State-of-the-Art Computational Models of Circle of Willis With Physiological Applications: A Review

Liu, H., Wang, D., Leng, X., Zheng, D., Chen, F., Wong, L. K. S., Shi, L. & Leung, T. W. H.

Original citation:
Liu, H, Wang, D, Leng, X, Zheng, D, Chen, F, Wong, LKS, Shi, L & Leung, TWH 2020, 'State-of-the-Art Computational Models of Circle of Willis With Physiological Applications: A Review', IEEE Access, vol. 8, pp. 156261 - 156273.
https://dx.doi.org/10.1109/ACCESS.2020.3007737

DOI 10.1109/ACCESS.2020.3007737
ESSN 2169-3536

Publisher: Institute of Electrical and Electronics Engineers

IEEE Access
Multidisciplinary ⋮ Rapid Review ⋮ Open Access Journal

Received May 30, 2020, accepted June 17, 2020, date of publication July 7, 2020, date of current version September 8, 2020.

Digital Object Identifier 10.1109/ACCESS.2020.3007737

State-of-the-Art Computational Models of Circle of Willis With Physiological Applications: A Review

HAIPENG LIU[1,2,3], DEFENG WANG[2,4,5,6], XINYI LENG[3], DINGCHANG ZHENG[1], (Member, IEEE), FEI CHEN[7], (Senior Member, IEEE), LAWRENCE KA SING WONG[3], LIN SHI[2], (Member, IEEE), AND THOMAS WAI HONG LEUNG[3]

[1]Research Center of Intelligent Healthcare, Faculty of Health and Life Science, Coventry University, Coventry CV1 5RW, U.K.
[2]Department of Imaging and Interventional Radiology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong
[3]Division of Neurology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong
[4]Research Institute for Frontier Science, Beihang University, Beijing 100191, China
[5]Beijing Advanced Innovation Center for Big Data-Based Precision Medicine, Beijing 100083, China
[6]Hangzhou Innovation Institute, Beihang University, Hangzhou 310000, China
[7]Department of Electrical and Electronic Engineering, Southern University of Science and Technology, Shenzhen 518055, China

Corresponding authors: Lin Shi (shilin@cuhk.edu.hk) and Thomas Wai Hong Leung (drtleung1@gmail.com)

This work was supported in part by the Research Grant Council (RGC) of Hong Kong under Grant 14204117 and Grant 14106019; in part by the National Natural Science Foundation of China (NSFC) under Grant 61828104; in part by the NSFC/RGC Joint Research Scheme under Grant N_CUHK421/16; in part by the Basic Research Foundation of Shenzhen under Grant GJHZ20180928155002157; in part by the Scheme Double First Class Program; in part by the Ministry of Education; in part by the Ministry of Finance; and in part by the National Development and Reform Commission, China.

ABSTRACT *Background:* Various computational models of the circle of Willis (CoW) have been developed to non-invasively estimate the blood flow and hemodynamic parameters in intracranial arteries for the assessment of clinical risks such as aneurysms, ischemia, and atherosclerotic plaque growth. This review aims to categorize the latest computational models of CoW and summarize the innovative techniques. *Summary of Review:* In traditional computational models of CoW, the computational complexity increased from zero-dimensional models to one-dimensional and three-dimensional models. The applications extend from estimating certain hemodynamic parameters to simulating local flow field. The innovative techniques include the combination of models with different dimensions, the extension of vascular structure including heart and veins, as well as the addition of distal fractality, cerebral autoregulation, and intracranial pressure. There are some nontraditional models based on fluid-solid-interaction, control theory, and in-vitro experiments. In all kinds of models, the in-vivo data and non-Newtonian rheological models of blood have been widely applied to improve the accuracy of hemodynamic simulation. *Conclusion:* Firstly, the selection of model depends on its application scenario. The balance between computational complexity and physiological accuracy deserves further investigation. Secondly, the improvement of CoW models relies on the large-scale validations and the combination of various innovative modeling techniques.

INDEX TERMS Brain modeling, computational modeling, circle of Willis (CoW), Windkessel effect, pulse wave, computational fluid dynamics (CFD), cerebral blood flow, intracranial arteries.

