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Decaying of phase synchronization in parkinsonian tremor

Avi Gozolchiani[a],*, Shay Moshel[a], Jeffrey M. Hausdorff[b], Ely Simon[b], Jürgen Kurths[c], Shlomo Havlin[a]

[a]*Minerva Center and Department of Physics, Bar-Ilan University, Ramat-Gan 52900, Israel*
[b]*Movement Disorders Unit, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel*
[c]*Institute of Physics, Potsdam University, Potsdam, Germany*

Abstract

We describe effects of the asymmetry of cycles and non-stationarity in time series on the phase synchronization method which may lead to artifacts. We develop a modified method that overcomes these effects and apply it to study parkinsonian tremor. Our results indicate that there is synchronization between two different hands and provide information about the time delay separating their dynamics. These findings suggest that this method may be useful for detecting and quantifying weak synchronization between two non-stationary signals.
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Keywords: Synchronization; Nonstationarity; Delay; Tremor; Synchronization decay

1. Introduction

Analysis of the synchronization between subsystems of a complex dynamical system is important for characterizing the system. Much effort has recently been focused on detecting and quantifying synchronization within non-stationary noisy systems (see e.g., Refs. [1–4]). In such systems, the traditional cross-correlation technique may not assure appropriate detection in all cases of interdependency [4]. The phase synchronization method has been found useful in identifying synchronization in several systems. It has been used to detect brain activity associated with parkinsonian tremor [5], to describe cardiorespiratory systems [6,7], to find relations between temperature and precipitation in different regions [8], and to study the binocular fixation eye movements [9].

Here, we further develop the synchronization decay method and apply it to clarify some questions related to parkinsonian tremor. Using the accelerometric and electromyographic (EMG) records of the hands during "rest tremor" (Fig. 1), we show that the two hands' tremor movements are synchronized and that the coupling mechanism has a broad range of time response scales starting at scales that are below the detection of the measuring apparatus (the sampling rate is 400 Hz) and reaching 0.5 s.

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*Corresponding author.

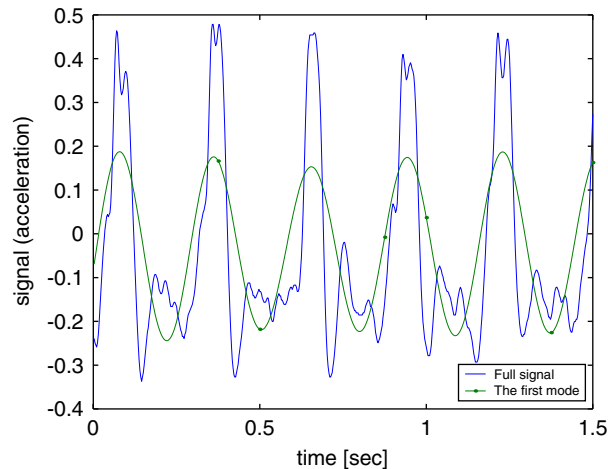*E-mail address:* gozolaa@shoshi.ph.biu.ac.il (A. Gozolchiani).

Fig. 1. Example of a parkinsonian tremor accelerometric record, and its first mode (in green).

2. Effects of asymmetry and nonstationarity

Direct application of the phase synchronization method [4] may encounter difficulties regarding consistent asymmetry of the density of points in each cycle, as discussed below. The phase synchronization method uses the concept of "analytic signal" (AS) [10] which is useful for detecting the phase in periodic and semi-periodic signals [4]. By computing the AS $S_A(t) = S(t) + iS_h(t)$ (where S is the original signal, and S_h is its Hilbert transform, see formulation in the *method* section) of two simultaneous records $S_a(t)$ and $S_b(t)$, and evaluating the phase differences series $\psi(t) = \phi_a(t) - \phi_b(t)$ (where the phase $\phi_{a,b}$ is the angle of the AS in complex space) one can generally estimate how strongly the signals are coupled, observing the variation of ψ. However, if the analytic signals are not folded equally over the cycle, their phases tend to stay longer in the more folded areas (see Fig. 2a, for an example of asymmetric folding). In this case, synchronized dynamics, where the completion of a cycle in S_a depends on the completion of a cycle in S_b, would be hard to detect. This difficulty arises because S_a may complete a very folded area (and remain in a very narrow region in phase space) while S_b completes a much less folded area (and therefore swaps a wide angle in the complex space). Thus, the phase differences series ψ [3] will not have a very dominant phase lag, and the synchronization might appear to be insignificant. The geometry of the AS might have, therefore, a significant impact on the ability to detect synchronization even when the dynamics of S_a and S_b are coupled.

