IMEKO TC6 International Conference on Metrology and Digital Transformation
September 19 – September 21, 2022, Berlin, Germany

MEASURING AND COMPUTING MODELS OF CEREBRAL AUTOREGULATION FOR DIGITAL PERSONALIZED MEDICINE

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Abstract – Development of personalized medicine is determined by the synergy of scientists from several fields of medicine, mathematics, computer science and instrumentation. Approaches based on modern methods of measuring, signal processing and machine learning complement the main methods for studying biological processes, make it possible to identify the mechanisms of the disease and personalize the treatment strategy. The article is devoted to the study of models and methods that characterize the processes of cerebral blood flow autoregulation for methodological support of measuring systems in the field of digital personalized medicine. Analysis of systemic arterial pressure and blood flow velocity in the arteries of the base of the brain signals, which characterize the cerebral blood flow autoregulation, makes it possible to determine the nature of the violation of cerebral autoregulation processes in patients. The article proposes to use fractal methods for signal analysis based on the calculation of the Hölder multifractal spectrum and the correlation dimension of signals. The advantage of fractal methods is that they can be applied to signals without a characteristic scale that are scale invariant.
Keywords**:** Mayer waves, cerebral autoregulation, multifractal spectrum, correlation dimension.

1. BASIC INFORMATION

The digitalization of medicine is a modern trend, which is based on the introduction of innovative technologies that contribute to the development of the health industry and preventive personalized medicine. Within the framework of the general concept of building cyber-physical systems in medicine, as a unified technological platform integrating new technologies for data accumulation and processing, the use of machine learning and artificial intelligence methods, it is required to develop new digital research methods and their application in medical information-measuring systems.

When studying the processes of cerebral autoregulation within the framework of the project for the development of digital personalized medicine, an expert-class Doppler system was used to monitor cerebral autoregulation, conduct special functional tests, monitor the detection of microemboli and conduct functional tests. The system has Doppler sensors designed to measure the blood flow velocity (BFV) in the main vessels of the brain for a long time. Sensors for measuring systemic arterial blood pressure (BP) are additionally connected to the external inputs of the system, which makes it possible to determine the relationship between the measured parameters of cerebral circulation [1]. Invasive measurement of BP is used in the examination of patients with neurosurgical pathology in the intensive care unit and resuscitation. For patients examined outside the acute stage of brain pathology, and for healthy volunteers from the control group, non-invasive methods for measuring BP based on the principle of transcutaneous photoplethysmography on the finger under normocapnia and hypercapnia are used.

The mechanisms of cerebral autoregulation are violated in patients with severe traumatic brain injury. In this case, pathological vascular reactions occur, leading to ischemia of some areas of the brain and hyperemia of others. Fluctuations in BP at low values of the autoregulation index are accompanied by synchronous changes in BFV, characteristic of a gross violation of cerebral autoregulation. Changes in BFV are noted in the acute period of traumatic brain injury with any severity. Computational models based on BP and BFV measurements can translate preclinical studies and clinical results into descriptive or predictive expressions. The importance of such models, also called digital evidence, has been increasingly recognized in medicine over the past decades. The signals that control cerebral autoregulation are in the range of 0.08 to 0.12 Hz and are called Mayer waves.

The study of the processes of cerebral autoregulation was carried out using a Doppler measurement system and a number of classical methods of signal analysis: correlation [2], short-term spectral [3], and wavelet analysis [4]. These methods consider scale-invariant signals, the statistical properties of which do not change when the scale of the time axis changes . These methods usually do not correctly show the relationship between signals with different scaling behavior [5], which is relevant because Mayer's fundamental frequency can vary by 50%. In our study, we use multifractal analysis of BP and BFV measurements to expand the diagnostic capabilities of the Doppler system. The system can be used in personalized medicine for advanced diagnostics, targeted therapy and prevention of circulatory disorders.

2. HÖLDER SPECTRUM BASED ON THE METHOD OF MAXIMA OF THE WAVELET TRANSFORM MODULI (MWT) FOR

Classical methods for controlling autoregulation processes, which use spectral correlation methods, do not take into account the fact that BP and BFV signals contain regions, in each of which they have the self-similarity property. If we represent the signals as a decomposition into sections with certain local scaling properties, then the quantitative description of such signals is a fractal decomposition. Such a decomposition is able to describe the regularity of the signal in the absence of an interval or ordinal scale of the phenomenon. The statistical properties of the signals should not change with individual differences in the frequency of autoregulation of the studied patient, taken from the Mayer waveband. A change in frequency can be seen as an expansion or contraction of the time axis. Classical methods do not allow solving this problem simply and clearly enough.