I. INTRODUCTION

The intracranial arterial stenosis (ICAS) could cause serious clinical events such as ischemic stroke. The pathology, diagnosis, and treatment of ICAS are still under investigation [1]. The circle of Willis (CoW) forms an interconnected structure of intracranial arteries and provides alternative routes of blood flow in case of ICAS, protecting the brain from ischemia [2]. However, the blood flow in CoW is difficult to observe. Recently, various models have been proposed to computationally investigate the blood flow in CoW. This review aims to categorize and summarize these models from a technical perspective.

A. ANATOMY OF CIRCLE OF WILLIS

The CoW connects the posterior and anterior cerebral circulations (Fig.1). In anterior cerebral circulation, the blood flows

The associate editor coordinating the review of this manuscript and approving it for publication was Xiaogang Jin.

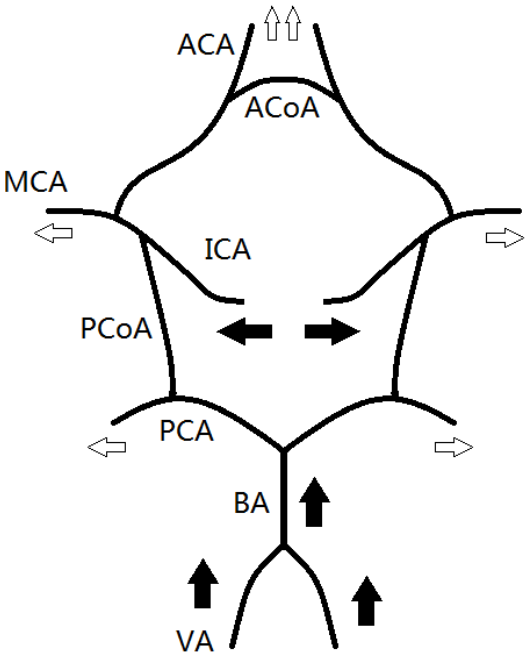


FIGURE 1. Structure of the circle of Willis (CoW). The solid and hollow arrows represent the directions of blood flows in afferent and efferent arteries. Afferent arteries: internal carotid artery (ICA), basilar artery (BA), vertebral artery (VA). Efferent arteries: middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA). Connecting arteries: anterior communicating artery (ACoA), posterior communicating artery (PCoA). All arteries are bilateral except ACoA.

from the left and right internal carotid arteries (ICA) into middle cerebral artery (MCA) and anterior cerebral artery (ACA). In posterior cerebral circulation, the blood flows from left and right vertebral arteries (LVA and RVA) into the basilar artery (BA) and finally the left and right posterior cerebral arteries (PCA). The anterior communicating artery (ACoA) connects bilateral ACAs. Each posterior communicating artery (PCoA) connects the ipsilateral PCA and ICA.

B. CLINICAL SIGNIFICANCE

The CoW is the primary collateral system protecting the brain from ischemia when occlusions occur in the intracranial arteries [2]. When a stenosis less than 86% occurs in an afferent artery, an intact CoW could re-route the blood flows in the circle to maintain the normal efferent flows [3]. However, with anatomical variations of CoW among individuals, intact CoW structure exists in less than 50% of general population [4], [5]. Due to the complicated hemodynamics, the arteries in CoW are susceptible to atherosclerosis and aneurysm [6]. Conversely, the existence of atherosclerotic plaques and aneurysms could influence the hemodynamics of CoW [7]. Therefore, the hemodynamic analysis is important to understand the physiological and pathological phenomena of CoW.

C. RATIONALE OF REVIEWING COMPUTATIONAL MODELS OF COW

Despite the clinical significance, the blood flow in CoW is difficult to observe, requiring invasive methods or expensive clinical imaging techniques. However, the blood flow in CoW could be non-invasively simulated with computational models. Furthermore, some hemodynamic parameters (pressure, wall shear stress, etc.) are impossible to be continuously recorded with current techniques, but could be estimated using computational models. Thus, computational modeling of CoW has attracted investigational interests in recent years. Various computational models of CoW have been developed and applied in the pathophysiological and clinical studies of intracranial arteries.

