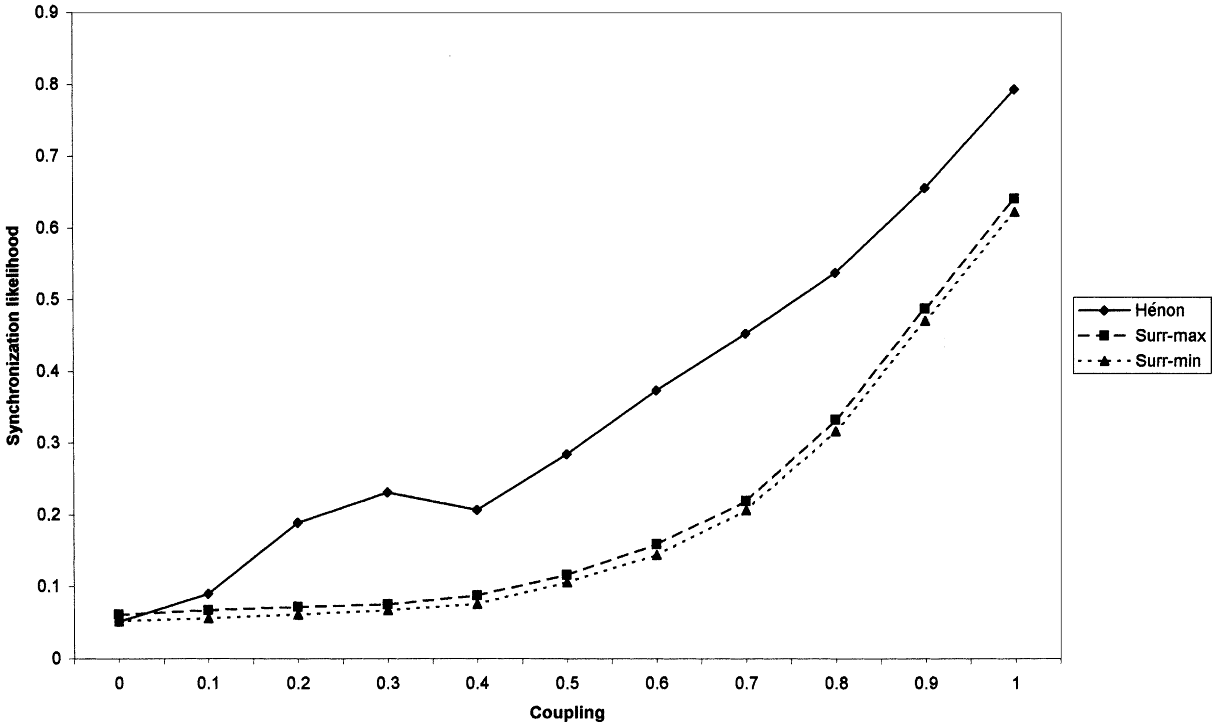


Fig. 2. Changes of S as a function of coupling strength C in non-identical ($B = 0.1$) unidirectionally coupled Hénon systems and 19 multivariate surrogate data sets. For the surrogate data only the maximal (Surr-max) and the minimal (Surr-min) values are shown. For $C > 0$ the synchronization for the original data is always well outside the distribution of S for the 19 surrogates, indicating significant non-linear coupling.

x_i is filtered with a low pass filter increasing in steps of 5 Hz from 5 to 50 Hz. For each setting of the filter S is computed as well as the asymmetric measures SXY and SYX as proposed by Arnhold et al. [1]. In all cases a time lag of 1 and an embedding dimension of 10 is used. For the computation of SXY and SYX a fixed number of nearest neighbours of 11 is used. The results are shown in Fig. 4. From this figure it is clear that the synchronization likelihood S does not depend upon the properties of the time series, and always fluctuates around the correct values of $p_{\mathrm{ref}} = 0.05$. For all values of the filter, $SYX \gg SXY$, and also $SYX \gg 0$. This would suggest that there exists a strong coupling between x_i and y_i; and that there is a driver/response relationship, with x driving y. Of course, because both time series are by construction uncorrelated, both conclusions are incorrect. Even worse, SXY shows a systematic dependence upon the value of the filter, increasing when the low pass filter increases. So, not only do absolute values of SXY and SYX have little meaning (values $\gg 0$ not necessarily implying coupling), changes in SXY and SYX may be due to changes in one of the time series without any changes in the coupling between them. On the other hand, S only reflects changes in coupling between the systems, and is not affected by intrinsic properties of the systems. The price that has to be paid for this is that S cannot detect asymmetric relationships between systems.

3.5. Dependence of synchronization likelihood on p_{ref} and on noise level

As in Section 3.1 we consider two unidirectionally coupled non-identical Hénon maps, with $B = 0.1$. Realizations of Eq. (8) were obtained for values of C increasing from $C = 0$ to $C = 1$ in steps of 0.1.