To characterize the local regularity of the BP and BFV signals, discrete wavelets were used, which allow estimating the Hölder exponent.

The multifractal wavelet method is interpreted as a generalization of classical algorithms for covering a set of signal samples with structural elements - wavelets [6], which have good time-frequency localization, a variety of function types, and fast calculation algorithms. The discrete wavelet transform of the function $f(n)$ is represented by a set of shifted and scaled functions $\psi\left(\frac{t-b}{a}\right)$, where b is the shift and a is the scale. The discrete wavelet transform of some function f(t) is given as:

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

The results of multifractal analysis are the most stable [7] if instead of the coefficients $w(a,b)$ we use their locally extreme values $Z(q,a)$ for each scale factor a, where q is a discrete array of empirically determined deformation parameters. The value $\mathrm{Z(q,a)} \propto a^{\tau(q)}$, where $\tau(q)$ is an estimate of the scaling exponent. The exponent $\tau(q)$ has the form of a linear dependence for monofractal signals and a nonlinear one for multifractal ones.

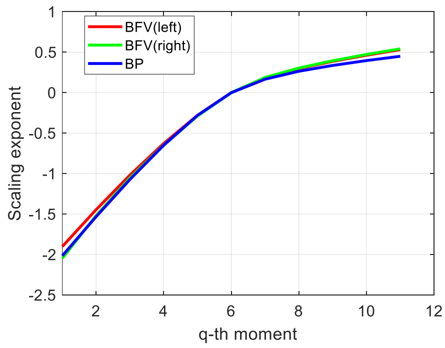


Fig.1.Example of the scaled exponents for BFV and BP signals for a healthy volunteer

The spectrum shows how much the local regularity of signals varies over time. A multifractal signal shows changes in signal regularity over time and has a multifractal spectrum with a wider support area. Signals with a wider support area are persistent, they have good memory and good properties.

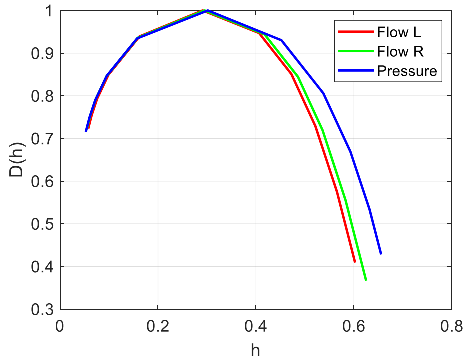


Fig.2. Example of the multifractal spectrum D(h): distribution of scaling exponents for BFV and BP signals for a healthy volunteer.

The Hölder (multifractal) spectrum for a healthy volunteer is shown in Figure 2.

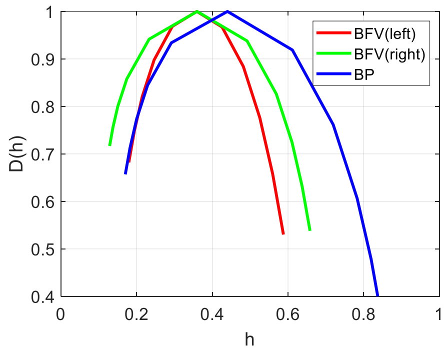


Fig.3. Example of the multifractal spectrum D(h): distribution of scaling exponents for BFV and BP signals for a patient with cerebral autoregulation disorder.

The Hölder spectrum for a patient with arteriovenous malformation of the left middle cerebral artery region is shown in Figure 3.

The reduction in the width of the multifractal spectrum compared to a healthy volunteer indicates that BFV signals in a patient with an arteriovenous malformation have a shorter memory and become less predictable, which indicates a reduction in the nonlinear dynamics of the signals.

The coefficients k_{Left}, k_{Right} characterize the relative difference between the BFV and BP singularity spectra: characterize the relative difference between the BFV and BP singularity spectra:

$$k_{Left} = \Phi(BFV_{Left}, BP) = \left|\frac{\sum_{i=1}^{N} BP(h_i) - BFV_{Left}(h_i)}{\sum_{i=1}^{N} BP(h_i)}\right|,$$

$$k_{Right} = \Phi(BFV_{Right}, BP) = \left|\frac{\sum_{i=1}^{N} BP(h_i) - BFV_{Right}(h_i)}{\sum_{i=1}^{N} BP(h_i)}\right|,$$

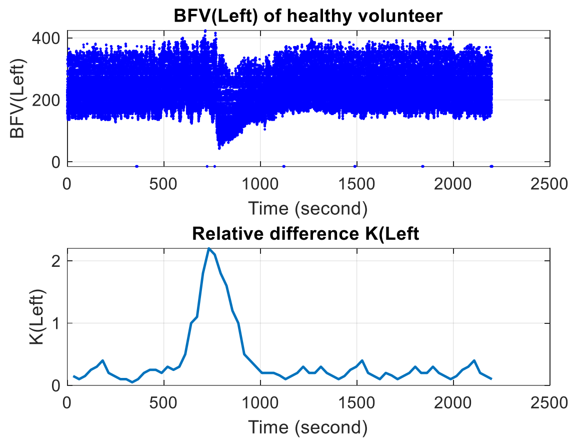
where N is the number of points for which all three quantities are calculated.

