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Statistical Memory Effects in Time Series Dynamics: Application to Parkinson's Disease

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In this work we present a new approach to the problem of diagnosing and forecasting various states in patients with Parkinson's disease. Recently we have achieved the following result. In real complex systems the non-Markovity parameter (NMP) can serve as a reliable quantitative measure of the current state of a complex system and can help to estimate the deviation of this state from the normal one. Our preliminary studies of real complex systems in cardiology, neurophysiology, epidemiology and seismology have shown, that the NMP has diverse frequency dependence. It testifies to the competition between Markov and non-Markov, random and regular processes and makes a transfer from one relaxation scenario to the other possible. On this basis we can formulate the new method of diagnosing deflections in the central nervous system caused by Parkinson's disease. We suggest the statistical theory of discrete non-Markov stochastic processes to calculate the NMP and the quantitative evaluation of various dynamic states of real complex systems. With the help of NMP we have found evident manifestation of Markov effects in a normal (healthy) state of the studied live system and its sharp decrease in the non-Markov states in the period of crises and catastrophes and various human diseases. The given observation creates a reliable basis for predicting crises and catastrophes, as well as for diagnosing and treating various human diseases, Parkinson's disease, in particular.

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1. Introduction

Various methods and models have been used in attempts to characterize physical peculiarities and physiological mechanisms of the treatment of patients. Today treatment of serious diseases of human nervous and motor systems attracts a lot of attention. Methods of biophysics, biochemistry and neurophysiology allow to receive more effective means of treating the majority of diseases, including Parkinson's disease. These new methods of treatment are an alternative to the regular treatment of Parkinson's disease. They substantially change the process of treatment of the patients.

The records of a tremor of human extremities are analyzed to study physiological changes at Parkinson's disease. The basic problems connected with the change of human gait dynamics as well as of various disorders of human motor activity, are considered in the papers of J. Hausdorff [1]-[6]. In the works the stride-to-stride variability and its temporal organization in children [1],

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the steady long-range correlation of fluctuations of young people's step interval [2], the increase of instability of elderly people's gait [3, 4], the changes of the fractal dynamics of human's gait with age and patients' gait [5, 6] are investigated. The use of nonlinear time series analysis for the study of normal and pathological human walking is considered in Refs. [7, 8]. In addition to the study of a muscle tremor of legs the scientists are engaged in the analysis of the time series of a physiological and pathological tremor of hands (and muscle activity) [9]-[13]. In Ref. [14] the periodic structure in the time series of a hand tremor in a patient with Parkinson's disease was found be means of a nonlinear signal and multimodal (independent) oscillations. The analysis of a physiological state of a patient with Parkinson's disease is also carried out by studying the time series of a pathological tremor of fingers [15]-[20].

The present work is based on a qualitatively different physical approach to the study of a physiological state of a patient with Parkinson's disease under different medical interventions. For the study of various dynamic states of a live system we consider the statistical effects of non-Markovity. The effects of non-Markovity in real complex systems: biological [21]-[24], physical [23, 25, 26], natural [27, 28], and live [27], [29]-[32] ones are of special interest for the correlation analysis. As a starting point we use separate concepts and points of the statistical theory of discrete non-Markov random processes in statistical physics [27]. The study of various dynamic features of complex systems in seismology [28], cardiology [29], neurophysiology [30, 32] and epidemiology [31] have allowed to propose a new method of diagnosing and forecasting Parkinson's disease. The essence of this methods consists in the following. As the first stage, statistical processing of initial time series of measurements of the observed physiological parameter is carried out. The second stage consists in defining a special identifier, in our case the non-Markovity parameter $\varepsilon_1(\omega)$ $(i = 1, 2, 3...)$. The first point of the non-Markovity parameter $\varepsilon_{\mathbf{1}} = \varepsilon_1(\omega)$ (further simply the non-Markovity parameter) is of special significance here. As a whole, the non-Markovity parameter is used for quantitative description of long-range memory effects in real complex systems. The initial idea of the present concept was to separate Markov (with short-range time memory) and non-Markov (with long-range time memory) stochastic processes. However, the study of real complex systems has allowed to reveal additional possibilities of this parameter. We have discovered unusual behavior of the non-Markovity parameter $(\varepsilon_1(0))$ in various physiological states of a human [29]-[32], when the greater values of the parameter $\varepsilon_1(0)$ are characteristic of stable physiological states of systems [29, 30] and the minimal values of this parameter are typical of pathological states of live systems [29, 30, 32]. Thus, by the increase or decrease of the non-Markovity parameter one can judge about physiological status 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 its normal state.

In this work the new method of diagnosing and forecasting is applied to live systems. The possibilities of the new approach are revealed when analyzing experimental data on various states of a patient with Parkinson's disease. Parkinson's disease is a chronic progressing disease of the brain observed in 1-2 % of elderly people. The 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". Complex biochemical processes characteristic of Parkinson's disease results 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 for Parkinson's disease form the so-called classical triad: tremor, rigidity of muscles (disorder of speech, amimia), and depression (anxiety, irritability, apathy). 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.

Earlier we found the way to define the liability of a person to frustration of the central nervous system due to Parkinson's disease [30]. The present 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 subjects. Treatment of patients with Parkinson's disease requires exact estimation of the current state of the person.

