Manifestation of Chaos in Real Complex Systems: Case of Parkinson's Disease

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In this paper we present a new approach to the research of manifestations of chaos in real complex system. Recently we have achieved the following information. In real complex systems the informational measure of chaos (IMC) can serve as a reliable quantitative estimation of the state of a complex system and help to estimate the deviation of this state from its normal condition. As the IMC we suggest the statistical spectrum of the non-Markovity parameter (NMP) and its frequency behavior. Our preliminary studies of real complex systems in cardiology, neurophysiology and seismology have shown, that the NMP has diverse frequency dependence. It testifies to the competition between Markovian and non-Markovian, random and regular processes and makes a crossover from one relaxation scenario to the other possible. On this basis we can formulate the new concept in the study of the manifestation of chaos. We suggest the statistical theory of discrete non-Markov stochastic processes to calculate the NMP and the quantitative evaluation of the IMC in real complex systems. With the help of the IMC we have found out the evident manifestation of chaos in a normal (healthy) state of the studied system, its sharp reduction in the period of crises and catastrophes and various human diseases. It means, one can improve the state of a patient (of any system) appreciably by increasing the IMC of the studied live system. The given observation creates a reliable basis for predicting crises and catastrophes, as well as for diagnosing and treatment various human diseases, Parkinson's disease, in particular.

1 Introduction

Today the research of manifestations of chaos in real complex systems of diverse nature has acquired great importance. The analysis of some properties and characteristics of real complex systems is impossible without quantitative estimate of various manifestation of chaos. The dynamics or evolution of the system can be predicted by the change of its chaosity or regularity. The discovery of the phenomenon of chaos in dynamic systems has changed the attitude to the functioning of complex systems, a human organism, in particular. The chaos is the absence of regularity. It characterizes randomness

and unpredictability of changes of the behavior of a system. At the same time, the presence of chaos in dynamic systems does not mean it can not be taken under control. Instability of dynamic systems in the state of chaos creates special sensitivity to both external and internal influences and perturbations. The series of weak perturbations of the parameters of the system allows to change its characteristics in the required direction. "Chaos" is frequently understood as a determined dynamic chaos, that is, the dynamics dependent on the initial conditions, parameters.

Lasers, liquid near to a threshold of turbulence, devices of nonlinear optics, chemical reactions, accelerators of particles, classical multipartite systems, some biological dynamic models are the examples of nonlinear systems with the manifestation of the determined chaos. Now manifestations of chaos are being studied in different spheres of human activity.

The control of the behavior of chaotic systems is one of the most important problems. Most of the authors see two basic directions in the solution of the problems [1, 2]. Both directions envisage a preliminary choice of a certain perturbation. The selected perturbation is used to exercise influence on the chaotic system. The first direction is focused on an internal perturbation, the choice of which is based on the state of the system. The perturbation changes the parameter or the set of parameters of the system, which results in the ordered behavior of the chaotic systems. The methods focused on the choice of such parameters (perturbations) are referred to as "methods with a feedback" [1]-[6]. They do not dependent on the studied chaotic system (model) as these parameters can be selected by observing the system for some period of time. The methods with a delayed feedback [3, 7] can also be referred to the first direction. The second direction presupposes that the choice of external perturbation does not dependent on the state of the studied chaotic system. By affecting the studied system with the similar perturbation, it is possible to change its behavior. The present group of methods is an alternative to the first one. These methods can be used in cases when internal parameters depend on the environment [1, 8, 9].

Generally, when choosing internal (external) perturbations it is possible to determine three basic stapes: the estimation of the initial information, the choice of perturbation and the bringing the chosen strategy of control into action (its practical realization). At the first stage the information on the state of the studied system is collected. At the second stage the received information is processed according to the plan or strategy of the control. On the basis of the achieved results the decision on the choice of the internal (of the external) perturbation is accepted. After that the chosen strategy of chaos control is put into practice [2].

The initial idea of the present concept was to separate Markovian (with short-range time memory) and non-Markovian (with long-range time memory) stochastic processes. However, the study of real complex systems has allowed to reveal additional possibilities of the given parameter. Actually,

the parameter of non-Markovity represents a quantitative measure of chaosity or regularity of various states of the studied system. The increase of the given parameter ($\varepsilon_1(0) \gg 1$) corresponds to the increase of chaosity of the state of the system. The decrease of the non-Markovity parameter characterizes greater ordering (regularity) of the state of the system. The given observation allows to define a new strategy of estimate of chaosity in real systems. The new approach in the theory of chaos can be presented as an alternative to the existing methods. Further analysis of the non-Markovity parameter allows to define the degree of chaosity or regularity of the state of the system.

In this work the new strategy for the study of manifestations of chaos is applied to real complex systems. The possibilities of the new approach are revealed at the analysis of the experimental data on various states of a human organism with Parkinson's disease. Parkinson's disease is a chronic progressing disease of the brain observed in 1-2 % of elderly people. The given disease was described in 1817 by James Parkinson in the book "An essay on the shaking palsy". In 19th century the French neurologist Pierre Marie Charcot called this disease "Parkinson's disease". The steady progress of the symptoms and yearly impairment of motor function is typical of Parkinson's disease. Complex biochemical processes characteristic of Parkinson's disease result in the lack of chemical substance of dopamine mediator which is a carrier of signals from one nerve cell to another. The basic symptoms typical of Parkinson's disease form the so-called classical triad: tremor, rigidity of muscles (disorder of speech, amimia), and depression (anxiety, irritability, apathy). The disease steadily progresses and eventually the patient becomes a helpless invalid. The existing therapy comprises a set of three basic treatments: medical treatment, surgical treatment and electromagnetic stimulation of the affected area of the brain with the help of an electromagnetic stimulator. Today this disease is considered practically incurable. The treatment of patients with Parkinson's disease requires an exact estimate of the current state of the person. The offered concept of research of manifestations of chaos allows to track down the least changes in the patient with the help of an exact quantitative level of description.

Earlier we found out an opportunity for defining the predisposition of a person to the frustration of the central nervous system due to Parkinson's disease [13]. Our work is an expansion and development of informational possibilities of the statistical theory of discrete non-Markov random processes and the search for parameters affecting the health of a subject.

