determine the synchronous contraction of various muscular groups of the motor system.

(4) Based on the developed model of an inferior olive neuron, a motion control and coordination system has been proposed for autonomous robotic machines. The basic idea here is to supply the control system with a discrete control block with the function to correct errors arising due to the operation of self-phase reset mechanisms (for motion along a rough surface, for example).

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Modeling nonlinear oscillatory systems and diagnostics of coupling between them using chaotic time series analysis: applications in neurophysiology

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1. Introduction

Using time series of experimental observables to identify and estimate interaction parameters between sources of complex (chaotic) oscillations [1–3] is a task of relevance to many disciplines, from physics and biology to geophysics, medicine, and engineering. A vibration analysis of machine elements can identify the source of the vibrations [4], whereas identifying interactions between various brain regions based on multichannel electroencephalogram analysis benefits epilepsy patients by locating the sites of pathological activity [5]. Particular attention in this area is paid to irregular signals because it is a long-recognized fact that the chaotic behavior of nonlinear systems is typical [3, 6, 7].

Reflecting the diversity of possible situations and the factors of noise and nonstationarity, a wide variety of approaches to identifying and assessing the 'intensity' of a coupling have been developed using mathematical statistics and spectral analysis [1], information theory [8, 9], and nonlinear dynamics [5, 10–12]. Among the most widely-used of these are the calculation of cross-correlation functions and of coherence functions [1], event sequence analysis with time series [13], the estimation of nearest neighbor distribution in the space of states [5], and the determination of characteristics of 'information transfer' between signals [8]. Whereas the techniques listed above process a signal 'directly', using appropriate working formulas and algorithms, there also exists an 'indirect' approach which proceeds from the original time series to produce predictive mathematical models and utilizes the properties of the series to estimate the coupling.

Each of the approaches has its preferred area of application [14–16]. In this talk we will be concerned only with employing mathematical models as a tool for estimating couplings (Section 2). The characteristics so obtained are in agreement with intuition regarding cause and effect relations between processes (e.g., coupling coefficients in dynamics equations). With an adequate model structure, this approach also turns out to be the most sensitive one, especially where nonlinearity and chaos are involved. Such a situation arises when practically important problems of physiology, such as pathology mechanisms of epilepsy and Parkinson's disease, are considered (Section 4).

In view of the importance of developing a model serving as a tool for identifying couplings, a number of problems of reconstructing equations are considered per se in Section 3.

2. Coupling diagnostics using predictive models

2.1 *A priori* known structure of the model

If the adequate mathematical model of the elements (subsystems) of the system under study is known in terms of its structure, and if the couplings whose parameters are being sought come in a finite number of structural forms, a simple item by item selection is a viable strategy. This strategy chooses for each particular coupling structure those values of model parameters (and coupling coefficients among them) for which the observed dynamics (for example, predicting next points from previous ones) are most accurately represented — ultimately selecting the most adequate model and its corresponding coupling characteristics. An example is estimating the coupling of two self-oscillatory time-delay systems [17] (see Fig. 1), each of which contains ring-connected nonlinear amplifier f, a delay line τ, and a filter ε (inertial element). The dashed lines represent different ways of connecting coupling elements to points I, II, and III (with k denoting the gains). Different types of coupling give rise to