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

The statistical theory of discrete non-Markov random processes [27]-[29] forms a mathematical basis for the present study of complex live systems. The theory allows to calculate a wide set of dynamic variables, correlation functions, memory functions, power spectra, statistical non-Markovity parameter, kinetic and relaxation parameters. The full interconnected set of these variables, functions and parameters allows to receive information on stochastic processes, connected with functioning of a live organism [29]-[32].

We use the non-Markovity parameter ε as a quantitative measure of non-Markov properties of a statistical system. The non-Markovity parameter ε, first appearing in [33], allows one to obtain valuable information concerning non-Markovian properties of the wide range of relaxation processes. The non-Markovity parameter allows to attribute real stochastic 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 non-Markovity parameter [34]. 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 us consider the first and the nth kinetic equations of the chain of connected non-Markov finite-difference kinetic equations [27, 29]:

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

$$\cdots$$

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

The first equation is based on the Zwanzig'-Mori's kinetic equation in nonequilibrium statistical physics [35]-[39]:

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

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

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

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

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

$$t = m\tau,$$

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

$$M_1(0) = 1,$$

$$\mathbf{A}_k^0(0) = (\delta x_0, \delta x_1, \delta x_2, \cdots, \delta x_{k-1}),$$

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

describes the statistical memory in complex systems with 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 us define the relaxation times of the initial TCF and of the first-order memory functions $M_1(t)$ [25]-[27] as follows :

$$\tau_a = Re \int_0^\infty a(t)dt = \Delta t \sum_{j=0}^{N-1} a(t_j),$$

$$\tau_{M_1} = Re \int_0^\infty M_1(t)dt = \Delta t \sum_{j=0}^{N-1} M_1(t_j), \cdots,$$

$$\tau_{M_n} = Re \int_0^\infty M_n(t)dt = \Delta t \sum_{j=0}^{N-1} M_n(t_j).$$

Then the spectrum of non-Markovity parameter $\{\varepsilon\}$ [34] is defined as a set of dimensionless numbers:

$$\{\varepsilon\} = \{\varepsilon_1, \varepsilon_2, ..., \varepsilon_i, ..., \varepsilon_{n-1}\}, \qquad (2)$$

$$\varepsilon_1 = \tau_a/\tau_{M_1}, \varepsilon_2 = \tau_{M_1}/\tau_{M_2}, \cdots, \varepsilon_{n-1} = \tau_{M_{n-1}}/\tau_{M_n},$$

$$\varepsilon = \tau_{rel}/\tau_{mem}.$$

Note, that $a(t) = M_0(t)$. The number ε_{n-1} characterizes the ratio of relaxation times of the nearest memory functions M_{n-1} and M_n. If at some $n-1$ the value of the parameter $\varepsilon_{n-1} \to \infty$, then this relaxation level is Markov. If ε_{n-1} changes in limits from zero to unity, then the relaxation level is defined as non-Markov ones. The times τ_{rel} (relaxation time) and τ_{mem} (memory life time) appear when the effects of statistical memory in 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.

The concept of the generalized non-Markovity parameter for a frequency - dependent case:

$$\varepsilon_i(\omega) = \left\{ \frac{\mu_{i-1}(\omega)}{\mu_i(\omega)} \right\}^{\frac{1}{2}}, \qquad (3)$$

was introduced in the work [27]. Here as $\mu_i(\omega)$ we designated the frequency power spectrum of ith memory functions:

$$\mu_1(\omega) = |Re \int_0^\infty M_1(t) e^{i\omega t} dt|^2$$
$$= |\sum_{j=0}^{N-1} M_1(t_j) \cos \omega t_j|^2, \cdots,$$

$$\mu_i(\omega) = |Re \int_0^\infty M_i(t) e^{i\omega t} dt|^2$$
$$= |\sum_{j=0}^{N-1} M_i(t_j) \cos \omega t_j|^2.$$

The new offered method of diagnosing and forecasting infringements of central nervous system for patients with Parkinson's disease is based on the use of the first point of the non-Markovity parameter. For a frequency - dependent case the first point of the non-Markovity parameter [27] is defined as follows:

$$\varepsilon_{\mathbf{1}} = \varepsilon_1(\omega) = \left\{ \frac{\mu_0(\omega)}{\mu_1(\omega)} \right\}^{\frac{1}{2}}. \qquad (4)$$

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

3. Using the non-Markovity parameter for quantitative estimation of a physiological state of live systems

In this work the study of live systems is carried out on the basis of interrelation which includes the non-Markovity parameter and information on a physiological state of a live system,

which defines a qualitative state of a real system. The existence of the given interrelation is very important for the analysis of a wide range of problems in medical science and physics of complex systems of diverse nature. The value of the first point of the non-Markovity parameter at zero frequency is defined as: $\varepsilon_1(0) = \left\{\frac{\mu_0(0)}{\mu_1(0)}\right\}^{\frac{1}{2}}$ (see, Eq. (4)). The physical sense of the given parameter consists in comparing the relaxation scales of the time correlation function ($a(\omega) = \mu_0(\omega)$) to the memory functions of the first order ($\mu_1(\omega)$). Depending on the values of this parameter one can discriminate Markov processes (with short-range memory) and non-Markov processes (with long-range memory effects). Thus memory is understood as information on the previous states of a system. The behavior of non-Markovity under various influences in a live system contains information about its physiological state (including its pathological state) [29]-[32]. The greater values of the parameter $\varepsilon_1(0) \sim 10^2$ are typical for normal physiological state. In a pathological state of a system the value of non-Markovity decreases $\varepsilon_1(0) \sim 10^0$. The change of non-Markovity reflects the change of a physiological state of a live system. Thus, the definition of the non-Markovity parameter for time series allows to define with high degree of reliability either a state of a live system is physiological or pathological one. It testifies to close interrelation of the non-Markovity parameter and information, characterizing the state of a system. The submitted interrelation is, in fact, a type of informational observation.

