NONLINEAR FRACTALS: APPLICATIONS IN PHYSIOLOGY AND OPHTHALMOLOGY

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RESUME

Fractal geometry and nonlinear dynamics have applications in the field of biology and medicine. Many complex structures of living systems exhibit fractal-like geometry, and special attention is paid to questions of nonlinearity of the anatomical structures of the human body and physiological functions. The review is provided of multidisciplinary studies demonstrating the multi-scale nonlinear complexity of physiological functions, and the fractal anatomy of different structures in the healthy organism, including the retina, which are simplified or complicated for diseases and in the process of human ageing. Pathological conditions tend to cause the development of highly periodic dynamics of processes, which is dominant on one time scale. In the development of applications of nonlinear dynamics in visual physiology and ophthalmology, author proposes the study of influence of fractal flickering background on electrical activity of the retina and visual cortex. It is assumed that this knowledge can form the basis of new methods of electrophysiological diagnostics and fractal therapy of visual system disorders.

Keywords: fractals, nonlinear dynamics, complex systems, retina, electrophysiology of visual system, fractal therapy

INTRODUCTION

Fractal geometry, which are capable to describe the natural objects, and nonlinear dynamics have many applications in the field of biology and medicine. Fractals are the geometric figures (or a set of points in Euclidean space), possessing the features of self-similarity and a fractional metric dimension. Self-similarity and scale invariance are the basic properties of fractals. They mean that the structure of the fractal object remains unchanged with the increase in the image regardless of the scale [1-3]. Examples of the simplest mathematical fractals are treelike structure with dichotomous self-similar branching, exhibiting properties of bifurcation (so-called “Pythagoras trees”). Since the notion of self-similarity is not applicable to describe many of fractal sets, for

example, of the Julia and Mandelbrot sets, the description of fractals extend through the conversion of a fragment of a fractal set to the entire set. The relief of the sea and river coastlines, of mountain ranges, the winding rivers networks, the Brownian crystal growth and lightning structure – are all belong to the natural fractals [4].

Fractal models for many natural objects are created using the L-systems and the system of iterated functions (SIF), which have the disadvantage of limiting their application to modeling natural objects – they are deterministic, while a coincidence is the inalienable property of the real world. For modeling of a wide range of “natural” fractals the main model is the fractal Brownian motion – the random process, widely spread in nature. The man-created fractals include music, painting, architecture, market shares. Natural fractal objects are the result of a process of self-organization in which the communication of structural levels of different scale occurs, resulting natural fractal objects also have a self-similar structure, that is, with the zooming such structures remains the same, regardless the scale. Natural fractals belong to a class of statistical or random fractals. The fractal dimension sets the link of fractal structures with the properties of the environment. Fractal dimension usually exceeds the objects topological dimension. Physical objects are rarely self-similar at increase of more than 4 orders of magnitude. In biology the new principles of self-organization are seen usually when increase of 2 orders [3].

FRACTALS IN PHYSIOLOGY

Many complex structures of living systems exhibit fractal-like geometry, and at present the special attention is paid to questions of nonlinearity of the anatomical structures of the man and his physiological functions [5-7, 13]. The physical human body is a rich source of nonlinear fractals. Examples of fractal anatomy include branching in venous and arterial vascular system of the heart, kidney, placenta and all the human body, the folds of the intestinal. Treelike fractals are used for description and modeling of the trachea-bronchial tree. Branching fibers of the His-Purkinje bundle is also self-similar structure, which provides the rapid and effective transmission of impulses from the pacemaker of the heart through a complex, spatially distributed network. Fractal structures, partly because of their redundancy and irregularity, are very stable structures that are more resistant to damage [5, 7].