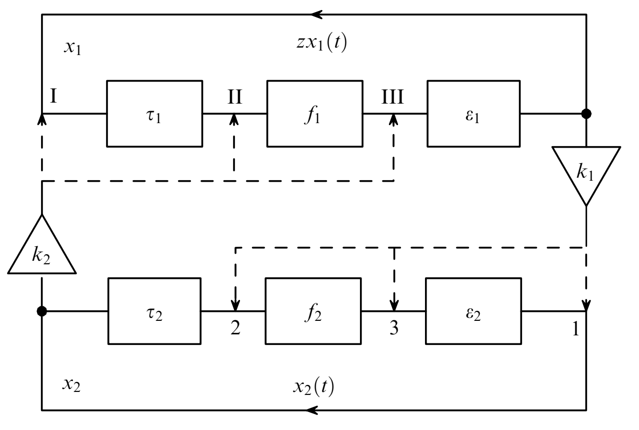

Figure 1. Block diagram of coupled time-delay systems X_1 and X_2. Elements τ_1 and τ_2, f_1 and f_2, ε_1 and ε_2 are responsible, respectively, for the delay and the nonlinear and inertial transformation of oscillations; elements k_1 and k_2 determine the amount of coupling between systems X_1 and X_2. At points 1–3, system X_1 acts on system X_2. At points I–III, system X_2 acts on system X_1.

mathematical models of different structures, as follows:

$$\varepsilon_{1,2}\,\frac{\mathrm{d}x_{1,2}(t)}{\mathrm{d}t} = -x_{1,2} + f_{1,2}\big(x_{1,2}(t-\tau_{1,2}) + k_{2,1}x_{2,1}(t-\tau_{1,2})\big)\,, \tag{1}$$

$$\varepsilon_{1,2}\,\frac{\mathrm{d}x_{1,2}(t)}{\mathrm{d}t} = -x_{1,2} + f_{1,2}\big(x_{1,2}(t-\tau_{1,2}) + k_{2,1}x_{2,1}(t)\big)\,, \tag{2}$$

$$\varepsilon_{1,2}\,\frac{\mathrm{d}x_{1,2}(t)}{\mathrm{d}t} = -x_{1,2} + f_{1,2}\big(x_{1,2}(t-\tau_{1,2})\big) + k_{2,1}x_{2,1}(t)\,. \tag{3}$$

Equation (1) describes the situation in which the first time-delay system exerts an influence on the second system at point 1, whereas the second system influences the first one at point I. We will denote this type of coupling as 1/I. Equations (2) and (3) describe coupled systems for the coupling schemes 2/II and 3/III, respectively. If systems X_1 and X_2 influence each other in different ways, they are described by different equations. For example, for the coupling scheme I/II system X_1 is described by Eqn (2), and system X_2 by Eqn (1).

Section 3 briefly describes a special technology for reconstructing delayed differential equations, which enables one to achieve the best result by choosing a model that correctly reflects the way to introduce couplings between self-excited oscillators in a physical experiment, and between reference dynamical systems in a numerical experiment [17].

2.2 Granger causality

In the absence of *a priori* information on the structure of the model equations, universal constructions can be utilized. A useful practical approach is a method based on constructing nonlinear prognostic models [18, 19], which extends the linear approach proposed by Granger [20–23] to identifying cause and effect relations. The basic idea is to use the time series $\{x_1(t_1),\ldots,x_1(t_N)\}$ and $\{x_2(t_1),\ldots,x_2(t_N)\}$ to construct prognostic models — 'individual' and 'joint'. A considerable improvement in the prognosis of the dynamics of the first system due to taking into account the values of a variable from the second system is an indication that the latter influences the former (provided such an improvement cannot be achieved by complicating the individual model). The following is one possible way in which this approach can be implemented (and which was used, for example, in Ref. [24]).

To assess the influence of the second system on the first, one starts by constructing an individual autoregression model in the form

$$x_1(t_n) = f_1\big(x_1(t_{n-1}), x_1(t_{n-2}),\ldots,x_1(t_{n-d_1}),\mathbf{a}_0\big) + \xi_n\,, \tag{4}$$

where f_1 is an algebraic polynomial of order K, d_1 is the dimensionality of the model, and ξ_n is a zero-mean noise. The coefficients $\mathbf{a}_0$ are estimated using the method of least squares, i.e., by minimizing the mean square of the prognosis error:

$$\sigma_1^2 = \frac{1}{N-n_0}\sum_{n=n_0+1}^{N}\Big(x_1(t_n) - f_1\big(x_1(t_{n-1}),\ldots,x_1(t_{n-d_1}),\mathbf{a}_0\big)\Big)^2, \tag{5}$$

where $n_0 = \max\,(d_1, d_2)$, and the quantity d_2 is defined below. As a next step, two series are taken to construct a joint model:

$$x_1(t_n) = g_1\big(x_1(t_{n-1}),\ldots,x_1(t_{n-d_1}), x_2(t_{n-1}),\ldots,x_2(t_{n-d_2}),\mathbf{a}\big) + \eta_n\,, \tag{6}$$

where d_2 indicates how many values of x_2 were taken into account, g_1 is a polynomial of order K, and η_n is a zero-mean noise. The minimum mean square of the prognosis error, as determined by the method of least squares, is defined as

$$\sigma^2_{2\to 1} = \frac{1}{N - n_0} \sum_{n=n_0+1}^{N} \Big(x_1(t_n) - g_1\big(x_1(t_{n-1}), \ldots, x_2(t_{n-d_2}), \mathbf{a}\big)\Big)^2 . \tag{7}$$

The improvement in the prognosis of the series x_1 due to taking into account the series x_2 is characterized by the difference of errors squared: $PI_{2\to 1} = \sigma_1^2 - \sigma^2_{2\to 1}$.

The difference from zero of the time series-based quantity $PI_{2\to 1}$ is often assessed in terms of statistical significance by using an analytical formula based on the assumption that the processes x_1 and x_2 are not coupled and that the (residual) prognosis errors of models (4) and (6) are due to normal white noise. Then, the normalized quantity

$$F_{2\to 1} \equiv \frac{(N - n_0)(\sigma_1^2 - \sigma^2_{2\to 1})}{(P_2 - P_1)\sigma^2_{2\to 1}} ,$$

where P_1 and P_2 are the respective numbers of coefficients in the individual and joint models, follows Fisher's F distribution with $(P_2 - P_1, N - n_0 - P_2)$ degrees of freedom. The significance of $F_{2\to 1}$ being different from zero is checked using the F test [9]. If this difference is significant at level p, then the fact of x_2 influencing x_1 has confidence probability $1 - p$. A fully similar situation occurs for the characteristic of the influence $1 \to 2$.

An alternative way to assess the existence of the discovered couplings for reliability is to use surrogate data, an ensemble of artificially obtained pairs of signals which, while mutually uncoupled, still retain some dynamical traits of the processes under study. These can be, for example, the initial time series biased relative to each other by a time interval larger than the autocorrelation time of the processes involved [13, 14].

When choosing the values of d_1, d_2, and K, the recommended way is to first construct models (4) and (6) for different values of these quantities (starting from unity) and then to select those values for which the mean square errors in the prognosis of the models [formulas (5) and (7)] get stabilized, i.e., cease to grow significantly with increasing d_1, d_2, and K. (Specifically, it makes sense to first select the values of d_1 and K by looking at the prognosis error of the individual model and then, with known d_1 and K, to select d_2 from the prognosis error of the joint model.) The functions f and g can be of any kind, for example, locally constant functions [18] or radial basis functions [19]. However, for short time series, typically encountered in biological and geophysical applications, the multiparametric nonlinear functions mentioned above are of limited use, as is increasing d_1, d_2, and K for polynomials. Therefore, informative results can usually be obtained (if at all) only for low dimensionalities and low-order polynomials [24].

2.3 Phase dynamics modeling

Considering that a model should be structurally adequate for the processes under study, the above-described necessitated use of the simplest possible models for estimating Granger causality limits considerably the effective application of the method. As a way out, however, the same approach can be profitably applied to the time series for the phases of the processes observed, rather than to the observed quantities themselves [25].

