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FRACTAL ANALYSIS IN THE STUDY OF THE REGULATION OF CEREBRAL CIRCULATION

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Abstract. A mathematical model of autoregulation of cerebral circulation in the human body for obtaining additional information to make decisions about choosing a treatment plan has been presented in the paper. The fractal analysis methods based on wavelet leaders, which made it possible to expand the traditional approach to assessing the interaction between systemic arterial pressure and linear blood flow velocity formed the basis of the developed nonlinear model of autoregulation. The application of the developed methods to assessing the state of the autoregulation system in a healthy volunteer and a patient with cerebral pathology was exemplified.

Keywords: autoregulation of cerebral blood flow, mathematical model, fractal analysis, wavelet leader

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ФРАКТАЛЬНЫЙ АНАЛИЗ В ИССЛЕДОВАНИИ РЕГУЛЯЦИИ МОЗГОВОГО КРОВООБРАЩЕНИЯ

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Аннотация. В работе представлена математическая модель ауторегуляции мозгового кровообращения в организме человека, позволяющая получать дополнительную информацию для принятия решений о выборе метода лечения. В основу разработанной нелинейной модели положены методы фрактального анализа на базе вейвлет-лидеров, которые дают возможность расширить традиционный подход к оценке взаимодействия системного артериального давления с линейной скоростью кровотока. Приведены примеры, иллюстрирующие применение разработанных подходов к оценке состояния системы ауторегуляции у здорового добровольца и пациента с церебральной патологией.

Ключевые слова: ауторегуляция мозгового кровообращения, математическая модель, фрактальный анализ, вейвлет-лидер

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Introduction

Most regulatory systems in the human body interact to maintain homeostasis. Effective regulation is impossible without feedback ensuring that organs or systems functions within the normal range. The body's regulatory systems tend to deteriorate with age. The age-related decline gradually destabilizes the body systems, increasing the risks of diseases and triggering physiological changes.

All types of regulatory systems within the healthy body are closely related. For this reason, it is rather difficult to determine the extent to which each of these systems participates in the regulatory response to changes in external conditions. Much attention is focused on regulation of cerebral blood flow, which is mediated by myogenic, metabolic and neurogenic mechanisms, and includes static and dynamic components.

The goal of the study is to construct and apply autoregulation models based on fractal analysis, allowing to monitor systemic and cerebral hemodynamics with the necessary accuracy in healthy or diseased subjects.

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Preliminary definitions

Synergetics of the regulatory system. The cornerstone of synergetics is that a structure is defined as a state resulting from uncertainties in the behavior of multi-component systems. The evolution of such systems does not obey either the second law of thermodynamics or Prigogine's theorem on minimum entropy production. New structures and systems may evolve as a result of this behavior, including more complex ones than the original [1–7]. The universal characteristic of the state of such a system is its entropy.

Entropy: definition and determination Entropy is a term widely used in the natural and exact sciences as a measure for irreversible dissipation of energy. It is customarily denoted by S . The relationship $dS = \delta Q/T$ is introduced in thermodynamics, where δQ is the infinitesimal amount of heat of the process, T is the absolute thermodynamic temperature; $\oint dS = 0$ for reversible processes. In statistical physics $S = k \ln \Gamma$, where k is the Boltzmann constant, Γ is the number of microstates.

In information theory, entropy is understood as a measure of uncertainty of the message source; it is defined as the probability of certain symbols appearing in the transmission. The function of such entropy is denoted by H .

Shannon's information entropy

$$H(p) = -K \sum_{i=1}^N p_i \ln p_i,$$

where p_i is the probability, K is a positive constant.

The Rényi entropy is expressed as

$$H_r(p) = \frac{1}{1-r} \sum_{i=1}^N \ln p_i^r.$$

This entropy tends to the Shannon entropy at $r \rightarrow 1$.

A balance between internal entropy production and exchange with the environment (dissipation) is reached in living organisms. This phenomenon is irregular. The irregularity is due to nonlinear and synergetic effects, which are characterized by dynamic chaos. Deterministic chaos is a vital part of the normal functioning of the body.

According to chaos theory, a dynamical system can be classified as chaotic if it has the following properties:

- sensitivity to initial conditions;
- topological transitivity (mixing);
- dense periodic orbits.

