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REVIEW

Approaches to vascular network, blood flow, and metabolite distribution modeling in brain tissue

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Abstract

The cardiovascular system plays a key role in the transport of nutrients, ensuring a continuous supply of all cells of the body with the metabolites necessary for life. The blood supply to the brain is carried out by the large arteries located on its surface, which branch into smaller arterioles that penetrate the cerebral cortex and feed the capillary bed, thereby forming an extensive branching network. The formation of blood vessels is carried out via vasculogenesis and angiogenesis, which play an important role in both embryo and adult life. The review presents approaches to modeling various aspects of both the formation of vascular networks and the construction of the formed arterial tree. In addition, a brief description of models that allows one to study the blood flow in various parts of the circulatory system and the spatiotemporal metabolite distribution in brain tissues is given. Experimental study of these issues is not always possible due to both the complexity of the cardiovascular system and the mechanisms through which the perfusion of all body cells is carried out. In this regard, mathematical models are a good tool for studying hemodynamics and can be used in clinical practice to diagnose vascular diseases and assess the need for treatment.

Keywords Cardiovascular system · Computational modeling · Arterial tree construction · Cerebral blood flow · Spatial metabolite distribution

Introduction

One of the main coordinating and integrating systems of the body is the circulatory system, which serves to transport and distribute the necessary substances in tissues and to remove metabolic byproducts. The circulatory system is also involved in such homeostatic mechanisms as body temperature and humoral regulation and the control of oxygen and nutrient concentration in various physiological states. The circulatory system performs these functions via the muscular pump, a series of distributing and collecting tubes, and an extensive system of thin vessels that allow rapid exchange between tissues and vascular bed.

The effective functioning of the circulatory system is largely determined by its structure and topology. Nutrient and oxygen transport depends on the blood flow, which primarily rely to the corresponding vessel geometric characteristics. In addition, the maximum distance between the vessels surrounding a certain tissue area should be small enough to adequately supply them, in particular, with oxygen. There are a huge number of biological mechanisms that control vascular network structure both at the main arteries and veins level, which location is determined by the influence of genetic factors during embryonic development, and smaller vessels that can form in the tissues of an adult organism during a number of physiological processes. Thus, in further blood flow modeling using various computational methods, it is necessary to take into account the vascular network structure as close as possible to the real one, which, in turn, can be a combination of instrumental methods for large vessel reconstruction and model systems describing small vessels up to the capillary bed.

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Vascular network formation

The formation and development of blood vessels is a multiscale process caused by endothelial cells (EC) activation by stimuli emitted by both surrounding cells and EC themselves. Vasculogenesis and angiogenesis are two main mechanisms involved in the blood vascular system formation (Fig. 1). The first process is the *de novo* primitive vasculature formation that results from directed and autonomous migration, aggregation, and organization of endothelial cells. The second describes new vessel formation from an existing capillary or post-capillary venule. Angiogenic remodeling is coordinated with blood flow establishment and can occur through the formation of new branches from the existing capillaries, cutting, changing the size of the capillary and the thickness of the capillary wall, or due to vessel lumen internal division.

As a result of experimental studies, the role of many factors influencing the vascular network formation, both in physiological and pathological situations, was revealed (Scianna et al. 2013). For example, vascular endothelial growth factors (VEGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), angiopoietins (Ang), ephrins, and others stimulate vascular growth (Gacche and Meshram 2014). However, the main stimulating factor of angiogenesis in both cases is the lack of oxygen (Krock et al. 2011).

The vasculogenesis begins in the embryo with the endothelial progenitor cells fusion into polygons with well-defined topological characteristics, which is due to the main function of the vascular system. These geometric properties are partially preserved in the adult human body, where the capillary network has the same shape as the smallest unit involved in the embryonic vasculature formation.

Due to angiogenesis in the embryonic period, the initial capillary network is formed into a mature and functional vascular bed, consisting of arteries, capillaries, and veins. At the same time, this process also plays a role in the adult life of the organism, when it participates in many physiological processes. However, when the basic control mechanisms are violated, angiogenesis becomes pathological and leads to the development of a huge number of diseases. Indeed, diseases such as cancer, psoriasis, arthritis, blindness, obesity,