Such an approach is effective if there are very distinct oscillation rhythms in the original time series (the power spectrum shows a marked rise in a narrow frequency band). In this case, the notion of the phases ϕ_1 and ϕ_2 of the observed oscillatory processes x_1 and x_2 has a clear meaning and they are most often calculated using the Hilbert transform and the introduction of an analytical signal [26]. The reason for the effectiveness of this approach is twofold. First, because the phases of the narrow-band processes described above are the most responsive variables to influences on a self-sustained oscillatory system, their use promises to make the method highly sensitive to weak coupling between the signal sources [3]. Second, a wide range of oscillatory processes are adequately described by a sufficiently simple system of stochastic difference equations in the form [25, 27, 28]

$$\phi_{1,2}(t+\tau) - \phi_{1,2}(t) = f_{1,2}\big(\phi_{1,2}(t), \phi_{2,1}(t - \Delta_{1,2})\big) , \tag{8}$$

where $f_{1,2}$ are moderate-order trigonometric polynomials; τ is a fixed time interval usually equal to the shortest of the characteristic oscillation periods, and $\Delta_{1,2}$ are the trial values of the influence delay time. The strengths of influence of the systems on each other are calculated from the estimates of the trigonometric polynomial coefficients, which are made on the basis of a time series by the method of least squares. The quantity $c^2_{2\to 1}$, the extent of influence of system 1 on system 2, is determined by the steepness of the dependence $f_1(\phi_2)$, and similarly for $c^2_{1\to 2}$, giving

$$c^2_{2\to 1,\,1\to 2} = \frac{1}{2\pi^2} \int_0^{2\pi} \int_0^{2\pi} \left(\frac{\partial f_{1,2}(\phi_{1,2}, \phi_{2,1})}{\partial \phi_{2,1}} \right)^2 \mathrm{d}\phi_1 \, \mathrm{d}\phi_2 . \tag{9}$$

Although simulation experiments [25] show the method to be very sensitive to weak coupling, the catch is that, for it to be applicable to initial systems with considerable levels of dynamical noise, the training series should be about 1000 times as long as the characteristic period at moderate noise levels. In actual practice, the method runs into difficulties when the time series under study are nonstationary. For electroencephalograms, the quasistationarity interval is not normally longer than 100 characteristic periods for any physiological 'rhythms' resolved, making it necessary to divide time series into relatively short segments and to obtain coupling estimates for each of these separately. If left unmodified, the model will in this case produce biased estimates [29]. For this reason, we have introduced [29] the new estimates $\gamma_{1\to 2,\,2\to 1} = c^2_{1\to 2,\,2\to 1} + r_{1,2}$, where the corrections $r_{1,2}$ depend on the noise level, oscillation frequencies, and the length of the time series. In the same work, approximate expressions for the 95% confidence intervals were obtained, with which results obtained for an individual time realization can be assessed for significance.

3. Model equation reconstruction from time series

Constructing empirical models of the type used for diagnostics of couplings in Section 2 is central to the broad field of research known as *system identification* in mathematical statistics [1, 30] and as *dynamical system reconstruction* in nonlinear dynamics [7, 31–33]. With the advent of the concept of dynamic chaos it became clear that complex chaotic behavior is exhibited by nonlinear equations of