In the case of biological processes, time series act as signals that determine the behavior of the system.

The main methods of time series analysis are the following.

Linear: statistical, spectral, correlational.

Non-linear: wavelet leaders, multifractal analysis, neural networks.

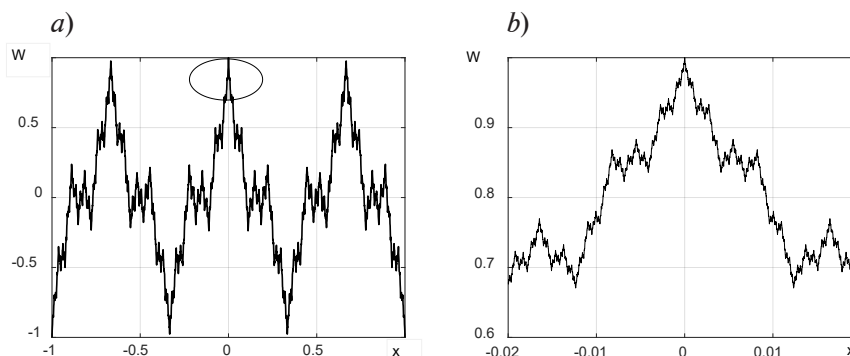


Fig. 1. Weierstrass function shown in two intervals of argument values: $[-1, +1]$ (a) and $[-0.02, +0.02]$ (b)



Fractal analysis. This analysis includes methods to determine the fractal dimension of the data. Initially, the concept of a fractal was associated with geometric objects that meet two criteria: self-similarity and fractional dimension [8].

The first known example of a fractal is the Weierstrass function (Fig. 1), defined as a Fourier series in the original paper [9]:

$$f(x) = \sum_{n=0}^{\infty} a^n \cos(b^n \pi x),$$

where $0 < a < 1$, b is an even positive number; $a \cdot b > 1 + 3/2\pi$.

The minimum value of the number b for which there is such a number a lying in the interval $0 < a < 1$ that these conditions are satisfied equals 7. Even though the Weierstrass function is nowhere differentiable, it is continuous, since the terms of the series defining it are limited to $\pm a^n$. The function is not monotonic between any two points. The graph in Fig. 1 exhibits fractal behavior, illustrating self-similarity: the area in the ellipse (see Fig. 1,*b*) is similar to the entire graph in Fig. 1,*a*.

Hölder continuity. It is convenient to write the Weierstrass function equivalently as

$$W_{\alpha}(x) = \sum_{n=0}^{\infty} b^{-\alpha n} \cos(b^n \pi x), \quad \alpha = -\frac{\ln(a)}{\ln(b)}.$$

Here the function $W_{\alpha}(x)$ introducing the exponent α is Hölder-continuous if

$$|W_{\alpha}(x) - W_{\alpha}(y)| \leq C|x - y|^{\alpha}.$$

A function f in a d -dimensional Euclidean space satisfies the Hölder condition, or is Hölder-continuous when there are non-negative real constants C , $\alpha > 0$, such that

$$|f(x) - f(y)| \leq C\|x - y\|^{\alpha}$$

for all x and y in the domain of f .

The number α is called the Hölder exponent. The function satisfying the condition $\alpha > 1$ in the segment is constant. If $\alpha = 1$, then the function satisfies the Lipschitz condition. It follows from the condition for any $\alpha > 0$ that the function is uniformly continuous [10].

Consider the properties of space C_H^{α} .

Let the function f be bounded on R , $x_0 \in R$, $a > 0$. Let $f \in C_H^{\alpha}(x_0)$.

Then there is a constant $C > 0$ and a polynomial P of degree less than a , such that in some neighborhood x_0 ,

$$|f(x) - P(x - x_0)| \leq C|x - x_0|^{\alpha}.$$

The Hölder exponent of a function f is a function h_f , defined for each value of x as

$$h_f(x) = \sup \{ \alpha : f \in C_H^{\alpha}(x) \}.$$

The method of fractal analysis introduces the reconstructed attractor instead of the signal. Fractal dimensions are used as numerical characteristics of the data, determining, for example, the probability of finding a point on the attractor. The information dimension and the associated information entropy, as well as correlation dimension and correlation entropy are typically used for this purpose.