Non-stationarity of S_a and S_b may lead to another difficulty. It is accepted that the global average of the AS must be removed before extracting the phase series, otherwise, the AS will appear to be "folded asymmetrically" even if it is a perfect circle (because the circle is not centered at the origin). If the center of the AS ring is non-stationary, this would be the case even after one removes the global average. A partial solution will be to identify small regimes, where the center of the ring does not wander too far, remove the average (detrending), and calculate the synchronization index in each regime. Finally, we average the synchronization index [5] over all regions. This compromise may still imply quite small synchronization indices when the signal is highly non-stationary. Non-stationarity will therefore also have high influence on the synchronization index.

The original work of Huygens [11] discussed the synchronization of pendulums due to interactions through the embedded media. In this case, a typical response time exists. The dynamics of one oscillator will generally follow the other oscillator in a time delayed manner. One, then, should expect that choosing the right time delay τ will improve the synchronization index of the signals $S_a(t)$ and $S_b(t - \tau)$. Thus, it is of interest to search in the region of time scales τ relevant for the supposed coupling mechanism for improved synchronization. One then generally expects to find a maximal value of the synchronization index in that region. Finding a remarkable time delay $\tau > 0$ will indicate that either S_a forces the dynamics of S_b, or an external field exists, and the coupling mechanism of this field with S_b is slower than the one with S_a. Some theoretical indications exist [12], that the time delay τ corresponding to the maximal computed synchronization index may
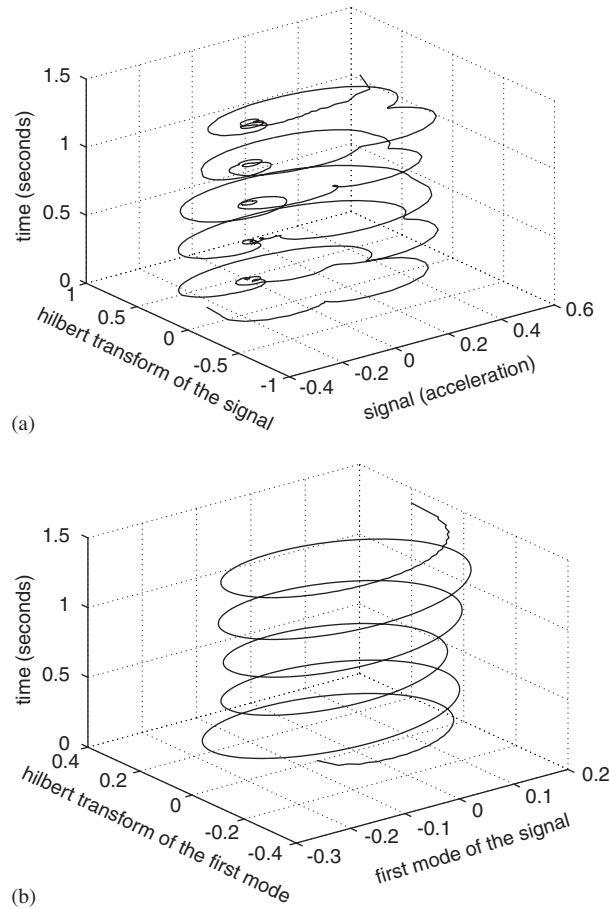
Fig. 2. Example of a parkinsonian tremor record's analytic signal as a function of time. The analytic signal always oscillates in a counter clock wise direction. (a) The full signal's transform. (b) Analytic signal of only first mode of oscillation.

overestimate the real delay that exists between the dynamics, by a quantity that depends on the coupling strength and the difference between the natural frequencies of the systems. This correction is connected with correlations between the noise existing in both systems and the phase difference [13]. The bigger the ratio between the coupling strength and the frequency mismatch will be, the smaller the correction to the time delay found will appear. While not knowing a priori these parameters, we can still use the exhaustive search result as an approximation. The correction form for the general case is still an interesting open question.

   We therefore describe a procedure (also used partially in Ref. [8], and fully used in Ref. [9]) with a related new index, which detects interdependencies between processes, taking into account asymmetry and non-stationarity, and providing a way to estimate the typical time delay. We will assume that interdependencies can be observed from phase differences alone, and that the process of mutual modification does not repeat itself exactly but has a stochastic component.