2 The statistical theory of discrete non-Markov random processes. Non-Markovity parameter and its frequency spectrum

The statistical theory of discrete non-Markov random processes [10]-[12] forms a mathematical basis for our study of complex live systems. The theory allows to calculate the wide quantitative set of dynamic variables, correlation functions and memory functions, power spectra, statistical non-Markovity parameter, kinetic and relaxation parameters. The full interconnected set of these variables, functions and parameters creates a quantitative measure of chaos used for the description of processes, connected with functioning of alive organism.

We use the non-Markovity parameter ε as a quantitative estimate of the non-Markov properties of the statistical system. The non-Markovity parameter allows to real statistical processes into Markov processes ($\varepsilon \to \infty$), quasi-Markov processes ($\varepsilon > 1$) and non-Markov processes ($\varepsilon \sim 1$). Besides the non-Markovity parameter we also use the concept of the spectrum of the non-Markovity parameter. We define the spectrum as a set of all values of the physical parameter used for describing the state of a system or a process. Let's consider the first and the nth kinetic equations of the chain of connected non-Markov finite-difference kinetic equations [10, 11]:

$$\frac{\Delta a(t)}{\Delta t} = \lambda_1 a(t) - \tau \Lambda_1 \sum_{j=0}^{m-1} M_1(j\tau) a(t - j\tau), \tag{1}$$

$$\dots$$

$$\frac{\Delta M_n(t)}{\Delta t} = \lambda_{n+1} M_n(t) - \tau \Lambda_{n+1} \sum_{j=0}^{m-1} M_{n+1}(j\tau) M_n(t - j\tau).$$

The first equation is based on the Zwanzig'-Mori's kinetic equation in nonequilibrium statistical physics:

$$\frac{da(t)}{dt} = -\Omega_1^2 \int_0^t d\tau M_1(j\tau) a(t - j\tau). \tag{2}$$

Here $a(t)$ is a normalized time correlation function (TCF):

$$\lim_{t \to 0} a(t) = 1, \lim_{t \to \infty} a(t) = 0. \tag{3}$$

The zero memory function $a(t)$ and the first order memory function $M_1(t)$ in Eqn. (1):

$$M_0(t) = a(t) = \frac{< \mathbf{A}_k^0(0) \mathbf{A}_{m+k}^m(t) >}{< |\mathbf{A}_k^0(0)|^2 >}, \quad t = m\tau,$$

$$M_1(j\tau) = \frac{< \mathbf{A}_k^0(0) \hat{L}_{12} \{1 + i\tau \hat{L}_{22}\}^j \hat{L}_{21} \mathbf{A}_k^0(0) >}{< \mathbf{A}_k^0(0) \hat{L}_{12} \hat{L}_{21} \mathbf{A}_k^0(0) >}, \quad M_1(0) = 1.$$

$$\mathbf{A}_k^0(0) = (\delta x_0, \delta x_1, \delta x_2, \cdots, \delta x_{k-1}),$$
$$\mathbf{A}_{m+k}^m(t) = \{\delta x_m, \delta x_{m+1}, \delta x_{m+2}, \cdots, \delta x_{m+k-1}\},$$

describes statistical memory in complex systems with a discrete time ($\mathbf{A}_k^0(0)$ and $\mathbf{A}_{m+k}^m(t)$ are the vectors of the initial and final states of the studied system). The operator $\hat{L}$ is a finite-difference operator:

$$i\hat{L} = \frac{\triangle}{\triangle t}, \quad \triangle t = \tau,$$

where τ is a discretization time step, $\hat{L}_{ij} = \Pi_i \hat{L} \Pi_j$ $(i, j = 1, 2)$ are matrix elements of the splittable Liouville's quasioperator, $\Pi_1 = \Pi, \Pi_2 = P = 1 - \Pi$ and Π are projection operators.

Let's define the relaxation times of the initial TCF and of the first-order memory functions as follows $M_1(t)$:

$$\tau_a = Re \int_0^\infty a(t)dt, \tau_{M_1} = Re \int_0^\infty M_1(t)dt, \cdots, \tau_{M_n} = Re \int_0^\infty M_n(t)dt. \quad (4)$$

Then the spectrum of non-Markovity parameter $\{\varepsilon\}$ is defined as an infinite set of dimensionless numbers:

$$\{\varepsilon_i\} = \{\varepsilon_1, \varepsilon_2, ..., \varepsilon_n, ...\},$$
$$\varepsilon_1 = \tau_a/\tau_{M_1}, \varepsilon_2 = \tau_{M_1}/\tau_{M_2}, \cdots, \varepsilon_n = \tau_{M_n}/\tau_{M_{n+1}},$$
$$\varepsilon = \tau_{rel}/\tau_{mem}. \quad (5)$$

Note, that $a(t) = M_0(t)$. The number ε_n characterizes the ratio of relaxation times of the memory functions M_n and M_{n+1}. If at some n the value of the parameter $\varepsilon_n \to \infty$, then this relaxation level is Markov. If ε_n changes in limits from zero to a unit value, then the relaxation level is defined as non-Markov. The times τ_{rel} (relaxation time) and τ_{mem} (memory life time) appear when the effects of the statistical memory in the complex discrete system are taken into account by means of the Zwanzig'-Mori's method of kinetic equations. Thus, the non-Markovity parameter spectrum is defined by the stochastic properties of the TCF.

In the work [10] the concept of the generalized non-Markovity parameter for a frequency - dependent case:

$$\varepsilon_i(\omega) = \left\{ \frac{\mu_{i-1}(\omega)}{\mu_i(\omega)} \right\}^{\frac{1}{2}} \quad (6)$$

was introduced. Here as $\mu_i(\omega)$ we have the frequency power spectrum of ith memory functions: $\mu_1(\omega) = |Re \int_0^\infty M_1(t) e^{i\omega t} dt|^2, \cdots, \mu_i(\omega) = |Re \int_0^\infty M_i(t) e^{i\omega t} dt|^2$.

The use of $\varepsilon_i(\omega)$ allows to find the details of the frequency behavior of the power spectra of time correlations and memory functions.

3 The universal property of informational manifestation of chaos in complex systems

In our work the discussion of manifestation of chaos is carried out on the basis of a statistical invariant which includes a quantitative informational measure of chaos and pathology in a covariant form. The existence of the given invariant is very important for the decision of the problems existing in medicine, and for the analysis of a wide circle of problems of physics of complex systems of various nature.