There is a large family of fractal dimensions. In particular, the Rényi dimensions are defined based on the concept of generalized entropy. The principle is to weigh the probability of the most frequently visited boxes by order of measurement [11].

Determining the delay time. Embedding should be carried out before any estimates of fractals from the data series. According to Takens's theorem, any state variable can be used to calculate the dynamical invariants [12]. However, in practice, this estimate is performed algorithmically, as useful information is effectively embedded into the given variable.

After the embedding dimension is selected, the next step is to determine the correct delay time. It can be estimated by the first zero crossing of the autocorrelation function or, preferably, by the first local minimum of mutual information.

A multifractal is a system of fractals, each characterized by its own dimension. Multifractal spectra can be used to describe multifractals without having to calculate the set of fractal dimensions comprising the multifractal [13, 14].

The fractal dimension can be determined by dividing the fractal into a certain number of cells of arbitrarily small size. The probability of cell population for a regular homogeneous fractal is $p_i(\varepsilon) \approx \varepsilon^\alpha$, where α is some exponent.

The probabilities p_i of cell population are not the same for a multifractal. Therefore, the exponent α can take different values, i.e., it becomes an argument of the function $f(\alpha)$. The physical meaning of the function $f(\alpha)$ is that it represents the Hausdorff dimension of a homogeneous fractal subset $L(\alpha)$ of the initial set L , characterized by the same probabilities of occupying cells $p_i(\varepsilon) = \varepsilon^\alpha$. The set of different values of the function $f(\alpha)$ in fact represents the spectrum of fractal dimensions.

The spectra constructed and the Hölder exponents α found serve as an additional source of information in various fields of science [15, 16]. As an example, consider the graphs of the Hölder exponent and the scaling factor (Fig. 2) for a system of three equations introduced by Lorenz:

$$\begin{cases} \frac{dx}{dt} = -\sigma x + \sigma y, \\ \frac{dy}{dt} = -xz + rx - y, \\ \frac{dz}{dt} = xy - bz. \end{cases} \quad (1)$$

The argument q in Fig. 2 expresses a discrete array of empirically determined deformation parameters. Evidently, the variation in the scaling exponent accompanying the variation in the deformation parameter is close to a linear relationship. Notably, in addition to formulating the fundamentals of chaos theory, Lorenz revolutionized numerical weather prediction.

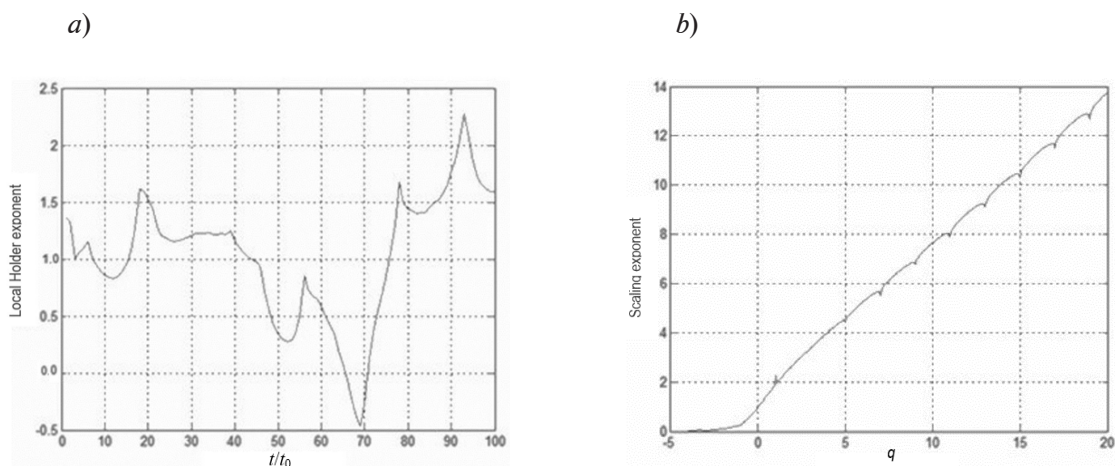


Fig. 2. Hölder exponent (a) and scaling exponent (b) for the system of Lorenz equations (1) at $\sigma = 10$, $r = 28$, $b = 8/3$