Geometric fractals are static figures and are not acceptable for the description of dynamical systems, that is, time-varying structures, of such natural phenomena as falling streams of water, turbulent eddies etc. If fractals describe the extreme irregularity or angularity inherent for geometric configuration, then to describe the state of unpredictable variability that occurs in a dynamic system, the concept of “chaos” is applied [3, 8]. The chaos implies some of the properties of deterministic dynamical

systems, the most important of which is its significant dependence on the initial conditions and internal unpredictability. Any chaotic phenomenon can be described with its trajectory at the analysis over time. The behavior of chaotic systems varies a seemingly random manner, but in the graphical image of the trajectory can be seen that there are clusters of repetition in certain regions of the phase space. The regions in the phase space, where the system trajectory are visually concentrated, are known as chaotic attractors (synonyms – strange attractor, the Lorenz attractor).

There was noted that the fractal architectures are also manifested in chaotic processes; and that the fractal concept can be applied not only to irregular geometric forms, but also to the complex processes that generate irregular fluctuations across multiple time scales, and such temporal variability is statistically self-similar [5]. The qualitative assessment of the self-similar nature of the fractal processes can be obtained with a graphical representation of their fluctuations at various time resolutions [9-11]. For example, in time-series of heartbeats rate of normal subject, at different scales of time the fluctuations of inter-beats interval has an irregular form, and these irregularities have the property of self-similar scale invariance in time.

Previously, the chaotic fluctuations were associated always with pathology, such as arrhythmia, sharply violated the dynamics of electrical activity of the heart. It was proved, however, that tachycardia and arrhythmia are relatively periodic, but not chaotic processes, and possess a vivid rhythmical nature, while the healthy heartbeat, on the contrary, exhibits the chaotic dynamics [5,12]. In the rhythm of a healthy heart, light variations are observable in the intervals between the beats, and a heart rate has a chaotic pattern, which has signs of self-similarity, while in a sick heart, the variability in heartbeat is absent and heart rate is constant, or it is extremely random. Analysis of the representations in the phase space for normal sinus rhythm in healthy subjects has shown the complexity of the variability in a wide spectrum of frequencies and compliance to the “strange” (chaotic) attractor [13].

Following these studies other studies were published, proving that pathological conditions tend to cause the loss in the complexity of the various processes and the development of their regularity [10, 12-15]. Fractal dimension characterizes the variability in the step-to-step interval in healthy persons, and the lack of dimension was seen in severe neurological diseases, which violate the coordination and gait, such as the Parkinson’s disease, Huntington’s disease [16-18]. Currently, one can speak about so-called «dynamic (periodic) diseases» that violate the system for coordination and control of various functions of the organism. These include diseases associated with the disorder of breathing (stridorous breathing, the Cheyne-Stokes and the Biot’s respiration), obstructive sleep apnea, sudden infant death syndrome, neonatal respiratory distress syndrome, tremor in Parkinson’s disease, disorders of the blood,

including the form of leukemia, which destroys the balance of red and white blood cells, platelets, and lymphocytes [cited by 6, 13, 17].

It is well known that the spectrum of electroencephalogram (EEG) is dominated by alpha-rhythm, which is the main component of the background electrical activity in the healthy waking human brain. Numerous studies have demonstrated [10, 19] that the alpha-rhythm possesses a fractal dimension. The dimensional analysis of EEG waveforms of healthy individuals shows a broad spectrum and the attractor in a phase space, which is similar to a strange attractor.

Moreover, different systems of a healthy brain, which are the sources of EEG rhythms, and also the activity of individual neurons and neural networks – all exhibit properly the chaotic behavior [19-24]. There was assumed that a chaotic trajectory inside the phase space makes neurons able to quickly switch between different status [21], providing the lability of the central nervous system and its resistance to external influences. When pathological conditions, such as schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, the reduction in the multiscale complexity of the background brain activity has been shown [25-30]. The dimensional analysis of EEG waveforms of healthy individuals shows a phase space portrait very similar to a strange attractor.

Thus, pathological conditions tend to cause complexity loss and development of highly periodic dynamics of the process, which is dominant on the same time scale. A multiscale nonlinear complexity of physiological functions is typically lost not only when diseases, but also in the process of human ageing, reducing the capacity of adaptation. It is assumed that the nonlinear regulatory systems operate in a state far from equilibrium. Chaos in health allows the body to adequately respond to rapidly and unpredictably changing circumstances. Disease and aging reduce the dimension or the degree of chaos. Pathology is not always associated with increasing regularity: violation of the fractal physiological monitoring mechanism can also lead to the extreme irregularity of fluctuations (for example, of heart rate during arrhythmia), which is not normally meets the criteria for nonlinear chaos [13].