In each live organism there is a universal informational property of the following form:

$$IMC + IMP = Invariant. \tag{7}$$

Here IMC is a informational (quantitative) measure of chaos for the given concrete live system, IMP is an informational measure of a pathological state of a live organism. As an informational (quantitative) measure of the degree of chaosity (regularity) we offer to use the first point of the non-Markovity parameter at zero frequency: $\varepsilon_1(0) = \left\{\frac{\mu_0(0)}{\mu_1(0)}\right\}^{\frac{1}{2}}$. The physical sense of the given parameter consists in comparing the relaxation scales of the time correlation function ($a(\omega)$) to the memory functions of the first order ($\mu(\omega)$). Depending on the values of this parameter one can discriminate Markov processes (with short-range memory) and non-Markov processes (with effects long-range memory). Thus, the phenomena distinguished by the greatest chaosity correspond to Markov processes. Non-Markov processes are connected with greater regularity. The informational measure of a pathological state (IMP) defines the qualitative state of a real live system.

The quantitative estimate of the degree of the chaosity of system IMC contains the information on a pathological state of the system. It testifies to the close interrelation of the given quantities. A high degree of chaosity is characteristic of a normal physiological state. In a pathological state the degree of chaosity decreases. A high degree of regularity is typical of this condition. Thus, the quantitative estimate of chaos in live systems allows to define their physiological or pathological state with a high degree of accuracy. In the right part of Eqn. (7) we have a statistical invariant, which reflects independence of the physical (as well as biophysical, biochemical and biological) laws in the given live organism from the concrete situations as well as the methods of description of these situations. The invariance, submitted in Eqn. (7), is formulated as the generalization of the experimental data. Among other physical laws the properties of invariance reflect the most general and profound properties of the studied systems and characterize a wide sphere of phenomena. Eqn. (7) reflects an informational observation. It consists of two informational measures: the measure of chaos and the measure of pathology (disease).

Let's use the operator of transformation $T(S', S)$ in both parts of Eqn. (7). It reflects the transition of the system from one state S to other S'. By

taking into account the statistical invariance $I(S') = T(S', S)I(S) = I(S)$ in the right part Eqn. (7) we receive:

$$\Delta P = P(S') - P(S) = -\Delta C = -\{C(S') - C(S)\}, \Delta P + \Delta C = 0. \quad (8)$$

Here the following designations are entered : $I(S) = Invariant$, $P(S) = IMP(S)$ is an informational measure of pathology (of disease) for the given state S, $C(S) = IMC(S)$ is an informational measure of chaos for the given state of patient S. Besides in Eqn. (8) into account we take the rules of transformation:

$$C(S') = T(S', S)C(S), P(S') = T(S', S)P(S). \quad (9)$$

Eqns. (7)-(9) are rather simple but they make the quantitative description of the state of a patient possible, both during the disease and under the medical treatment. Eqns. (7)-(9) have a general character. They are true for many complex natural and social systems. It is possible to develop the algorithms of prediction of various demonstrations of chaos in complex systems of diverse nature on the basis of these equations.

4 The quantitative factor of quality of treatment

One of the major problems of the medical physics consists in the development of a reliable criterion of quality of medical treatment, diagnostics and forecasting of the behavior of real live complex systems. As one can see from the previous section, the criterion should include the parameter of the degree of randomness in a live organism. The creation of a quantitative factor of the quality of treatment Q_T is based on the law of behavior of the non-Markovity parameter $\varepsilon_1(0)$ in the stochastic dynamics of complex systems. The greater values of the parameter $\varepsilon_1(0)$ are characteristic of stable physiological states of systems. The minimal values of this parameter are peculiar for pathological states of live systems. Thus, by the increase or reduction of the non-Markovity parameter one can judge the physiological state of a live organism with a high degree of accuracy. Therefore the non-Markovity parameter allows to define a deviation of the physiological state of a system from a normal state.

The factor Q_T defines the efficacy or the quality of the treatment and is directly connected with the changes in the quantitative measure of chaos in a live organism. We shall calculate it on a concrete example. Let us consider **1** as the patient's state before therapy, and **2** the state of the patient after certain medical intervention. Then $\varepsilon_1(\mathbf{1})$ and $\varepsilon_1(\mathbf{2})$ represent quantitative measures of chaosity for the physiological states **1** and **2**. The ratio δ of these values ($\delta = \frac{\varepsilon_1(\mathbf{2})}{\varepsilon_1(\mathbf{1})}$) will define efficacy of therapy. Various j processes occur simultaneously in therapy. Therefore the total value of δ can be defined in the following way:

$$\delta = \prod_{j=1}^{n} \frac{\varepsilon_1^j(\mathbf{2})}{\varepsilon_1^j(\mathbf{1})}, \tag{10}$$

where $j = 1, 2...n$ is the number of the factors affecting the behavior of the non-Markovity parameter. However, the natural logarithm $\ln \delta$ is more convenient for use.

Then we have:

$$\delta > 1, \ln \delta > 0;$$
$$\delta = 1, \ln \delta = 0;$$
$$\delta < 1, \ln \delta < 0.$$

The above mentioned three values of δ correspond to the three different situations of quality of treatment: effective, inefficient and destructive treatment. They reflect an increase, preservation and reduction of the measure of chaosity in therapy. Thus, one can define $Q_T(\varepsilon) = \ln \delta$ according to the equation (10) as follows:

$$Q_T(\varepsilon) = \ln \prod_{j=1}^{n} \frac{\varepsilon_1^j(\mathbf{2})}{\varepsilon_1^j(\mathbf{1})}. \tag{11}$$

However, the total factor Q_T is defined both by the quantitative measures of chaos and by other physiological and biochemical data. Now we shall consider the transition of the patient from state **1** into state **2**. Then by analogy, one can introduce physiological parameter $k(\mathbf{1})$, determined for state **1**, and $k(\mathbf{2})$ for state **2**. In case of Parkinson's disease one can introduce the amplitude or the dispersion of the tremor velocity of extremities (hand or leg) of the patient as this parameter. In other cases any medical data, which are considered for diagnostic purposes, can be used. For greater reliability it is necessary to use the combination of various parameters $k^j(\mathbf{1})$ and $(k^j(\mathbf{2}))$.

The value:

$$Q_T = \ln \prod_{j=1}^{n} \frac{\varepsilon_1^j(\mathbf{2})}{\varepsilon_1^j(\mathbf{1})} * \left\{ \frac{k^j(\mathbf{2})}{k^j(\mathbf{1})} \right\} \tag{12}$$

will be considered as a generalized quantitative factor of quality of the therapy.