4. Quantitative factor of the quality of treatment

One of the major problems of medical physics consists in the development of a reliable criterion defining quality of medical treatment, diagnosing and forecasting of live complex systems behavior. As one can see from the previous section, the criterion should include the parameter of non-Markovity of alive organism. The creation of a quantitative factor of the quality of treatment Q_T is based on the behavior of the non-Markovity parameter $\varepsilon_1(0)$ in the stochastic dynamics of live complex systems.

The factor Q_T defines the efficacy or the quality of the treatment and is directly connected with the changes of the non-Markov effects in a live organism. We shall calculate Q_T for the 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 randomness 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 the efficacy of the therapy. Various j processes occur simultaneously in the therapy. Therefore the total value of the parameter δ can be defined in the following way:

$$\delta = \prod_{j=1}^{n} \frac{\varepsilon_1^j(\mathbf{2})}{\varepsilon_1^j(\mathbf{1})}, \tag{5}$$

where $j = 1, 2...n$ is the number of 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 the quality of the treatment: effective, inefficient and destructive treatment. Thus, one can define the value $Q_T(\varepsilon) = \ln \delta$ according to Eq. (5) as follows:

$$Q_T(\varepsilon) = \ln \prod_{j=1}^{n} \frac{\varepsilon_1^j(\mathbf{2})}{\varepsilon_1^j(\mathbf{1})}. \tag{6}$$

However, the total factor Q_T is defined both by the non-Markovity parameter (stochastic contribution) and by other physiological and biochemical data. Now we shall consider the transition of the patient from state **1** to 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 amplitude or dispersion of the tremor velocity of extremities (hand or leg) 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 $k^j(\mathbf{2})$.

So, the value:

$$Q_T = \ln \prod_{j=1}^{n} \frac{\varepsilon_1^j(\mathbf{2})}{\varepsilon_1^j(\mathbf{1})} * \left\{ \frac{k^j(\mathbf{2})}{k^j(\mathbf{1})} \right\}, \qquad (7)$$

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

However in real conditions it is necessary either to increase or weaken the magnitude of contribution, determined by the non-Markovity parameter or physiological contributions to Eq. (7). For this purpose we shall take the simple ratio:

$$\ln \prod (a^n b^m ...) = n \ln a + m \ln b + ...$$

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

$$Q_T = \ln \prod_{j=1}^{n} \left(\frac{\varepsilon_1^j(\mathbf{2})}{\varepsilon_1^j(\mathbf{1})} \right)^{m_j} * \left\{ \frac{k^j(\mathbf{2})}{k^j(\mathbf{1})} \right\}^{p_j}. \qquad (8)$$

If experimental data in some situations are incomplete one can assume $p_j = 1$ (attenuation of the physiological contribution). The value of $m_j > 1$ can mean the amplification of the stochastic contribution, determined by the non-Markovity parameter. Otherwise, if we want to weaken the contribution, determined by the non-Markovity parameter, we should take $(m_j = 1)$, and if we reinforce the physiological contribution we come to $(p_j > 1)$. We have presented the results of the concrete calculations of the quantitative factor Q_T in 6th Section.

5. The experimental data

We have taken the experimental data from Refs. [40, 41] (see, also http://physionet.org/physiobank/database/). They represent the time records of the tremor velocity of an index finger of a patient with Parkinson's disease. The effect of the chronic high frequency deep brain stimulation (DBS) on the rest tremor was investigated [40, 41] for a group of subjects with Parkinson's disease (PD) (16 subjects). Eight PD subjects with a high amplitude tremor and eight PD subjects with a low amplitude tremor were examined by a clinical neurologist and tested with a velocity laser to quantify time and frequency domain characteristics of a tremor. The participants received DBS of the internal globus pallidus (GPi), the subthalamic nucleus (STN) or the ventrointermediate nucleus of the thalamus (Vim). A 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. A rest tremor was recorded on the most affected side with a velocity-transducing laser [42, 43]. 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 tremor velocity changing 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 tremor velocity is observed: 1) in a natural condition of the patient (a), 2) 15 (45) minutes after the stimulator was switched off. Lower speed of the tremor is in cases: 1) when both methods (stimulation, medication) are used, 2) when each of these methods is used separately, 3) 30 (60) minutes after the stimulator was switched off. The similar results are received in Refs. [40, 41].

6. The results of application of the theory

In this 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 all other subjects.

6.1. The non-Markovity parameter and a pathological tremor in patients with Parkinson's disease

In this subsection the calculation technique of quantitative and qualitative criteria under various conditions that influence the state of a patient with Parkinson's disease is presented. The basic idea of the approach consists in defining the non-Markovity parameter to receive the information on a physiological state of a patient. As one of the examples we shall consider the velocity of the changes of the subject's index finger tremor 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 feature. The value of the non-Markovity parameter $\varepsilon_1(0)$ decreases with the increase of the tremor velocity of fingers (deterioration of the physiological state) and increases 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 $\mu_0(\omega)$, the non-Markovity parameter $\varepsilon_1(\omega)$, and the time dependence of local relaxation parameter $\lambda_1(t)$ as additional sources of information.