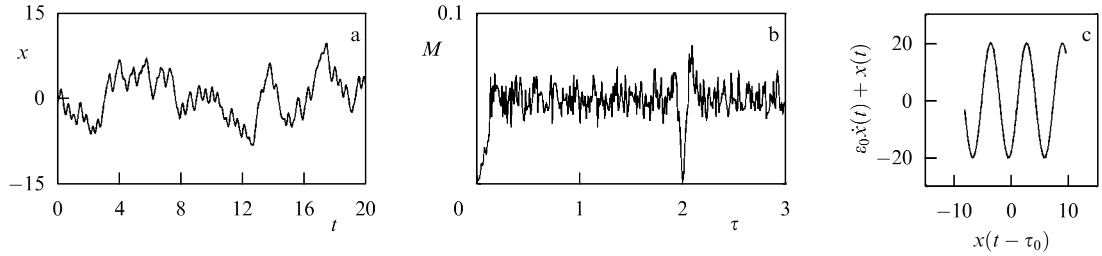

Figure 2. Example of reconstructing a time-delay system: (a) time realization of the Ikeda equation (11) for $\tau_0 = 2$; (b) the number $M(\tau)$ of extremum pairs normalized to the total number $M_{\min} = M(2, 0)$ of extrema in the series; (c) reconstructed nonlinear function. Numerical experiments including additional noise show that noise-to-signal ratios of up to 20% allow a reconstruction.

even low dimensionality, resulting, in recent years, in empirical modeling often being performed based on nonlinear difference equations (discrete maps) $\mathbf{x}_{n+1} = \mathbf{F}(\mathbf{x}_n, \mathbf{c})$ or ordinary differential equations $\mathrm{d}\mathbf{x}/\mathrm{d}t = \mathbf{F}(\mathbf{x}, \mathbf{c})$, where $\mathbf{x}$ is the D-dimensional state vector, $\mathbf{F}$ is a vector function, $\mathbf{c}$ is a P-dimensional parameter vector, n is a discrete time, and t is a continuous time.

It was believed for some time that universal approaches suitable for any system could be developed. Thus, the general algorithm for constructing the nonlinear models mentioned above is in many respect similar to the smooth-curve approximation algorithm for points in a plane, albeit it comprises additional steps. The initial stages of the reconstruction procedure include a preliminary analysis of experimental data and a choice of the structure of the model: the type and number of equations, the form of the function $\mathbf{F}$, and how the dynamic variables $\mathbf{x}$ are linked with the observable quantities. This done, model fitting is performed — by selecting those values of the equation parameters $\mathbf{c}$ with which the model reproduces the observed signal best. In practice, various versions of the maximum likelihood method and of the method of least squares are most often used. (In one of the simplest approaches, the mean square of the one-step-ahead error of the prognosis is minimized.) Finally, the quality of the model is checked using a specially distinguished test series.

In practice, however, hopes for a universally workable method were dashed. Mathematical models often turn out to be cumbersome and nonrobust, and in the sequence described above each operation may run into difficulties. Note also that the higher the degree of uncertainty, the more complex the situation is. The most complex case is that of a 'black box', in which the structure of the possible adequate model is totally unknown. The basic difficulty here, poignantly termed the 'curse of dimensionality', is that increasing the dimensionality of the model sharply complicates the problem and requires that stationary time series of greater length be used.

Success is more likely to be achieved by developing ad hoc approaches for certain narrow classes of objects and utilizing targeted modeling techniques, as will be shown by an example below. The uncertainty in choosing the structure of a model can be reduced, for example, by using *a priori* information on the properties of a certain chosen class of systems and by preliminarily analyzing the series involved.

The broad class of complex dynamic processes is modelled by the system described by a first-order differential equation with a time-delay argument:

$$\varepsilon \frac{\mathrm{d}x(t)}{\mathrm{d}t} = -x(t) + F\big(x(t-\tau_0)\big)\,. \tag{10}$$

For such a system, the time realizations of oscillations of its dynamic variable x have been shown [34] to characteristically lack extrema time-spaced by τ_0, with τ_0 being the delay time (Fig. 2). Knowing the position of the minimum in the τ dependence of the number of τ-spaced extrema provides an estimate for the delay time: $\tau \approx \tau_0$ (Fig. 2b), from which it is an easy matter to estimate the inertiality parameter ε and to approximate the nonlinear function F [34].

Figure 2 shows, as an example, the results of reconstructing equations of the form (10) by a chaotic time realization (Fig. 2a) of the Ikeda equation

$$\varepsilon_0 \frac{\mathrm{d}x(t)}{\mathrm{d}t} = -x(t) + \mu \sin\big(x(t-\tau_0) - x_0\big) \tag{11}$$

describing the dynamics of a passive optical cavity. The reader is referred to Ref. [35] for more details on the technology of reconstructing time-delay systems.