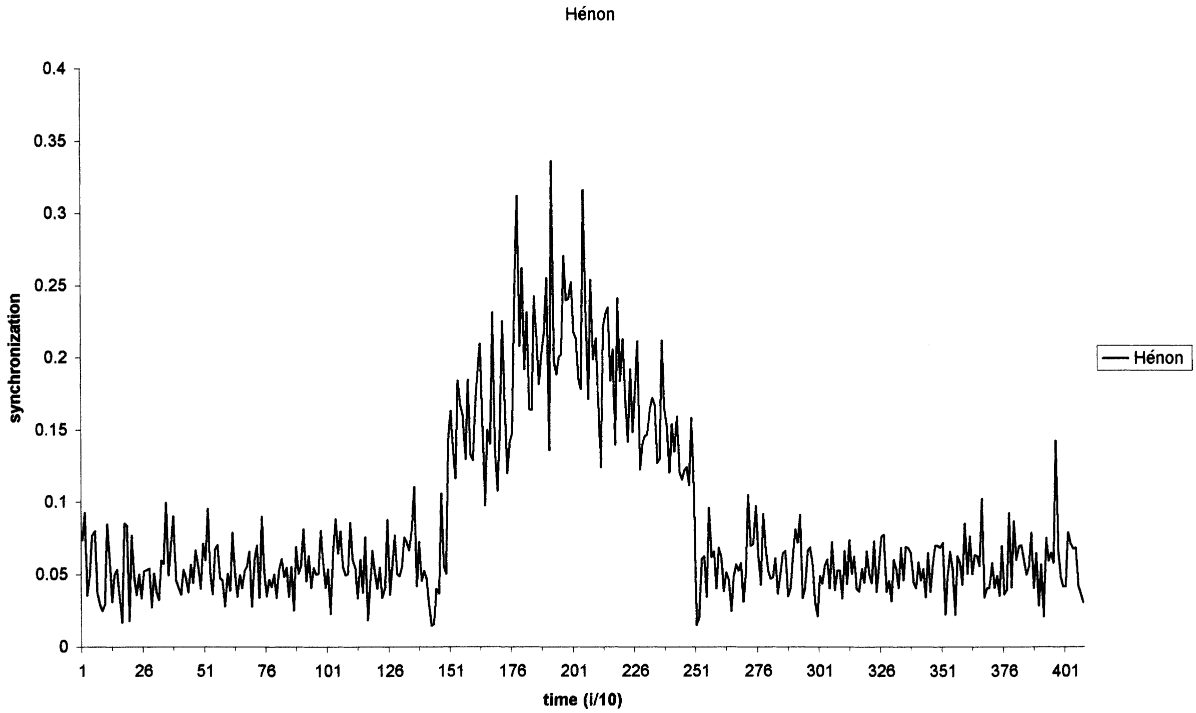


Fig. 3. Time dependence of S_i in identical ($B = 0.3$) unidirectionally coupled Hénon systems. The coupling parameter $C = 0$ except for an interval between $t = 150$ and $t = 250$ where $C = 0.5$. The results are averaged over 10 realizations. S shows a clear and instantaneous increase at $t = 150$ and clear decrease at $t = 250$.

For each of these realizations the synchronization likelihood was estimated ($l = 1$; $m = 10$) for the following values of p_{ref}: 0.01; 0.05; 0.10; 0.15; 0.20. The results are shown in Fig. 5. As expected, for $C = 0$ $S_{k,i}$ is approximately equal to p_{ref}. For all values of p_{ref}, $S_{k,i}$ increases with increasing C. However, the local maximum at $0.2 < C < 0.3$ is only seen for relatively low values of p_{ref} (0.05 and 0.01). The influence of observational noise on the performance of synchronization likelihood was studied in the same unidirectionally coupled non-identical Hénon maps. Here the parameter settings for the synchronization likelihood were: $l = 1$; $m = 10$; $p_{\mathrm{ref}} = 0.05$. $S_{k,i}$ was computed for the noise-free time series, as well as for the following signal-to-noise ratios: 5, 4, 3, 2 and 1. The results are shown in Fig. 6. For low noise levels (SNR = 5–3) there is a moderate decrease of $S_{k,i}$ compared to the noise-free case. For relatively high noise levels (SNR = 2–1) the decrease in $S_{k,i}$ is more pronounced. However, for an SNR of 2 $S_{k,i}$ can still detect increases in the coupling strength C. So the behaviour of $S_{k,i}$ is fairly robust even in the case of considerably noisy data.

4. Application to EEG and MEG

4.1. Epilepsy

In this section we demonstrate the potential applicability of S to human multichannel EEG and MEG data. An important field for application of synchronization measures is epilepsy. During epileptic seizures (and possibly even in the 10–20 min preceding a seizure [28]) the activity of different brain regions becomes highly synchronized. Previous studies have suggested that at least some of the dynamical dependencies during a seizure are non-linear [8]. As an example we