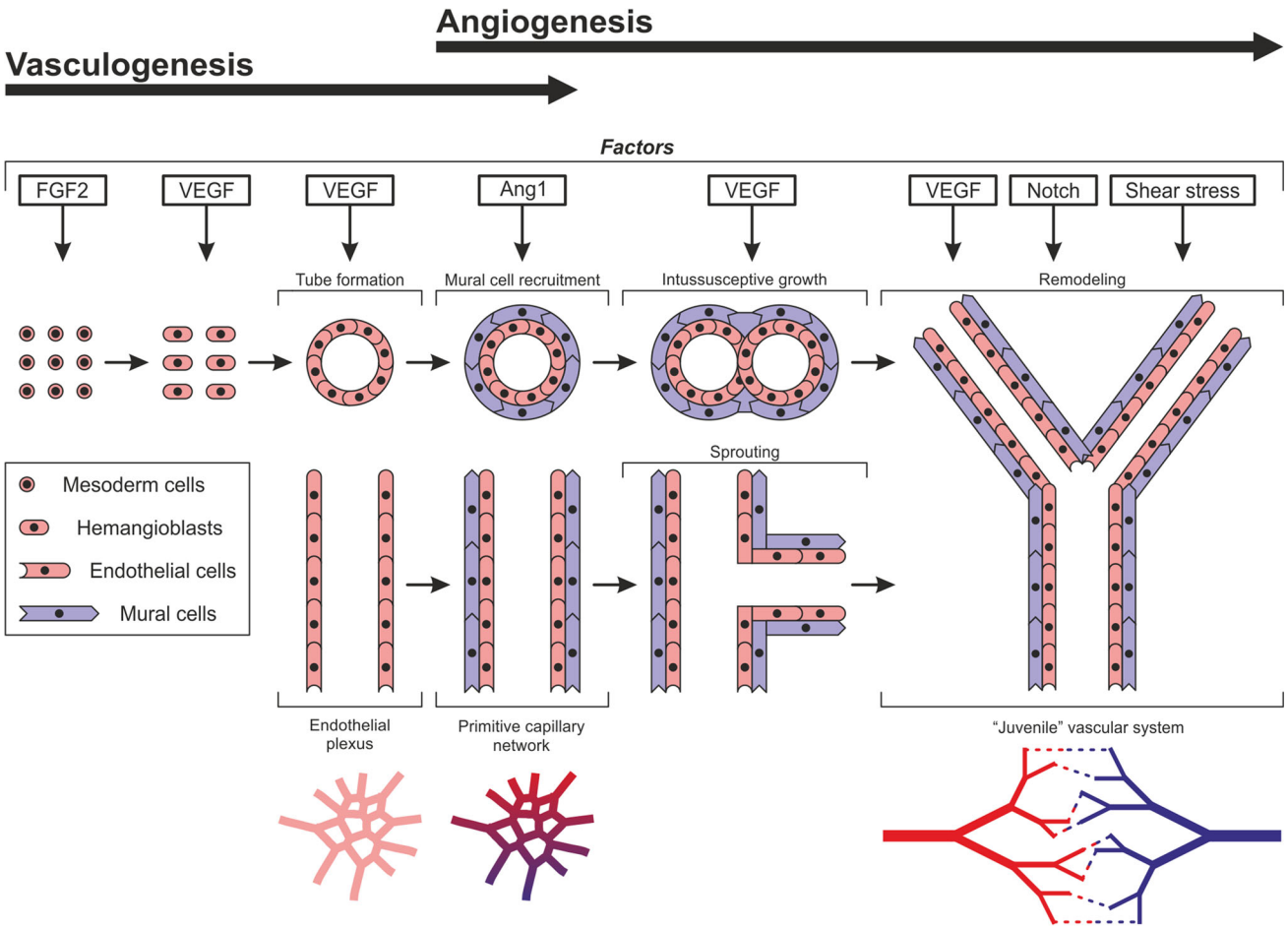

Fig. 1 Scheme of the vascular network formation

asthma, atherosclerosis, and infectious diseases are characterized by increased angiogenesis (Carmeliet 2003). In addition, inadequate vascular growth and abnormal vascular regression not only cause cardiac and cerebral ischemia, but can also lead to neurodegeneration, hypertension, respiratory failure, osteoporosis, and other disorders (Carmeliet 2003). A large number of mathematical models have been proposed to describe various aspects of vasculogenesis and angiogenesis (Ambrosi et al. 2005; Pillay et al. 2017; Nakazawa et al. 2022). Early models, including a highly simplified angiogenesis mechanism, are based predominantly on a deterministic method for two-dimensional vascular structure generation (Chaplain 2000). The vascular system construction is modeled, for example, as a growth process in response to angiogenic factors secreted by ischemic tissue cells (Nekka et al. 1996). In the case of generating a network based only on the distribution of angiogenesis factors without introducing any restrictions on its further geometry, the resulting models are too regular, which does not correspond to the anatomical data. To solve this problem, a number of complex algorithms for creating a vascular system in accordance with biophysical properties with good resolution have been proposed (Szczerba and Szekely 2005; Lloyd et al. 2008). In this case, the implementation can be roughly divided into two stages: the primary capillary plexus creation and the vessel growth in accordance with biophysical and hemodynamic rules, including the non-Newtonian properties of blood and the effect of shear stress.

As mentioned above, the process of vascular network formation includes several phases, for the modeling of which it is necessary to take into account the role of various cell types. Thus, in the review by Heck et al. (2015), three classes of models were considered: in the first of which the vasculature formation is determined by tip cell migration; in the second, the effect of stalk cell is also taken into account; and the last group of models takes into account the cell shape changes. Later, when evaluating the rate of tip cell migration and the rate of stem cell proliferation on the formation of the vascular network, it was shown that the latter has a greater influence on the spread and extent of vascular growth, but a balance between the two processes is also necessary (Norton and Popel 2016). In turn, the endothelial cell shape can change significantly during angiogenesis due to numerous biochemical and biomechanical interactions (Santamaria et al. 2020), which makes it necessary to take this factor into account. One of the popular approaches to describe the dynamics of endothelial cells is the Cellular Potts model (CPM), which allows one to reproduce the proliferation, migration, and interaction of EC with the extracellular matrix (ECM) (Boas et al. 2013; Daub and Merks 2013). Thus, using a hybrid model based on CPM and diffusion of growth factors in the ECM, it was possible to accurately reproduce the sprouting pattern and angiogenesis primary events by taking into account the original effect of EC proliferation (Salavati and Soltani 2019). Shear and tensile stress induced by fluid flow, which have a significant effect on the vasculature development and regression in areas with low blood flow, were considered in a recent work as biomechanical stimuli affecting EC (Abdi and Vahidi 2022). The process of vascular network formation in brain tissues is a separate and rather complex task. Thus, the goal of the study by Alberding and Secomb (2021) was to model the process of angiogenesis in brain tissues. The development of the cortical network, including angiogenesis, structural adaptation, and pruning, occurs in response to diffusion growth factors, the production rate of which depends on the local oxygen concentration. However, despite the fact that the proposed models demonstrate a high similarity with real circulatory systems, the simplifications underlying the approaches still do not allow one to form vascular morphologies in full accordance with experimental data. In addition, these methods allow the reproduction of sufficiently small vascular networks.

A number of works are devoted to modeling angiogenesis in tumor tissues (Curtis et al. 2015; Akbarpour Ghazani et al. 2020; Phillips et al. 2020). The study of this issue is a rather important task, since, as mentioned above, tumor capillary networks differ significantly from those formed under normal conditions. These networks are characterized by excessive branching and randomness, while the vessels are significantly dilated, tortuous, and have an uneven diameter (Carmeliet and Jain 2000). In addition, in tumors, the fraction of hypoxic tissues is significant, and the endogenous VEGF level is usually elevated (Pries and Secomb 2014). Thus, 3D tumor growth models were proposed that combine the description of blood flow, angiogenesis, vascular remodeling, transport of nutrients/growth factors, movement and interaction between normal and tumor cells, as well as cell cycle dynamics (Perfahl et al. 2011). Based on the experimental data, the original geometry of the circulatory network was reconstructed, which then developed under the influence of nutrients and chemical factors through germination, anastomosis, and pruning. The formation of the embryonic capillary plexus was modeled using an agent-based model that takes into account the role of endothelial growth factor, pro- and anti-angiogenic signals of inflammatory chemokines, and the plasminogen-activating system of enzymes and proteases (Kleinstreuer et al. 2013). In general, the current models of tumor-induced angiogenesis reproduce changes in vessel geometry in response to various stimuli. For example, the work (Vilanova et al. 2017) takes into account the influence of tumor angiogenic factor (TAF) not only on the new capillary growth, but also on their natural regression and re-growth. This model, based on the non-conservative phase-field theory, predicts the dynamics of the vascular network development on a long-term scale, consis-

tent with experimental data. Furthermore, taking into account the role of interstitial flow in the tumor capillary network development, the authors showed that interstitial flow can affect angiogenesis, leading to an increase in tumor malignancy (Vilanova et al. 2018). To generate 3D networks of blood vessels at macroscopic scales, corresponding to the topological, morphological, and hydrodynamic properties observed in real samples, an open source software based on a multiscale approach combining several previously described models has been proposed (Fredrich et al. 2018). In a recent study, using a complex computational model of spatiotemporal FDG transport, it was shown that as a tumor grows, its microvascular density increases, which is a marker of tumor angiogenesis (Kashkooli et al. 2022). Tumor vascularization models are described in more detail in the reviews by Rieger and Welter (2015) and Bhat et al. (2021). In general, it should be noted that the comparison of the obtained circulatory networks in the case of modeling the process of angiogenesis in tumors with experimental data is difficult, since these vascular structures are highly specific.