It is known that in nonlinear systems the noise may increase the degree of orderliness of the system, and this can be used in a therapy of different pathological conditions. Stochastic resonance refers to such phenomena: the response of a nonlinear system on a weak external signal is amplified when the increase in the intensity of the noise in the system [14, 31]. There is the optimal noise magnitude at which the system response on a weak signal is maximal. Studies have shown that the stochastic resonance represents a fundamental physical phenomenon, typical for nonlinear systems, in which the use of the noise helps control one of the characteristic scales of the system (for example, the switching time between metastable states).

On the theory of dynamic systems, when varying the intensity of the noise, one can provide a mode, when the average time of crossing the barrier is close to the period of external influence. The system switching will generally occur with a frequency of the external influence, and the noise will serve as an “amplifier” of the external signal. There is the compliance (resonance) of the external impact and perceiving system (nonlinear dynamic system and noise). Stochastic resonance occurs in bistable systems in situations in which a small periodic force is used simultaneously with the considerable broadband stochastic force (noise). There is an optimal amplitude of noise at which the system response to a weak signal is maximal [14, 31].

The therapy based on the stochastic resonance is known: vibrating soles to ensure coordination and gait in the elderly, patients with diabetic neuropathy, as well as in the period of rehabilitation after a stroke [32-34]. This treatment improved subjectively the equilibrium sense and stability gait of patients, and it caused objectively a significant increase in the fractal dimension and in the complexity of the step-to-step interval fluctuations.

FRACTALS IN OPHTHALMOLOGY

During the aging and disease, the fractal anatomical structures in the retina, similarly to other fractal structures in the human body, altered the degree of their complexity. An example of the change in the complexity of the retina structure is the retina remodeling in *retinitis pigmentosa*, which is characterized by the truncation of the dendrites and axons of retina neurons and the alterations in the wiring of the neural network and synaptic connections [35, 36]. An interesting phenomenon is the recently discovered reduction in the complexity of a dendritic branching and length in magnocellular and parvocellular layers of the lateral geniculate nucleus (LGN) when modeling glaucoma in non-human adult primates (*Macaca fascicularis*) [37]. Interesting that these changes in complexity were modified by NMDA (N-methyl-D-aspartate) receptor blockade. The blockade of NMDA open channel receptor with memantine attenuated decrease in the dendrite complexity and length in relay LGN neurons in primate glaucoma [cited by 37].

Violation of dendritic branching is one of the characteristics and potential mechanisms of neurodegeneration not only for glaucoma, but it is also observed in Alzheimer’s disease and induces infringement of architecture of neural networks in these patients [38]. Disturbances to dendrite branching can disrupt neural network organization and lead to neural dysfunction, as in human neurological disorders including Alzheimer’s disease. Because the fractal geometry describes the morphogenetic laws of complex structures, it was assumed even 20 years ago, that these laws can be used for mathematical modeling of retinal vessels formation (normal vascularization of the retina) during development and in the elaboration of automatic methods of diagnosis of retinal

diseases. Fractal analysis of the retina is a mathematical method to assess the degree of complexity in the geometry of vascular networks. Numerous evidences have been received that a branched vascular nets of normal retina is statistically self-similar and exhibits the properties of fractals, and that a fractal analysis can be used for automated diagnosis of vascular retinal diseases [39-48].

