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COMPLEX SYSTEMS BIOPHYSICS

Application of Fractal Analysis to Evaluate the Rat Brain Arterial System

V. S. Kopylova[a], *, S. E. Boronovskiy[a], and Ya. R. Nartsissov[a]

[a] *Institute of Cytochemistry and Molecular Pharmacology, Moscow, 115404 Russia*

**e-mail: kopilova.veronika@yandex.ru*

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Abstract—Vascular networks possess properties of self-similarity, which allows one to consider them as stochastic fractals. The box-counting method based on calculations along the vessel centerlines is traditionally used to evaluate the parameters of the fractal structure. Such an algorithm does not allow one to consider structural differences between different bifurcation levels of the system, characterized by the natural property of changing the blood vessel caliber. In this case, the discrepancy between the values of the fractal dimension may exceed 20%. In this paper, an approach that allows one to avoid underestimating the complexity of the system for low bifurcation orders and large vessels is proposed. Based on the constructed arterial tree of the rat brain, it was shown that the fractal dimension increases with an increase in the values of both bifurcation exponent and length coefficient. The obtained values most fully reflect the properties of the arterial tree considering the real geometry of the vessels; they are proposed for use in estimating three-dimensional vascular networks.

Keywords: arterial system, bifurcation of blood vessel, computer modeling, fractal dimension

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INTRODUCTION

The main function of the vascular system is to provide all cells of the body with oxygen and other vital metabolites. For this to occur most effectively, the arterial tree should be a branching system, while bifurcation is the most common form of division at each step [1]. Due to the extreme complexity and multilevel topology of the vascular network, there is no unequivocal opinion about which parameters to use for describing the structure of blood vessels. In addition, there is a demand for a criterion of normal development that allows one to diagnose diseases. To solve these problems, fractal analysis has been used to evaluate various healthy and pathological circulatory systems [2, 3]. Vascular networks are not strictly fractal, since they do not exhibit large-scale invariance in the infinite range; however, they have self-similarity properties, since the branching process is the same at each stage, therefore, the vascular system is fractal in nature and can be considered as a pseudofractal [4]. It was shown that at least the arterial system of the brain is a combination of two components: a capillary network that fills the space uniformly and a branched fractal structure of larger vessels [5]. In fractal geometry, the properties of self-similar structures observed in a wide spectrum of successive bifurcations are quantified using fractal dimension (*FD*), which is a measure of the complexity of structures [6]. It can be considered as a quantitative determination of the space filling, similar to the analysis of the vascular density [7]. Thus, in the case of a two-dimensional branching network, the closer the fractal dimension is to two the more efficiently the tree fills the space, since the upper limit of the fractal dimension corresponds to the topological dimension. The estimation of the fractal dimension was used to characterize human retina [8], various tumor formations [9, 10], as well as to analyze a three-dimensional arterial tree of human lungs obtained using the data of computer tomography [11]. In addition, the fractal dimensions of 2D projections of the lung vascular system of patients were evaluated in several studies [12]. The estimation of the fractal dimension is widely used to characterize vascular networks in various diseases. As an example, a decrease in the fractal dimension of the pulmonary arterial tree according to CT angiography is associated with a decrease in survival in the study of people with pulmonary hypertension [13], as well as with an increased risk of stroke [14]. It was hypothesized that any pathological morphology of the vascular tree leads to a decrease in the fractal dimension [15]. In the present work, fractal analysis was applied to estimate the structure in the model of the rat brain arterial tree.