Approaches to structural modeling of vascular systems

With the improvement of numerical modeling methods and the development of algorithms for visualizing the results of medical research, a comprehensive study of vascular networks has become possible, taking into account complex structure and differences in the blood vessel scales. Three-dimensional images of real biological circulatory systems can be obtained using various imaging techniques, such as phase-contrast magnetic resonance imaging (Wymer et al. 2020), computed tomography angiography (Gao et al. 2022), corrosion casting technique (Kafarov et al. 2023), and time-of-flight magnetic resonance angiography (Tang et al. 2019). These methods are used to visualize sufficiently large blood vessels with sizes from 1 mm, but they lack resolution for the microvasculature reconstruction (Vigneshwaran et al. 2019). 3-photon fluorescence microscopy (Zhang et al. 2022) and long-wavelength reflectance confocal microscopy (Xia et al. 2018) have a higher resolution, but they have a number of significant limitations associated with the appearance

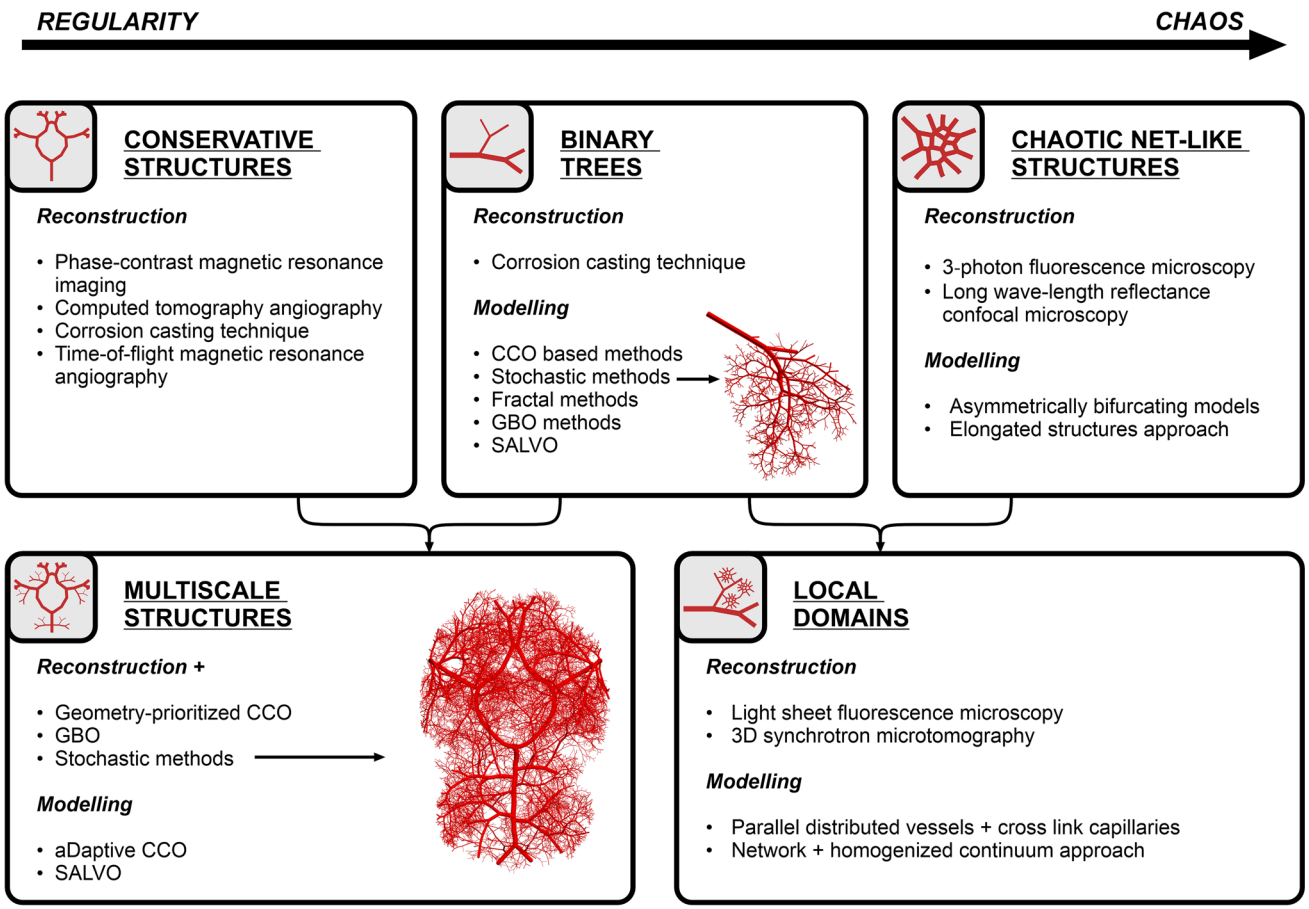

Fig. 2 Different scale modeling of vasculature structure. Examples of represented arterial system models were created using approach described in Kopylova et al. (2019b)

of artifacts during image processing and the lack of adequate quantification methods (Chico and Kugler 2021). In this regard, there is a need to study the structure of circulatory systems using computer models. The main approaches used to model the vascular structure at various scales are presented in Fig. 2.