The change in the width of the singularity spectrum is defined as the ratios:

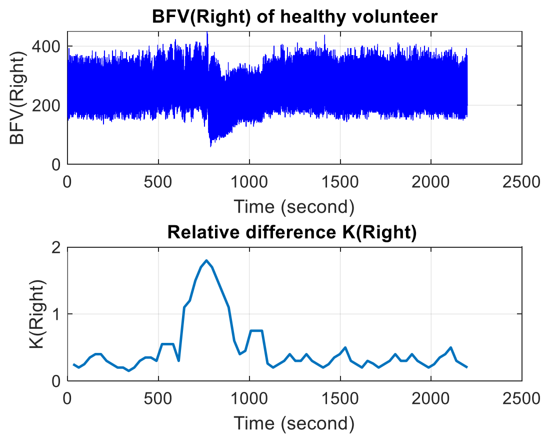
$$l_{Left} = \left| \frac{h_{Left}(1) - h_{Left}(N_{max})}{h_{BP}(1) - h_{BP}(N_{max})} \right|,$$

$$l_{Right} = \left| \frac{h_{Right}(1) - h_{Right}(N_{max})}{h_{BP}(1) - h_{BP}(N_{max})} \right|,$$

where $h_{Left}(1), h_{Left}(N_{max})$ are the minimum and maximum value of the Hölder exponent.



a)



b)

Figure 4. Results of BFV measurements and the corresponding values of the relative difference between BFV and BP singularity spectra; a) - for the left artery; b) - for the right artery.

Figure 4 shows the results of the BFV measurement and the corresponding values of the coefficients k_{Left}, k_{Right}. These coefficients change their values during the experiment on artificial enhancement of cerebral autoregulation.

To test the method, an experiment was performed, consisting in measuring BP and BFV for a healthy volunteer with an interval of 0.01 s for 35 minutes. A special test was performed by a healthy volunteer to determine the performance of the proposed multifractal method for diagnosing autoregulation processes. To do this, hyperventilation of the lungs was reproduced in the interval from 12 to 14 minutes, which artificially enhances the cerebral autoregulation. For the wavelet transform, the bior-1.5 biorthogonal wavelet decomposition leaders were used. Wavelet leaders make it possible to obtain more stable results of multifractal analysis and increase sensitivity to cerebral autoregulation disorders. The sensitivity of the method depends on the type of wavelets, increasing the length of wavelets and the length of their filters contributes to an increase in sensitivity and an increase in complexity and implementation time. In this sense, a compromise must be reached.

3. CORRELATION DIMENSION OF AUTOREGULATION SIGNALS

Let us apply the methods of the apparatus of the theory of dynamic systems, deterministic chaos and dynamic chaos, namely, the restoration of the attractor and the determination of its correlation dimension. This value makes it possible to judge the synchronism and variability of the processes of autoregulation of cerebral circulation. The value of the correlation dimension characterizes the level of chaos in the autoregulation system. The higher the value of the correlation dimension, the higher the level of chaotic complexity of the system.

According to the Taken's theorem [4], the evolution of the entire system can be judged by the dynamics of a single signal by constructing a pseudo-attractor that has the same metric characteristics as the attractor of the system in the phase space. The characteristic of the attractor, which carries information about the degree of complexity of the behavior of a dynamical system, is the correlation dimension D_c.

The algorithm for calculating D_c is based on the calculation of the correlation integral, which is a function $C(\delta)$ for each δ equal to the normalized number of pairs of points, the distance between which does not exceed δ:

$$C(\delta) = \frac{1}{N^2} \sum_{i=1}^{N} \sum_{j=i+1}^{N-1} \theta\left(\delta - |y_i - y_j|\right),$$

where $\theta\left(\delta - |y_i - y_j|\right)$ is the Heaviside function, $|y_i - y_j|$ - distance between samples y_i and y_j signal in the reconstructed space. If the dependence $C(\delta)$ has a power-law form $C(\delta) \sim \delta^{D_c}$, then the set under study is fractal, and the value D_c is a correlation dimension.

For the practical calculation of the correlation dimension on the graph $\ln(C(f)) = f(\ln(\delta))$ the area of linear dependence (scaling area) and the approximating straight line by the least squares method are selected. The tangent of the slope of the line approximating this dependence characterizes the correlation dimension D_c.