Fig. 2 represents the power spectra of the initial TCF for various conditions of the experiment. One can observe a powerful peak for all figures at the frequency $\omega = 0.07 f.u.(f.u. = 1/\tau, \tau = 10^{-2}$ second). The figures are submitted according to the initial time series. The given peak testifies to a pathological state of the studied system. The similar picture is observed in patients with myocardial infarction [29]. The least amplitude $75\tau^2$ corresponds to the condition (ON, ON) (deep brain stimulation on and medication on; see, Fig. 2b). The highest amplitude $4.34 * 10^4 \tau^2$ corresponds to the greatest speed of a tremor (see, Figs. 1e, 2e). The comparison of these values reflects the amplitude of the tremor velocity at the initial record of time. The similar picture is observed for all other patients.

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 (see, Section 6.2) are submitted (the technique of the analysis of the given behavior is considered in Ref. [32]). For the observed data of a tremor of the right index finger of the patient's hand (the second subject: stimulation and medication of the brain are not applied) with Parkinson's disease, we divide the entire time evolution data into nonoverlapping epochs of 256 data points each. For each epoch, we have calculated the power spectra of the TCF $a(\omega)$. The time evolution of the spectra is shown in three-dimensional diagrams. 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 $\mu_0(\omega)$

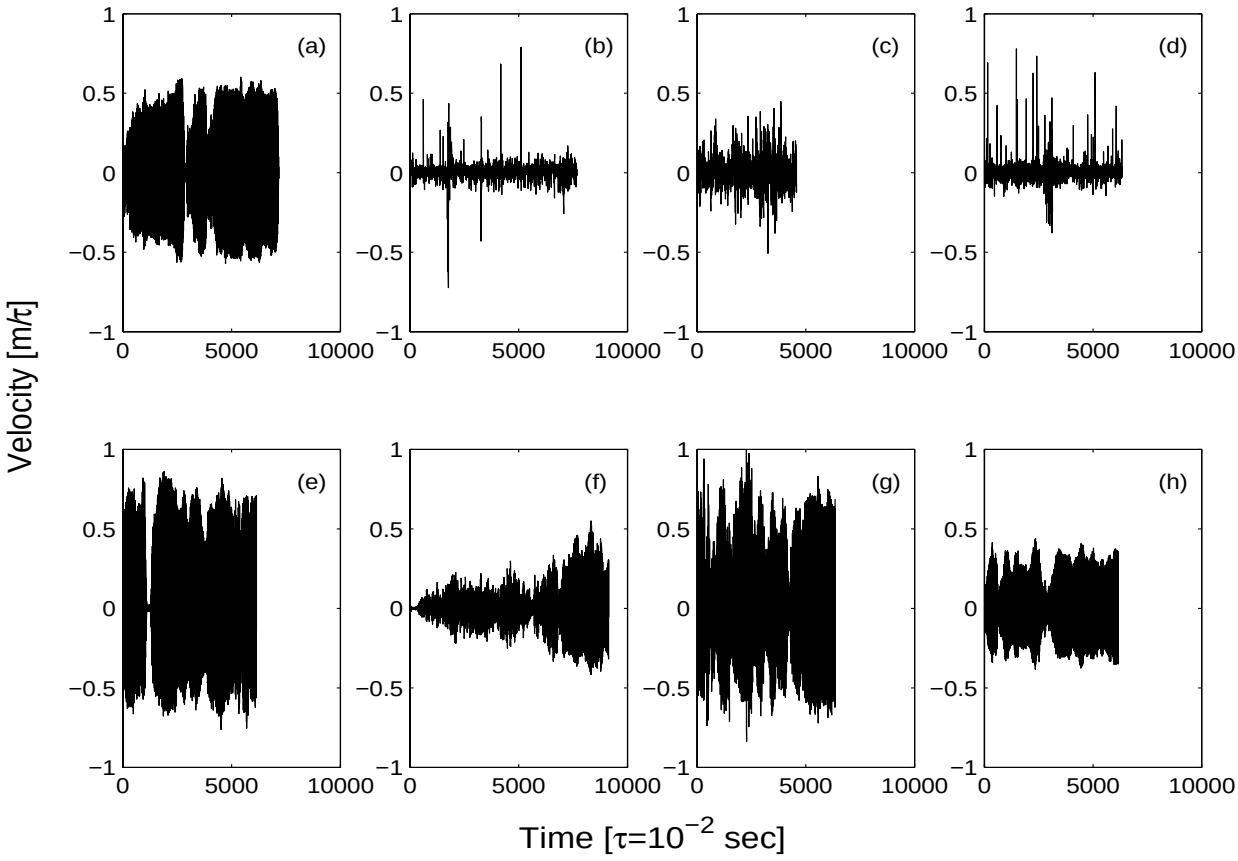

FIG. 1. The tremor velocity change of the right index finger of the patient's hand (the second subject) with Parkinson's disease under various conditions of the experiment. (a)-deep brain stimulation off, medication off; (b)-the subject was receiving stimulation of the GPi, medication on; (c)-deep brain 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.

corresponds to the regions with least velocity of the tremor.