Fractal analysis in health monitoring

There are diverse techniques for tracking the abnormalities in various organs and regulatory systems of the human body. It is equally important to monitor the overall health status of the patient, assessing the risks of critical conditions. Heart rate variability was used in our previous studies as a predictor for the onset of such conditions. Customized software was developed to implement the technique based on multifractal analysis [17–20]. The algorithm is based on the moving window method. The program automatically determines the necessary parameters by analyzing the trajectories of the system with the following coordinates:

$$X_i^m = \{x_{ti}, x_{ti+1}, \dots, x_{ti+m-1}\}.$$

The correlation dimension D_{cr} is determined as follows in terms of the correlation integral $C(\varepsilon)$:

$$C(\varepsilon) = \lim_{\varepsilon \rightarrow \infty} \frac{1}{m^2} \sum_{i=1}^m \sum_{j=1, i \neq j}^m \chi(\varepsilon - |x_i - x_j|),$$

$$D_{cr} = \lim_{\varepsilon \rightarrow 0} \frac{\log C(\varepsilon)}{\log(\varepsilon)}.$$

Here $m_\varepsilon(x_i)$ is the number of points in the sequence falling into a sphere with the radius ε centered at point x_i belonging to the same sequence; ε is the radius of the sphere centered at point x_i , χ is the Heaviside function.

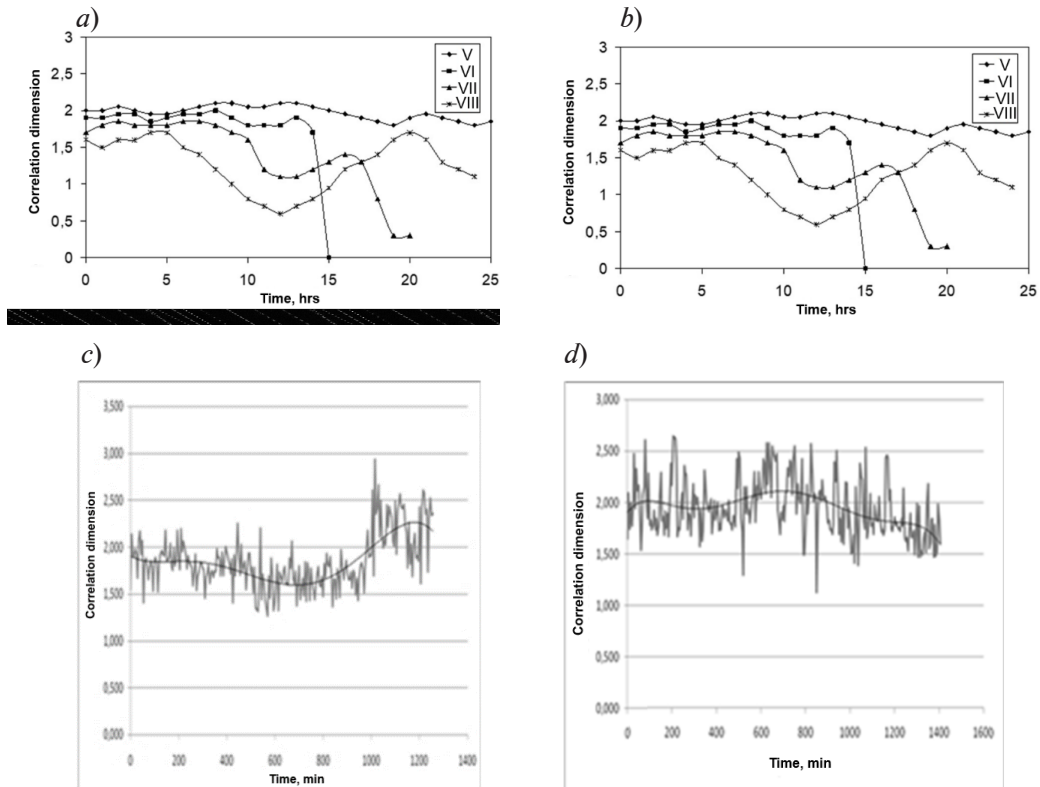


Fig. 3. Correlation trend for dimension of heart rate attractor
 The time evolution of this quantity is given in hours for healthy (a) and critically ill (b) subjects, and in minutes for patients after stroke (c) and in persistent vegetative state (d).
 Curve numbers (I–VIII) correspond to eight subjects (details are given in the table)

Several estimates of the correlation dimension are calculated with the embedding dimension until the correlation dimension approaches a constant value. A window $w(m)$ ($m = 0, 1, \dots, M$) with the length of 16,500 samples is used for signal processing. The window duration is $t = 165$ s. The window step is 20.5 s.