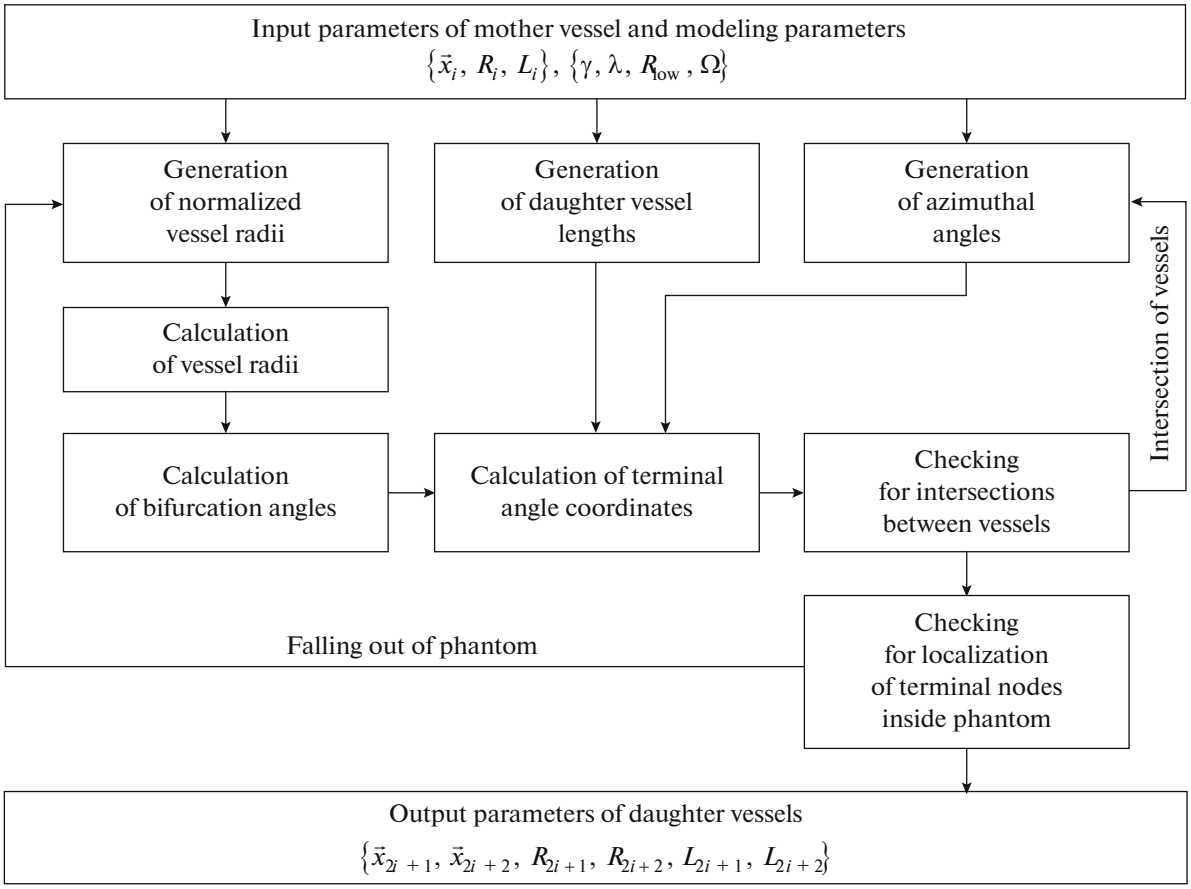

Fig. 1. The single bifurcation modeling algorithm.

MATERIALS AND METHODS

In order to reflect the structure of the cerebral network anatomically correctly, the model representation of the arterial tree was divided into deterministic and stochastic parts depending on the caliber of the vessel. The main arteries of the brain, which have a larger radius and quite conserved topology in most samples, are a deterministic structure that allows one to reproduce the typical topology of large arteries with maximum accuracy. The representation of arteries of the deterministic part was created in the form of an ordered set of cylinders; the radii and coordinates of the centers of their bases were assigned for each, where the radius of the cylinder corresponded to the radius of the vessel. The diameters of the main arteries of the rat brain used to construct the basal level were calculated based on the images of rat brain vessels.

Smaller vessels, which are branches from the main arteries, were isolated into a separate stochastic structure. The stochastic part was implemented in the form of a binary tree since it is consistent with the data of morphometric analysis which shows that bifurcation is almost always formed during the vascular system branching [16, 17]. Under this form of branching, the mother branch (i) is divided into two daughter vessels ($2i + 1$, $2i + 2$), each of which in turn forms a bifurcation up to the level corresponding to the minimum radius of the vessel, which in this model corresponds to 8 μm. At the same time, the process of generating each individual bifurcation consists of several key stages (Fig. 1). The input parameters are the radius, length, and coordinates of the nodes of the mother branch, as well as the values of the key parameters of the model, which determine the branching geometry of the tree as a whole. The decrease in the length of the daughter vessels relative to the length of the mother branch is characterized by the length coefficient (λ):

$$L_{2i+1,\,2i+2} = \lambda L_i. \quad (1)$$

The relationship between the radius of the mother branch and the radii of the left and right daughter branches is established by the bifurcation law, which is also known as Murray's law [18]:

$$R_i^{\gamma} = R_{2i+1}^{\gamma} + R_{2i+2}^{\gamma}, \quad (2)$$

where γ is the bifurcation exponent, whose values, according to the literature, vary from two to three [19, 20]. The generation of normalized radii of the daughter vessels occurs in the range defined by the radius of the mother branch and the minimum radius:

$$\begin{cases} r_{\text{low}} = \dfrac{R_{\text{low}}}{R_i} \\ r_{\text{high}} = \left(1 - r_{\text{low}}^{\gamma}\right)^{\frac{1}{\gamma}} \end{cases} \quad (3)$$

$$\Rightarrow \begin{cases} r_{2i+1} = r_{\text{low}} + (r_{\text{high}} - r_{\text{low}})U(0,1) \\ r_{2i+2} = \left(1 - r_{2i+1}^{\gamma}\right)^{\frac{1}{\gamma}} \end{cases},$$

where R_{low} is the minimum radius in the arterial system and $U(0, 1)$ is the standard uniform distribution. Along with the radii and lengths of the daughter vessels, azimuthal angles are generated:

$$\begin{aligned} \phi_{2i+1} &= 2\pi U(0,1), \\ \phi_{2i+2} &= \phi_{2i+1} + \pi. \end{aligned} \quad (4)$$

Further, bifurcation angles between the daughter branches are calculated based on the normalized radii:

$$\begin{cases} \theta_{2i+1} = \arccos\left(\dfrac{r_{2i+1}^2}{2} + \dfrac{r_{2i+1}^{-2}}{2}\left(1 - \left(1 - r_{2i+1}^{\gamma}\right)^{\frac{4}{\gamma}}\right)\right) \\ \theta_{2i+2} = \arccos\left(\dfrac{r_{2i+2}^2}{2} + \dfrac{r_{2i+2}^{-2}}{2}\left(1 - \left(1 - r_{2i+2}^{\gamma}\right)^{\frac{4}{\gamma}}\right)\right) \end{cases}. \quad (5)$$

Using the obtained coordinates of the terminal nodes, intersections between vessels are eliminated by calculating the distances to the nearest bifurcations. In this work, the arterial system is generated in a space limited by the geometric dimensions of the rat brain phantom; therefore, at the last stage, the localization of terminal nodes inside a given area is checked:

$$\Omega = \bigcup_i E_i; \quad E_i = \left\{ \vec{x} : \sum_{j=1}^{3} \left(\frac{x_j - c_{i,j}}{R_{i,j}} \right)^2 \le 1 \right\}, \quad (6)$$

where $c_{i,j}$ and $R_{i,j}$ are the coordinates of the center and the semiaxes values of the i-th ellipsoid. A rat brain phantom was constructed using the approximation of the brain with the system of ellipsoids, the geometric parameters of which were obtained based on the digitization of the rat brain images.