Vascular systems, no matter how they are formed, tend to a state of optimality; therefore, it is possible to bypass the stage of vascular growth and directly simulate a fully formed circulatory network. The main approaches for a branched arterial system generation are usually based on the optimality principles for various biological functionals (Kopylova et al. 2017). In most cases, the arterial network is implemented as a binary tree, since according to experimental data, bifurcation is the most common form of branching (Cassot et al. 2006). In favor of using the optimality principles to branches that form a bifurcation is the fact that the junctions of blood vessels are the main structural element of the vascular system. And, therefore, finding each node in an optimal state leads to the optimality of the entire system. One of the first developed methods was a fast algorithm for constructing three-dimensional computer models of vascular trees with their inherent physiological and hemodynamic features, which is based on the geometric optimization of each newly created bifurcation and the recalculation of blood pressure and vessel radii in the entire tree (Kretowski et al. 2003). The most popular algorithm is Constrained Constructive Optimization (CCO), first described by Schreiner (1993). The main idea of CCO is the gradual growth of the tree, during which geometric and structural optimizations are performed, aimed at minimizing the total intravascular volume and ensuring uniform perfusion of the area under consideration. One of the key parameters of the model is the bifurcation exponent, the value of which remains constant throughout the entire tree growth process. However, later it was shown that its variation depending on the branching order makes it possible to obtain vascular trees whose diameters are in better agreement with experimental data (Meneses et al. 2017). Subsequently, several extensions of this approach have been proposed, one of which is Global Constructive Optimization (GCO) (Georg et al. 2004), which improved the global structure of the vasculature, since with CCO application, the original branching structure can be maintained throughout the optimization. Another extension of this computational method is the Staged Growth (SG) mechanism (Karch et al. 2000), in which the generation of new terminal regions occurs using an additional time-dependent boundary condition that determines the sequence of vessel growth regions within a given perfusion volume. An analysis of various topological and metric properties of Voronoi polytopes associated with the distal ends of the terminal segments of arterial trees generated using CCO has also been proposed (Karch et al. 2003). However, CCO, even with the additions described, cannot be used to build the arterial system of an organ or tissue that is supplied by a number of arteries. In this connection, a number of algorithms have been proposed to solve this problem. For example, a mathematical model was used to divide the area of perfusion into domains, in each of which an arterial network was created using the CCO method (Blanco et al. 2013). In this model, the domain boundaries remain unchanged, and each of the subregions is supplied by only one artery, which does not correspond to experimental observations (Bokkers et al. 2010), as it leads to a complete lack of blood supply to part of the tissues in the event of blockage of the vessel. Despite these limitations, CCO-based algorithms have been successfully used to model the vasculature of the liver (Schwen and Preusser 2012; Crookston et al. 2019; Correa-Alfonso et al. 2022) and kidneys (Queiroz and Aquino 2018; Cury et al. 2021). In recent work, CCO has been improved using a parallel strategy to create extensive circulatory networks, since the original method allows one to efficiently generate systems containing no more than twenty thousand segments. In addition, the accelerated CCO approach has been applied to create multiple and independent interpenetrating networks that can be used to create vascularized artificial tissues through 3D printing technology (Guy et al. 2020). Another algorithm based on the reconstruction of optical fluorescence cryomicrotome images was used to construct the arterial system of the heart (Mackenzie 2022).

In addition to the optimization algorithms described above, a realistic vascular tree structure can be obtained using a fractal model. Due to the fact that the branching process is repeated at each step in the arterial network, they have the properties of self-similarity and have a fractal character (Kopylova et al. 2020). A model of this kind lays down the principles of optimal formation of blood vessels, and although they represent a certain geometric simplification, they can be used to study hemodynamics (Gabrys et al. 2005). Using the fractal model, it was shown that the first level of the vasculature has the greatest influence on the thermal anamnesis of the tumor (Wang et al. 2015). In addition, fractal methods were used to estimate the distribution of blood flow both in an ideal binary tree and in networks of various structures (Li et al. 2021). It should be noted that the assessment of the fractal properties of real vascular networks is widely used in experimental studies (Moledina et al. 2011; Cheung et al. 2014; Leontidis et al. 2015).

The most interesting is the modeling of the cerebral arterial system, since the brain is one of the most important organs and maintaining its stable perfusion in humans is provided by 15–20% of cardiac output (Xing et al. 2017). The vascular system is in many ways unique and more heterogeneous in the brain than in most other organs, with the brain tissue having the most extensive capillary network. The circle of Willis (CoW) is the central system of anastomoses between the major arteries in the brain, which connects the

two internal carotid arteries (ICA) and the two vertebral arteries (VA) (Pascalau et al. 2019). The two VAs merge to form the basilar artery (BA), which gives rise to the left and right posterior cerebral arteries (PCA). The ICA, in turn, branches into the middle cerebral arteries (MCA) and anterior cerebral arteries (ACA). The two posterior communicating arteries and the anterior communicating artery complete the CoW. According to the generally accepted compensatory theory, the circle of Willis can potentially compensate for insufficient blood supply in case of occlusion or stenosis of large supplying arteries (Hoksbergen et al. 2000; Alastruey et al. 2007). However, there is a hypothesis that CoW acts as a pressure absorber that protects against damage to the cranial microvasculature and blood-brain barrier (Vrselja et al. 2014). In this regard, it is necessary to reproduce the structure of the arterial system of the brain, taking into account the characteristic topology of large arteries.

An algorithm developed for constructing the abdominal vascular system (Steele et al. 2007) was used to model the arterial system of the human brain (David et al. 2009). In this case, using a binary self-similar tree characterized by several parameters, only small arteries originating from the middle cerebral artery were described. Also, an attempt was made to model the human brain vasculature with a physiologically correct arrangement of the main arteries using a CCO-based algorithm with additional time-dependent constraints (Bui et al. 2010). The circulatory system of the brain was modeled by combining a three-dimensional hydrodynamic model of the circle of Willis with a one-dimensional branching tree model of the peripheral vasculature, created on the basis of CCO (Sutalo et al. 2009, 2014). The main disadvantage of this algorithm is the insufficiently accurate representation of the main arteries distribution on the cerebral cortex. One way to obtain a procedurally generated optimal configuration of the cerebral arteries required to supply the brain tissue is the Simulated AnneaLing Vascular Optimization algorithm (SALVO), which is based on the principle of minimizing the energy required to maintain blood flow (Keelan et al. 2019). The resulting vasculature has a similar spatial arrangement of the middle, anterior, and posterior cerebral arteries and correctly reproduces the perfusion territories of these vessels. Due to the high computational complexity of global optimization, the algorithm was used to create an arterial tree of one of the hemispheres, and the other was symmetrized. In addition, the geometric parameters of the main arteries feeding each of the brain subregions can be obtained from a 3D experimental data and then used to develop vascular models within the brain mesh-surface of the adult human for use in internal dosimetry (Correa-Alfonso et al. 2023).