The signals of neurophysiological systems look quite complicated, they are quite similar to random ones. Nevertheless, according to the Taken's theorem, it is possible to restore some properties of the attractor from the time sequence of one of the signal components BP, BFV.

The embedding dimension is the smallest integer dimension of the space containing the entire attractor. It corresponds to the number of independent variables, which uniquely determines the steady motion of a dynamic system. The value of the correlation dimension D_c is directly proportional to the level of chaos in the system, that is, a higher value of D_c represents a high level of chaotic complexity in the system.

Graphs of the correlation integral of the radius of the neighborhood were obtained using Matlab. To calculate the correlation dimension, the values of the minimum and maximum radius were determined.

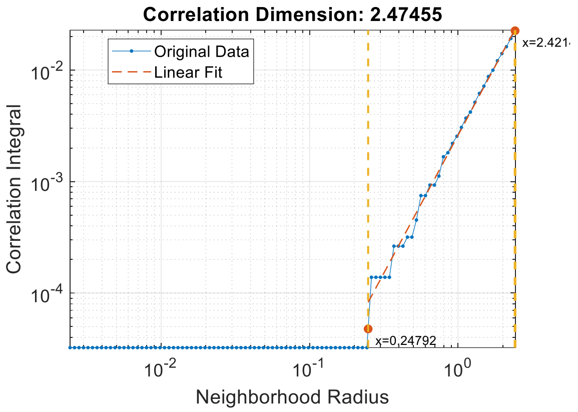


Figure 5. Dependence of the correlation integral on the radius of the neighborhood for the results of measuring the patient's BP

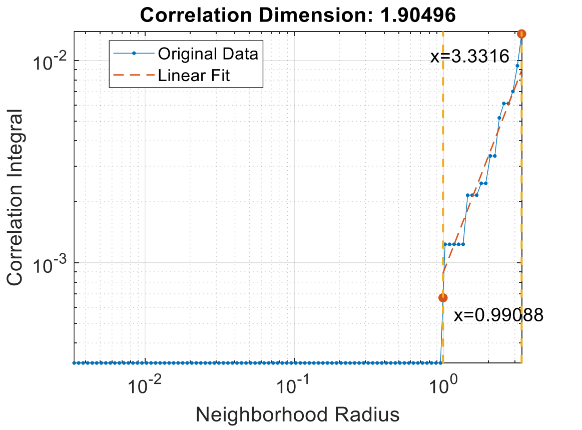


Figure 6. Dependence of the correlation integral on the neighborhood radius for the patient's BFV(Right) measurement results

The radius range is obtained by linearly fitting the original data line. Graphs of the dependence of the correlation integral on the radius of the neighborhood for the measurement results of BP and BFV (Right) of the patient are shown in Figures 5 and 6.

The calculation results are summarized in Table 1. The patient had arteriovenous malformations (AVM) on the left with a pronounced asymmetry of BFV and a phase shift in the M-wave range.

Table 1. Fractal dimension and similarity radius for a healthy volunteer and patients

Test subject	Measured value	x_{min}	x_{max}	Correlation dimension
Healthy volunteer	BP	0.95	8.15	2.51
	BFV(Left)	1.00	9.75	1.79
	BFV(Right)	1.00	9.76	1.80
Patient with left-sided cerebral AVM	BP	0.25	2.42	2.47
	BFV(Right)	0.990	3.33	1.90
	BFV(Left)	1.11	1.99	1.26

Table 1 shows the values characterizing the fractal dimension for healthy volunteer and for patient. The minimum and maximum similarity radius make it possible to obtain a correlation dimension that characterizes the measure of discrimination between deterministic chaos and random noise. This characteristic makes it possible to detect potential changes in cerebral autoregulation.

4. CONCLUSIONS

An expert-class Doppler system made it possible to measure BP and BFV signals in real time.

Digital processing of these signals in the Mayer wavelength range, based on traditional algorithms for spectral, correlation and wavelet analysis of signals, does not always reliably diagnose the development of autoregulation disorders in patients. Traditional algorithms should be supplemented with fractal analysis algorithms that allow determining the width of the multifractal spectrum and the correlation dimension of the BP and BFV signals.

The proposed methods are aimed at the development of digital medicine of preventive personalized medicine.

ACKNOWLEDGMENTS

The authors are grateful for the financial support of the study. This research work was supported by project No. 19-29-01190\19 on the topic "Development and application of methods of mathematical analysis of physiological parameters for the operational diagnosis of pathological conditions of patients with an assessment of the risks of their transition to critical conditions in real time" proposed by Russian Foundation for Basic Research.

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