In Fig. 4 the frequency dependence of the first point of the non-Markovity parameter $\varepsilon_1(\omega)$ (see, Eq. (4)) is submitted for the second subject under various conditions of the experiment. The figures are submitted according to the initial time series. The value of the parameter $\varepsilon_1(0)$ on zero frequency is special importance for our study of manifestations of randomness. 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 a well-defined frequency structure of the non-Markovity parameter can be seen. This structure is completely neutralized and disappears only when therapy is applied. The characteristic frequency of fluctuations corresponds, approximately, to the frequency of $\omega = 0.07 f.u., 1 f.u. = 100 Hz$. These multiple peaks are most appreciable at low frequencies. At higher frequencies these fluctuations are smoothed out. As can be seen in these figures, 2nd subject has a strong peak which remains stable over time. The similar structure of the frequency dependence of the non-Markovity parameter testifies to the presence of the characteristic

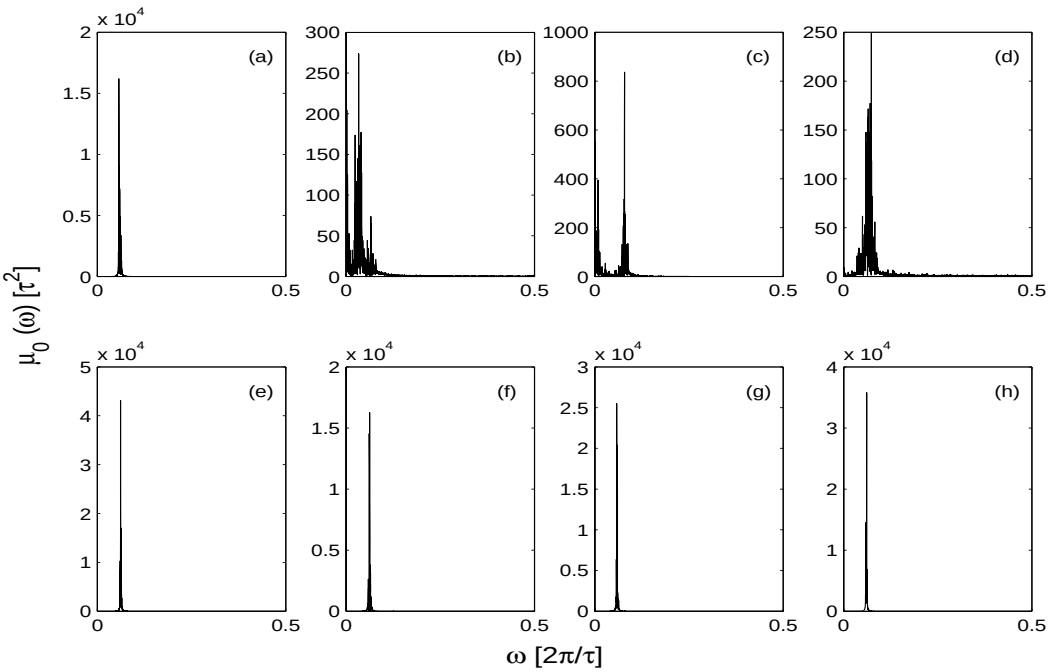

FIG. 2. The power spectrum of the initial TCF $\mu_0(\omega)$ for the tremor velocity changing of the second subject under various conditions that influences an organism. (a)-deep brain stimulation off, medication off; (b)-deep brain stimulation on, medication on; (c)-deep brain stimulation off, medication on; (d)-deep brain stimulation on, 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.

frequency of pathological tremor fluctuations of human extremities [15]-[17]. Parkinson's disease is a serious neurological disorder with a broad spectrum of symptoms. One of the most obvious and disabling symptoms is a large amplitude and a low frequency tremor [40, 41]. Such periodic structure is defined by a nonlinear signal and multimodal (independent) oscillations [14].

Table 1. The interval of dispersion of the values $\varepsilon_1(0)$ 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 for the group of 16 subjects. 1 - Deep brain stimulation, 2 - Medication. Conditions are submitted according to the initial time series.

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

In Table 1 the interval of dispersion $(\varepsilon_1(0)_{min} \div \varepsilon_1(0)_{max})$ of values $\varepsilon_1(0)$ and the average value $(\varepsilon_{av.val} = \sum_{i=1}^{16} \varepsilon_1(0)_i/16)$ for the whole group of subjects (for all 16 subjects) are shown. Let us consider 2 conditions: (OFF, OFF) and (OFF, ON). The interval of dispersion and the average value of parameter $\varepsilon_1(0)$ in the first case are minimal. It means the presence of a high degree of pathology of a physiological state of the patient (see, Fig 1a). The value of the non-Markovity parameter appreciably grows with application of any method of treatment. The maximal value of the non-Markovity parameter 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