Nevertheless, currently there is a lack of a comprehensive review on the computational models of CoW regarding to their computational (or theoretical) basis, advancements, limitations, and applications. To comprehensively understand and categorize the state-of-the-art techniques applied in the modeling of CoW, and to summarize the technical innovations, we reviewed the related literature on simulation and modeling of CoW in recent 6 years.

II. LITERATURE SEARCH

With the keywords ''circle of Willis'' combined with ''modeling'' or ''simulation'', publications between 2013 and 2019 were searched on the database of PubMed, Web of Science Core Collection, IEEE Xplore Digital Library, and https://scholar.google.com. More than 80 articles were found. Excluding the unrelated results, and those written in other languages with parallel English versions, 80 items were finally selected. There were 3 book chapters, 4 theses, and 73 journal articles or conference papers. Two journal articles were written in Japanese and German [8], [9]. All the other items were in English.

The reviewed models were classified into traditional and nontraditional models. Traditional models could be categorized by their dimensions: the zero-dimensional (0D, or lump-parameter) models based on the Windkessel effect, the one-dimensional (1D) models based on simplified Navier-Stokes equations, and three-dimensional (3D) computational fluid dynamics (CFD) models based on the 3D geometry of arteries. Nontraditional models include the fluid-structure-interaction (FSI) models, the in-vitro experimental models, and the models based on control theory. To improve the accuracy of simulating blood flow and hemodynamic parameters, innovative modeling techniques such as combination of 0D, 1D, and 3D modes, addition of intracranial pressure, and non-Newtonian rheological models of blood, have been applied in the CoW models.

In the following sections, the 0D, 1D, 3D, and nontraditional models were discussed categorically. In each category, the computational basis and model composition were introduced. The details of technical innovations were analyzed regarding to the applications in physiological and pathological studies. Finally, from a technical view, we summarized the innovations and limitations of the models in different categories, and suggested some directions for future works.

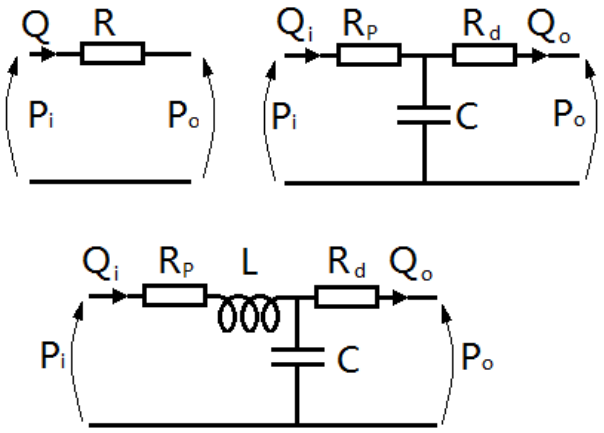


FIGURE 2. Three 0D (Windkessel) models of intracranial arteries. The P, Q, R, C, and L denote blood pressure, flow rate, resistance, capacitance, and inductance. The subscripts of i, o, p, and d denote inlet, outlet, proximal, and distal. The resistance (R), capacitance (C), and inductance (L) elements simulate the effects of vessel resistance, vessel compliance, and blood inertia.

III. TRADITIONAL MODELS

A. ZERO-DIMENSIONAL MODELS

1) MODEL STRUCTURE

The structure and parameters of 0D (lump-parameter, or Windkessel) models are derived from the electrical analogy of elastic intracranial arterial walls. The resistance (R), capacitance (C), and inductance (L) elements simulate the effects of vessel resistance, vessel compliance, and blood inertia. Fig.2 shows three common 0D models of intracranial arteries: the R, RC, and RCL models. In the RC and RCL models, the resistances are divided into the proximal (p) and distal (d) parts. According to the Poisueille's law, the flow resistance in an artery is inversely proportional to the square of its cross-section area: $R = 8\mu l/A^2$, where R, μ, l and A denote the flow resistance, the blood viscosity, the length and cross-section area of the artery [10]. The distal resistance (Rd) is in 1-2 higher magnitude order than the proximal resistance (Rp) [11]. Compared with 3-element 0D RC models, adding more R, C, and L elements to simulate distal branches could improve the accordance of derived flow velocity with the physiological measurement results, in the cost of increased computational complexity [12].