2.1. The method

   In order to evaluate the significance of the synchronization indices measured, we compare it with the "natural" values of the index obtained when the signals are not coupled. We therefore use the concept of "the synchronization decay" [8,9]. This concept assumes that since the coupling is local in time, finding the synchronization of the first time series $s_1(t)$ with the future (past) of the second time series $s_2(t)$ will give a synchronization value that is related to the geometric structure of the signal, and not to the influence of the systems on each other. The decay of synchronization is, therefore, just a plot of the "simple phase

synchronization" indices (as defined below) as a function of the time differences between the records. The algorithm we use to estimate the decay of synchronization is as follows:

Let s_1, s_2 be two time series of length N. Firstly, we choose a reasonable time shift τ_{max} within which we expect the local influence of one oscillator on the other to be negligible. We set the time shift τ to be $-\tau_{max}$.

(1) Take the signals $s_1(t)$, $s_2(t - \tau)$ when

$$t \in \begin{cases} [0, N - \tau_{max} - 1] & \text{if } \tau < 0, \\ [\tau_{max}, N - 1] & \text{if } \tau \geqslant 0, \end{cases}$$

where $\tau \in [-\tau_{max}, \tau_{max}]$.
(2) Evaluate the analytic signals

$$S_A^\tau(t) = S^\tau(t) + iS_H^\tau(t) = S^\tau(t) + \frac{i}{\pi q} * S^\tau(q),$$

where the superscript τ represents the time shift that is taken between the signals, and "$*$" is a convolution with the integration variable q. Evaluation is done using the AS form in the frequency domain

$$\int dt\, e^{-2\pi i f t}\left(S(t) + i \int dq \frac{S(q)}{\pi(t - q)}\right) = \iint dt\, dq\, e^{-2\pi i f t} S(q)\left(\delta(t - q) + \frac{i}{\pi(t - q)}\right)$$

$$= \left(\delta(q) + \frac{i}{\pi q}\right) * S(q) = (1 + \text{sgn}(f))\mathbf{S}(f) = 2\Theta(f)\mathbf{S}(f)$$

where

$$\Theta(x) = \begin{cases} 0 & \text{where } x \leqslant 0 \\ 1 & \text{where } x > 0 \end{cases}$$

is the Heaviside function.
(3) The analytic signals can be represented in the form $S_A^\tau(t) = A(t)\exp(i\phi^\tau(t))$. The phase series $\phi^\tau(t)$ can be easily obtained by the trigonometric relation

$$\phi^\tau(t) = \arctan\left(\frac{S_H^\tau(t)}{S^\tau(t)}\right) + \frac{\pi}{2}(1 - \text{sgn}(S^\tau)).$$

(4) Calculate the series

$$\psi_{mn}^\tau(t) = \text{mod}_{2\pi}(m\phi_1^\tau(t) - n\phi_2^\tau(t)),$$

where m, n are integers ($\neq 0$). The ratio $m{:}n$ equals to the ratio between the dominant frequencies $\omega_2{:}\omega_1$. One should choose m and n based on a physical guess (e.g. if both oscillators are theoretically similar, one should choose $\omega_2{:}\omega_1 = 1$ and hence $m = n = 1$) and on the dominant peaks in the power spectrum of the records.
(5) Evaluate the probability density P of $\psi_{mn}^\tau(t)$, by choosing a fine division of $[0, 2\pi]$ to N_b bins (as described in Ref. [14]), and evaluating the probability P_i of finding $\psi_{mn}^\tau(t)$ within the ith bin [15].
(6) Evaluate the Shannon entropy [16] of the probability histogram

$$S^\tau = -\sum_i P_i \log P_i.$$

Derive the synchronization index ρ [5] by scaling the entropy S^τ to be in $[0, 1]$ where 0 stands for lack of synchronization and 1 stands for full synchronization, using the relation