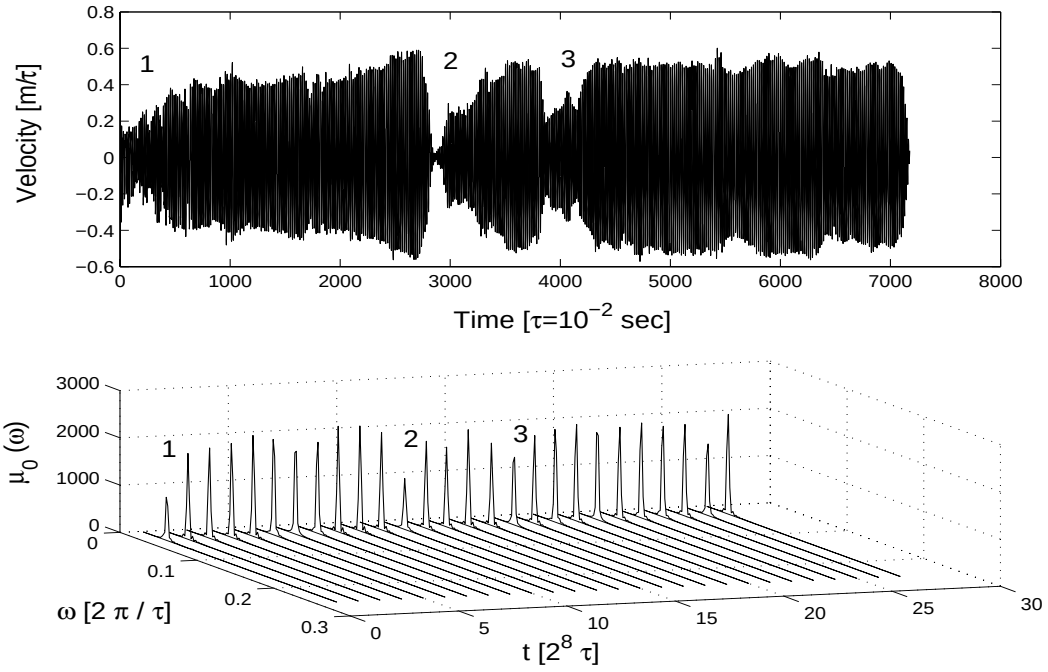

FIG. 3. The initial time series and the window-time behavior of the power spectrum of the TCF $\mu_0(\omega)$. Two figures are submitted to illustrate the case of subject 2: stimulation and medication of the brain are not applied. The change of regimes in the initial time series is reflected in the decrease of the tremor velocity (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).

individual case can be found. In our case for the second patient it is a treatment by medication. It is necessary to note, that this reasoning is true only for the study of the component, determined by the non-Markovity parameter ($Q_T(\varepsilon)$; see, Eq. (6)). The most trustworthy information about the quality of treatment can be given by the total quantitative factor Q_T which takes into account other diagnostic factors (see, Eq. (8)).

Results of the calculation of the quantitative factor Q_T are given in Table 2. The data are submitted separately for the second patient and for the whole group. Here $Q_T(\varepsilon)$ is a contribution to the quantitative factor, determined by the non-Markovity parameter (see, Eq. (6)). Q_T is a total quantitative factor (see, Eq. (8)), where $\varepsilon(\mathbf{1})$ and $\varepsilon(\mathbf{2})$ are contributions, determined by the non-Markovity parameter, for the tremor amplitudes $k(\mathbf{1}), k(\mathbf{2})$. The total factor Q_T provides detailed information about the quality of the treatment. The present factor includes both the stochastic component $Q_T(\varepsilon)$ and the physiological (diagnostic) contribution $Q_T(k)$ (it also speaks divergences with component $Q_T(\varepsilon)$). $Q_T(k)$ allows to take into account those features of the system which the component $Q_T(\varepsilon)$ does not contain. The calculation $Q_T(k)$ is described in Section 4. One can define the quality of the treatment by means of Q_T. The positive value of the given factor defines an effective method of treatment (the greater the given factor, the more effective is the method of treatment). For a separate patient and for the whole group the parameter Q_T has the maximal value under condition of (ON, ON). Thus, taking into account all the contributions, determined by the non-Markovity parameter as well as by the physiological factors it is possible to tell, that the best method of treatment is the combination of two medical methods: electromagnetic stimulation and medication.