In several research groups strong evidence was presented that the fractal dimension of blood vessels in the normal human retina is about 1.7. The same fractal dimension was detected for the process of diffusion-limited growth of blood vessels in embryogenesis, which may be important in embryological development of retinal vascular system [cited by 48]. In the study of Daxer A., ten patterns of retinal vascular network of patients with diabetic retinopathy (DR) and neovascularization at or on the optic disk (NVD) were compared with the structure of the vascular networks of 14 normal eyes. After digitizing, the fractal dimensions were calculated by means of the 'density-density' correlation function method [40]. The fractal dimension was significantly higher than for the structure of blood vessels with NVD (D=1.845±0.056, M±SD) as compared with the control group (D=1.708±0.073). The value of the dimension of 1.8 was received as the threshold, where higher values could indicate proliferative changes. The sensitivity of the method for detection of NVD amounted to 90%. The presence of NVD in the eyes of patients with DR is a criterion of a high risk of severe vision loss and the evidence of necessity of panretinal laser photocoagulation. Thus, the fractal analysis gives the opportunity to develop a new strategy for computerized automatic diagnosis and quantitative assessment of proliferative DR.

In recent decades, various methods of retinal image analysis were proposed, having different levels of efficiency when using in medical visualization. A standardized method for processing and vascular segmentation of red-free retinographies was presented by Jelinek H. and coauthors [cite by 49], which was designed for fractal analysis of retinal vessels without ocular disease and when retinal neovascularization, and for development of methods of automated diagnostics of vascular retinal diseases. In this study, the box-counting fractal dimension of vascular branching in the fundus followed a Gaussian distribution and amounted to 1.43±0.04 (the mean value and standard deviation – M±SD), what was significantly below the value of the fractal dimension obtained in other studies [41,44-48]. For example, in [50] the average value of the mean fractal dimension for arteriovenous retinal vascular network was 1.698±0.003.

When comparing the patterns of vascular branching in patients with mild to moderate non-proliferative DR (NPDR) a significant difference between them was found only in the macular region. In this case, the simplification of vascular network architecture and the reduction of the fractal dimension occurred. The alteration in the value of the fractal

dimension of vascular branching in the macular region was suggested by the authors as a prediction tool and a method of NPDR diagnosis [39].

There are various changes in the geometric parameters of retinal microvessels that can be used for predicting the DR before the appearance of microaneurysms or hemorrhages [51, 52]. Prognostic criteria include changes in arterioles and venules calibers, vascular curvature tortuosity, length-diameter ratio, branching angles, and fractal dimension. In 'the Wisconsin Epidemiology Study of Diabetic Retinopathy', the increase by 10 microns in venular caliber was associated with the development of diabetic retinopathy during 6 years, progressing of DR and with the presence of proliferative retinopathy [53]. Longitudinal studies of another group have shown that the higher retinal arteriolar caliber [54], a change in the length-diameter ratio and a vessel tortuosity [55] predicted the development of DR. In cross-sectional studies, the increase in vascular tortuosity [56] and fractal dimension [57] was also associated with an increased risk of DR, regardless of the known risk factors for microvascular complications.

The mechanisms underlying these changes in the retinal geometric parameters are unclear, but it is assumed that they may be associated with endothelial cell dysfunction, neovascularization or relative tissue hypoxia [55, 56].

In another work [58], the two methods (box-counting and information fractal dimensions) were applied to the whole retina and to nine anatomical regions of the retina in 5 individuals with mild NPDR and in 28 diabetics without clinical signs of retinopathy (controls, age 31-86 years). The retina images were obtained from the Digital Retinal Images for Vessel Extraction (DRIVE) database. The results of this study have shown that the fractal dimension was not sensitive enough parameter to be of use for an early diagnosis of NPDR.

The associations of retinal vessels' fractal dimension with the risk of DR was studied prospectively in 590 patients aged 12-20 years with type 1 diabetes without retinopathy, when the beginning of DR have been diagnosed on subsequent visits. On average, during 2.9±2.0 years 262 participants developed mild stage NPDR. After adjusting for age, sex, duration of diabetes, A1C, and other risk factors, the authors found no association between the fractal dimension of the retina vessels and the beginning of retinopathy in children and adolescents [59].