$$\rho^\tau = \frac{S_{max} - S^\tau}{S_{max}},$$

where $S_{max} = \log N_b$.
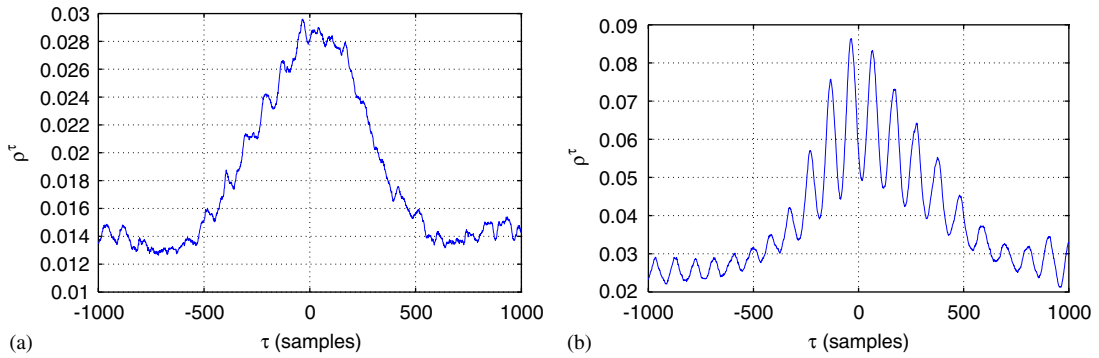(7) Set $\tau = \tau + 1$, return to step 1.

Fig. 3. Synchronization index ρ vs. time shift τ. (a) Synchronization decay between oscillations in both hands. Records here are not filtered. (b) Synchronization decay of first mode in both hands. There are clearly decaying tails, but the figure is modulated by a strong oscillation. In both cases one sees that ρ^0, the standard synchronization index, is extremely smaller than the maximal value 1, but is significantly larger than the background noise. The left tail in both figures is taken to be in the region between -1000 and -500 samples and the right tail is taken to be in the region between 500 and 1000 samples.

The algorithm should be applied on relatively short time scales so that the slips of the center of the AS' ring can be ignored. In order to avoid using the edges of each window (because estimation of the Hilbert transform is poor at the edge), the window should contain a few cycles more than the maximal window size allowed due to the slipping of the center criterion (allowing us to crop the edges after the transform is done). The decay of the synchronization index for all time windows should be averaged over all windows. A detailed picture of the development of coupling in time can be achieved by observing the individual time windows.

A "synchronized state" is a local state. It occurs when the synchronization index ρ^τ vs. time shift τ has two significantly falling tails and one or a few maxima (e.g., see Fig. 3). A well pronounced synchronization occurs when the difference between the tails and the maxima is larger than the standard deviation of the tails. We quantify the significance by evaluation of

$$\frac{\langle \rho_{k \in middle} \rangle - \langle \rho_{k \in tails} \rangle}{\sqrt{\langle \rho_{k \in tails}^2 \rangle - \langle \rho_{k \in tails} \rangle^2}}.$$

We consider the regions of τ where the synchronization index ρ^τ stabilizes to be the tails, and the other regions of τ to be the center. This dichotomy should be defined for all pairs of the same kind in a unique way. We define the thresholds of the center region for our records (see Fig. 3) so that the center is exactly half of the time window.

If one sets $\tau_{max} = 0$ and takes only one window, then the method reduces to the standard phase synchronization method (and the significance will be infinite).

3. Application to tremor in Parkinson's disease

Parkinsonian rest tremor accelerometric records, being non-stable, gave rise to an interesting question regarding the synchronization between hands, where the synchronization decay diagrams might give some indication for the answer. We analyzed 29 records, from 3 male and 2 female patients, with ages between 55 and 69. Each record has a duration of 330 s, and a sampling rate of 400 Hz. The EMG records were filtered using a low-pass butterworth filter, to avoid high-frequency noise.

The parkinsonian rest tremor accelerometric and EMG records in different extremities have been found to be non-coherent [17], despite their concurrent motion. It can be shown that the low coherence between two time series imposes a very low synchronization index as well. "Synchronization Decay" diagrams can indicate that although the synchronization indices are indeed low, the hands' dynamics might be coupled. We find that

synchronization between the hands appears to be maximal with a time delay which suggests a non-mechanical coupling (generally bellow 0.5 s).