At present, a more realistic approach is to combine anatomical and physiological imaging techniques with computer simulation technology. The finite element method was used to plot the arteries of the circle of Willis based on MRI data, and the rest of the vessels were modeled using the CCO algorithm (Cebral et al. 2003). The main problem is to determine the volume of perfusion for each of the arteries. In the work described above, it was done by manually labeling voxels of brain MRI images, which is a very complex and time-consuming task. In a recent study, modeling of the arterial-venous system was performed using a similar hybrid approach, in which the brain hemispheres were extracted from MRI images, the large-sized vessels were reconstructed from 4D-CT angiography images, smaller vessels were generated based on simplified and geometry-prioritized CCO, and multilevel region-confined algorithm was applied to link from the micro to macroscale systems (Ii et al. 2020). Also, a recently developed growth-based tree generation algorithm (GBO) has been used to create the human cerebrovascular system (Kim et al. 2023). In this case, the geometry, as in the works described above, was obtained from medical image data. The algorithm is based on tissue growth followed by vascular growth, which makes it possible to generate vascular trees in accordance with the metabolic needs of the surrounding tissues. However, various algorithms based on CCO have been also used to model individual parts of the human brain circulatory system, such as the microcirculatory system of human secondary cortex (Linninger et al. 2013) and gray matter vasculature in the superior frontal gyrus (Talou et al. 2021).

It should be noted that when studying the circulatory system of the brain, animals were often chosen as the object of modeling, while rats and mice are most widely used for studying cerebral vessels due to their neuroanatomy similar to that of humans (Vandamme 2014). For example, a hybrid model of the arterial system of the rat brain was proposed, based on the reconstruction of the main arteries, according to microphotographs and the stochastic generation of smaller vessels in accordance with the principles of optimality (Kopylova et al. 2018). The optimal values of the key parameters used were predicted, allowing to reproduce the physiologically correct vascular network, both in terms of the structural characteristics of a single vessel and the topology of the arterial tree as a whole (Kopylova et al. 2019a, b).

Approaches for the microvasculature modeling, usually, differ from those described above, since the capillary system does not obey bifurcation laws and is a chaotic net-like structure; therefore, it cannot be described by a binary tree (Grinberg et al. 2009). However, in the work of Lee et al. (2018), by comparing with experimental data, it was shown that the asymmetrically bifurcating model can be used to calculate microvascular blood transport. As a rule, to solve applied problems, the microvascular network is implemented as elongated structures or linear vessels oriented in one of three directions (Espinoza et al. 2013). In this case, arterioles can be represented as parallel segments of different diameters, which are connected by stochastically distributed

capillaries (Cai et al. 2015). In addition, brain microvascular network architecture was reproduced using a hybrid model including a network of interconnected tubes describing arterioles and venules, as well as a porous medium modeled using a homogenized continuum approach and representing a capillary bed (Peyrounette et al. 2018). It is worth noting that the structure of the cortical gray matter microvasculature can be reconstructed from imaging data; however, in most cases, such studies are performed on animals, such as primates (Guibert et al. 2010), mice (Dorr et al. 2012; Gagnon et al. 2015; Kirst et al. 2020), and rats (Blinder et al. 2010).

Approaches for blood flow description in the cardiovascular system

Mathematical modeling of the circulatory system is an extremely complex problem, since the functions that it performs involve a huge number of biophysical mechanisms. For adequate blood flow description in the cardiovascular system, it is necessary to take into account the conservation laws of mass, momentum, and energy, the movement of blood through the vessels caused by heart contractions, the flexibility of the vessels, which significantly affect blood flow dynamics, and the interaction of the flow with the viscoelastic vessel wall. In addition, as already described earlier, the vasculature includes a huge number of vessels that have different properties. In this regard, in the numerical simulation of the cardiovascular system functions, models of various classes are used, each of which is suitable for a specific type of problem or a specific part of the circulatory network. In general, the dimension of the model representation varies from 0D to 3D, and it is chosen depending on the purpose and the required accuracy of the study. The brief description of the key features of different approaches is represented in Fig. 3.

Zero dimensional models (point models, spatially averaged models) are described by ordinary differential equations that depend only on time. Due to the fact that 0D models do not allow estimating the spatial distribution of the studied parameters, they are used to establish the time dependences of such values as volumetric blood flow, pressure, and volume. These models often use electrical analogy, and one of the models of this kind is the Windkessel model, which takes into account the impedance of the microvascular bed, its elasticity, and the hydrodynamic resistance (Westerhof et al. 2009). Zero-dimensional models are widely used to describe blood flow in the heart (Formaggia et al. 2006), liver (Audebert et al.