Systems experiencing external action are another example of specialized reconstruction technologies targeting to a certain distinguished class of objects [36]. We will not here describe in detail the existing modeling techniques and note only that, importantly, along with the key stage of choosing the most adequate model structure, technical problems arise at various stages of the reconstruction procedure, as exemplified by our studies on improving accuracy in estimating parameters [37], including the case of hidden parameters [38]; on optimizing the structure of a model [39], and on choosing dynamic variables for modeling [40]. Works by a number of groups (see, for example, review papers [41–45]) provide vast information on the subject.

4. Coupling diagnostics in neurophysiological applications

Many nervous system disorders, including epilepsy and Parkinson's disease, are due to the pathological synchronization of large groups of cerebral neurons. A sign of Parkinson's disease is the neuron synchronization in the thalamus and basal ganglia nuclei [46]. However, the functional role of this synchronization in the generation of Parkinsonian tremor (uncontrollable, regular 3-to-6-Hz limb oscillations) remains a subject of discussion [47]. The hypothesis that neuron synchronization causes tremors has not yet received convincing empirical support [47]. If there is no effect from medicines, the standard therapy consists in high-frequency (above 100 Hz) continuous electric deep brain stimulation (DBS) [48]. Discovered purely empirically, the standard DBS is not yet understood in terms of how it works [49], nor is it without its limitations — in particular, due to side effects [50,

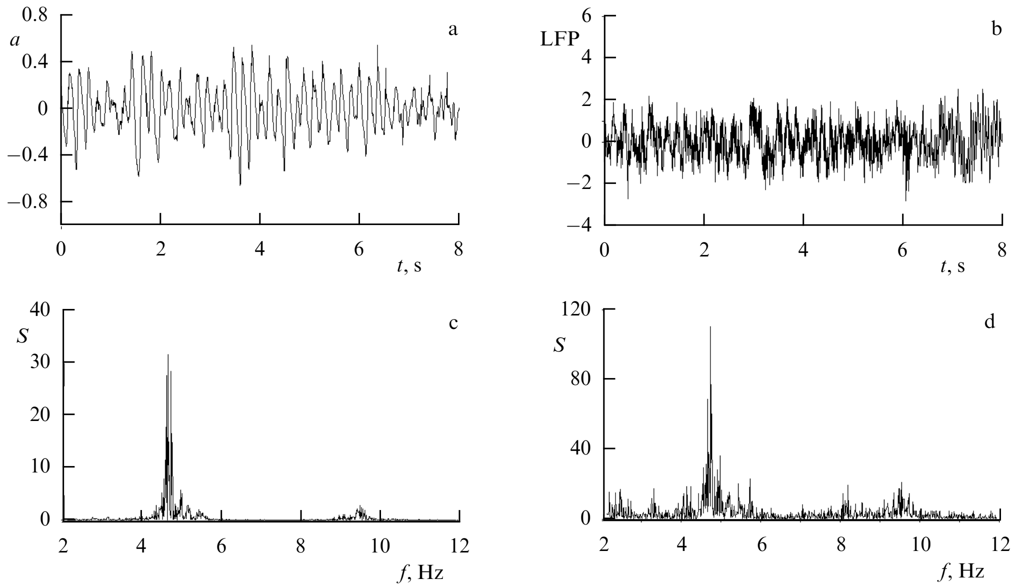

Figure 3. Interval of spontaneous Parkinsonian tremor (total duration 80 s) [52]: (a, b) signal from an accelerometer and an LFP from one of the electrodes in arbitrary units (only first 8 s are shown); (c, d) power spectrum estimates of the signals.