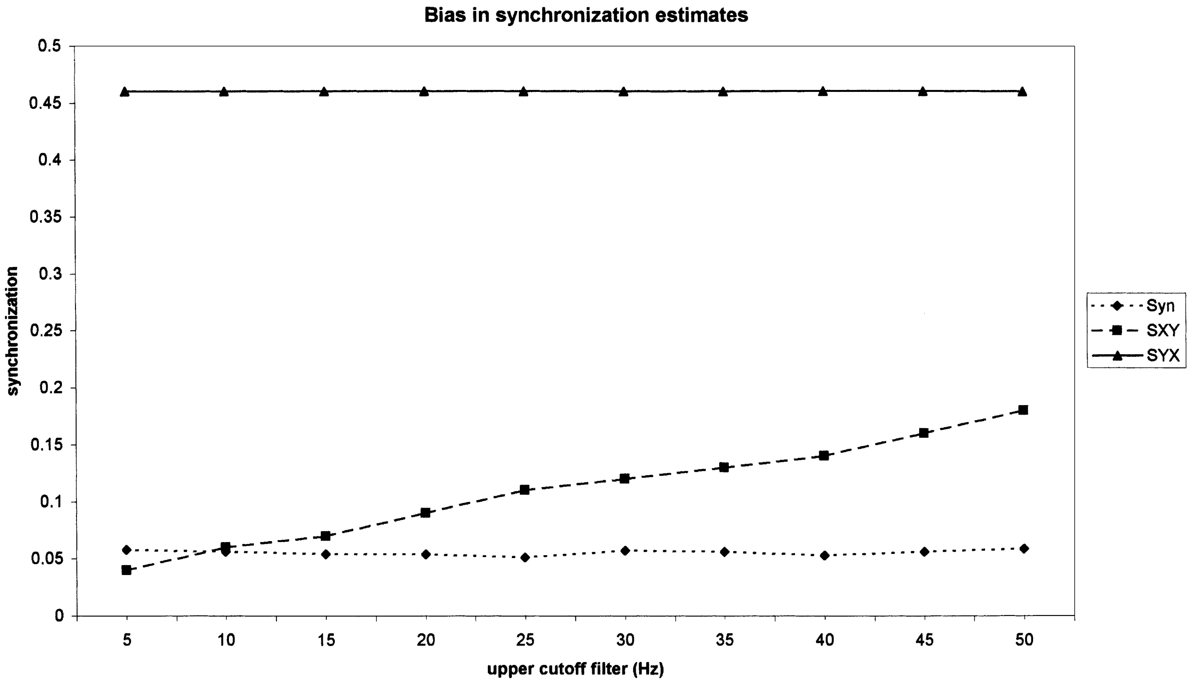


Fig. 4. Estimated interdependencies between two uncorrelated time series X and Y, one of which is white noise (Y), and other (X) is white noise filtered with a low pass filter as indicated on the abscissa. For all values of the filter, S is around 0.05 indicating correctly the absence of any coupling between the two time series. However, for all filter settings, $SYX \gg SXY$ incorrectly suggesting a strong driving of Y by X. Also, SXY increases for higher values of the low pass filter, incorrectly suggesting an increase in coupling (where in fact no coupling exists).

study an EEG at the transition between normal background activity and a generalized seizure (3 Hz spike wave discharges characteristic of so-called absence epilepsy). First we analyse the preictal and ictal epochs separately. For each epoch the synchronization likelihood S is computed (averaged over all k and i). Epoch duration is 4096 samples; the sample frequency was 500 Hz; 16 bit A–D precision; all 21 channels are included in the analysis; average reference electrode. The data was not normalized. Filter settings: band pass between 0.5 and 30 Hz. Parameters for the calculation of S were: the lag was chosen equal to 10 samples; the embedding dimension was chosen equal to 10; w_1 was 100; w_2 was 400; p_{ref} was 0.05. For each of the two epochs 19 multivariate surrogate data sets were generated and S was computed for each of them. The results are shown in Fig. 7. The synchronization was relatively low for the preictal epoch. The values of S for the surrogate data were in the same range, indicating weak, mostly linear coupling during the preictal phase. During the ictal phase there was a huge increase in S as expected. The synchronization for the surrogate data also increased, however much less than S for the ictal EEG. The highest value of S for the 19 surrogates is much lower than S during the ictal period, which indicates that during the seizure interactions between brain regions become much stronger as well as highly non-linear. The detailed time evolution of S can be studied by skipping the averaging over i. The result is shown in Fig. 8. During the preictal phase S_i fluctuates at low levels which are however clearly above p_{ref} and which reflect the weak coupling of EEG background activity. During the seizure there is a clear rise in S_i. Interestingly, the detailed time course of S_i shows that synchronization already starts to increase before the actual spike wave discharges become visible, similar to the observations in other studies, e.g. [28].

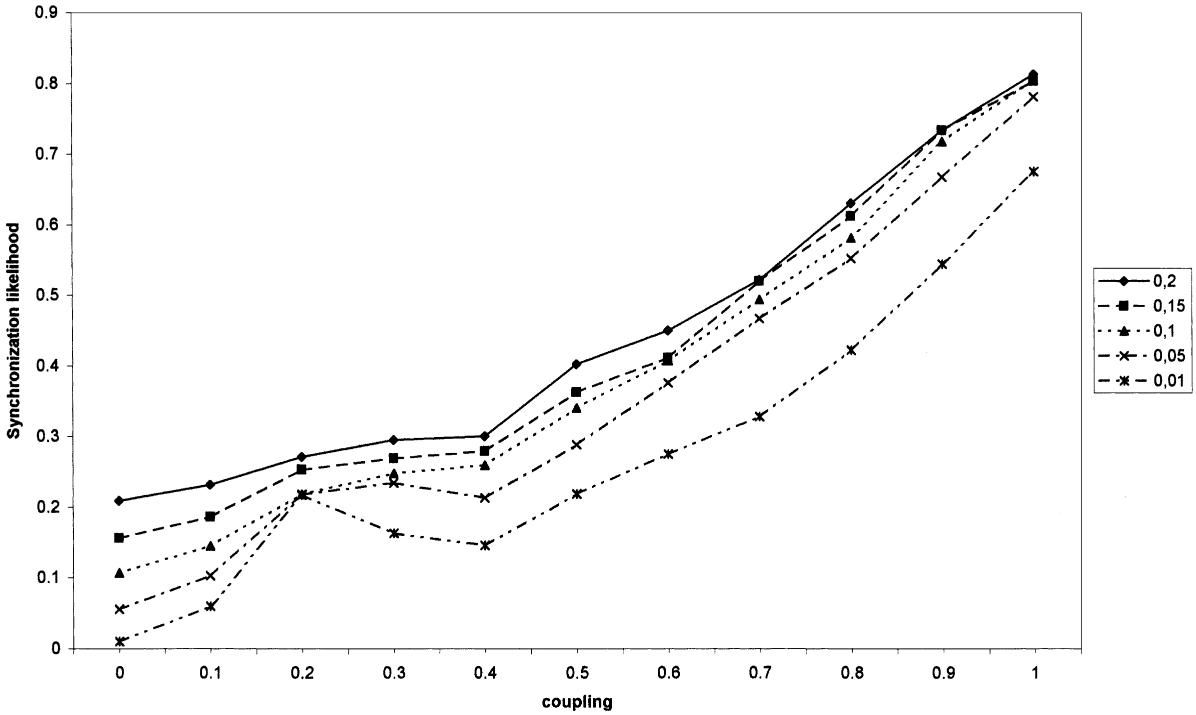


Fig. 5. Influence of different choices of p_{ref} on the synchronization likelihood computed from unidirectionally coupled, non-identical Hénon maps according to Eq. (8). The abscissa indicates the coupling strength C and the ordinate the synchronization likelihood. Parameters for the calculation of the synchronization likelihood were: $l = 1$; $m = 10$.