The results obtained by applying methods of multifractal analysis to diagnostics of both the overall health and the regulatory systems of the body's vital organs are given in [21, 23]. An electrocardiogram (ECG) is regarded as a time series, serving for analyzing heart rate variability.

Fig. 3 shows analysis of fractal components for ECG in healthy subjects and in patients at risk of grave complications. The ECG data were obtained during clinical trials. The curve numbers in Fig. 3, *a, b* correspond to eight subjects examined (see Table).

Cerebral regulation is the property of cerebral arteries maintaining relatively constant cerebral

Table

Examined healthy subjects and patients (see Fig. 3)

Curve	Subject	Age, years	Status
I	Child	5	Healthy
II	Adolescent	15	Healthy
III	Adult male	35	Healthy
IV	Adult female	65	Healthy
V	Adult female	49	Coma after clinical death and emergence from coma
VI	Adult male	57	Sudden cardiac arrest and death
VII	Adult male	88	Life-threatening arrhythmia
VIII	Adult female	69	After general anesthesia during surgery

blood flow with the perfusion pressure varying from 50 to 170 mm Hg [24]. The time parameters characterizing the evolution of autoregulation range from 1–2 minutes to 25 seconds.

Methods for analyzing the regulation of cerebral circulation can be divided into two groups with different theoretical foundations: the first one is based on linear analysis of interaction of two signals, and the second on synergetics, relying on fractal analysis.

From a physical standpoint, any wave process is a sum of oscillations with different frequencies. Mathematical analysis of such processes is based on the concept of time series. The carrier frequency (fluctuation of blood pressure) can also be modulated by respiratory and slow waves.

Specifics of cerebral circulation

The functional organization of the cerebral vascular system has certain specifics separating it from the vascular system in the rest of the body (to maintain homeostasis) on the one hand, and allowing to protect sensitive nerve cells from ischemia on the other hand.

A particularly intriguing aspect of cerebral autoregulation (CAR) are periodic spontaneous slow fluctuations of blood flow velocity (BFV) in cerebral arteries in the range of M-waves and intracranial-pressure B-waves, where the variation insysteming arterial pressure (SAP) acts as the carrier frequency. SAP is the resultant of cardiac output (SV) and systemic vascular resistance (SVR): $SAP = SV \cdot SVR$.

SAP is found by analyzing the pulse wave by non-invasive techniques, using special devices. BFV is measured by transcranial Doppler ultrasonography, in particular, using Multi-Dop X-class class systems (Germany).

The oscillation period of B-waves ranges from 20 to 120 s. They arise due to slow changes in the lumen of cerebral vessels; this is reflected by the indicators of systemic and cerebral hemodynamics, in particular BFV (Fig. 4).

Detailed overview of the methods for CAR analysis is presented in [25].