However in real conditions it is necessary to increase or weaken the magnitude of chaotic, or physiological contributions to the equation (12). For this purpose we shall take the simple ratio:

$$\ln \prod (a^n b^m ...) = n \ln a + m \ln b + ... \tag{13}$$

By analogy, we can reinforce or weaken various contributions depending on the concrete situation:

$$Q_T = \ln \prod_{j=1}^{n} \left(\frac{\varepsilon_1^j(\mathbf{2})}{\varepsilon_1^j(\mathbf{1})} \right)^{m_j} * \left\{ \frac{k^j(\mathbf{2})}{k^j(\mathbf{1})} \right\}^{p_j} . \quad (14)$$

If incomplete experimental data are available in some situations, so one can assume $p_j = 1$ (attenuation of the physiological contribution). The value of $m_j > 1$ can mean the amplification of the chaotic contribution. Otherwise, if we want to weaken the chaotic contribution, we should take ($m_j = 1$) and if we reinforce the physiological contribution we come towards ($p_j > 1$). We have presented the results of the calculation of the quantitative factor Q_T in the 6th section.

5 Experimental data

We have taken the experimental data from Ref. [15]. They represent the time records of the velocity of tremor of an index finger of a patient with Parkinson's disease (see, also http://physionet.org/physiobank/database/). The effect of chronic high frequency deep brain stimulation (DBS) on the rest tremor was investigated [15] in group of subjects with Parkinson's disease (PD) (16 subjects). Eight PD subjects with high amplitude tremor and eight PD subjects with low amplitude tremor were examined by a clinical neurologist and tested with a velocity laser to quantify time and frequency domain characteristics of tremor. The participants received DBS of the internal globus pallidus (GPi), the subthalamic nucleus (STN) or the ventrointermediate nucleus of the thalamus (Vim). Tremor was recorded with a velocity laser under two conditions of DBS (on-off) and two conditions of medication (L-Dopa on-off).

All the subjects gave informed consent and institutional ethics procedures were followed. The selected subjects were asked to refrain from taking their medication at least 12 h before the beginning of the tests and were allowed to have no more than one coffee at breakfast on the two testing days. Rest tremor was recorded on the most affected side with a velocity-transducing laser [16, 17]. This laser is a safe helium-neon laser. The laser was placed at about 30 cm from the index finger tip and the laser beam was directed perpendicular to a piece of reflective tape placed on the finger tip. Positive velocity was recorded when the subjects extended the finger and negative velocity when the subjects flexed the finger.

The conditions, counterbalanced across subjects, included the following:

1. The L-Dopa condition (no stimulation).
2. The DBS condition (stimulation only).
3. The "off" condition (no medication and no stimulation).
4. The "on" condition (on medication and on stimulation).
5. The effect of stopping DBS on tremor (time record of the tremor after 15, 30, 45, 60 min since switching off of the stimulator).

In **Fig. 1.** the time records of the velocity of changing tremor of an index finger of the second patient's hand (man, 52 years old) under various conditions of influence on the organism are submitted as an example. High velocity of tremor is observed: 1) in a natural condition of the patient **(a)**, 2) in 15 (45) minutes after the stimulator was switched off. Lower speed of tremor is in cases: 1) when both methods (stimulation, medication)are used, 2) when each of these methods is used separately, 3) in 30 (60) minutes after the stimulator was switched off. The similar results are received in Refs. [15].

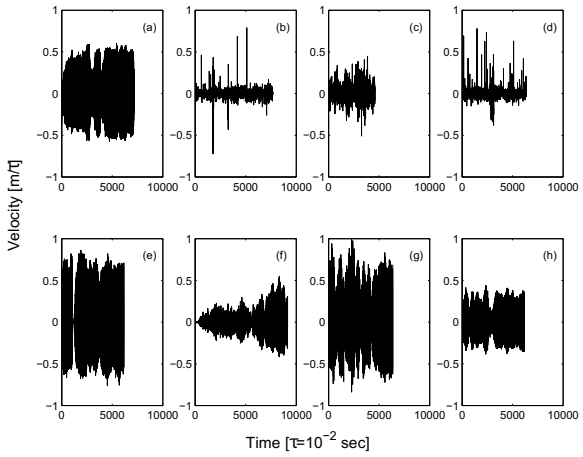

Fig. 1. The velocity of the change of tremor of the right index finger of the patient's hand (the second subject) with Parkinson's disease under various conditions of the experiment. **(a)**-deep brain stimulation off, medication off; **(b)**-the subject was receiving stimulation of the GPi, medication on; **(c)**-deep brain stimulation off, medication on; **(d)**-the subject was receiving stimulation of the GPi, medication off; **(e)-(h)**-the recording of rest tremor in the right index finger of the subject 15 (30, 45, 60) minutes after the stimulator was switched off, this subject was off medication for at least 12 hours.

6 Results

In the given section the results of processing of the experimental data for one of the patients (the subject 2) are shown. The similar pictures are observed in the experimental data of other subjects.

6.1 The non-Markovity parameter as a quantitative measure of defining chaos

In this subsection the technique of the calculation of quantitative and qualitative criteria under various conditions that influence the state a patient is given. The basic idea of the given approach consists in defining the quantitative ratio between chaosity and regularity of the observed process. It allows to judge the physiological (pathological) state of a live system by the degree of chaosity or of regularity. The highest degree of chaosity in the behavior of a live system corresponds to a normal physiological state. Higher degree of regularity or specific ordering is characteristic of various pathological states of a live system. In the given work we use the non-Markovity parameter $\varepsilon_1(0)$ as a special quantitative measure defining chaosity or regularity of the studied process. The examples [10]-[14], [18] which have been investigated by us earlier serve as a basis for such reasoning. As one of the examples we shall consider the tremor velocity of the changing of the subject's index fingers in case of Parkinson's disease.

The comparative analysis of the initial time record and the non-Markovity parameter for all the submitted experimental data allows to discover the following regularity. The value of the non-Markovity parameter $\varepsilon_1(0)$ decreases with the increase of the tremor velocity of the patient fingers (deterioration of the physiological state) and grows with the decrease of the tremor velocity (improvement of the state of the patient). We shall also consider the power spectra of the initial TCF $\mu_0(\omega)$ under various conditions that influence an organism, the window-time behavior of the power spectrum $\mu_0(\omega)$ and the non-Markovity parameter $\varepsilon_1(\omega)$, the time dependence local averaging relaxation parameter $\lambda_1(t)$ as an additional sources of information.