4.2. Synchrony changes due to eye-opening

Apart from its applicability in the field of epilepsy, synchronization measures may also be useful to study task-dependent changes in synchrony in healthy subjects. To investigate this possibility EEGs of 10 healthy subjects during an eyes-closed and an eyes-open condition were examined. For each condition a single epoch of 8 s was analysed (EEG details as above; filters settings: band pass between 8 and 12 Hz; data were not normalized). The results are shown in Fig. 9. The distribution of S over the different channels k shows a highly characteristic profile, which is essentially the same during eyes-closed and eyes-open conditions. During eye-opening there is a highly significant decrease in alpha band synchronization at almost all electrodes. These findings are consistent with the EEG literature on task-dependent alpha band changes and suggest S might be used to study changes in synchronization.

4.3. Gamma band synchronization in MEG data

Currently there is accumulating evidence that synchronous activity in the gamma band (around 40 Hz) may play a crucial role by integrating the information represented in different brain regions in a unitary concept. Modern MEG systems with more then 100 channels are especially suited to study this gamma activity. As an illustration of the potential possibilities of the synchronization likelihood measure applied to multichannel MEG data we show results for a healthy subject and a patient suffering from early Alzheimer's disease in Fig. 10a and b, respectively. In the healthy subjects episodes of synchronous activity in the gamma band lasting between 100 and 500 ms can be seen with a constantly changing spatial pattern. In the Alzheimer patient there is a dramatic reduction of gamma band synchronization, which may reflect the disturbances in information processing characteristic for this disease.

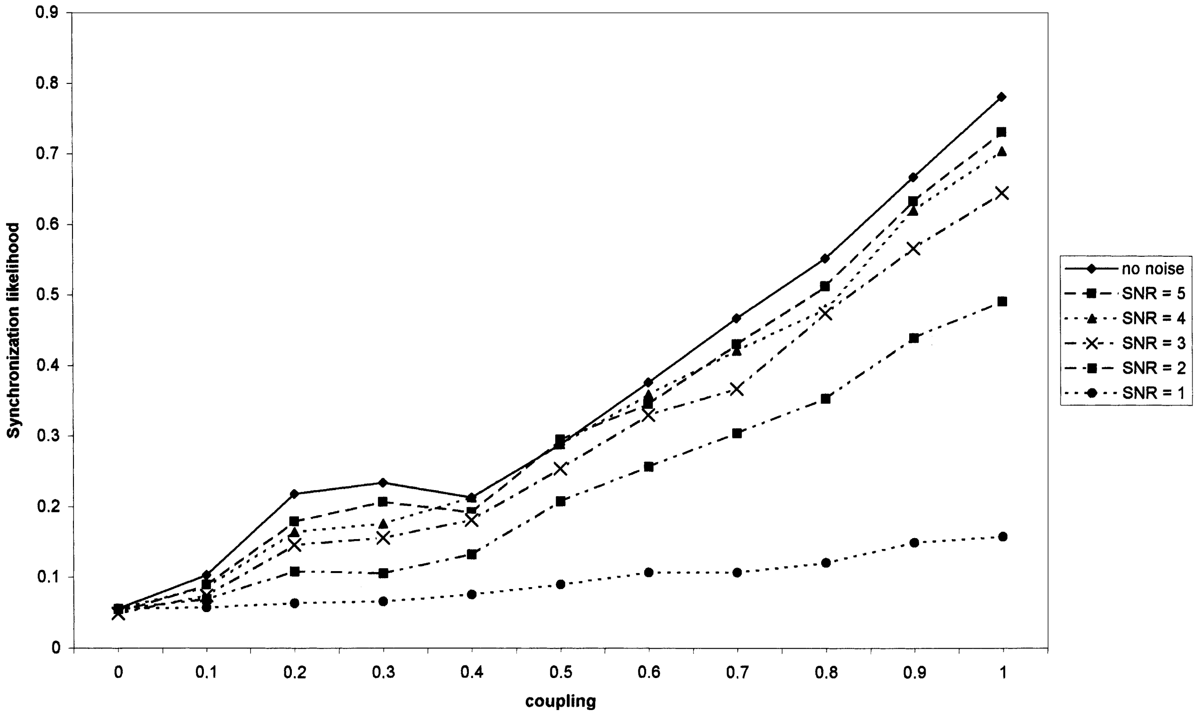


Fig. 6. Influence of different noise levels on the synchronization likelihood computed from unidirectionally coupled, non-identical Hénon maps according to Eq. (8). The abscissa indicates the coupling strength C and the ordinate the synchronization likelihood. Parameters for the calculation of the synchronization likelihood were: $l = 1$; $m = 10; p_{\text{ref}} = 0.05$.

5. Discussion

We proposed a novel measure of dynamical interdependencies between time series which preserves some of the strengths of other algorithms based on the concept of generalized synchronization while avoiding the bias as noted by Pereda et al. [3]. A minimum requirement for any synchronization measure is that it changes in a systematic way when the coupling strength between two dynamical systems increases. We used two coupled Hénon systems as a test bank following [19]. While this is a very simple test system, it has all the essential elements such as chaotic dynamics, non-linear and asymmetric coupling and parameter differences between the two subsystems. Increasing the coupling strength from results in a systematic increase of synchronization likelihood both for identical and non-identical systems. In the case of identical systems, values of $C > 0.7$ are associated with identical coupling and S reaches a maximum value of 1. However, in the case of non-identical systems the relationship between x_i and y_i remains very complex even in the case of maximum coupling (Fig. 5 of [19]); S increases with C, but never becomes 1. There is a remarkable local maximum of S for $C = 0.3$. Schiff et al. [19] also detected two maxima in the coupling between non-identical systems ($B = 0.1$), and explain this in terms of minima of the largest sub-Lyapunov exponent (Fig. 10A and B of [19]).