However, in another work by the same scientific group [57] the study of stereoscopic retinal photographs of seven fields was performed in 729 young patients with type 1 diabetes, among which 137 people had signs of DR (105 – with mild NPDR). Median retinal fractal dimension was 1.46214. After adjustment for age, sex, duration of

diabetes, A1C, blood pressure, it was shown that the increasing fractal dimension of the retinal vascular network was associated with the increasing odds of developing retinopathy. Thus, greater fractal dimension of the retina, representing increased geometric complexity of its vascular system, was associated, according the results of this study, with early signs of DR in type 1 diabetes.

In a comprehensive study, which was attended by 2,735 people, parameters retinal vascular network were studied in the older age population of Asian Malay persons aged 40 to 80 years [60]. Vascular tortuosity, branching angle, caliber and fractal dimension were measured using a semi-automated computer-based program. In patients with diabetes there were more direct (less winding) arterioles, wider caliber in arterioles and venules, than in those without diabetes. Among diabetics, patients with retinopathy had more wide venular caliber, than persons without retinopathy. Parameters of the vascular network varied depending on the severity of diabetes and retinopathy. Results of this study may suggest that in the older adults the architecture of retinal vascular network is simplified in diabetes, and these changes are more pronounced in case of clinical manifestation of retinopathy.

The alteration in retinal vessels fractal dimensions can act as a surrogate marker for diseased cerebral vessels. In a recent cross-sectional study [61], fractal properties of the retina blood vessels were investigated in lacunar stroke. Lacunar strokes account for 25% of all ischemic strokes and may be the cerebral manifestation of a systemic small vessel vasculopathy. In this study, digital photos of both eyes in patients with lacunar stroke (86 persons) and small cortical stroke (80 persons as the control group) were used, and the monofractal and multifractal analysis were conducted. The mean value of the Dbox (monofractal dimension) amounted to 1.42 (SD 0.02) and the average D0 (multifractal dimension) was 1.67 (SD 0.03). Multivariate analysis showed that the reduction of the fractal dimensions, reflecting the reduced complexity of branching, is associated with a large age of patients, and with a subtype of lacunar, but not the cortical stroke [61].

In another paper, there was also obtained the evidence for lower fractal dimension and simplification of retinal vascular network in human aging and in diabetes mellitus complications [62]. The cross-sectional study of the association of the retinal fractal dimension and the development of microvascular and macrovascular complications in 208 long-term type 1 diabetes from a population-based study Danish cohort was carried out. This study provided the evidence that fractal dimension may have some role as a global measure of retinal vasculature and its association with systemic disease. These results have shown that lower fractal dimension reliably associated with advanced age (influence of ageing), the development of proliferative retinopathy and neuropathy [62]. There was also a trend correlation of simplification in the figure vascular network with

the presence of nephropathy, but not with macrovascular diseases (coronary heart disease, stroke, peripheral artery disease).

Studies of fractal dimension were also undertaken to assess the effectiveness of treatment. For example, it was suggested that vitamin D deficiency mediates changes in retinal vessels and can influence retinal geometric parameters [63], because calcitriol, the active form of vitamin D, inhibits retinal neovascularization and reduce endothelial cell viability and function in adults with type 2 diabetes [64]. However, the value of the fractal dimension was only slightly higher in patients without a deficit, than with vitamin D deficiency [63].

Thus, *summarizing the results* of the research of retinal vessels fractal geometry, note the following regularities:

In the proliferative DR, there was proven an increase of the fractal dimension rather than its simplification in contrast to the abovementioned for physiological functions. Because pathological conditions are not always associated with simplification in the complexity of the structure and function, and can also lead to the extreme irregularity of fluctuations (for example, for heartbeat when arrhythmia and fibrillation), this fact seems logical for process of neovascularization of the retina and the optic nerve. Moreover, a considerable increase in the fractal dimension of the newly formed vessels may reflect the participation in neovascularization of mechanisms, which similar to the mechanisms taking place in normal vasculogenesis in the retina development that, as is known, are accompanied by an increasing complexity of its structure [42].