We tested whether coupling between the dynamics of the extremities exists. There is evidence in human hand tremor [18] and in neuronal activity of MPTP monkey models [19] that the first two modes of oscillations (e.g., 4 and 8 Hz) exhibit different dynamics which cannot always be described as harmonics. We therefore computed the synchronization decay between the hands and between each of the modes of the left hand and each of the modes of the right hand. When asserting phase synchronization decay between the two full signals, one can refer to the phases extracted as "effective phases", and to the phases of the individual modes as "phases". We attribute interdependence for cases in which the decay of synchronization is larger than 1.5 standard deviations of the tails. We found that out of 29 records of the entire signal, 19 were synchronized. The first mode of the tremor hand was synchronized with the first mode of the relatively healthy hand in 16 of the records, and with its second mode in 11 cases. The second mode of the tremor hand was synchronized with the first mode of the relatively healthy hand in 6 cases, and with its second mode in 7 cases. These results suggest that different extremities oscillate dependently. A close look at Fig. 4 reveals that synchronization of the first mode of the tremor hand and any of the modes of the relatively healthy hand is in some cases more sharp (above 3 standard deviations) than the synchronization of the second mode of the tremor hand with any of the modes of the relatively healthy hand. The appearance of a significant interdependence between oscillators, when their coherence is insignificant [17], is a surprising result of the analysis. The other possibility, that coherence can exist without synchronization, has been recognized before [4]. The reason for this new possibility is due to our different (less strict) demand for observing inter-dependency. We suggest that it is sufficient to demand that synchronization decays as time shift grows.

We assume above that our findings are related to the disease state, and that the outcoming mechanical oscillation is indeed a reflection of the neuronal activity. However, an alternative explanation is that the mechanical system itself (the hands and the body) causes the relations found and not the pathology. Thus, we must exclude the possibility that the coupling we tracked can be fully explained by the mechanical coupling between the hands through the body media. Our suggestion that it is due to neuronal activity is supported by three results: (a) The range of response times (between times less than 2 ms and up to 0.5 s) that was found is recognized as typical neuronal time scale. Even if there is a correction to the computed delay, as suggested by Ref. [12], theory suggests that the correction is negative (so the time scale of the coupling we found is still less than 0.5 s). (b) In two of the cases, there was an order of magnitude difference between the response time of second mode (in both hands) and the response time between the first mode in one hand and the second mode in the other. Thus, even the same person, with the same mechanical parameters shows extremely different response times (which also supports the claim that there are indeed several sources which rule each hand, see Ref. [18]), and therefore, a mechanical coupling cannot explain such delays. (c) We also tested the synchronization decay between the EMG signals. The EMG records are quite noisy, and in most cases analysis gave no sign of a synchronization such as that found between the accelerometric records. However, there were 6 (out of 29) records which did show good synchronization decay. Such interdependence is better explained by the interdependence of neuronal activity rather than mechanical couplings (because we measure the signal from the brain, and not the actual movement).