A second important requirement is that synchronization measures must capture non-linear as well is linear interactions between dynamical systems. In fact, the ability of these novel measures to capture non-linear coupling is a major reason for preferring them over well know linear measures such as coherency. A common way to investigate non-linear properties of time series or their couplings is the use of phase-randomized surrogate data [26,29].

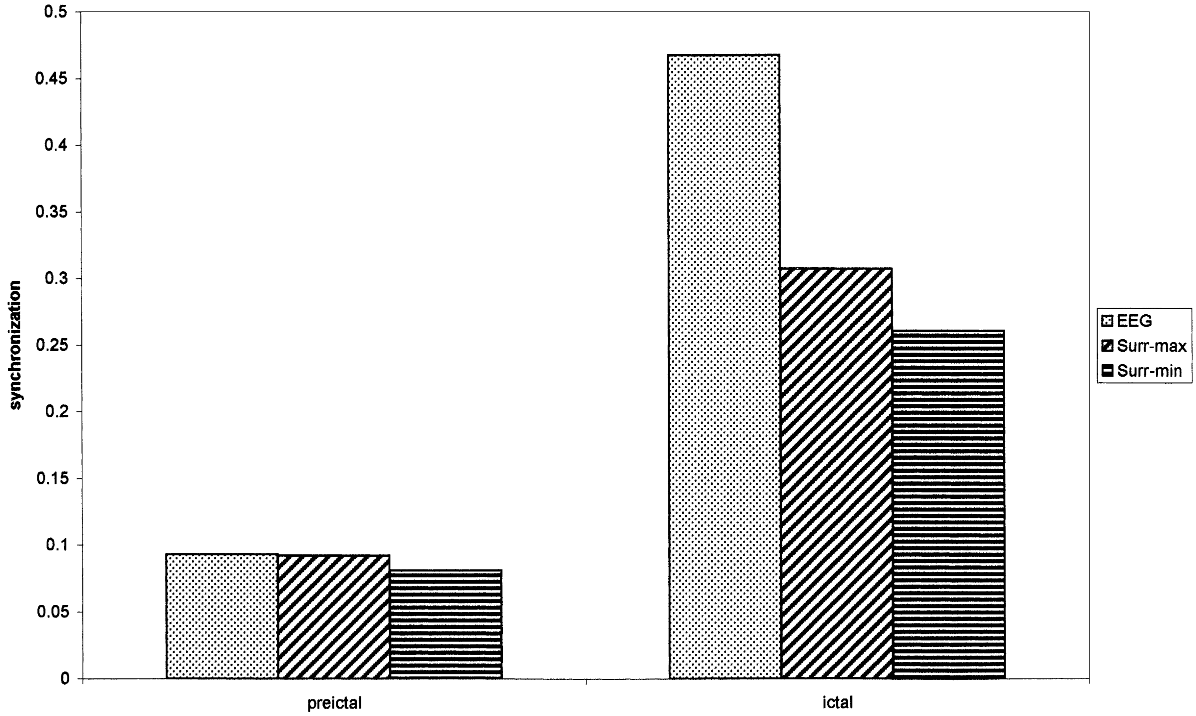


Fig. 7. Synchronization, averaged over all channels and all time points, for an epoch of preictal and ictal EEG. The maximum and minimum values corresponding to an ensemble of 19 surrogate data are also shown. Synchronization during the ictal epoch is much higher than during the preictal epoch. For the preictal epoch there is no clear difference with the surrogate data, suggesting only linear coupling. During the ictal epoch there is a very clear difference with surrogate data, indicating highly non-linear coupling.

A measure S_{data} is applied to the original data set (in this case: two non-linearly coupled chaotic systems) and an ensemble of surrogate data which have the same power spectra and cross-spectra as the original data, but are otherwise random. When S_{data} is larger then any of the 19 $S_{\text{surrogate}}$, this is a non-parametric test of significant non-linearity at a significance level of $p = 0.05$ (for a two-sided test, 38 surrogates would be required). Normally this kind of test is used to investigate the properties of an experimental data set; in this case the properties of the data set are known and we have used this test to demonstrate that the synchronization likelihood is indeed able to detect the non-linear coupling.

All of the recently proposed synchronization measures based upon reconstructing the dynamics underlying the time series are characterized by averaging over a time index i. By skipping this time averaging step it is possible to obtain the coupling strength as a function of time. This is analogous to computing the dimension in a time-dependent way [30]. Pawelzik [22] has computed the generalized mutual information (based upon the correlation integral) in a time-dependent way and shown the usefulness of this approach for non-stationary data. In a similar way, the synchronization likelihood may also be estimated as a function of time and for a large number of channels. The proposed measure allows the detection of changes in coupling between systems with a high time accuracy, as can be seen in Fig. 3. We should stress that the use of the window w_2 (Section 2) enhances the contrast between low and high coupling but is not essential for the time resolution. Being able to detect changes in coupling with a high time resolution is very important for the characterization of normal and disturbed brain dynamics.