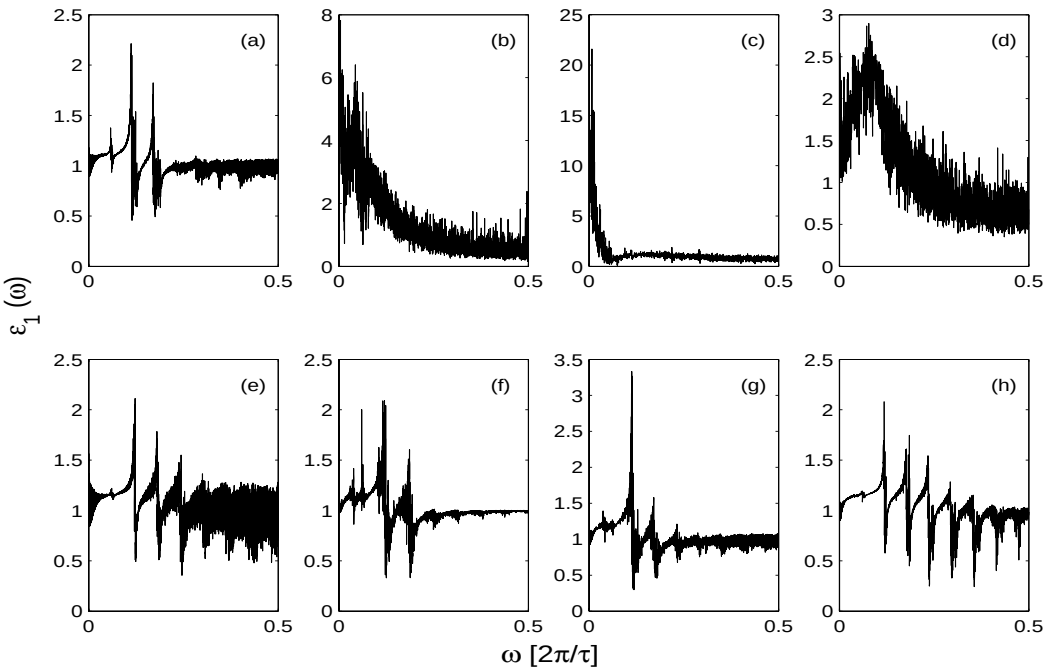

FIG. 4. The first point of the non-Markovity parameter $\varepsilon_1(\omega)$ for the second subject under various conditions of the experiment: (a)-deep brain stimulation off, medication off; (b)-deep brain stimulation on, medication on; (c)-deep brain stimulation off, medication on; (d)-deep brain stimulation on, 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 (for example, 6.02 in the second case and 1.0043 in the last one) define the physiological state of the second patient.

For the second patient under condition (15, OFF) (see, Table 2) 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.

6.2. Definition of the predictor of the sudden changes in time series dynamics 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 are used) and the procedure of localization of the relaxation parameters were considered. These procedures allow to determine specific predictors of the change of regimes in the initial time records.

Table 2. 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. $m_j = 1, p_j = 1$. Conditions are submitted according to the initial time series.

		The 2 patient		
Value	OFF OFF	ON ON	OFF ON	ON OFF
$Q_T(\varepsilon)$	-	1.756	2.556	0.785
Q_T	-	2.654	2.013	1.763
Value	15 OFF	30 OFF	45 OFF	60 OFF
$Q_T(\varepsilon)$	0.291	0.438	0.041	0.017
Q_T	-0.013	0.883	-0.004	0.856
		The whole group		
Value	OFF OFF	ON ON	OFF ON	ON OFF
$Q_T(\varepsilon)$	-	1.810	1.326	1.077
Q_T	-	4.071	2.883	3.661
Value	15 OFF	30 OFF	45 OFF	60 OFF
$Q_T(\varepsilon)$	0.544	0.728	0.671	0.731
Q_T	1.473	1.734	1.624	1.742

The idea of the first procedure is that the optimum length of the time window ($2^8 = 256$

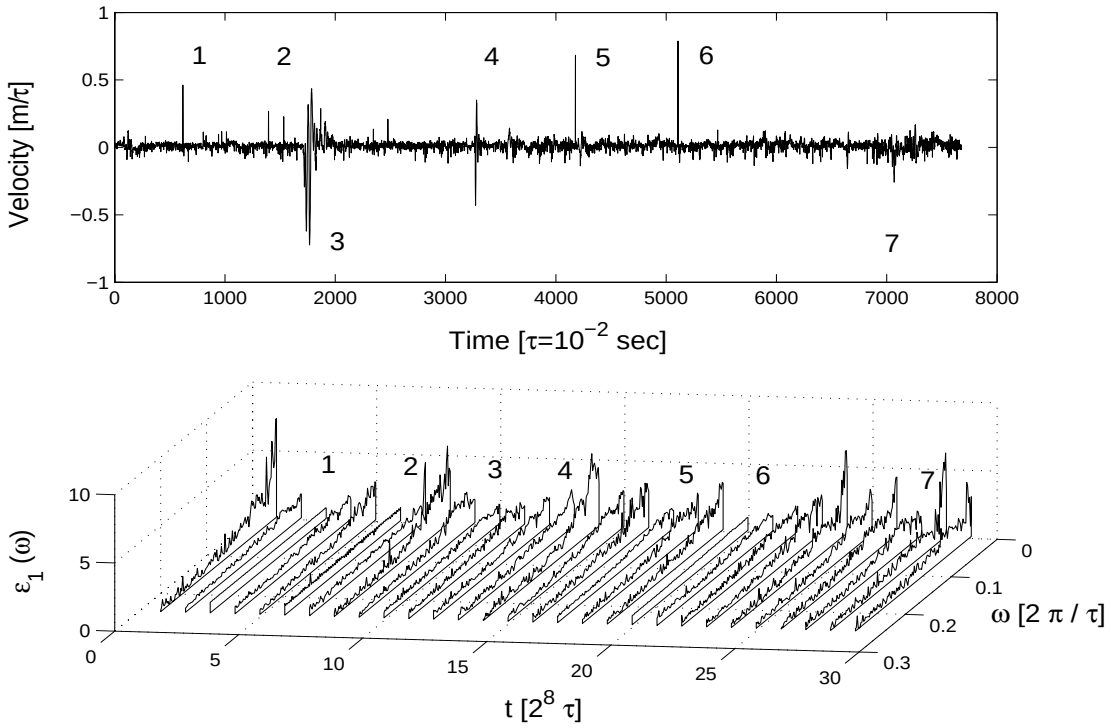

FIG. 5. The initial signal is the change of tremor velocity when the second patient is treated by two methods and the window-time behavior of the first point of non-Markovity parameter $\varepsilon_1(\omega)$. At the time of the sharp change of the mode (sharp increase of tremor velocity) in the initial time series behavior (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.

points) is found first. In the initial time series the first window is cut out. For a given window (the array of points is from 1 to 256) the construction of the frequency dependence of the non-Markovity parameter is executed. Then the second window is cut out (from point 257 to point 512) and the same procedure is repeated. In total 30 windows are constructed (see, Fig. 5). For more detail see Ref. [32]. 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 unity. One can observe that the value of the non-Markovity parameter starts to decrease by 2-2.5 sec before the increase of the tremor velocity.