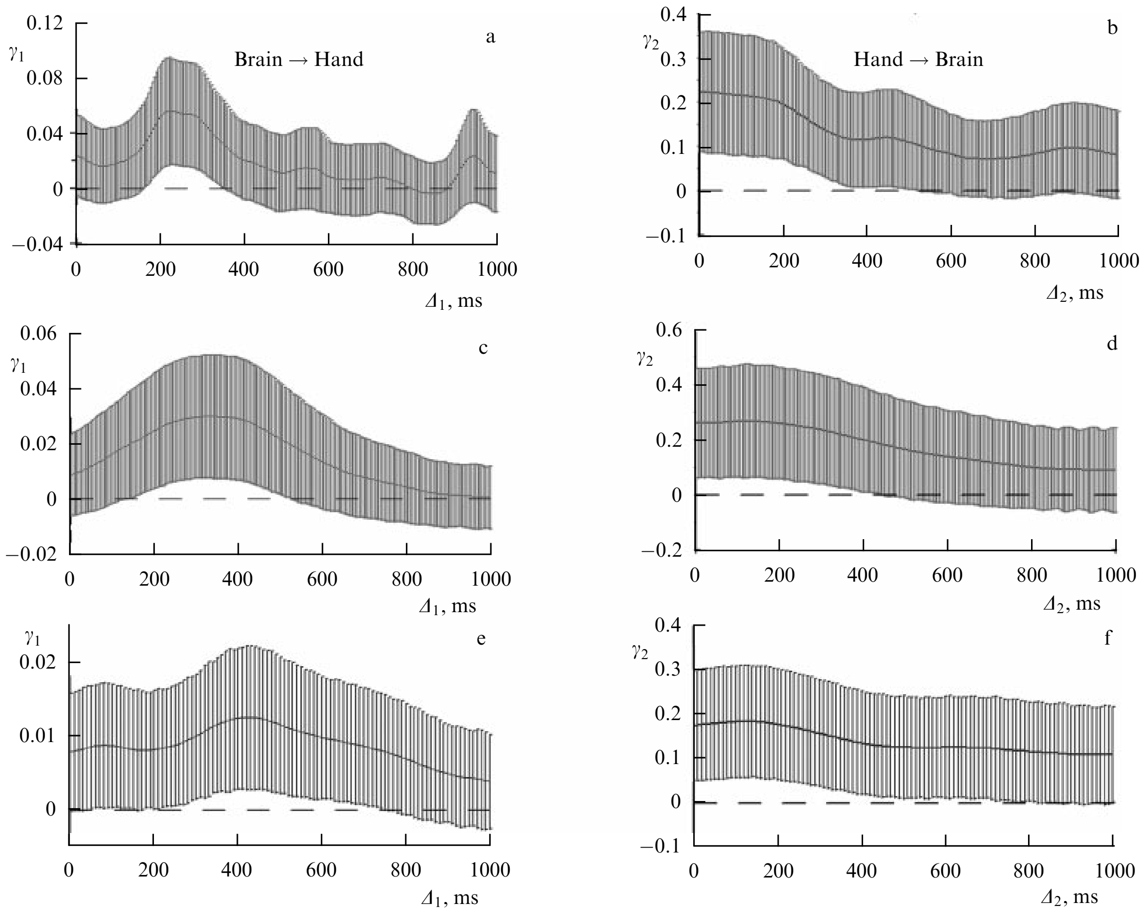

Figure 4. Measure of influence of thalamic activities on hand oscillations (a, c, e) and vice versa (b, d, f) estimated for three patients [respectively (a, b), (c, d), and (e, f)] as a function of test delay time [52]. Estimates averaged over an ensemble of 10 to 15 intervals of violent tremors are shown, as are the 95% confidence intervals of the estimates (dimensionless quantities).

51]. A more specific follow-up idea was to suppress tremors by means of desynchronizing DBS [2], for instance, using coordinated reset stimulation [50]. The confirmation that a tremor is caused by the synchronized activities of the neurons in thalamus and basal ganglia nuclei could presumably lead to milder, low-side-effect therapies. In this connection, to determine how various parts of the brain are linked to the patient's muscles is becoming a topical task.