4. Discussion

4.1. Oscillations in the synchronization decay plot

It is worth noting that one can usually identify the artifacts of non-stationarity by looking at a synchronization decay plot. For example, in Fig. 3b one can see that the synchronization index does fall dramatically. The falling profile is modulated with an oscillation. This oscillation can be explained with a reasoning similar to that we gave for the index falling due to geometry in the discussion above. When shifting the records so that folded areas fall together most of the time, one obtains "better" synchronization. When folded area of one record overlaps the unfolded areas of the other record (and vice versa, of course), the index
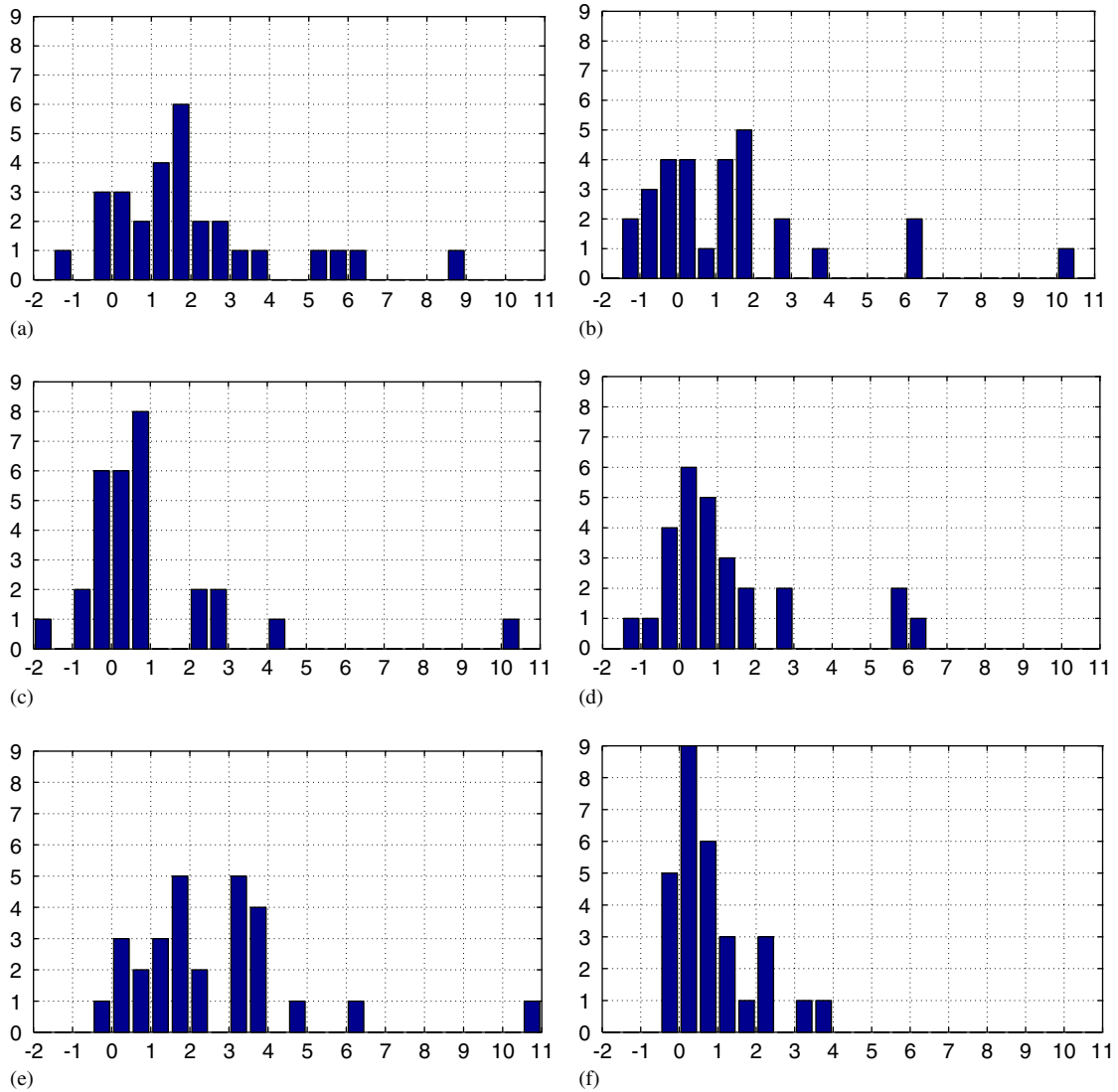
Fig. 4. Distribution of the difference between center and tails mean values (in standard deviation units) in the synchronization decay diagram testing interdependency between. (a) First mode of healthy hand vs. first mode of tremor hand. (b) Second mode of healthy hand vs. first mode of tremor hand. (c) First mode of healthy hand vs. second mode of tremor hand. (d) Second mode of healthy hand vs. second mode of tremor hand. (e) Full tremor signals of both hands. (f) Full EMG signals of both hands.

falls. Therefore, the index falls and grows alternately as we shift the records (in the process described above). Oscillation is, therefore, due to geometry.

4.2. Why two perfect sines are not synchronized?

Synchronization of two sines (or of two pendulums with the same rod length), using our new general restriction (that existence of synchronization is indicated by the fact that the cycles of one oscillator are less coherent with the future cycles of the other oscillator than they are with its present) is very low (because there will be no change in the synchronization index between different time shifts). Synchronization means therefore a process of local (in time) feedbacks.

A simple illustration for this point is given in Fig. 5. A triangular wave is given by

$$u(t) = \frac{2h}{\tau}\left\{\sum_{i=0}^{\infty}\left[\text{sgn}\left(-t + (1+2i)\frac{\tau}{2}\right) - \text{sgn}(-t + i\tau)\right]\left(t - (0.5 + 2i)\frac{\tau}{2}\right)\right.$$

$$\left. + \left[\text{sgn}\left(-t + (2+2i)\frac{\tau}{2}\right) - \text{sgn}\left(-t + (1+2i)\frac{\tau}{2}\right)\right]\left(-t + (1.5 + 2i)\frac{\tau}{2}\right)\right\},$$

where $h/2$ is the amplitude, and τ is the period. A decay of synchronization index between the two first modes of oscillation of a perfect triangular periodic wave does not exist because each cycle of the first mode is perfectly synchronized with each cycle of the second mode, and not just with the relatively close cycles (τ is not a function of time, therefore each cycle is identical in its phase dynamics with previous cycles). Each point on the decay of synchronization plot is a local maximum.