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 local relaxation parameters λ_1 for the given sampling and carry out the operation of "a step-by-step shift to the right". Then we calculate the local relaxation parameter λ_1. After that we execute one more "step-by-step shift to the right" and continue the procedure up to the end of the time series. Thus the local parameters (in the work one of them is considered) have high sensitivity to the effects of intermittency and of non-stationarity. Any non-regularity in initial time series is reflected instantly in the behavior of the local parameters. The use of this procedure requires a choice of the optimal length of a

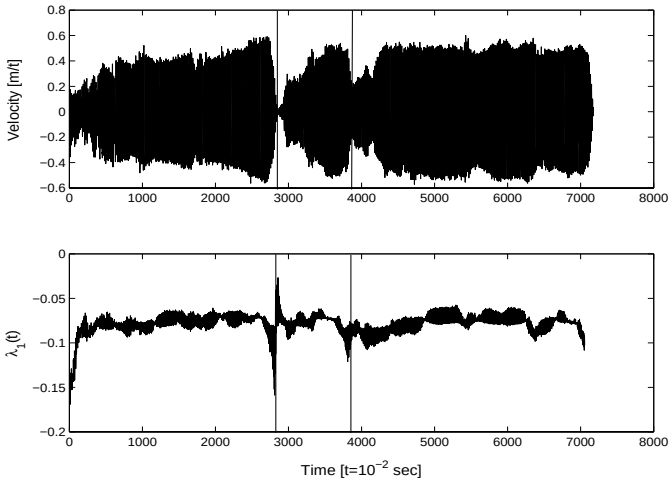

FIG. 6. The change of the tremor velocity for the second patient (stimulation of the brain and medication are not used) and the time dependence of the local relaxation parameter $\lambda_1(t)$. The procedure of localization allows to find sudden changes of relaxation regimes of the researched system. The amplitude values of the local relaxation parameter are in the region of the lowest tremor velocity. 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.

sampling which enables to receive most trustworthy information. If a sampling is too short, noise effects do not allow to obtain qualitative information. Besides with a short length sampling we have significant errors. On the other hand with a great length of a sampling the local parameters lose "sensitivity" necessary for the study. As a result of the study of local samplings of different length we have received the optimal length which makes 120 points, for more detail see Ref. [31]. In Fig. 6 the initial time record and the time dependence of the local relaxation parameter $\lambda_1(t)$ are submitted for one case. 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 the tremor velocity.

7. Conclusions

In the present paper we offer new physical method of diagnosing and forecasting Parkinson's disease. It is based on the application of the statistical theory of discrete non-Markov stochastic processes, the statistical non-Markovity parameter and its spectrum. This approach allows to define the difference between a healthy person and a patient by means of numerical values of the non-Markovity parameter. This observation gives a reliable tool for the strict quantitative estimates for diagnosis and quantification of the treatment of patients. As an example we have considered the changes of various dynamic states of patients with Parkinson's disease. The quantitative and qualitative criteria used for the definition of various physiological states of live systems, allow 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. It makes possible the investigation of various dynamic states of complex systems in real time.

The statistical parameter of non-Markovity $\varepsilon_1(0)$ bears in itself certain information on a physiological state of a live system, that may be used to diagnose and forecast a system state. In case of Parkinson's disease the variation of this parameter defines the change of a physiological state of

the system. The increase of the non-Markovity parameter reflects the decrease of pathology and improvement of the patient's state. The decrease of non-Markovity parameter defines a high degree 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 carry in themselves the information, which defines the degree of pathological variations in a human organism.

The new procedures (the window-time procedure and the procedure of localization) 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 sec earlier. It happens when the non-Markovity parameter approaches a unit value. The procedure of time localization 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 sec earlier. These predictors allow to lessen the probability of ineffective use of different methods of treatment.

General conclusions, which are taking into account the total factor of the quality of treatment Q_T (determined by parameter of non-Markovity and by physiological factors), consist in the following. If we consider the whole of group of patients, the combination of two different methods (medication, electromagnetic stimulator) produce the most effective result ($Q_T = 4.071$) in comparison with the effect of medication or stimulation given separately. Used separately, stimulation is more effective ($Q_T = 3.661$), than the use of medication ($Q_T = 2.883$). In some cases both medication and stimulation exert a negative influence on the state of the subject. The effectiveness of various medical procedures and the quality of treatment can be estimated quantitatively for each subject separately with utmost precision. For the second patient the best method of treatment is the combination of two method of treatment ($Q_T = 2.654$). For the given patient the separate effect of a medicine ($Q_T = 2.013$) is more effective, than the separate use of stimulation ($Q_T = 1.763$). The given conclusion corresponds to the results of work [15]. After the stimulator is switched off its aftereffect has an oscillatory character with characteristic low frequency.

When estimating the quality of treatment, we take into account the non-Markovity parameter ($Q_T(\varepsilon)$) only, the results will be a little different. It is due to the fact that the total factor of the quality of treatment Q_T takes into account the diagnostic (physiological) factors of the studied system.

In conclusion we would like to state that our study gives a unique opportunity for 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 method of study of live systems opens up great opportunities for alternative analysis, diagnosis and forecasting of the stochastic behavior of live complex system.

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