Fig. 2. represents the power spectra of the initial TCF for various conditions of the experiment. One can observe the powerful peak for the all figures at the characteristic frequency $\omega = 0.07 f.u.(\omega = 2\pi\nu, 1 f.u. = 2\pi/\tau, 1\tau = 10^{-2}$ second). The amplitude values of this peak for $\mu_i(\omega)$ $(i = 1, 2, 3)$ are given in **Table 1**. The given peak testifies to a pathological state of the studied system. The similar picture is observed in patients with myocardial infarction [11]. The comparison of these values reflects the amplitude of velocity of tremor at the initial record of time.

In **Table 1** the second patient's amplitude values $\mu_0(\omega)$ for the initial TCF and the memory functions of the younger order $\mu_i(\omega)$ $(i = 1, 2, 3)$ at frequency $\omega = 0.07 f.u.$ are submitted. Terms in Table content define the conditions under which the experiment is carried out. Under all conditions the peak of power on the frequency $\omega = 0.07 f.u.$ can be observed. Amplitude values of the given peak (in power spectrum $\mu_0(\omega)$ in particular) reflect the amplitude of tremor velocity. For example, the least amplitude 75 τ^2 corresponds to the condition (ON, ON; or: deep brain stimulation on, medication on). The highest amplitude $4.34 * 10^4 \tau^2$ corresponds to the greatest speed of tremor (see, **Figs. 1e, 2e**). Thus, the given parameter can be used for the estimate

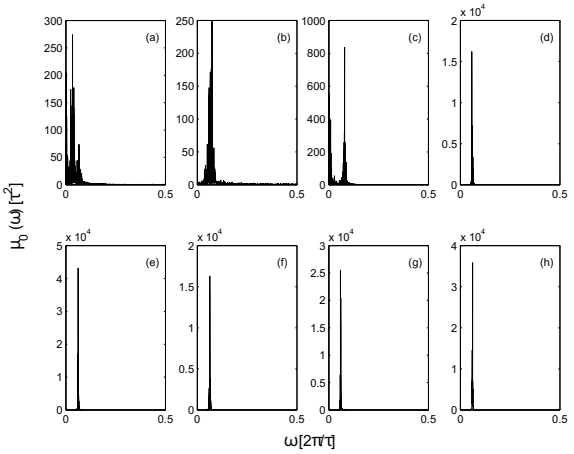

Fig. 2. The power spectrum of the initial TCF $\mu_0(\omega)$ for the velocity of changing of tremor of subject (2) under various conditions that influences an organism. **(a)**-deep brain stimulation on, medication on; **(b)**-deep brain stimulation on, medication off; **(c)**-deep brain stimulation off, medication on; **(d)**-deep brain stimulation off, medication off; **(e)-(h)** the power spectrum of the initial TCF $\mu_0(\omega)$ for the recording of rest tremor in the right index finger of the subject 15 (30, 45, 60) minutes after the stimulator was switched off, medication off. On frequency $\omega = 0.07 f.u., 1 f.u. = 100 Hz$ (the characteristic frequency) peak is found. The presence and amplitude of the peak are determined by the state of the patient.

of the physiological state of a patient. The similar picture is observed in all other patients.

Table 1. The value $\mu_0(\omega)$ for the initial TCF and $\mu_i(\omega)$ $(i = 1, 2, 3)$ for the memory functions of junior orders on the frequency $\omega = 0.07 f.u.$ 1 - Deep brain stimulation, 2 - Medication (the subject 2). For example, OFF OFF - no DBS and no medication.

	ON ON	ON OFF	OFF ON	OFF OFF	15 OFF	30 OFF	45 OFF	60 OFF
μ_0	75	250	812	$1.71 * 10^4$	$4.34 * 10^4$	$1.53 * 10^4$	$2.51 * 10^4$	$3.68 * 10^4$
μ_1	19	52	$1.28 * 10^3$	$1.17 * 10^4$	$3.21 * 10^4$	$1.32 * 10^4$	$1.82 * 10^4$	$2.8 * 10^4$
μ_2	42	60	113	71	300	62	137	224
μ_3	37	54	141	73	147	74	152	186

In **Fig. 3.** the initial time record (the normal state of the subject; OFF, OFF) and the window-time behavior of the power spectrum of the TCF (the technique of the analysis of the given behavior is considered in Ref. [18]) are submitted. In these figures Regions 1, 2, 3, which correspond to the least values of the tremor velocity are shown. The minimal amplitude of the peaks of the power spectrum $\mu_0(\omega)$ corresponds to the regions with the least velocity of tremor.

In **Fig. 4.** the frequency dependence of the first point of the non-Markovity parameter $\varepsilon_1(\omega)$ is submitted for the second subject under various

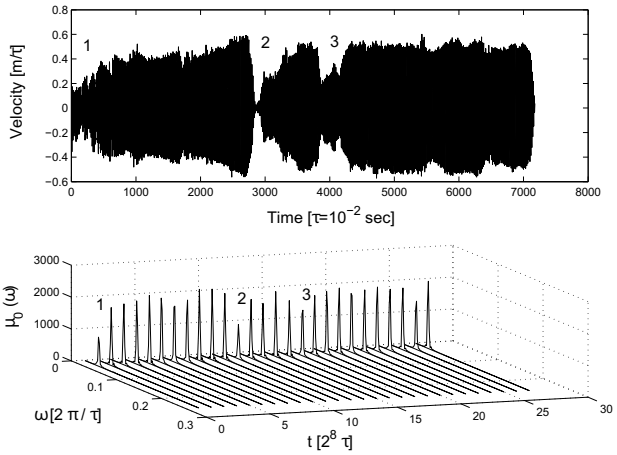

Fig. 3. The initial time series and the window-time behavior of the power spectrum of the TCF $\mu_0(\omega)$. Two figures are submitted to illustrate the case of subject 2: stimulation of and medication of the brain are not applied. The change of regimes in the initial time series is reflected in the decrease of the velocity of tremor (regions 1, 2 and 3) and becomes visible as a sharp reduction of the power of spectrum $\mu_0(\omega)$ (see, the $1th, 12th, 17th$ windows for more detail).