2) METHODS TO IMPROVE ACCURACY

Fractality is an important property of the cerebrovascular flow resistance [13]. With decreasing diameter, the flow resistance show fractal growth in small arteries, arterioles, and capillaries. The 0D fractal structure of distal flow resistance can be used as the outlet condition in 1D and 3D models (Fig.3b, c). The 0D models with fractal distal flow resistance have been applied in calculating the transfer function and the arrival time map of the brain [14], and in estimating the effect of arterial obstructions in CoW on the blood flow in distal tissues [15].

The effect of bifurcation on flow resistance is often neglected in 0D models, which could cause inaccurate estimation of blood flow. Chnafa *et al.* investigated the pressure drop at intracranial arterial bifurcations. The results indicated that, compared with 3D models, lower dimensional (0D and 1D) models could overestimate the blood flow due to the omission of pressure drops at arterial bifurcations [16].

To improve the accuracy of simulating blood flow in CoW, physiological regulation of cerebral blood flow has been considered in some 0D models. Autoregulation is an important mechanism to maintain the intracranial blood flow within the normal range. A static simulation based on 0D RC model showed that autoregulation could effectively preserve the intracranial blood flow during arterial occlusion (blood flow reduction: 1.0% and 7.1% with and without autoregulation) [17]. Besides the CoW, another anatomical structure for cerebral circulation regulation is the leptomeningeal anastomoses (LA) which connect the terminal cortical branches of major intracranial arteries. Phan *et al.* compared the ability of LA and CoW in maintaining the cerebral blood flow when occlusion occurred in ICA, MCA, and distal branches [2]. They concluded that CoW could maintain the blood flow perfusion in distal branches when occlusion happened in large intracranial arteries, while LA could maintain the perfusion even when occlusion happened in distal small branches.

The intracranial pressure (ICP) could influence cerebral blood flow by changing the contraction of arterial wall, therefore has been included in some 0D models. ICP is defined as the pressure on the brain tissues and outside the intracranial arterial wall, which influences the intracranial arterial blood flow and could be simulated by 0D models. Sethaput simulated the intracranial artery blood flow with traumatic brain injury and hydrocephalus [18]. The results indicated that both the elasticity of arterial wall and the ICP contributed to the Windkessel effects in intracranial arteries. Another study of ICP based on 0D model included two technical innovations [19]. Firstly the non-Newtonian effect was considered. The blood is a non-Newtonian fluid due to its shear-thinning caused by the distinct behavior of erythrocytes under different shear rates. The Newtonian fluid model is widely applied for simplification. Here the non-Newtonian viscosity was derived from the hematocrit value. Secondly, veins were included in the model. The limitations were the static simulation and the lack of in-vivo validation.

3) APPLICATIONS

The 0D models of CoW have been applied in the simulation of different physiological conditions by adding in-vivo boundary conditions, refined flow resistances, and regulating mechanisms of cerebral blood flow. Zhang *et al.* used an intracranial RCL network to study the effects of body position changes on the intracranial blood flow, and concluded that CoW plays a significant role in maintaining the balance of cerebral blood supply during postural change [20]. As aforementioned, 0D models have been widely used in simulating the occlusion of intracranial arteries. Using RCL models, Abdi *et al.* built an arterial tree which started from common carotid artery with a heart model added, to investigate the effect of ICA occlusion [10], [21] and aneurysm [22] on