Arterial trees constructed using the proposed approach were used to estimate the fractal dimension by the box-counting method [21]. For a given fractal structure embedded in a d-dimensional volume, the method consists in dividing the space of the structure into a d-dimensional grid of variable size. The number of nonempty cells $N(r)$ of size r needed to cover the fractal structure depends on r:

$$N(r) \sim r^{-FD}, \quad (7)$$

where FD is the fractal dimension of the given structure. The box-counting algorithm counts the number of nonempty cells for different values of r. The value of the fractal dimension is calculated based on linear approximation of the logarithmic curve:

$$FD = \lim_{r \to 0} \frac{\log N(r)}{\log \frac{1}{r}}. \quad (8)$$

Figure 2 shows an example of calculating the fractal dimension of a two-dimensional arterial tree constructed based on the algorithm presented above. In the described example, for calculation each vessel was represented by the centerline, which does not allow considering the influence of the vessel radius on the value of the fractal dimension (Fig. 3a). It should be noted that the radius of the vessel is one of the most important geometric characteristics of a single branch, which determines the topology of the arterial tree as a whole. In this regard, an approach that allows more accurate assessment of the complexity of the vascular network was developed. The surface of each vessel is uniformly divided into polygons with the mean value of the edge length is about two micrometers (Fig. 3b).

RESULTS AND DISCUSSION

The main influence on the spatial arrangement of blood vessels and the topology of the arterial tree is caused by the bifurcation exponent (γ) and length coefficient (λ). This is greatly referred to the stochastic part of the system, since the geometry of large arteries is less variable. Additional parameters that limit the complexity of the system are the space for constructing the vascular system (Ω) and the minimum possible radius of the vessel (R_{low}), which are biological features of the studied object. To assess the direct influence of the key parameters of the model on the topology of the vascular system without taking limiting factors into account, two-dimensional single daughter trees were constructed based on the principles described above for various values of the bifurcation exponent (Fig. 4) and the length coefficient (Fig. 5). In the presented models, the radius of the mother vessel was taken equal to 40 μm; the vascular tree was then constructed until the specified radius of the branch, which corresponded to 5 μm, was reached. It can be seen from the above models that the density of the blood vessels noticeably increases with an increase in the bifurcation exponent. In turn, an increase in the length coefficient leads to the formation of a vascular system that provides a large coverage area. In order to quantitatively determine the filling of the space, the fractal dimension values were calculated for each of the constructed trees. The fractal dimension increases with an increase in both the bifurcation exponent and the length coefficient. This is consistent with experimental data on various pathological morphologies of the vascular

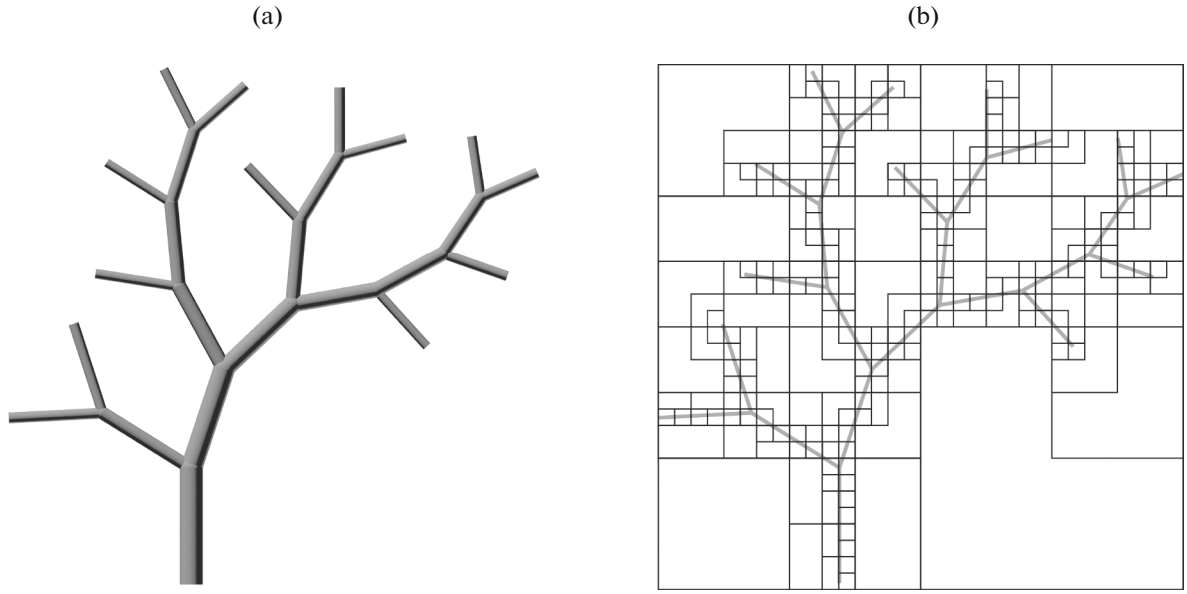

Fig. 2. A schematic representation of the method for measuring fractal dimension by an example of two-dimensional arterial network using the box-counting method: (a), two-dimensional arterial tree constructed using the proposed approach; (b), sequential subdividing of the space into a grid of variable size with the isolation of cells covering the structure of the arterial tree.

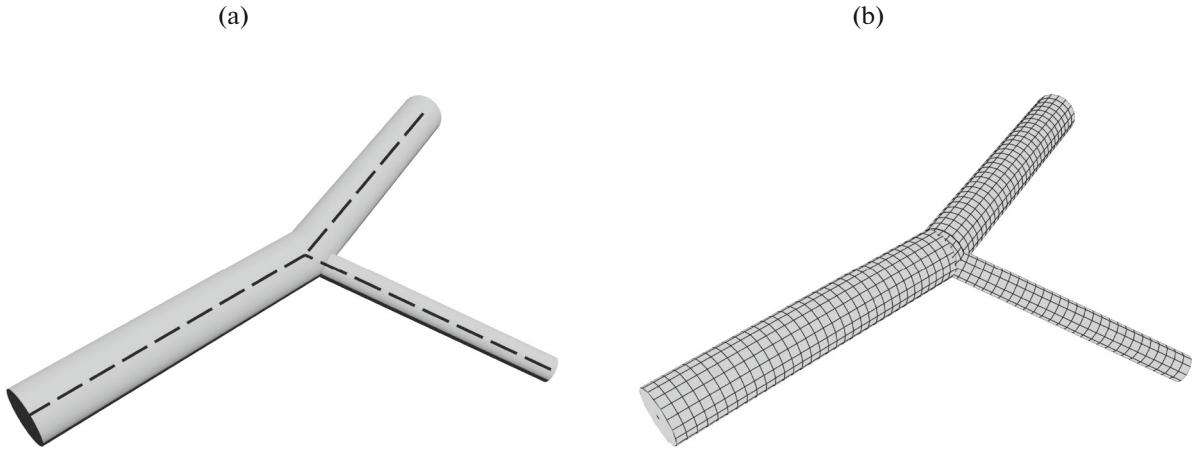

Fig. 3. A representation of single bifurcation for calculating fractal dimension: (a), vessels are approximated by the centerline; (b), vessel surface is represented by a set of polygons.