Even if you perturb by adding ($u'(t) = u(t) + \varepsilon\eta(t)$ when $\eta(t)$ is some white noise) or multiplying ($h = h(t)$) the wave by some random noise, you will not get decay of the synchronization index, because phases stay the same (detection of the phases might differ a bit, but not consistently enough to reduce significantly the synchronization index). In Fig. 5a–c there is a superposition of several noisy triangular waves (τ is fixed for each of them, and $h = h(t)$). It is obvious that the synchronization index is not 1 all over the diagram (because detecting is not perfect) but there is no decaying (Fig. 5c). Nevertheless, perturbing the frequency [20] ($\tau = \tau(t)$) Fig. 5d–f) mimics a dependency between the two modes of oscillation, because a local change in the proceeding of one mode is seen simultaneously in the other mode. In real systems, such "simultaneous" local changes are the kernel of a dynamical synchronization process. This simple example suggests that harmonies of a signal with changing local period synchronize (in the sense of decaying synchronization) in order to build the wave form. Indeed, the decaying of the synchronization index plot in Fig. 5f shows sharp decay in both tails. Simultaneous local (in time) changes in two time series (and therefore—the measure of synchronization decay) indicate interdependence.
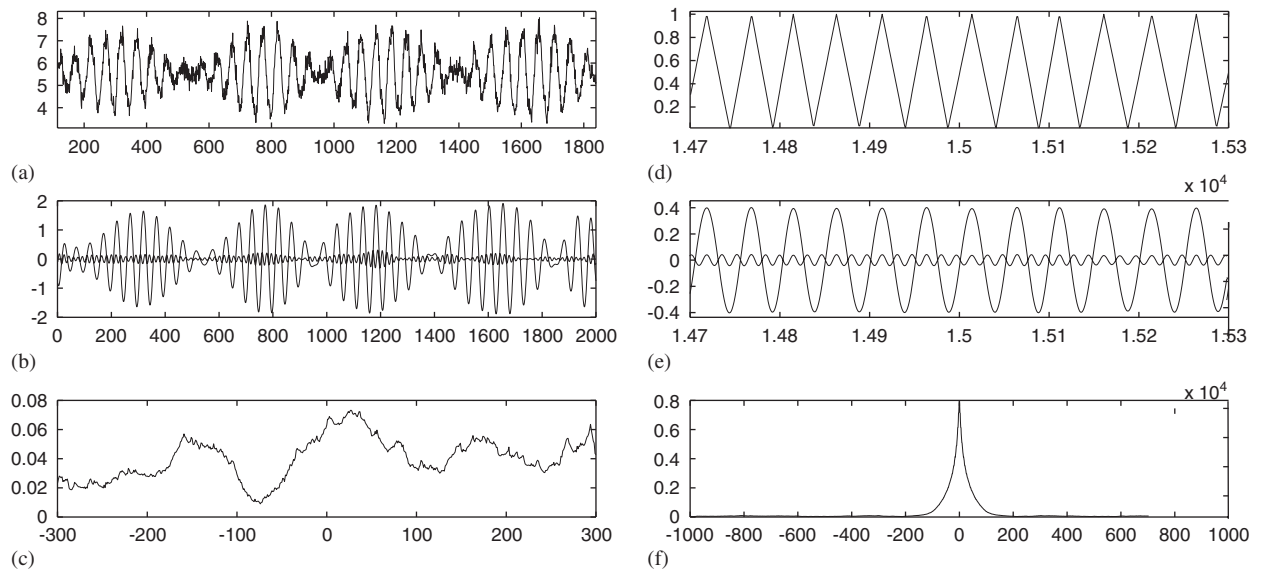

Fig. 5. We apply the synchronization decay method to follow the synchronization between the harmonies of a wave form. Time and time shifts appear in all six figures in arbitrary units. (a–c): A superposition (with random in time coefficients) of 10 triangular waves each with slightly different wavelength, the separation into two dominant modes and the decay of the synchronization index plot. (d–f): A triangular wave, its separation to modes and the decay of the synchronization index plot. On each cycle, a new wavelength is chosen randomly.

Acknowledgements

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