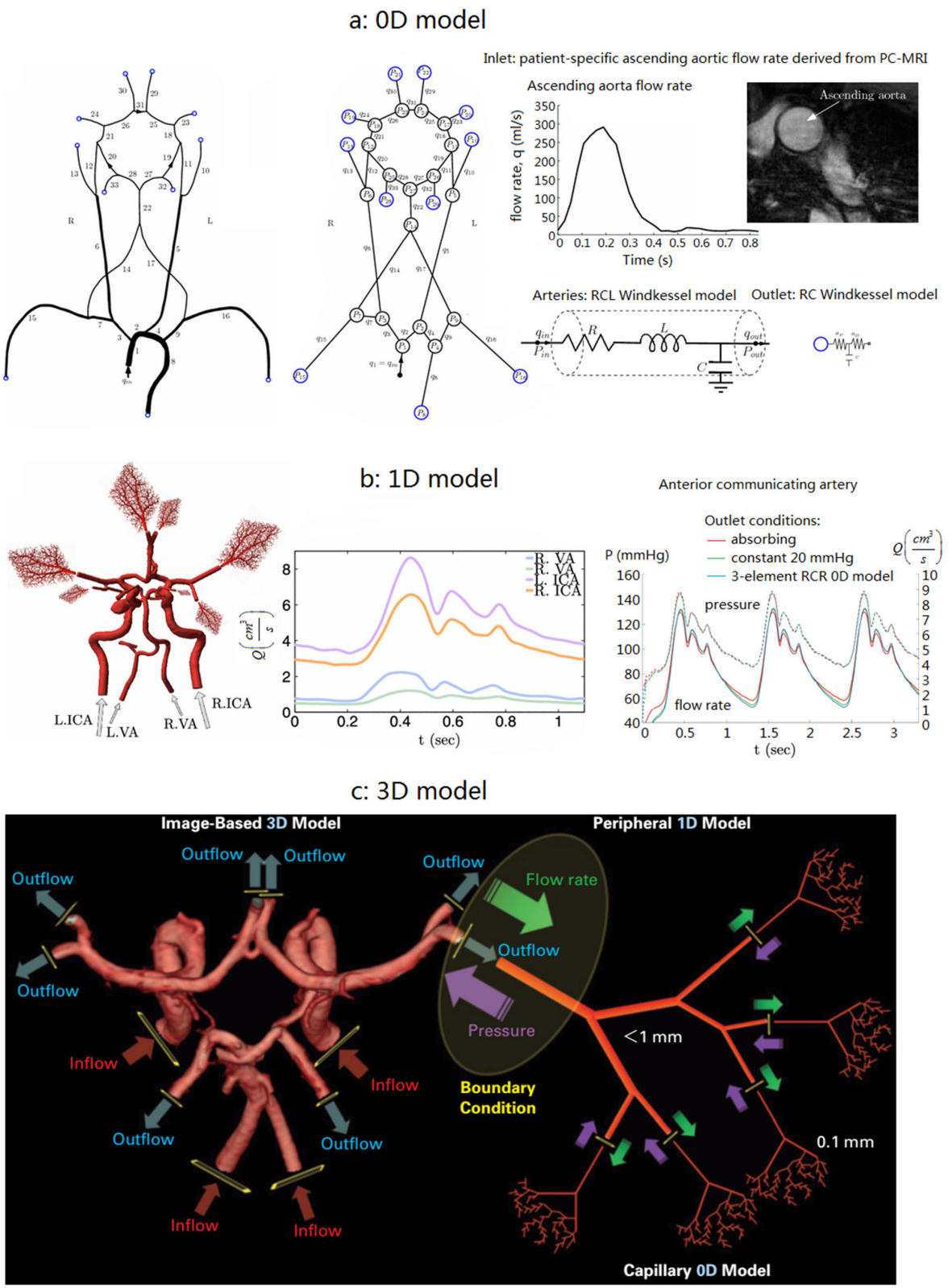


FIGURE 3. Computational models of CoW and boundary conditions. (a) A 0D model. The structure of arterial tree (left), the 0D elements (middle), and boundary conditions (right). Arteries and outlets were simulated by RLC and RC elements. The patient-specific inlet flow rate at ascending aorta was derived by the PC-MRI [24]. (b) A 1D model. The 0D fractal tree model was adopted as outlet condition (left). In-vivo flow rates at ICAs and VAs were applied at the inlets (middle). Three different outlet conditions were used: absorbing, constant pressure of 20mmHg, and a three-element RCR 0D model. The flow rate and pressure were derived in three different outlet conditions and compared (right) [30]. (c) A 3D model. The inlet flow was derived from PC-MRI. At the outlet, the 1D and 0D models simulated the distal intracranial arteries and microcirculation (arterioles, capillaries, and venules) respectively [9].