tree, in which the fractal dimension is decreased [22–24]. It should be noted that the range of *FD* changes of the system is wider with a change in the bifurcation exponent value ($\Delta FD = 0.13$) and the complexity of the system is largely determined by its branching.

In the case of analysis of medical images of vascular systems, the fractal dimension is usually estimated based on two-dimensional projections [13, 25]. This is associated with both the difficulty of obtaining a full three-dimensional structure and the impossibility of automatic segmentation of a separate vessel for volumetric representation, which leads to the need for linear approximation. Despite this, estimating the complexity of a system from two-dimensional projections is least expensive in terms of computational resources and provides an effective way to initially estimate parameters of the model based on available experimental data. An example of application of the box-counting algorithm for calculating the fractal dimension of the axial projection of the rat brain arterial system is presented in Fig. 6. The dependences of the

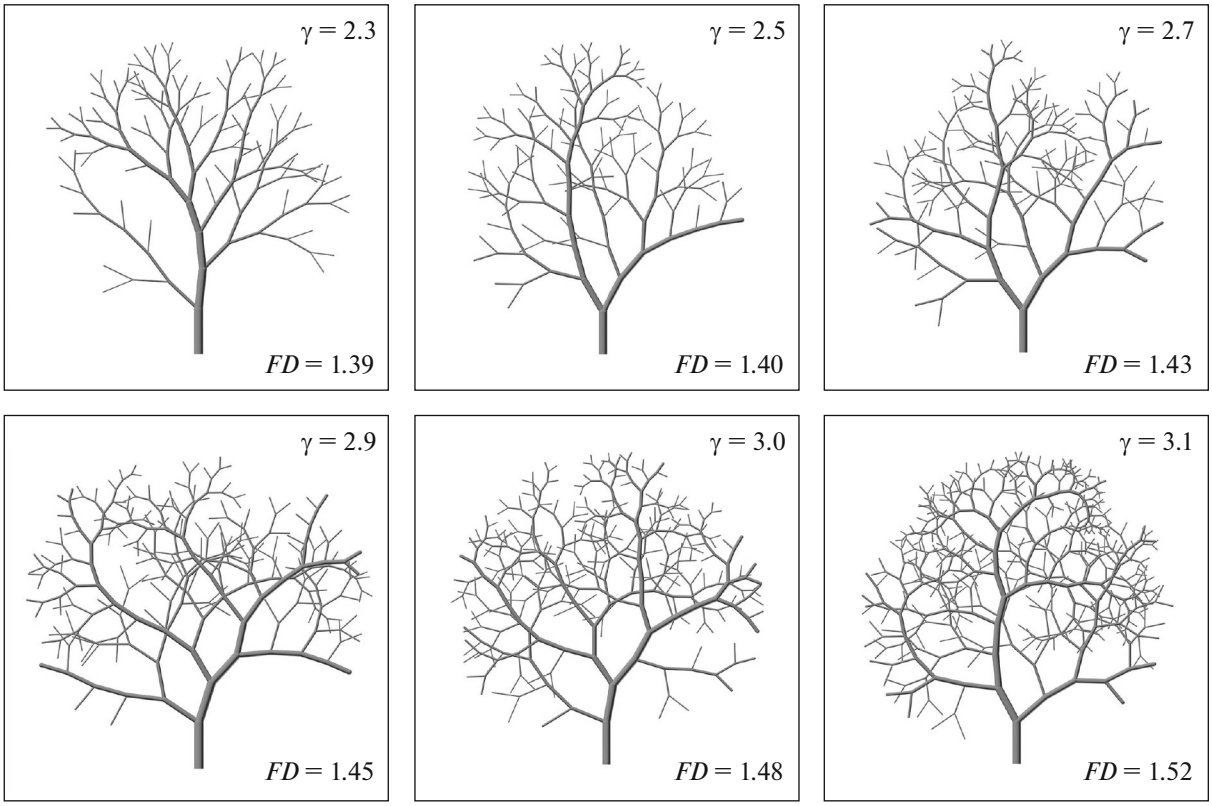

Fig. 4. Two-dimensional vascular trees constructed for different values of the bifurcation exponent (γ). The value of the length coefficient (λ) was taken equal to 0.90. The present values of the fractal dimension are obtained by the box-counting method along the vessel centerlines.

fractal dimension on the bifurcation exponent and the length coefficient for the case of the axial projection were obtained (Fig. 7). The pattern of *FD* growth is comparable with the case of single two-dimensional trees; however, the absolute values are on average higher by 0.36, and the decrease in the ΔFD range is associated with the presence of a low variable structure of large arteries that escape the principle of bifurcation branching. At high values of γ and λ, the fractal dimension is approximately 1.83, which is consistent with experimental data and modeling results, according to which the fractal dimension exceeds 1.80 [26, 27].