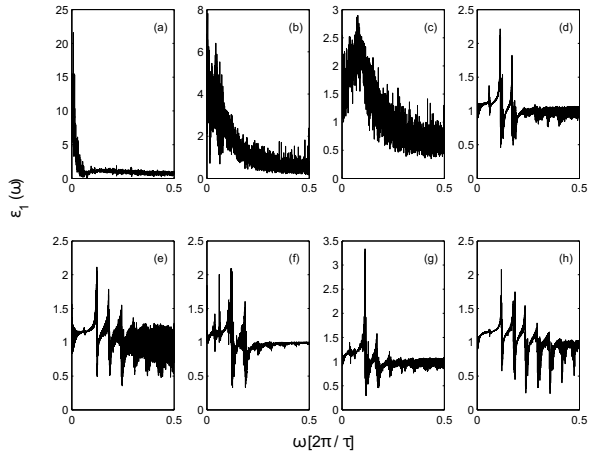

Fig. 4. The first point of the non-Markovity parameter $\varepsilon_1(\omega)$ for the second subject under various conditions of the experiment: **(a)**-deep brain stimulation off, medication on; **(b)**-deep brain stimulation on, medication on; **(c)**-deep brain stimulation on, medication off; **(d)**-deep brain stimulation off, medication off; **(e)-(h)**-the recording of rest tremor in the right index finger of the subject 15 (30, 45, 60) minutes after the stimulator was switched off, medication off. The non-Markovity parameter at zero frequency $\varepsilon_1(0)$ has a special role. These values (6.02 in the first case and 1.0043 in the last one) define chaosity or regularity of the studied states. The amplitudes of these values also characterize the state of the subject.

conditions of the experiment. The value of the parameter $\varepsilon_1(0)$ on zero frequency is of special importance for our the research of manifestations of chaos. It is possible to judge the change of the state of a subject by the increase (or by the decrease) of this value. The comparative analysis of the initial time records allows to come to the similar conclusions. In **Figs. 4d-h** well defined frequency structure of the non-Markovity parameter can be seen. The given structure is completely suppressed and disappears only at treatment. The characteristic frequency of fluctuations corresponds, approximately, to $\omega = 0.06 f.u.$ These multiple peaks are most appreciable on low frequencies. On higher frequencies these fluctuations are smoothed out. As can be seen in these figures, the 2nd subject has a strong peak which remains stable over time. As our data show, the comb-like structure with multiple frequencies can observed in all patients with high velocity of tremor. In a group of patients with low velocity of tremor it disappears, and a wider spectrum that presents some fluctuations over time is observed. The present structure testifies to the presence of characteristic frequency of fluctuations of tremor of human extremities.

In **Table 2** the interval of dispersion of values and the average value $\varepsilon_1(0)$ for the whole group of subjects (16 subjects) are submitted. Let's consider 2 conditions: OFF, OFF and OFF, ON. The interval of dispersion and average value $\varepsilon_1(0)$ in the first case are minimal. It means the presence of a high degree of regularity of a physiological state of the patient. The degree of regularity is appreciably reduced at application of any method of treatment. Here the degree of chaosity grows. The maximal degree of chaosity corresponds to the condition OFF, ON (medication only is used). The difference of $\varepsilon_1(0)_{av.val}$ with medication and without it (OFF, OFF) is 3.8 times (!). On the basis of the comparative analysis of the given parameters the best method of treatment for each individual case can be found. It is necessary to note, that the given reasoning is true only for the research of the chaotic component of the quantitative factor of the quality of treatment Q_T. The most trustworthy information about the quality of treatment can be given by the full quantitative factor Q_T which takes into account other diagnostic factors.

Table 2. The interval of dispersion of values and the average value of the first point of the non-Markovity parameter $\varepsilon_1(0)_{int}$ and $\varepsilon_1(0)_{av.val}$ under various conditions of the experiment realization for the group of 16 subjects. 1 - Deep brain stimulation, 2 - Medication.

	OFF OFF	ON OFF	OFF ON	ON ON	15 OFF	30 OFF	45 OFF	60 OFF
$\varepsilon_1(0)_{int}$	1 - 1.8	2 - 18	2 - 22	1.5 - 8	1.5 - 3	1.8 - 5	1.7 - 4.5	2 - 6
$\varepsilon_1(0)_{av.val}$	1.41	4.14	5.31	3.17	2.43	2.92	2.76	2.93

The results of calculation of the quantitative factor Q_T are submitted in **Table 3**. The data are submitted for one patient and for the whole group. Here $Q_T(\varepsilon)$ is a chaotic contribution to the quantitative factor (see Eqn. (11)).

Q_T is a total quantitative factor (see Eqn. (14)), where $\varepsilon^{(1)}(\mathbf{1})$ and $\varepsilon^{(1)}(\mathbf{2})$ are chaotic contributions for the tremor amplitudes $k^{(1)}(\mathbf{1}), k^{(1)}(\mathbf{2})$; $\varepsilon^{(2)}(\mathbf{1})$ and $\varepsilon^{(2)}(\mathbf{2})$ are dispersions of tremor amplitude $k^{(2)}(\mathbf{1}), k^{(2)}(\mathbf{2})$ (physiological contributions). The full factor Q_T provides detailed information about the quality of treatment. The present factor includes both the chaotic component $Q_T(\varepsilon)$, and the physiological contribution $Q_T(k)$. The calculation $Q_T(k)$ is described in **Section 4**. One can define the quality of treatment by means of Q_T. The positive value of the given factor defines an effective method of treatment. For a separate patient and for the whole group Q_T has the maximal value under condition of ON, ON. The total quantitative factor is supplemented by a diagnostic (physiological) component. It allows to take into account those features of the system which the chaotic component does not contain. For the second patient under condition 15 OFF (see, **Table 3**) the factor Q_T has a negative value. It testifies to the negative influence of the given method of treatment on the organism of the patient. Thus, the best method of treatment is the combination of the two medical methods: electromagnetic stimulation and medication.

Table 3. The quantitative factor $Q_T(\varepsilon)$ and the total quantitative factor Q_T for the second patient and for the whole group (16 subjects). 1 - Deep brain stimulation, 2 - Medication. $m_j = 1, p_j = 1$.