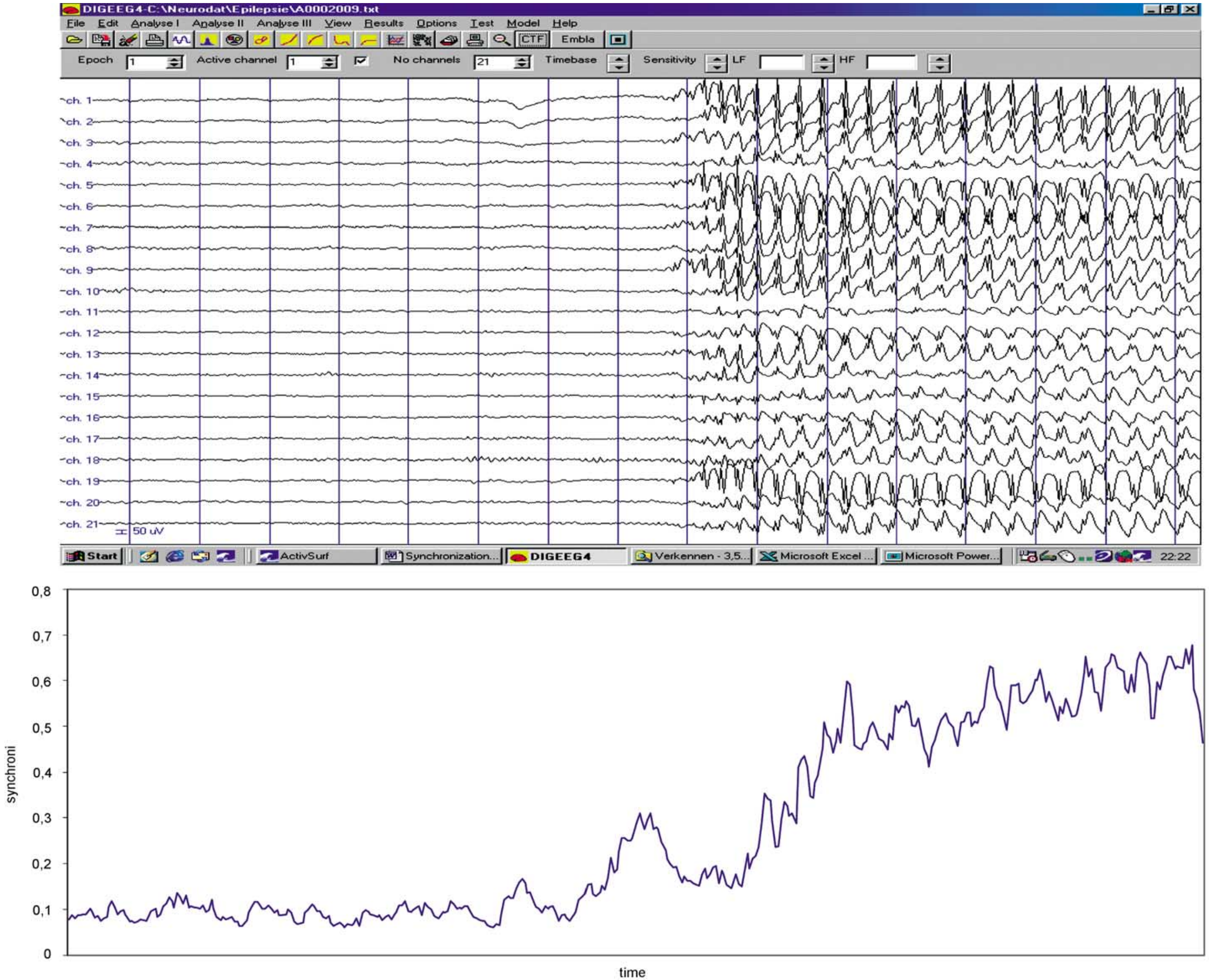


Fig. 8. Detailed time course of S_i, averaged over all channels, during the transition between normal background activity and generalized seizure activity. The seizure is clearly associated with a large increase in synchronization. The increase in synchronization begins already before the high amplitude spike and wave discharges become evident in the raw tracing. This early rise is due to low amplitude synchronous EEG activity.