Analysis of the fractal dimension of the full three-dimensional vascular system is of the greatest interest. In this regard, the dependence of the fractal dimension on the model parameters for the three-dimensional arterial tree of the rat brain was studied (Fig. 8). As can be seen from the above curve, the fractal dimension exceeds 2.05 for the values of the bifurcation exponent close to three in the case of estimation along the centerline of the vessel (FD_{line}). Despite the fact that a change in the bifurcation exponent primarily affects the branching of the network and, as a consequence, the fractal dimension, an increase in the calibers of daughter vessels under an increase in γ is significant. In addition, the average and modal values of the relative length of blood vessels for the rat brain arterial system are 16 and 10, respectively [28]. This suggests that for a large number of vessels linear approximation is not effective and the underestimation of the fractal dimension value in the calculation along the centerline is significant. To assess the effect of the vessel radius on the complexity of such a system, the surface of each vessel was presented as a set of polygons. All the dependencies are characterized by an increase in FD_{poly}, and the average difference in estimating the fractal dimension between two calculation methods is 0.11. The obtained values of the fractal dimension fully reflect the influence of the parameters of the arterial tree considering the exact geometry of the vessels and it is proposed to use them to assess three-dimensional vascular networks.

As was shown earlier, the space of parameters {γ, λ} should be strictly limited from the bottom for maximum correspondence with the bifurcation model of the rat brain arterial tree. Systems with a low value of the bifurcation exponent ($\gamma < 2.9$) show insufficient

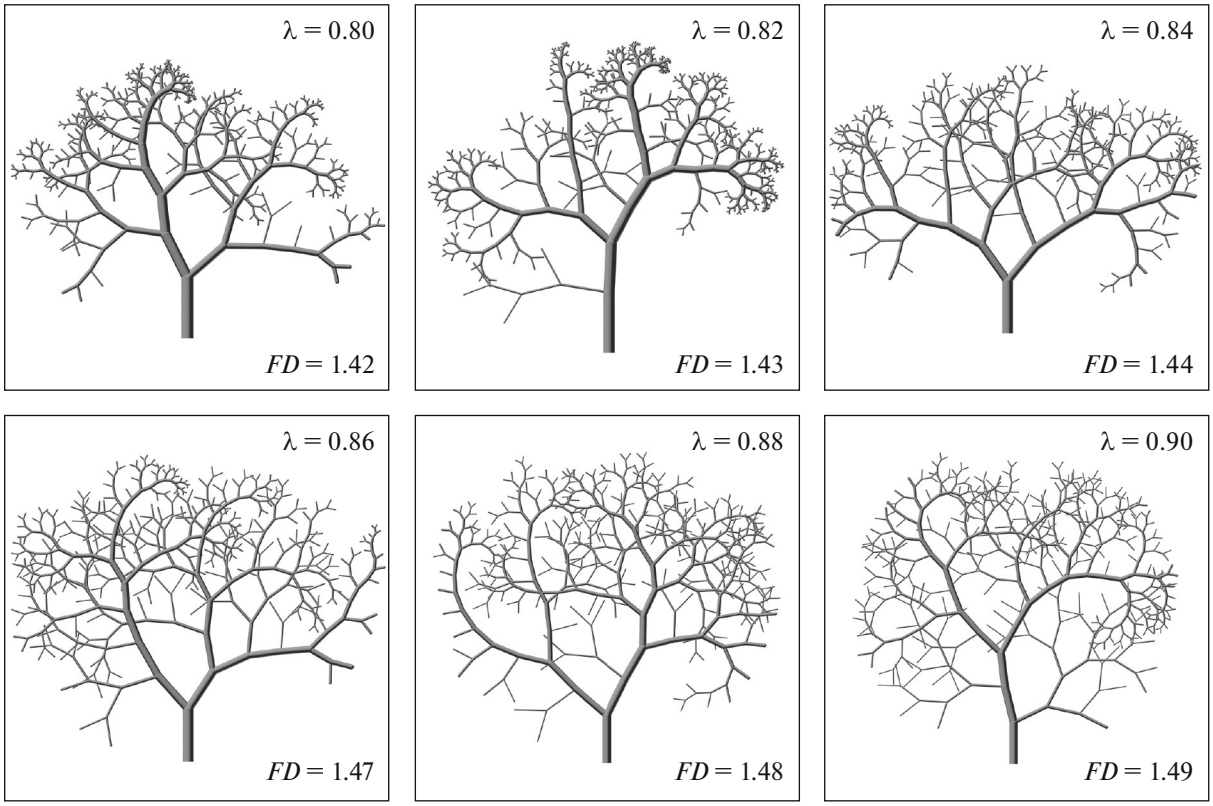

Fig. 5. Two-dimensional vascular trees constructed for different values of the length coefficient (λ). The value of the bifurcation exponent (γ) was taken equal to 3.0. The present values of the fractal dimension are obtained by the box-counting method along the vessel centerlines.

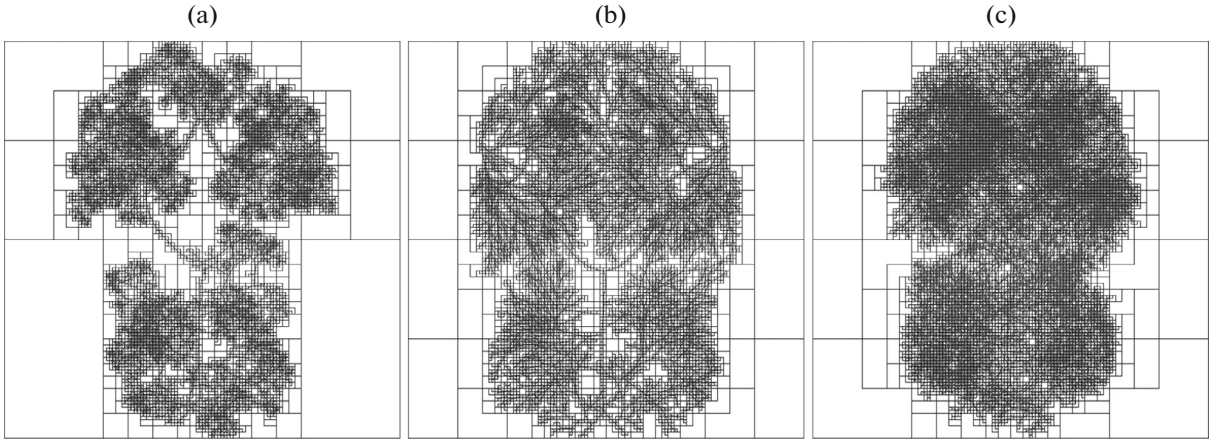

Fig. 6. An example of the box-counting algorithm application for calculating fractal dimension of axial projection of model rat brain arterial systems for various values of key parameters: (a), γ = 3.0, λ = 0.80; (b), γ = 2.3, λ = 0.90; (c), γ = 3.0, λ = 0.90.