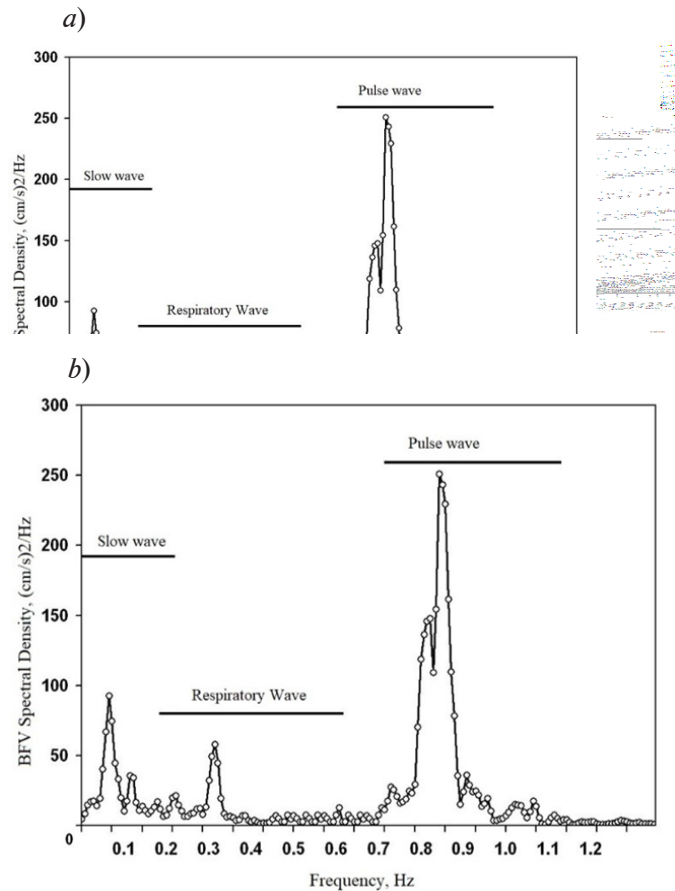


Fig. 4. BFV in the middle cerebral artery (a) and spectral density (b) of BFV in the range of slow, respiratory and pulse waves, calculated by fast Fourier transform (results for a patient without any CAR abnormalities)

Multifractal analysis of autoregulation processes. The multifractal approach to CAR analysis assumes that the signals of blood pressure and blood flow velocity can be divided into segments with self-similar properties observed in each of them. Multifractal signals have certain characteristics that cannot be analyzed using the frequency spectrum or the correlation function. Methods of fractal analysis have been developed to study such signals [26–29].

A signal with a nonlinear scaling rule is characterized by a multifractal spectrum. The multifractal structure of blood pressure signals and blood flow velocity can be determined by the wavelet transform modulus maxima method (WTMM). The latter consists in generalizing the algorithms for decomposing a set of signal samples with wavelets. Wavelet transforms have a number of useful properties: good time-frequency localization, diverse types, and fast algorithms.

The wavelet transform is based on the scaling function ψ from the space $L^2(\mathbb{R})$. In this case, the scale replaces the concept of frequency used in spectral analysis. A functional shift is introduced to partition the time domain with wavelets. The discrete wavelet transform of some discrete function $g(n)$ is set as

$$W(a, b) = \frac{1}{\sqrt{a}} \sum_{n=1}^N g(n) \psi\left(\frac{n-b}{a}\right).$$

The multi-fractal spectrum based on wavelets yields more accurate results if it is built on wavelet leaders rather than on wavelet coefficients. Wavelet leaders are the suprema of absolute discrete wavelet coefficients localized in time or space.

The second step of the WTMM algorithm consists in estimating the value of $Z(q,a)$ characterizing the scale parameters with respect to the extrema of the analyzed signals. The estimate is obtained by calculating the maximum absolute coefficients of the wavelet transform along each line of the local extremum l on all scales:

$$Z(q,a) = \sum_{l \in L(a)} (\sup |W(a', x_i(a'))|)^q, \tag{2}$$

where $L(a)$ is the set of all lines l of the local absolute wavelet coefficients $W(a,b)$ existing on the scale a ; q is the discrete array of empirically determined deformation parameters.

Expression (2) can be represented as $Z(q,a) \approx a^{\tau(q)}$. Constructing the $Z(a)$ dependences for each q on a double logarithmic scale, we can estimate the scaling exponent $\tau(q)$. This dependence is linear for monofractal signals nonlinear for multifractals.

The fractal dimension is determined by partitioning a fractal into a certain number of cells with a sufficiently small size. The probabilities p_i of visiting cells are not the same for a multifractal. Therefore, the exponent can take different values of $f(\alpha)$: $N(\alpha) = \varepsilon^{-f(\alpha)}$. The function $f(\alpha)$ with various arguments α can be regarded as the Hausdorff dimension of a homogeneous fractal subset $L(\alpha)$ from the initial set L . The set of different values of the function $f(\alpha)$ is a spectrum of fractal dimensions. The Hölder exponent α serves as a characteristic of the multifractal spectrum of the signal.