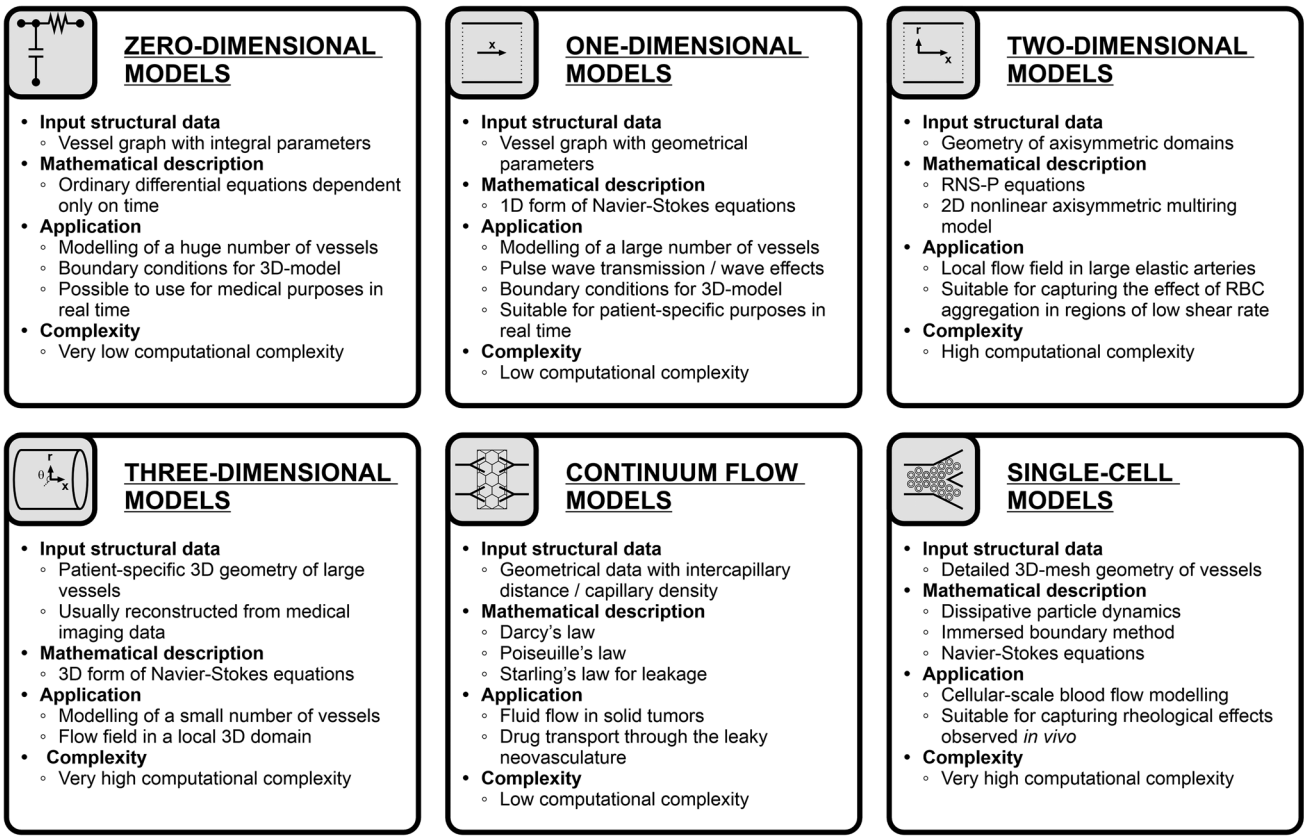

Fig. 3 The main approaches used in blood flow modeling in vascular systems of varying degrees of complexity and detail

2017), arteries of the circle of Willis (Ursino and Giannessi 2010), and a complete arterial system of the brain (Ryu et al. 2015). Also, 0D is used to model blood flow in a closed system containing arterial and venous components (Borzov et al. 2012), as well as to study the complete human circulatory system, including arterial and venous networks, heart, pulmonary circulation, and microcirculation (Muller and Toro 2014). In general, zero-dimensional models are quite simple and contain a large number of simplifications; however, due to this, their implementation requires significantly less computing power, which allows them to be used to solve a huge number of problems. Thus, in a recent work, a precision medicine framework that allows obtaining information about the hemodynamic parameters of a particular patient based on neuroimaging data and subsequent zero-dimensional modeling was created (Frey et al. 2021). A detailed description of the spatially averaged models used to describe various characteristics of the cardiovascular response is given in several reviews (Shi et al. 2011; Capoccia 2015).

One-dimensional models are also simplified, but unlike 0D models, they take into account the propagation and reflection of the pulse wave in the vascular system. These models are based on averaging the long-wavelength Navier–Stokes equation by integrating over the cross-sectional area of the vessel (Sherwin et al. 2003). A more detailed mathematical representation of one-dimensional models can be found in the review by Quarteroni et al. (2016). From the point of view of blood flow dynamics studying, these models physiologically correctly describe the effect of wave transmission in large arteries, such as, for example, the arteries of the circle of Willis, due to the large wavelength of the arterial pulse compared to the artery diameter (Alastruey et al. 2008). 1D models are a good compromise between accuracy and computational cost, while still being able to reproduce all of the features of the waveforms observed *in vivo*. Thus, this approach was used in modeling the human arterial tree, which includes all the main arteries (Reymond et al. 2009), the main components of the cardiovascular system (Mynard and Nithiarasu 2008), namely, the coronary and systemic arterial circulation, ventricular pressure and aortic valve, as well as cerebral arteries (Liang et al. 2011). It was shown that correct one-dimensional models can lead to simple and reliable predictions of blood circulation in the circle of Willis (Devault et al. 2008). Today, the 1D approach makes it possible to obtain accurate patient-specific models used for various medical applications. Thus, Simakov and Gamilov (2019) considered the effect of atherosclerosis disease in the internal carotid and vertebral arteries on blood flow in the middle and posterior cerebral arteries. CT angiography data were used to reconstruct various variants of the circle of Willis anatomical structure, which has been shown to have a significant impact on blood flow in the main arteries in atherosclerosis. In addition, based on a one-dimensional hemodynamic model, it was concluded that due to communicating arteries in the CoW, the pulse wave shape is aligned in different states of cardiovascular stress (Muskat et al. 2021).

As for two-dimensional models, they are rarely used in hemodynamic studies of blood flow. With this approach, the velocity change is calculated in the radial and axial directions using the two-dimensional Navier–Stokes equations, which makes it possible to take into account the effect of the vascular wall elasticity on the blood flow at any point of the vessel (Rosales-Alcantar and Hernández-Dueñas 2023). In addition, there are simplified 2D models that assume axially symmetric flows in compliant arteries (Casulli et al. 2012; Tian et al. 2013). Similar models can be applied to study the effect of stenosis on blood flow characteristics in arteries (Sharma and Yadav 2019). A reduced-order multiring model has also been proposed to calculate blood flow characteristics in axisymmetric rigid and elastic arteries, based on coupled long-wave Navier–Stokes equations (Ghigo et al. 2017). Mirramezani et al. (2019) used this approach to assess the pressure drop in the coronary arteries in stenosis.

The most complex and computationally expensive methods for all types of modeling are three-dimensional models. In this case, it is necessary to take into account the correct boundary conditions, the complex geometry of the vessel, the pressure of the surrounding tissues, the rheological properties of blood, the properties of the vascular wall, and many other physiological and anatomical features. In addition, detailed blood flow models should reproduce the fluid–structure interaction (FSI) by combining the equations of hydrodynamics and motion of the viscoelastic vessel wall (Chen et al. 2021). The 3D geometry of blood vessels is typically reconstructed from medical imaging data. Together, this leads to an extreme complication of the mathematical model, the implementation of which requires powerful computing resources. In addition, three-dimensional models include a huge number of parameters, some of which are patient-specific and not always amenable to experimental measurement. Thus, despite the fact that models of this class most accurately describe the blood flow in vessels with real geometry, their scope is limited to local areas. Quite often, software such as ANSYS (Sheh Hong et al. 2020) and COMSOL Multiphysics (Shin et al. 2018) are used for 3D modeling. Computational fluid dynamics (CFD) models have been used to analyze blood flow in bifurcations (Bahrami and Norouzi 2018; Lopes et al. 2019), in aneurysms (Rahma and Abdelhamid 2023; Rostamian et al. 2023), in particular in aneurysms of the middle cerebral artery (Sadeh et al. 2023), in stenosed arteries (Nadeem et al. 2018; Dwidmuthe et al. 2021), as well as in the arteries of the circle of Willis (Berg et al. 2014; Rahma et al. 2022). For example, Gaidzik et al. (2021) proposed a data assimilation approach combining 4D phase-contrast magnetic resonance imaging and CFD modeling data to assess blood flow parameters in the subject-specific CoW. Similarly, with the structural

models described above, rodents are a very common object of hemodynamic studies in large cerebral arteries (Cherevko et al. 2016). Thus, it was shown that type 1 diabetes affects the architecture and hemodynamics of the circle of Willis arteries, leading to cerebral blood flow asymmetry in the long course of the disease (Yankova et al. 2021).