branching and degrees of symmetry and do not provide the required arterial cerebral blood volume (CBV) [29, 30]. In turn, the arterial system, which is effective from the point of view of the vascular topology, can be obtained only with the optimal value of both key parameters (γ = 3.0; λ = 0.90) [28]. The limitation of the vessel radius at the level of metarterioles is associated with the fact that microcapillary beds, as a rule, escape the bifurcation laws of branching and are chaotic net-like structures [31]. An example of an optimal arterial tree is shown in Fig. 9.

The above results allow us to estimate both the values of the fractal dimensions for various arterial trees as a whole and to consider the influence of the main

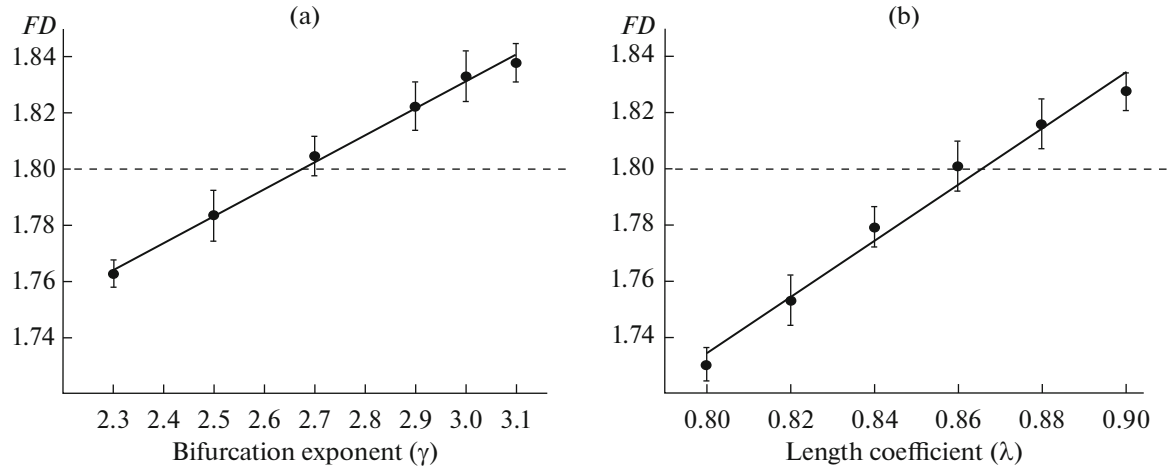

Fig. 7. (a), The dependence of the fractal dimension of the arterial tree axial projection on the bifurcation exponent (γ); (b), dependence of the fractal dimension of the arterial tree axial projection on the length coefficient (λ). The results are presented as $M \pm SD$ for 20 independently generated rat brain arterial systems for each calculation.

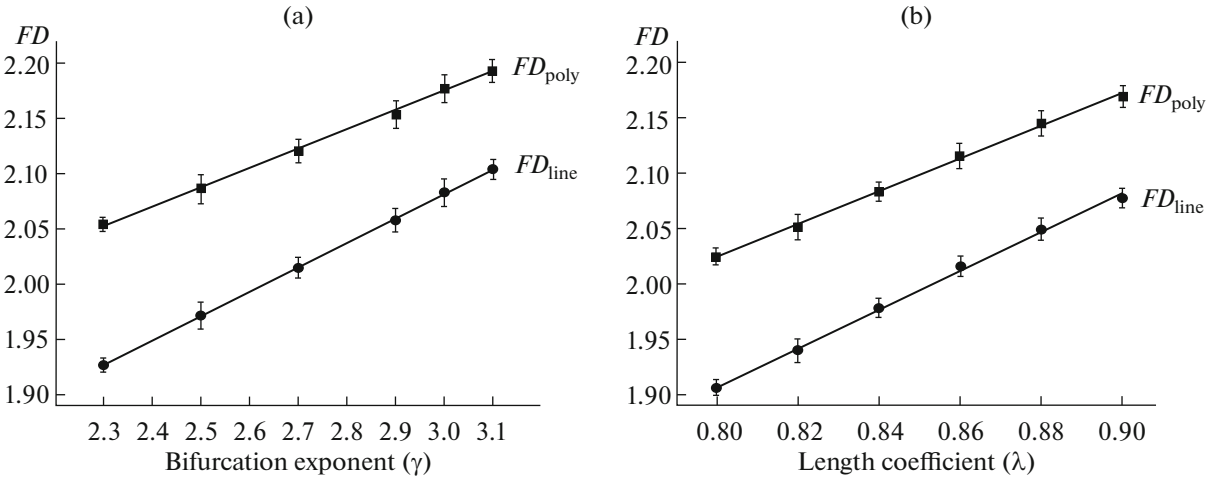

Fig. 8. (a), The dependences of the fractal dimension of three-dimensional arterial tree on the bifurcation exponent (γ); (b), dependences of the fractal dimension of three-dimensional arterial tree on the length coefficient (λ). The results are presented as $M \pm SD$ for 20 independently generated rat brain arterial systems for each calculation.

bifurcation parameters on the complexity of the system. In turn, the fractal dimension of local regions can vary significantly within the same arterial system despite the fact that both branching laws (the division of the mother branch strictly into two daughter vessels) and key parameters within the same tree remain unchanged.