the intracranial blood flows. Zhang *et al.* used RCL models to evaluate the compensatory capability of CoW during unilateral ICA occlusion by observing the symmetric degree of blood flows in bilateral hemispheres [23]. Transcranial Doppler measurements were used for validation. The results presented the formation of collateral circulation through the ACA and the ipsilateral PCoA during ICA occlusion.

In different applications, the 0D models differ in structural complexity. RCL models could be patient-tailored by adjusting the parameters with Kalman filters according to the in-vivo data [24].

When focusing on the aorta blood flow, the CoW could be omitted in simulation due to its limited effect on extracranial blood distribution [25]. With 0D Windkessel elements and 1D wave transmission elements, Manini *et al.* built a vessel network from the aorta inlet to the veins [26]. The capacitance of vein was delineated by a non-linear pressure-diameter relationship. Moreover, the extravascular pressure was included. Considering its ability to simulate the surgical operations, further validation of this model based on in-vivo data is significant for clinical applications.

B. ONE-DIMENSIONAL MODELS

Due to the simplified structure, 0D models could not reflect the pulse wave propagation and the changes of hemodynamic parameters along the arteries. These hemodynamic effects are important in patient monitoring by diagnostic devices such as transcranial Doppler or continuous blood pressure monitor [27]. One-dimensional models were therefore proposed.

1) MODEL STRUCTURE

The 1D models represent the changes of hemodynamic parameters along the arteries, using simplified Navier-Stokes equations:

$$\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial z} = 0$$

$$\frac{\partial Q}{\partial t} + \frac{\partial}{\partial z}\left(\frac{Q^2}{A}\right) + \frac{A}{\rho}\frac{\partial P}{\partial z} + K_R\frac{Q}{A} = 0$$

where A, Q, P, t, z, and ρ denote the arterial cross-section area, flow rate, pressure, time, length along the arterial axis, and blood density. K_R is a resistance parameter related to the viscosity of blood [28].

To make the system solvable, another equation of A and P, which indicate the material property of artery wall, is added:

$$P - P_0 = \frac{Eh_0}{r_0\left(1-\sigma^2\right)}\left(\sqrt{\frac{A}{A_0}} - 1\right)$$

where h is the thickness of the arterial wall, and the subscript 0 denotes the reference state. E is Young's modulus and σ is the Poisson ratio. The equations can have different forms [27], [29].

2) METHODS TO IMPROVE ACCURACY

With different parts of arteries included, 1D models of CoW differ in their geometrical and structural complexity. Some models included only the intracranial arteries and used the in-vivo flow rate at the inlets [30], [31]. Many models started from the aorta [3], [27], [32]–[36] while veins could be added [8]. In some models, with the veins at the outlets, 0D heart models were added at the inlet [28], [37], [38]. Autoregulation could be simulated by using flow-dependent resistance at the outlets [27]. Huang *et al.* proposed a comprehensive cardiovascular system model which included a lumped model of the circulation between the heart and the lungs, 1D models of arteries and veins, and 0D Windkessel models of microcirculation [39].

Besides comprehensive vascular structure, the viscoelastic arterial wall model and the combination with physiological parameters have been applied in some 1D models. With the patient-specific 1D model based on the geometry derived from magnetic resonance angiography, Huang *et al.* compared a linear elastic wall model and a viscoelastic Kelvin-Voigt biomechanical wall model. Compared with the in-vivo measurement of cerebral blood flow velocity, the average root-mean-square relative differences of linear elastic wall model were less than 4.3%. The viscoelastic wall model achieved even lower differences [40]. To estimate ICP from cerebral blood velocity and blood pressure, Wang *et al.* combined a 1D CoW model with a Windkessel model which included cerebral blood flow, cerebrospinal fluid, and ICP. They developed a data-augmented method with a Bayesian data assimilation (DA) framework based on Kalman filtering, and successfully estimated ICP from in-vivo measurement of blood pressure and blood velocity in MCA, with error less than 2mmHg [41]. In summary, 1D models could non-invasively estimate more hemodynamic parameters which are difficult to measure, compared with 0D models.