				The 2 patient				
	OFF OFF	ON OFF	OFF ON	ON ON	15 OFF	30 OFF	45 OFF	60 OFF
$Q_T(\varepsilon)$		0.758	2.556	1.756	0.291	0.438	0.041	0.017
Q_T		1.763	2.013	2.654	-0.013	0.883	-0.004	0.856
				The all group				
$Q_T(\varepsilon)$		1.077	1.326	0.810	0.544	0.728	0.671	0.731
Q_T		3.661	2.883	4.071	1.47	1. 734	1.624	1.742

Fig. 5. reflects the behavior of the parameter $\varepsilon_1(0)$ for the four subjects. The points lying above the horizontal line, testify to the improvement of the state the subject and the efficacy of the method of treatment. The points, lying below the horizontal line, testify to the deterioration of the state of the subject and inefficiency of the applied method. For example, **Fig. 5b** corresponds to the sevenfold change of the quantitative measure of chaos for the 9th patient. In case of the 8th patient (see **Fig. 5c**) no influence could change the measure of chaos, therefore there was practically no change in the state of the subject either. In some cases (see **Figs. 5b, 5d**) the DBS or the medication reduces the measure of chaos which testifies to the deterioration of the state of the subject. This approach allows to define the most effective (or inefficient) method of treatment in each individual case.

6.2 The definition of the predictor of the sudden changes of the tremor velocity

In this subsection the window-time behavior of the non-Markovity parameter $\varepsilon_1(\omega)$ for a certain case (the second patient, two methods of medical treatment

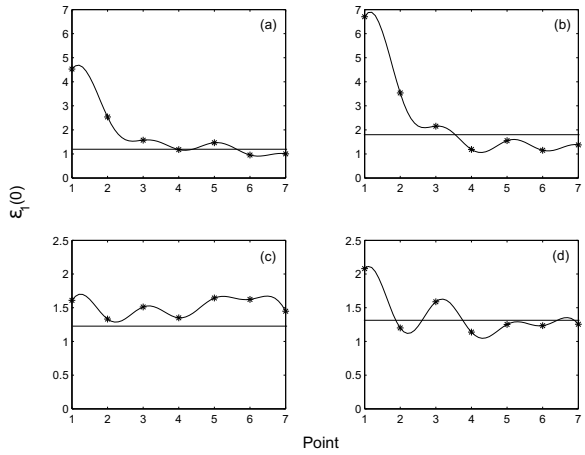

Fig. 5. The behavior of the parameter $\varepsilon_1(0)$ for four various patients: **(a)**-the second subject, high amplitude tremor, **(b)**-the 9th subject, low amplitude tremor (the stimulation of the GPi); **(c)**-the 8th subject, high amplitude tremor, **(d)**-the 15th subject, low amplitude tremor (the stimulation of the STN). The value $\varepsilon_1(0)$ for seven consecutive conditions of the experiment: 1 point - both methods are used; 2 - treatment by medication is applied only; 3 - the DBS only is used; 4 (5, 6, 7) - value of the parameter 15 (30, 45, 60) minutes after the stimulator was switched off; the horizontal line corresponds to the value of the parameter when no method is used. This representation allows to define the most effective method of treatment for each patient.

were used) and the procedure of local averaging of the relaxation parameters were considered. These procedures allow to determine specific predictors of the change of regimes in the initial time records.

The idea of the first procedure is, that the optimum length of the time window ($2^8 = 256$ points) is found first. In the studied dependence (in our case the frequency dependence of the first point of the non-Markovity parameter) the first window is cut out. Then the second window is cut out (from point 257 points to point 512) etc. This construction allows to find the local time behavior of the non-Markovity parameter. At the critical moments when the tremor velocity increases the value of the non-Markovity parameter comes nearer to the value of a unit. One can observe that the value of the non-Markovity parameter starts to decrease by 2-2.5 sec before the increase of the velocity of tremor (see **Fig. 6.**).

The idea of the second procedure consists in the following. One can consider the initial data set and take an N-long sampling. We can calculate kinetic and relaxation parameters for the given sampling. Then we can carry out the operation of "step-by-step one shift to the right". Then we calculate kinetic and relaxation parameters. After that we execute one more "step-by-step shift to the right" and continue the procedure up to the end of the time

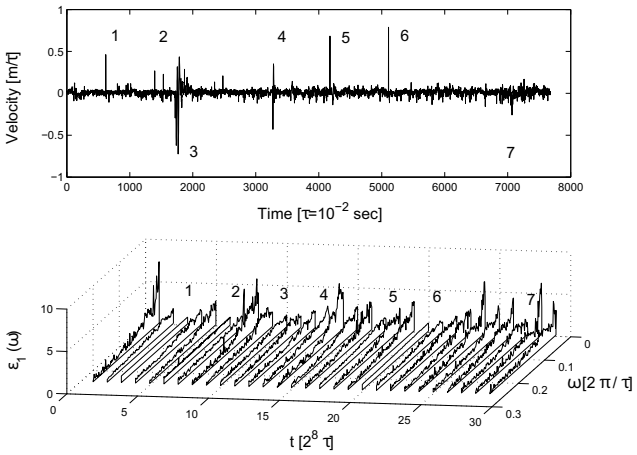

Fig. 6. The initial signal - the change of velocity of tremor when the second patient is treated by two methods and the window-time behavior of the first point of non-Markovity parameter $\varepsilon_1(\omega)$. At the time of the sharp change of the mode (sharp increase of velocity of tremor) in the behavior of the initial time series (regions 1-7) gradual decrease of the non-Markovity parameter up to the value of a unit (the $3th, 6th, 10th, 14th, 17th, 20th, 27th$ windows) is observed. The decrease of the non-Markovity parameter begins 2-2,5 sec earlier of acceleration of tremor on an initial series.