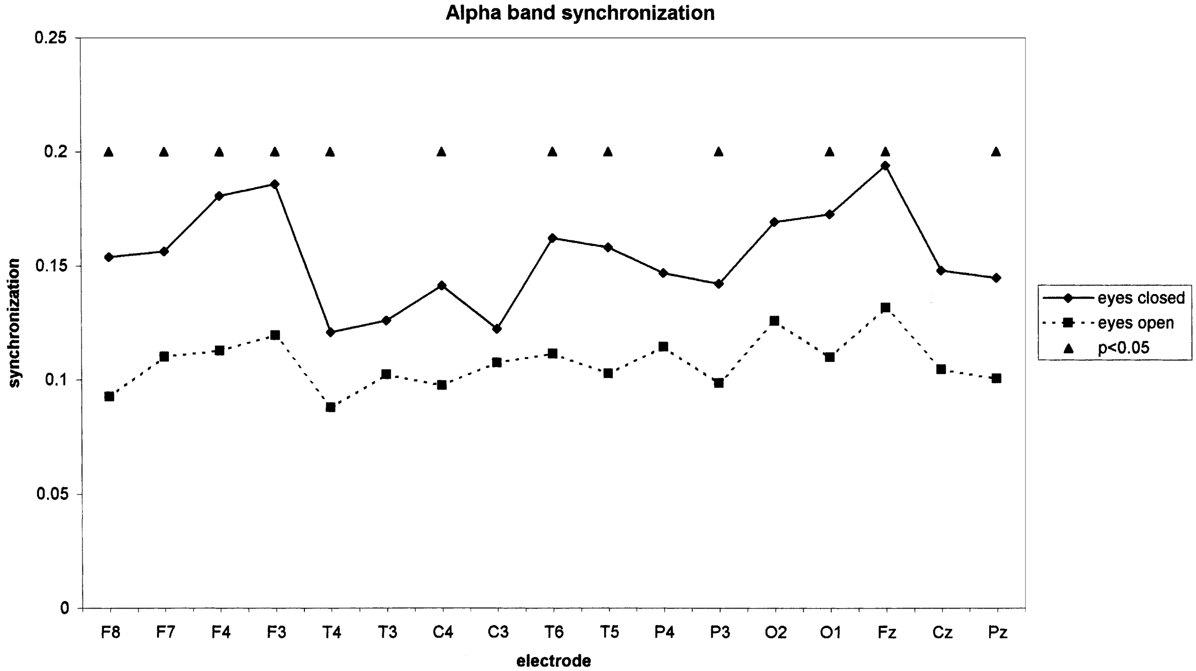
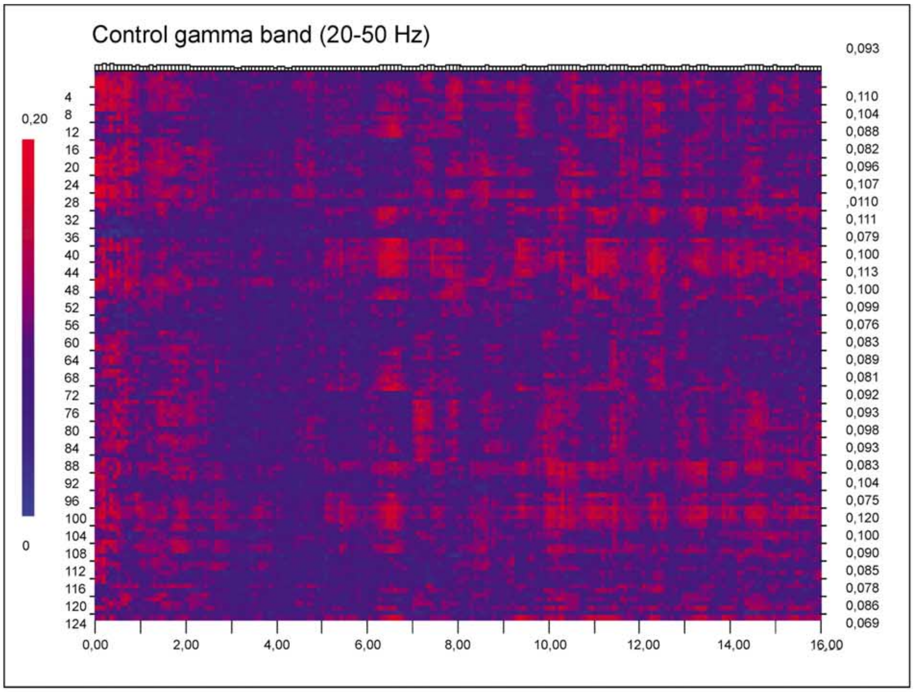


Fig. 9. Average alpha band (8–12 Hz) synchronization likelihood for 10 subjects during an eyes-closed (blue) and an eyes-open state (red). The synchronization likelihood was computed for each subject, for both conditions and for all channels. Each channel was compared with all other channels, and the mean of this comparison was used. The red triangles indicate the individual EEG channels where the differences between both states is significant at the $p < 0.05$ level (t-test).

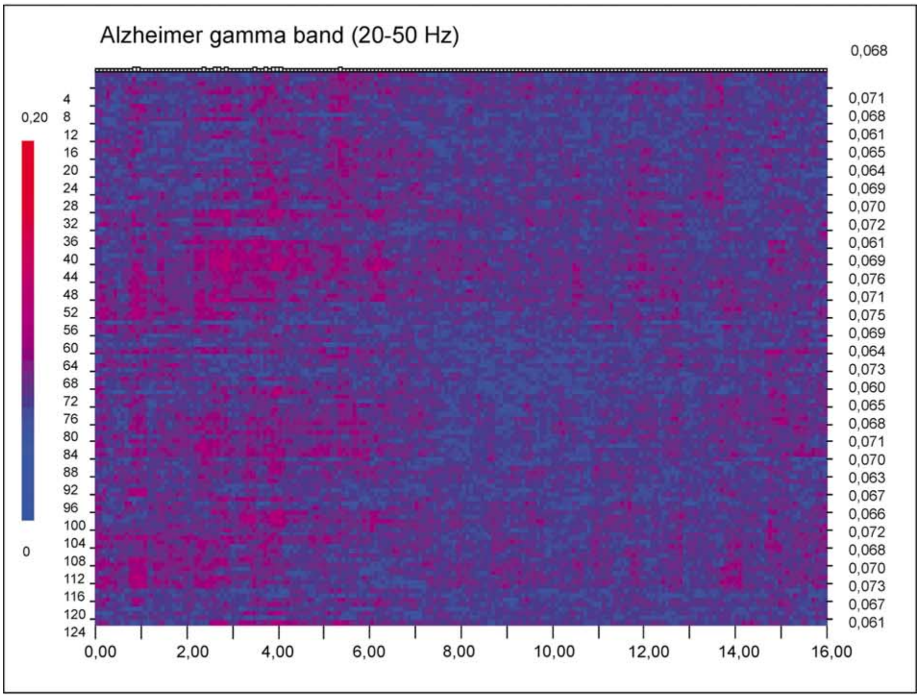
The concept of generalized synchronization was defined in the context of asymmetric, driver response type interactions between dynamical systems [18]. All of the measures that have been proposed so far for the detection of generalized synchronization claim to be able to detect asymmetric coupling. This ability is very important because it would allow to detect causal interactions between systems. However, asymmetry is not proof of causal interactions, and the straightforward identification of generalized synchrony in experimental data is not so simple [19]. Even worse, Pereda et al. [3] have shown that measures of synchronization are typically biased by the dynamical properties of the individual systems. An illustration of this problem can be seen in Fig. 4. There is a spurious detection of strong and asymmetric coupling, when in fact there is no coupling at all.