The dependence of the fractal dimension on the bifurcation level for two variants of the vessel representation was analyzed for an arterial tree with optimal values of both parameters (Fig. 10). As can be seen from the above curves, the *FD* value increases with an increase in the bifurcation level and the maximum growth of the complexity of the system is observed on the first fifteen bifurcation orders in both cases. However, the range of changes in the fractal dimension is significantly larger with the calculation method along the centerline (from 1.42 to 2.08), while it is from 1.77 to 2.18 when using the polygonal representation. It should also be noted that the boundary bifurcation level which divides the arterial system into distributing and delivering vessels [32, 28] corresponds to growth of the complexity of 61% and 55% for linear and polygonal representations, respectively.

The caliber of the vessel does not directly depend on the bifurcation level, since the symmetry of the vessels increases significantly with an increase in the bifurcation order [29, 33]. This is associated with the different functions of two types of vessels: vessels with predominantly asymmetric bifurcations give a rela-

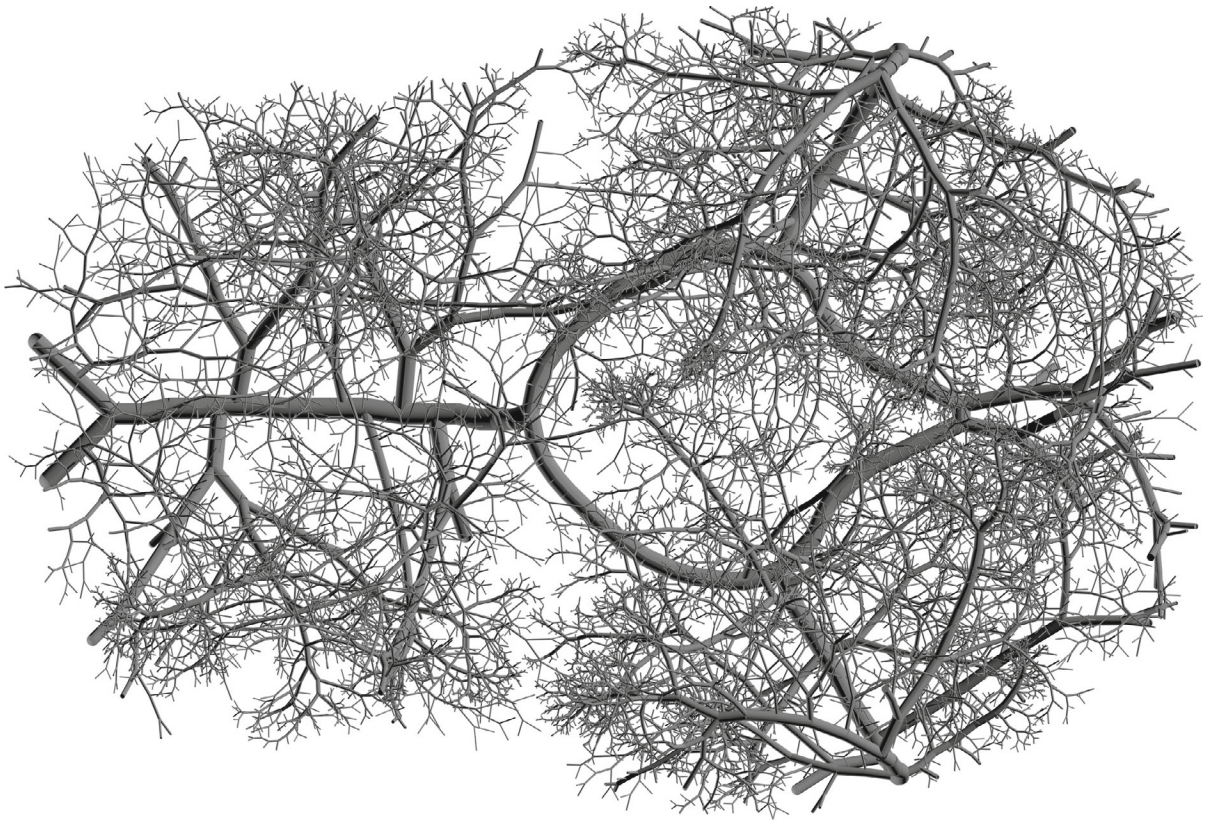

Fig. 9. A model of the arterial tree of the rat brain constructed based on the optimal values of bifurcation parameters ($\gamma = 3.0$, $\lambda = 0.90$). The minimum vessel radius is limited to 8 μm, which corresponds to the level of terminal arterioles.

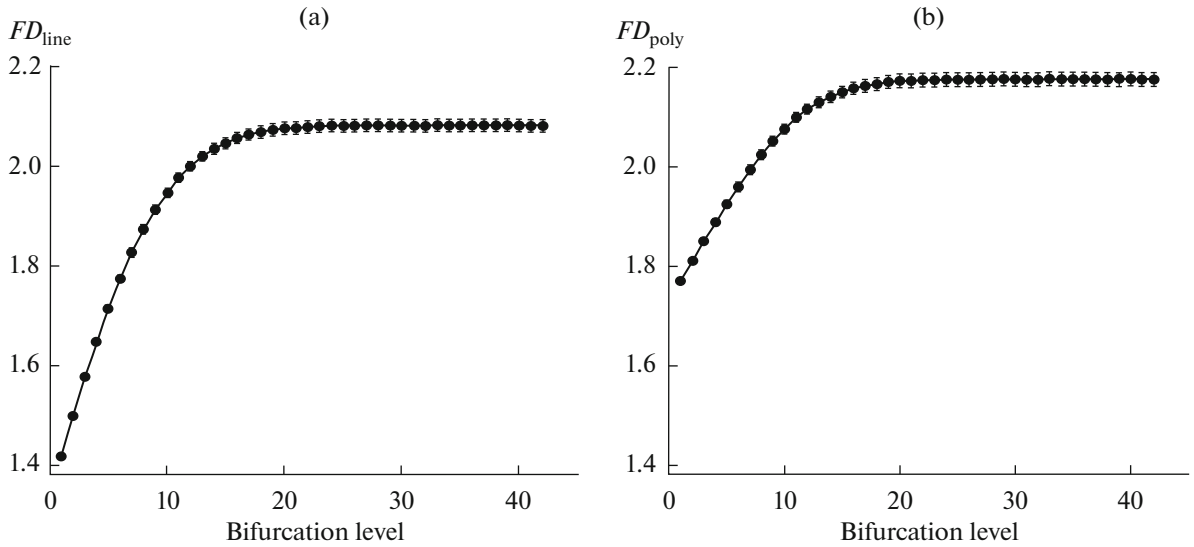

Fig. 10. The dependences of the fractal dimension of the three-dimensional arterial tree of the rat brain on the bifurcation level: (a), *FD* calculation along the vessel centerlines; (b), *FD* calculation based on polygonal representation of the vessel.