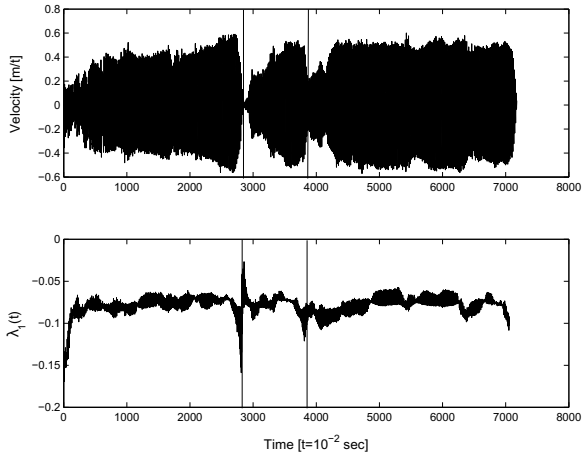

Fig. 7. The change of the tremor velocity for the second patient (stimulation of the brain and medication are not used) and the time dependence of the local relaxation parameter $\lambda_1(t)$. The procedure of localization allows to find sudden changes of relaxation regimes of the researched system. The amplitude values of the local relaxation parameter are in the region of the lowest velocity of tremor. The change in the time behavior of the parameter $\lambda_1(t)$ begins 2-3 sec earlier than the change of the regimes in the initial time series appears.

series. Thus the local averaged parameters have high sensitivity to the effects of intermittency and non-stationarity. Any non-regularity in the initial time series is reflected instantly in the behavior of local average parameters. The optimum length of the sampling is 120 points. In **Figs. 7, 8** the initial time record and the time dependence of local relaxation parameter $\lambda_1(t)$ are submitted for two cases. The change in the time behavior of the parameter $\lambda_1(t)$ begins 2-3 sec prior to the change of the regimes of the time record of the tremor velocity . The increase of speed of relaxation ($\lambda_1(t)$) testifies to the decrease of velocity of the tremor.

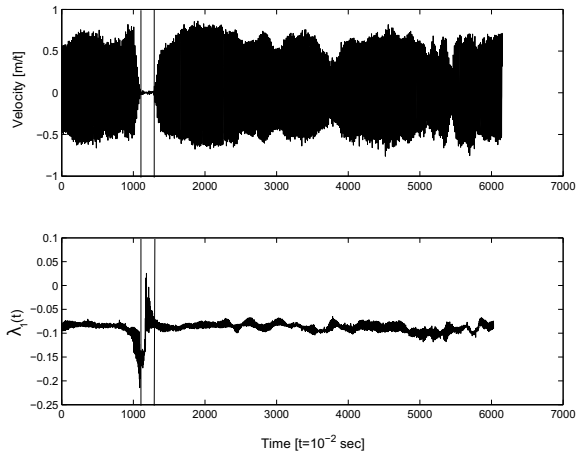

Fig. 8. The change of the tremor velocity for the second patient (15 minutes after the stimulator was switched off, medication off) and the time dependence of the local relaxation parameter $\lambda_1(t)$. The site characterizing the minimal velocity of the tremor is allocated. The increase and decrease of the local relaxation parameter occurs 2.5 sec before the decrease or increase of the velocity of tremor. The similar behavior of the parameter $\lambda_1(t)$ can be explained by its high sensitivity to nonstationarity of the initial signal.

7 Conclusions

In the given work we offer a new concept of the study of manifestations of chaos. It is based on the application of the statistical non-Markovity parameter and its spectrum as an informational measure of chaos. This approach allows to define the difference between a healthy person and a patient by means of a numerical value of the non-Markovity parameter. This observation gives a reliable tool for the strict quantitative estimates for the diagnosis and quantification of the treatment of patients. As an example we have con-

sidered the changes of various dynamic conditions of patients with Parkinson's disease. The quantitative and qualitative criteria used by us for the definition of chaosity and regularity of investigated processes in live systems, allows to reveal new informational opportunities of the statistical theory of discrete non-Markov random processes. The new concept allows to estimate quantitatively the efficacy and the quality of treatment of different patients with Parkinson's disease. She allows to investigate various dynamic states of complex systems in real time.

The statistical parameter of non-Markovity $\varepsilon_1(0)$ can serve as a reliable quantitative informational measure of chaos. It allows to use $\varepsilon_1(0)$ for the study of the behavior of different chaotic systems. In case of Parkinson's disease the change of the given parameter defines the change of a quantitative measure of chaosity or regularity of a physiological system. The increase of chaosity reflects the decrease of the quantitative measure of pathology and improvement of the state of the patient. The increase of the regularity defines high degree of manifestation of pathological states of live systems. The combined power spectra of the initial TCF $\mu_0(\omega)$, the three memory functions of junior orders and the frequency dependence of the non-Markovity parameter compose an informational measure which defines the degree of pathological changes in a human organism.

The new procedures (the window-time procedure and the procedure of local averaging) show evident predictors of the change of the initial time signal. The window-time behavior of the non-Markovity parameter $\varepsilon_1(\omega)$ reflects the increase of the tremor velocity 2-2.5 s earlier. It happens when the non-Markovity parameter approaches a unit value. The procedure of local averaging of the relaxation parameter $\lambda_1(t)$ reflects the relaxation changes of physiological processes in a live system. The behavior of the local parameter $\lambda_1(t)$ reacts to the change of relaxation regimes in the initial time record 2-3 s earlier. These predictors allow to lower the probability of ineffective use of different methods of treatment.

In the course of the study we have come to the following conclusions. The application of medication for the given group of patients proved be the most efficient way of the treatment of patients with Parkinson's disease. The combination of different methods (medication, electromagnetic stimulator) is less effective in comparison with application either of medication or of stimulator. After the stimulator is switched off its aftereffect has an oscillatory character with characteristic low frequency corresponding to the period of 30 min. Used separately stimulation is less effective, than the use of medication. In some cases both medication and stimulation exert a negative influence on state of subject. The efficacy of various medical procedures and the quality of treatment can be estimated quantitatively for each subject separately with utmost precision.

However, if we take both chaotic and physiological components into account, the general estimation of the quality of treatment will be more uni-

versal. Two methods (DBS and medication, $Q_T = 4.071$) produce the most effective result in comparison with the effect of DBS (3.661) or of medication (2.883) given separately. This is connected with additional aspect of estimation of the quality of treatment due to the study both of chaotic and diagnostic components of a live system. The given conclusion corresponds to the results of work [15].

In conclusion we would like to state that our study gives a unique opportunity for the exact quantitative description of the states of patients with Parkinson's disease at various stages of the disease as well as the treatment and recovery of the patient. On the whole, the offered concept of manifestations of chaos opens up great opportunities for the alternative analysis, diagnosis and forecasting of the chaotic behavior of real complex system of a live nature.

8 Acknowledgements

This work supported by the RHSF (Grant No. 03-06-00218a), RFBR (Grant No. 02-02-16146) and CCBR of Ministry of Education RF (Grant No. E 02-3.1-538). The authors acknowledge Prof. Anne Beuter for stimulating criticism and valuable discussion and Dr. L.O. Svirina for technical assistance.

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