Thus, we considered the following characteristics of the signals:

- the singularity spectrum, calculated based on the wavelet leaders obtained by wavelet filters;
- scaling functions.

Evaluating the differences in the multifractal spectra of SAP and BFV signals allows to determine the degree to which the cerebral regulatory system deviates from the normal.

Wavelet leaders L were used to obtain stable results, determined from the wavelet coefficients $d_x(j,k)$ of scale 2^j .

Here k is the discrete time, which corresponds to the relation

$$L_x(j,k) = \sup_{\Lambda} |d_x(j,k)|, \quad \Lambda = \lambda_{jk-1} \cup \lambda_{jk} \cup \lambda_{jk+1}.$$

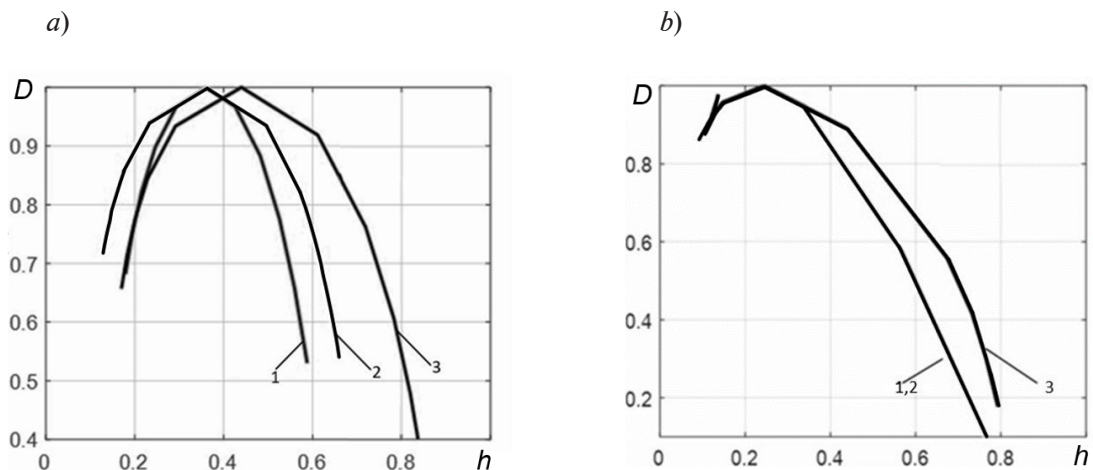


Fig. 5. Hölder (multifractal) $D(h)$ spectra obtained from a healthy subject (a) and from a patient with arteriovenous malformation in the left middle cerebral artery (b)



The estimate of the Hölder exponent α , obtained by a computational algorithm, is denoted by h . Evaluating the differences in multifractal spectra, we can separate healthy subjects from those suffering from autoregulatory system disorders.

Fig. 5 shows a comparison of the multifractal spectrum $D(h)$ (distribution of scale indicators) for SAP and BFV of a healthy volunteer and a similar spectrum for a patient with AVM in the left middle cerebral artery. A pronounced difference can be observed in the spectra of the considered signals.

Arteriovenous malformation is an anomaly in the cerebral circulatory system, where shunt vessels appear between the arteries and veins instead of a capillary network [30].

The multifractal spectrum in the patient with AVM has a different width from the corresponding spectrum in the healthy volunteer, suggesting a shorter memory for BFV signals in the patient AVM and a lower predictability of these signals. This difference indicates a decrease in nonlinear dynamics of signals and a consequent decrease in the activity of the entire autoregulation system.

Conclusion

Applying the multifractal approach to regulation of cerebral circulation, we drew the following conclusions.

The multifractal dimension of SAP and BFV signals can serve as a characteristic of cerebral autoregulation processes, allowing to detect the deviations from the normal in patients. This approach shows promise for applications, along with other well-known methods calculating the cross-correlation FFT spectra of SAP and BFV signals.

Wavelet transformations can be used to determine the relationship between these signals by analyzing their multifractal spectrum.

Based on these findings, we can formulate the directions for future research. Significant statistics should be collected for different types of autoregulatory dysfunction in patients with various disorders. The accumulated statistical data are to be used for training artificial neural networks and evaluating the necessary characteristics to improve the recognition quality for the given deviations.

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