Synchronization likelihood avoids this problem by keeping the probability measure of Eq. (2) at the same fixed level for all time series (in this case: $p_{\text{ref}} = 0.05$).

Fig. 10. Synchronization likelihood in the 20–50 Hz band for (a) a control subject and (b) an Alzheimer patient. In both parts the ordinate corresponds with the 117 MEG channels. The abscissa represents time (in seconds). The value of the synchronization likelihood for each channel and each time point is indicated with a colour scale. The synchronization likelihood reflects how strongly a channel at a particular time is synchronized to all other channels. The numbers on the right are the average synchronization values for each channel. The curve on top reflects the time course of the synchronization likelihood averaged over all channels. In part (a) the graph shows a complex pattern of synchronization clusters involving several channels and lasting typically hundreds of milliseconds and in (b) the graph shows a much reduced occurrence of synchronization clusters.


Control gamma band (20-50 Hz)
0,093
0,20
0
4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 112 116 120 124
0,110 0,104 0,088 0,082 0,096 0,107 ,0110 0,111 0,079 0,100 0,113 0.100 0,099 0,076 0,083 0,089 0,081 0,092 0,093 0,098 0,093 0,083 0,104 0,075 0,120 0,100 0,090 0,085 0,078 0,086 0,069
0,00 2,00 4,00 6,00 8,00 10,00 12,00 14,00 16,00

(a)


Alzheimer gamma band (20-50 Hz)
0,068
0,20
0
4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100 104 108 112 116 120 124
0,071 0,068 0,061 0,065 0,064 0,069 0,070 0,072 0,061 0,069 0,076 0,071 0,075 0,069 0,064 0,073 0,060 0,065 0,068 0,071 0,070 0,063 0,067 0,066 0,072 0,068 0,070 0,073 0,067 0,061
0,00 2,00 4,00 6,00 8,00 10,00 12,00 14,00 16,00

(b)

Fig. 10.

When there is no coupling between the time series, $S = p_{\mathrm{ref}}$, irrespective of the properties of the individual time series as can be seen in Fig. 4. The price that has to be paid for this is that S is not sensitive to any asymmetry in the coupling. However, because S is not dependent upon the degrees of freedom of the coupled systems, it is also suitable to study interdependencies between different types of systems such as for instance heart rate variability and respiration. We should note that by choosing the critical distance $\varepsilon_{k,i}$ in a different way, for instance as a percentage of the mean intervector distance, S can be expected to become sensitive to asymmetric coupling but also to the bias. In fact, the same problem affects the generalized mutual information as implemented by Pawelzik [22]. The strength of the synchronization likelihood is that it measures coupling and only coupling, allowing a straightforward interpretation. Is it possible to avoid the bias and still detect asymmetric coupling? The dimension of the driver system is expected to be smaller than the dimension of the response system [20]. So a possible approach would be to use S to detect the existence of a dynamical coupling, and then compute dimensions to identify the most likely driver and response system. Although such an analysis might be informative, it cannot give conclusive evidence of causality.

The ultimate test of any new measure is its performance with real data. A prominent application of non-linear time series in general and synchronization measures in particular is in the field of epilepsy. The importance of non-linear EEG analysis has recently been stressed by the discovery that this approach allows the detection of epileptic seizures 10–20 min before their actual occurrence [28]. Epileptic seizures are characterized by pathologically increased synchronization between neural networks in the brain. Measures of dynamical interdependencies between time series are obvious candidates for the detection of such hypersynchronization [2]. We have shown that the synchronization likelihood can detect the strong increase in coupling associated with a generalized seizure (Fig. 7). Not only does the synchronization increase in strength, it also changes from a linear to a strongly non-linear coupling. Le Van Quyen et al. [8] also found a highly non-linear coupling during the seizure. The high time resolution of S allows the detection of subtle increases in synchronization preceding the actual spike wave discharges (Fig. 8). When these findings can be substantiated in a larger data set and for a variety of different seizures, they may lead to interesting clinical applications in the field of automatic seizure detection and possibly even prediction. A major question that will have to be addressed by future research is whether strong and highly non-linear coupling is a sensitive as well as a specific feature of all types of seizures, irrespective of their detailed morphology.

Another important field for the application of synchronization measures is the study of normal and disturbed higher brain functions, such as perception, attention, memory, etc. It is now generally accepted that higher brain functions require delicate cooperation between distributed neural networks in the brain, and that synchronous oscillations play an important part in this process. A well known example of this phenomenon are the changes in alpha band synchronization which are associated with eye-closure and eye-opening. In a group of 10 healthy subjects the synchronization likelihood demonstrated a clear and widespread decrease in alpha band (8–12 Hz) synchronization associated with eye-opening (Fig. 9). A greater challenge is the application of this measure to multichannel MEG data and high frequency gamma activity. As an example we have shown preliminary results for a healthy subject and an Alzheimer patient. From Fig. 10 it is clear that the MEG of the healthy subject is characterized by a complex pattern of spatio-temporal synchronizations in the gamma band; these synchronization are virtually absent in the Alzheimer patient. Further studies will have to substantiate these findings. However, this approach does seem to be interesting for the characterization of neurophysiological changes in the early stages of dementia.

Acknowledgements

The EEG data analysed in this paper were recorded at the Department of Clinical Neurophysiology of the

Leyenburg Hospital, The Hague. The MEG data were recorded at the MEG Centre of the Vrije Universiteit, Amsterdam. Subjects were referred by the outpatient clinic for memory disorders of the Vrije Universiteit (Prof. Ph. Scheltens; Dr. Y.A.L. Pijnenburg). We would like to thank the two anonymous referees for helpful comments on an earlier draft of this paper.

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