Our study [52] investigated ensembles of intervals of spontaneous Parkinsonian tremor in three patients. Limb oscillations were identified by accelerometer signals recorded with sampling frequencies of 200 Hz and 1 kHz, and information on brain activity was represented by local field potentials (LFPs) recorded from four in-depth electrodes implanted in the thalamus or basal ganglia. The data were obtained at the Department of Stereotaxical and Functional Neurosurgery, University of Cologne, Cologne, and at the Institute of Neuroscience and Biophysics-3 (Medicine), Juelich Research Center, Juelich (both Germany).

Signals from the accelerometer and the LFP from one of the electrodes, which were recorded in the course of violent Parkinsonian tremor, are shown in Fig. 3, together with their spectra. The accelerometer signal displays oscillations, corresponding to which there is a distinct 5 Hz peak in the power spectrum. A tremor frequency peak, although somewhat broader, is also seen in the LFP spectrum. Both the signals allow a phase to be correctly introduced. Analysis based on the phase dynamics modeling approach (see Section 2.3) reveals that a limb influences the brain in a statistically significant way with a delay of no more than a few dozen milliseconds. The influence of the brain on a limb, which is also seen, is characterized by a delay time falling between 200 and 400 ms (of the order of 1 to 2 characteristic oscillation periods). Results are reproduced qualitatively very well for all three patients (Fig. 4).

That a limb influences the activities of the thalamus and basal ganglia was established earlier using the linear estimation of Granger causality [53]. With phase dynamics modeling, however, new results were obtained: the existence of reciprocal influence was established, and the delay time estimated. Because this delay is large compared to the time it takes the signal to travel from the brain to a limb along nerve fibers, it was interpreted [52] as an indication that thalamic and basal ganglia activities exert indirect influence on limb oscillations (via signal processing in the brain cortex). Moreover, this means that, rather than merely being passive signal receivers, the thalamic and basal ganglia nuclei are links of a 'feedback ring' which determines the oscillations of the limb. Therefore, the application of desynchronizing DBS to these target structures [2, 50] appears to exert a more specific and milder influence which, as theoretical studies predict, can even make the stimulated neuron networks 'unlearn' pathological activity [51] and produce a long-term positive effect. Another possible applications of the directed coupling analysis include determining the target point for stimulation (so as to enable a more effective arrangement of stimulating electrodes).

Surrogate data tests [54] have confirmed the statistical significance of the conclusions reached [54] and have shown in addition that linear methods fail to reveal the influence of thalamic and basal ganglia activities on limbs.

We refer the reader to Ref. [55] for similar preliminary results demonstrating the potential of the method for localizing the epileptic focus by recording local field potentials.

5. Conclusions

The problem of modeling from time series, of much importance in both applied and fundamental terms, is often solved using ideas and methods from nonlinear dynamics. Among the applications of this modeling the most known is the *prognosis* of the behavior of a system (see, for example, Ref. [56]). There are others, too, including the identification of quasistationary sections in a nonstationary signal [44], bifurcation prognosis for weakly nonautonomous systems [57], and multichannel confidential transmission of information [43]. In this talk it was shown that the approach can also be applied to the practically important problem of diagnosing interaction between oscillating systems.

Although mathematical modeling will always be, to a large extent, an art, still some general principles and specific recipes can be identified with which a 'good' model is more likely to be developed. Some such considerations were given above. The corresponding techniques have been successful in the study of real systems (see, for example, Refs [31 – 33, 41 – 45]), such as nonlinear electrical circuits, climate processes, and functional systems of living organisms. In the present talk, a new result illustrating the efficiency of the method as applied to problems in neurophysiology (specifically, to the study of mechanisms of a Parkinsonian tremor) was presented.

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