With regard to the early stages of DR, a significant discrepancy is observed between the results of different studies. Some authors claim that the fractal dimension is not sensitive enough criterion for early NDPR diagnosis in type 1 diabetes; in other studies a larger fractal dimension (and increasing the geometrical complexity of the retina vascular network) associated in young patients with early signs of retinopathy; and in the third investigations it was proved that when NPDR of mild to moderate degree, significant difference in the values of the fractal dimension takes place only in the macular area. These discrepancies may be related to the fact that, as a rule, even in studies of a large cohort of patients the associations were analyzed between the fractal dimension of retinal vascular network with different parameters in patients with diabetes, including the presence and degree of retinopathy, but these data commonly were not compared with fractal dimension of the retina in healthy individuals without diabetes. At the same time, the presence of diabetes, even in the absence of signs of DR in the fundus, is likely to lead to the alterations of anatomical structures. In addition, it should be noted also some discrepancies in the fractal dimension of the vascular network for normal retina that have been obtained in different scientific groups, which depends

among others on the applied method of vessels segmentation in the digitized image and of the method of calculating the dimension.

The long-term investigation in a large cohort of older adult and elderly patients has shown not the increase, but some decrease in the fractal dimension and the reduction in complexity of retinal vascular network architecture. Moreover, these changes correlated not only with age (confirming the de-complication of the structure at physiological aging), but also with the presence of diabetes without retinopathy. Perhaps, the alterations in patterns of fractal complexity of the retina are different for various age periods in a human life.

Thus, the importance of analysis of fractal geometry of the retina for ophthalmology is proved today in numerous works, and further investigations are required for the expansion of the fundamental knowledge about its changes in the course of normal aging and pathology of the visual system.

Unlike fractal anatomy of the visual system, which has been studied for over 20 years, chaotic dynamics of its nonlinear physiological processes remains practically not studied. Meanwhile, the knowledge of visual functions nonlinear dynamics and regularities of their changes can promote the expansion of our understanding of the pathogenesis of neurodegenerative disorders and the new pathogenetic substantiation of adequate therapeutic strategies, in particular, using the property of plasticity of the nervous tissue.

It should be noted that some authors previously suggested that the exciting prospects may be related to novel therapeutic interventions, based on the fact that certain mathematical or physical systems with complex dynamics can be controlled by properly timed external stimuli: chaotic dynamics can be made more regular (chaos control) and periodic ones can be made chaotic (chaos anti-control) [66-68]. For example, there was proposed the using of chaos anti-control protocols to treat or to prevent cardiac arrhythmias or epilepsy based on the hypothesis that restoration of a kind chaotic-like variability may actually be advantageous [67].

In the study of Rilk A.J. [65], the long-term time-series of retina evoked responses at standard flickering stimuli were recorded, and then the fluctuation of the inter-peak intervals in the flicker electroretinogram (ERG) were mathematically analyzed. This study differed from the well-known common analysis of heartbeat intervals in electrocardiogram and of alpha-rhythm in EEG, because it described the evoked but not spontaneous activity. The author showed non-linear response of the visual system to adequate stimulation in the norm and also the change of the flicker ERG responses embedded in a phase space (phase portrait as a graphic trajectory representation of the

flicker ERG inter-peak intervals in the phase space) when retinitis pigmentosa and Stargardt disease [65].

For development of applications of nonlinear dynamics in physiology of visual system and ophthalmology, we expect to conduct research in another direction: to study (in norm and pathology) the ERGs and visual evoked cortical potentials (VEPs) of different kinds, registered not on homogeneous, but on chaotically flickering background with a given nonlinear dynamics of inter-stimuli interval fluctuations, which can be called as the dynamic light fractal. To adequately assess the regularities in the influence of flickering light background having the time invariance property upon the retina and visual cortex electric activity, it is necessary to compare the responses on a standard homogeneous background with the responses on the background of fractal flickering, rhythmic (regular) flickering of constant frequency, and inhomogeneous broadband flashing (white noise).

The retrieving of previously unknown fundamental data about the influence of light environment, which possesses property of time invariance, on the retina and brain evoked responses in norm and neurodegenerative disorders may contribute to the development of new technologies of diagnostics and pathogenetically adequate dynamical fractal therapy.

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