As in 0D models, some 1D models applied in-vivo data [28], [30], [40]–[42] while the majority 1D models still need in-vivo validation [3], [8], [27], [28], [31], [34]–[39], [43]. 1D fractal arterial trees could be applied as the outlets of intracranial arteries [30]. Compared with 0D models, the arterial radius is variable in 1D models [32]. In 0D models, fractal structures were mainly used to simulate distal resistance. Misgeld *et al.* included the fractals of resistances, capacitances, and inductances in their 1D model [8], [44]. They derived the fractal parameters from the biomechanical properties of arterial walls and investigated the pulse wave transmission.

Similar with 0D models, 1D models could not reflect the flow distribution on the cross-sections of the arteries or the shear thinning effect. Therefore, Newtonian fluid model was widely used in 1D models for simplification while non-Newtonian fluid models were applied in some models to simulate the Fåhræus–Lindqvist rheological effect [30], [32].

3) APPLICATIONS

1D models present the transmission of pulse wave in CoW. Related physiological phenomena could be simulated: the multiple stenosis in intracranial arteries [42], the effects of arterial occlusion [33], [34] or abnormal structure of

CoW [39] on intracranial blood flow, the effect of distal flow resistances on the collateral flow pattern in normal CoW [35], the collateral flow patterns in dysplastic CoW [3], the detection of cerebral vasospasm [43], the estimation of intracranial pressure from cerebral blood flow velocity and blood pressure [41], the aging effect on cerebral blood flow [37], and the pharmacokinetics in the intracranial arteries [36].

C. THREE-DIMENSIONAL CFD MODELS

1) MODEL STRUCTURE

The 0D and 1D models could simulate the overall distribution of blood flow but not the local flow field. The three dimensional (3D) models were therefore proposed to describe the local flow field, and to estimate some hemodynamic parameters such as wall shear stress.

3D models are based on the Navier-Strokes equations:

$$\rho\left(\frac{du}{dt}+u\cdot\nabla u\right)=-\nabla p+\mu\nabla^2 u+f$$
$$-\nabla u=0$$

where ρ and μ are the density and viscosity of blood, while u, p and f denote the velocity, pressure and body force [45]. With boundary conditions added, the 3D equations could be numerically solved using CFD method (Fig.3c). In this part, our discussion was limited to the 3D CFD models with rigid wall assumption. The FSI models and 3D in-vitro models would be detailed later as nontraditional models.

2) METHODS TO IMPROVE ACCURACY

Geometry is a decisive factor of the accuracy of CFD simulation. Individual differences in intracranial arterial anatomy limited the efficiency of manual extraction of arterial geometry for CFD simulations [46]. In the 3D models, the geometric models could be categorized into the idealized and in-vivo ones. The idealized models are built by the computer-aided design (CAD) tools. An idealized model could be a simple one based on several geometric parameters [47], a local 3D geometry coupled with 0D artery tree at inlet and outlets [48], or a structure rebuilt from the in-vitro model [49], [50]. More patient-specifically, some idealized models were reconstructed from the central lines extracted from the clinical imaging of intracranial arteries [51]–[53] or an intact arterial structure starting from the aorta [5], or derived from changing the topology of CoW reconstructed from patient-specific CT images [54]. In-vivo geometric models were reconstructed directly from the patient-specific imaging data. They can present intracranial arteries only [9], [55]–[62] or with aorta and extracranial arteries included [45], [63].