Microvasculature blood flow modeling has a number of features associated with the specifics of blood flow through small vessels. A number of works are devoted to the mathematical description of rheological effects observed *in vivo*, such as plasma skimming at bifurcation (Lee et al. 2017), Fåhræus (Farina et al. 2023) and Fåhræus-Lindqvist effect (Farina et al. 2021), and the presence of a cell free layer near the vascular wall (Balogh and Bagchi 2019). In general, the approaches of the capillary hemodynamics study can be divided into two main classes: single-cell methods (Bryngelson et al. 2019) and continuum flow models (CFM) (Gkontra et al. 2019) (Fig. 3). In the first case, the movement of individual erythrocytes, which are an incompressible viscous liquid surrounded by an elastic membrane, is analyzed. Due to the large number of particles considered, this method is computationally expensive and is usually used only for blood flow modeling in a single vessel (Vahidkhah et al. 2016) or bifurcation (Lykov et al. 2015). In the case of CFM, the capillary network is represented as a homogeneous medium with appropriate characteristics, which makes it possible to analyze local transport. In addition, a hybrid approach that takes into account hemodynamics both in the arteriolar tree and in the capillary bed has been proposed (Shipley et al. 2020). In the present case, a discrete model is used to describe the blood flow in larger vessels, and the blood flow in the capillary bed is based on CFM. This approach can be used to calculate pressure in microvascular networks, especially, in cases where the capillary bed structure is unknown (Sweeney et al. 2022). Microcirculatory blood flow modeling methods are presented in more detail in the reviews by Arciero et al. (2017) and Gompper and Fedosov (2016).

It is worth emphasizing that in multiscale modeling of various aspects of blood flow in the cardiovascular system, a coupling strategy that combines 3D-1D (Malossi et al. 2013; Caforio et al. 2022), 3D-0D (Esmaily Moghadam et al. 2013; Augustin et al. 2021), and 1D-0D models (Guan et al. 2016; Manganotti et al. 2021) is often used (Fig. 4). For example, a three-dimensional representation was used for the electromechanics model of the heart (Caforio et al. 2022; Augustin et al. 2021) and an abdominal aorta model (Malossi et al. 2013), a one-dimensional model described the blood flow in large arteries (Malossi et al. 2013; Caforio et al. 2022; Manganotti et al. 2021), and a zero-dimensional approach representing the heart (Manganotti et al. 2021) and closed-loop circulation (Augustin et al. 2021). Also, coupling 3D CFD model of the CoW and 1D branching tree model of the peripheral cerebral vasculature was used to assess cerebral hemodynamics in possible pathological conditions (Sutalo et al. 2014). The use of such hybrid approaches can significantly reduce the computational complexity and makes it possible to use them for medical purposes in real time. In addition, analytical solutions exist only for fairly simple geometries, and in all other cases, numerical methods are used for hemodynamic modeling.

A vascular structure and a spatial-time distribution of metabolites concentrations in a brain parenchyma

The described approaches can be used for generation of a vascular network concerning an arterial part of the blood system. However, the main purpose of the blood vessels is to fulfil an exchange of metabolites in a living tissue. Initially, the arterial part of a vasculature brings nutrients as the supplements of biochemical reactions. As the key metabolites, glucose and oxygen are among the most important nutrients suppling the brain functioning. Both of them are tightly coupling with energy demands and ATP production. The alteration in their levels get the essential changes in a nervous tissue metabolism. The adult human brain has high energetic needs that must be met by appropriate delivery of fuel to maintain function, and a rapid decline in brain glucose levels typically leads to cognitive dysfunction such as seizures and coma (Ostergaard et al. 2016). However, the mechanisms of a spatial-time distribution forming for oxygen and glucose are quite different.

For oxygen, one may consider nearly free reaction-diffusion out of a blood stream without essential non-penetrate barriers. Nevertheless, the gradients of O_2 near the arterioles and capillaries essentially depend on cerebral blood flow (CBF) and a vasculature architecture. The cerebral microvasculature plays a vital role in adequately supplying blood to the brain. Determining the health of the cerebral microvasculature is important during pathological conditions, such as stroke and dementia (Abbott et al. 2006). Despite the obvious fact that ischemic stroke is a particularly dangerous pathology, its therapy should start at the lowest level of vasculature (Abbott et al. 2010). A biophysical modeling of oxygen transport in tissue shows that capillary flow disturbances may contribute to the profound changes in cerebral blood flow after traumatic brain injury; thereby, elevated capillary transit time heterogeneity can cause critical reductions in oxygen availability in the absence of "classic" ischemia (Lucker et al. 2018a). A capillary dysfunction may be an early and shared feature of cerebral small vessel disease risk factors, and a source of neurodegeneration, stroke, and cognitive decline, despite considerable differences in the aetiologies and clinical presentations of these

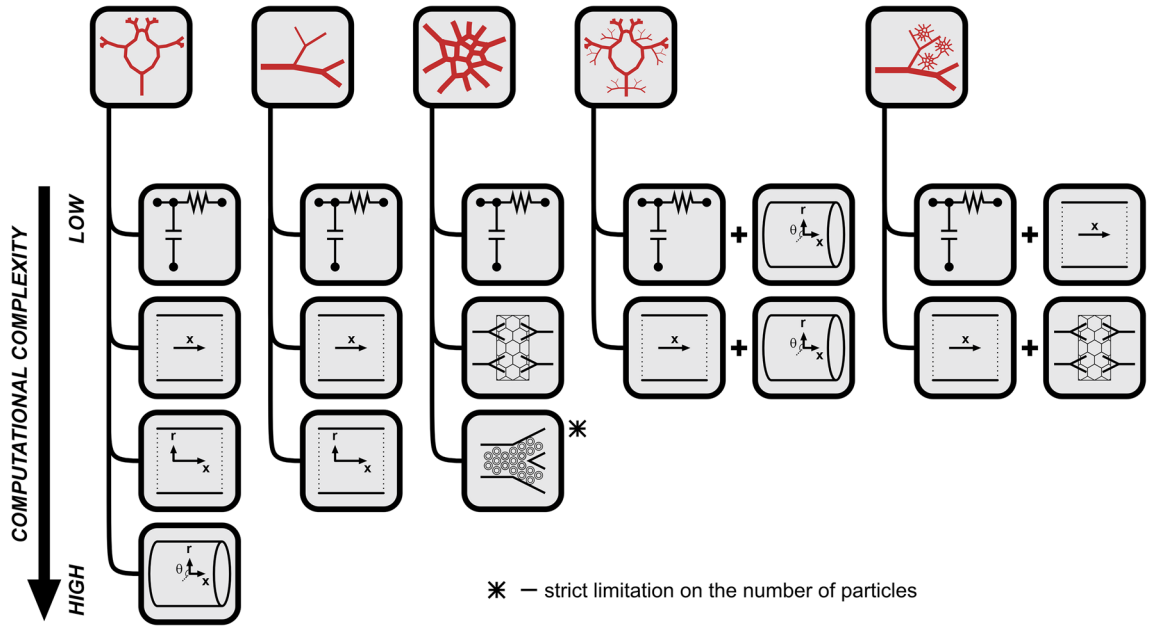

Fig. 4 Application diagram of the blood flow description approaches for vascular systems of various scales