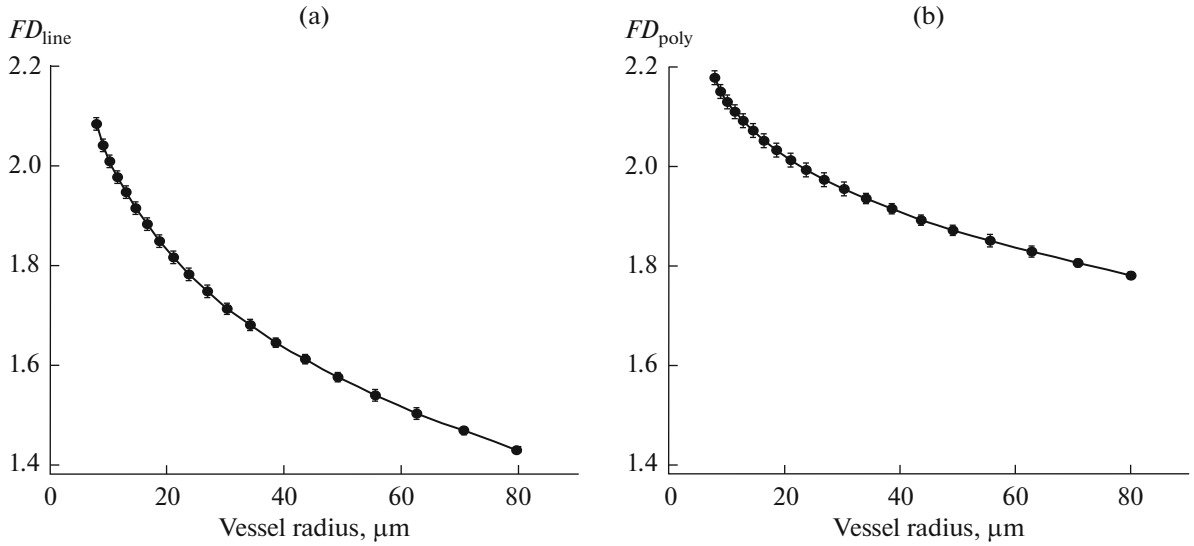

Fig. 11. The dependences of the fractal dimension of the three-dimensional arterial tree of the rat brain on the vessel radius: (a), *FD* calculation along the vessel centerlines; (b), *FD* calculation based on polygonal representation of the vessel.

tively small flow to the lateral branches during division and, therefore, are able to carry blood over long distances; the more symmetrical bifurcation structure splits into numerous small branches that supply the surrounding tissue with blood. The dependence of the fractal dimension on the radius of the vessel was analyzed (Fig. 11). The minimum radius corresponds to the radius of terminal arterioles, which in the proposed model is equal to 8 μm, and the maximum value corresponds to arteries. Using the obtained dependences, one can estimate the fractal dimension of the arterial tree of various degrees of the complexity. Thus, for example, the fractal dimension of a system consisting only of arteries with a radius of 50–80 μm varies from 1.78 to 1.87 (Table 1). As in the case of the previous analysis, higher dispersion of the *FD* values allows us to conclude that the complexity of the system is underestimated when calculated along the centerline, especially for low bifurcation orders and large vessels.

CONCLUSIONS

The method of calculating the fractal dimension, which allows quantification of the efficiency of space filling, was used as a criterion for estimating the structure of the constructed vascular tree. This approach is widely used to identify pathological abnormalities of vascular networks in various diseases. It was previously established that even a slight decrease in the fractal dimension is a negative factor in the prognosis for a number of diseases [34]. In this work, it was shown that the value of the fractal dimension increases with an increase in the bifurcation exponent (γ) and the length coefficient (λ). The results indicate that the construction of the arterial network model in the tis-

Table 1. The fractal properties of the main types of vessels of the rat brain arterial system

Type	Functions	Radius, μm	FD_{line}	FD_{poly}
Arteries	Transfer of blood from the heart and supply of various parts of the brain with blood	50–80	1.43–1.57	1.78–1.87
Arterioles	Regulation of blood pressure and blood distribution in the capillary bed	10–50	1.57–2.01	1.87–2.13
Metarterioles	Regulation of supply for individual groups of capillaries	8–10	2.01–2.08	2.13–2.18

sue based on the optimal values of both key parameters is justified not only by physicochemical, but also physiological features of the branched structures. The box-counting method based on calculations along the center line of the vessel is most often used to assess the fractal properties of arterial systems. This method is simple from the point of view of computational complexity; however, the linear representation of the vessels does not allow one to take the differences between the bifurcation levels of the system into account, which are characterized by the different calibers of the vessels. In this paper, an approach was proposed that allows one to avoid underestimating the complexity of the system for low bifurcation orders and large vessels, which at the level of large arteries can exceed 20%. The obtained values of the fractal dimension most fully reflect the properties of the arterial tree considering the real geometry of the vessels and allow both estimation of the fractal dimension of arterial trees of varying degrees of complexity and determination of the presence of vascular pathologies during medical research.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

Statement on the welfare of animals. This article does not contain any studies involving animals performed by any of the authors.

Statement of compliance with standards of research involving humans as subjects. This article does not contain any studies involving humans as subjects of research.

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