syndromes (Ostergaard et al. 2016). The perturbations of capillary flow will always, on average, decrease the tissue P_{O_2} in both homogenous and heterogeneous capillary networks (Terman et al. 2021). In normal brain, functional activation has been shown to result in CBF increases disproportionately larger than the increase in oxygen utilization as measured by positron emission tomography, and elaborate modeling suggests that this apparent "uncoupling" of oxygen consumption from the extent of functional hyperemia owes to biophysical limitations of oxygen diffusion from blood to tissue (Lucker et al. 2017). For a given red blood cells flux (RBS) in a capillary, the P_{O_2} in the surrounding tissue increases with increasing hematocrit, as a consequence of decreasing intravascular resistance to diffusive oxygen transport from RBCs to tissue (Lucker et al. 2017). Diffusive interaction contributes greatly to the microcirculation's ability to achieve tissue oxygenation, despite heterogeneous capillary transit time and hematocrit distribution (Lucker et al. 2018a). Recently, it was shown that capillary transit time heterogeneity influences capillary outflow saturation heterogeneity strongly reduced on a small spatial scale by a diffusive interaction yet does not determine it (Lucker et al. 2018b).

Another metabolite which can be considered with nearly the same mechanism of a spatial distribution near the blood vessels is nitric oxide (NO). In blood vessels, NO is a potent vasodilator involved in the minute-to-minute and long-term control of vascular function mediated by its generation in the endothelium by the endothelial NO synthase (eNOS) (Figueroa et al. 2013). eNOS activity is essential for a blood vessel tone, but the rate of production can be insufficient to supply vasorelaxation in the large blood vessels (Seraya and Nartsissov 2002; Seraya et al. 2003). The model incorporating the production of NO by synthesis in neurons and by mechanotransduction in the endothelial cells and the loss of NO due to its reaction with superoxide and interaction with hemoglobin was recently proposed (Tamis and Drapaca 2021). It was shown that changes in blood flow during hypoxia or hyperoxia could be explained by altered NO degradation in the parenchyma (Haselden et al. 2020).

On the contrary, glucose is transported inside the brain parenchyma by both a free diffusion and membrane transporters of GLUT family (Nartsissov 2021a). This feature is a sequence of the complex structure of the border between a vasculature and the brain tissue. The brain is protected by being separated from the rest of the body by a set of barriers (so called the blood-brain barrier (BBB)). These barriers hinder entry of unwanted substances from the circulation but at the same time provide for the removal of potentially toxic substances that have inadvertently entered or been produced within the brain. These barriers will of course present challenges for delivery of nutrients, essential for normal brain growth, metabolism, and function (Hladky and Barrand 2018). In the brain and spinal cord of mammals including humans, the BBB is created by the endothelial cells that form the walls of the capillaries (Abbott et al. 2010), and BBB is a part of well-structured neurovascular units (NVU) formed by neurons, glia, and microvessels (Abbott et al. 2006). It is well known that NVU are involved in the regulation of cerebral blood flow.

Having passed the initial BBB glucose is distributed through the extracellular space (ECS) and intra-cell diffusion-

consumption. The importance of intra-cell diffusion is supported by the experimental data confirming that the value of diffusion coefficients for glucose measured in purified rat astrocytes is consistent with the view that cytosolic diffusion may allow glucose and glucose metabolites to traverse from the endothelial cells at the blood-brain barrier to neurons and neighboring astrocytes (Kreft et al. 2013). In the model coupling a blood flow dynamic and a convectional reaction-diffusion of metabolites, it was shown that a rapid decrease of a capillary blood flow yields an enhanced level of glucose in a near-capillary nervous tissue if the contacts between astrocytes end-feet are not tight (Nartsissov 2022).

However, the problem to estimate the gradient in a large area including a complex branched arterial tree is still non-trivial. For this purpose, especial approaches need to be established. In particular, the brain concentration of glucose and oxygen can be estimated an approach to obtain the probability density functions based on structural segmentation of the diffusion region using Delaunay triangulation and the spherical source diffusion field (SSDF) method (Kopylova et al. 2022). This method had been applied for the first time to evaluate a concentration of glucose near rat pial blood vessels (Nartsissov et al. 2013), and it was validated using the finite element method (FEM) revealing the difference on 7% under the most appropriate conditions (Nartsissov 2021b). If the metabolites have no ability to pass through the cell membrane fluently, it is commonly accepted to apply the approach introduced by Nicholson (2001). Diffusion in ECS of the brain is constrained by the volume fraction and the tortuosity, and a modified diffusion equation represents the transport behavior of many molecules in the brain (Sykova and Nicholson 2008).

Thus, the dependence of spatial-time metabolite gradients on vascular architecture in a brain parenchyma is clearly indicated both experimentally and theoretically. It is essential to note that the geometry and the distribution of CBF have an important role not only for a general supply of the nutrients but also for a stability and a formation of the gradients.

Conclusion

The continuous improvement both for visualization methods and reconstruction of medical images, as well as computing power growth, make it possible to investigate more comprehensively and with much greater accuracy the principles of formation, architecture, and biophysical patterns of the circulatory system functioning using computer models. At the same time, a wide range of mathematical approaches is used to study these issues. Agent-based modeling makes it possible to reproduce various aspects of vasculogenesis and angiogenesis, and at the current stage, the number of factors taken into account in these models is continuously growing. Stochastic and optimization algorithms are used to build a formed circulatory network of varying degrees of complexity. Computational fluid dynamics methods allow to describe blood flow both in local areas and throughout the cardiovascular system as whole. As well as single-cell models take into account the dynamics of individual erythrocyte movement and deformation, which leads us to understand the processes that take place at the lowest level of the vascular hierarchy. It should be noted that the choice of a specific approach is determined by the application area and is often due to a trade-off between computational complexity and physiological accuracy. The mathematical models proposed to date can be used for a detailed study of blood supply at different stages, levels, and scales in both physiological and pathological situations. Moreover, some of the models are patient-specific, which makes it possible to predict the dynamics of the disease, as well as to choose the best option for surgical intervention.

Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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