Boundary conditions are important for 3D CFD simulation. 0D [48], [59], [62] and 1D models [47] were adopted as boundary conditions in some 3D models. Yamada *et al.* jointed 1D models to the outlets of their 3D model, and attached 0D models to the outlets of 1D models, forming a cascading arterial tree (Fig.3c) [9]. Berg *et al.* used the in-vivo flow rate at the inlet and distributed it to outlets by 0D flow resistances according to Murray's law [55]. To simulate the reversed Robin Hood syndrome, Piechna *et al.* used the 0D flow resistance with autoregulation as the outlet condition [49].

The differences in boundary conditions between in-vivo and literature data, and between individuals, could lead to inaccuracy in CFD simulations [64]. The flow rates derived from in-vivo measurement were widely adopted as the inlet condition [9], [51], [55], [58], and could be applied at the aorta inlet and external carotid artery outlet [45].

Various hemodynamic parameters, such as in-vivo velocity [63], unified velocity for all the afferent arteries [56], and blood pressure [5], [52], [53], [61], were adopted as outlet conditions. Zero pressure was not a physiologically realistic outlet condition [45] but could be used to estimate the pressure drop along the arteries [58]. In Ghaffari *et al.*'s model, the outlet pressure was adjusted according to in-vivo measurements to achieve patient-specific simulation [51]. Mamatyukov *et al.* used the blood pressure and flow velocity measured by a 0.014-inch dual-sensor wire for model validation [65]. In some studies, the inlet and outlet conditions were set according to the results of in-vitro experiments [50], [54], [57] or 1D simulation [60], [66].

3) APPLICATIONS

Firstly, 3D CFD models could simulate physiological and pathological phenomena such as the anatomical variation of CoW [52], [54], the intracranial stenosis and aneurysm [9], [50], [54], [55], [67], the carotid stenosis [48], the surgery of aneurysm [65], the Reversed Robin Hood Syndrome [49], and the travel trajectories of intracranial emboli under steady flow [56]. Secondly, 3D CFD could simulate some clinical treatments such as the bypass surgery for moyamoya disease [58], the cardiopulmonary bypass procedure [63], and the endovascular mechanical recanalization [62].

Some hemodynamic phenomena could only be investigated with 3D models. Reorowicz *et al.* included the turbulence effects in their model [5]. Considering the tortuosity and varying radius of intracranial arteries, Ghaffari *et al.* proposed a new meshing method that could improve the efficiency and accuracy of CFD calculation [51].

4) COMPARISON BETWEEN 0D, 1D, AND 3D MODELS

The differences between 0D, 1D and 3D models are summarized in Table 1. Firstly, the 0D and 1D models present only the flow and pulse wave while the 3D CFD models present the flow field. Therefore 3D models could be used to estimate any hemodynamic parameter. Secondly, 0D and 1D models are highly simplified in geometry, whereas 3D models basically preserve the real geometry of intracranial arteries despite the inaccuracies in imaging, segmentation, and amendments.

Especially, the 3D models are more appropriate to simulate the complex geometry of CoW. The intracranial arteries are highly curved, making CoW particularly susceptible to atherosclerosis and aneurysms [60], [62]. 0D and 1D models simulate the pulse wave propagation at low

TABLE 1. Comparisons between 0D,1D, and 3D models of the circle of Willis.

	0D models	1D models	3D models
Computational basis	Electrical analogy (Ordinary differential equations)	Simplified Navier–Stokes equations (Partial differential equations)	Navier–Stokes equations (Partial differential equations)
In-vivo data	In-vivo physiological measurements [23, 24]	In-vivo physiological measurements [28, 30, 31]	In-vivo 3-D geometry [9, 55-62], in-vivo physiological measurements [9, 45, 51, 55, 58]
Rheological models	Hematocrit-based non-Newtonian model [19]	Mainly Newtonian models Hematocrit-based non-Newtonian models [30, 32]	Carreau model [45, 53, 54], Carreau-Yasuda model [55], power-law model [5], Casson model [47], Hematocrit-based non-Newtonian models [9, 68].
Clinical applications	The ICA occlusion [10, 21] and aneurysm [22], the effect of positions on intracranial blood flow [20], the leptomeningeal anastomoses (LA) [2], the effects of stenosis on the blood flow in distal tissues [15], intracranial blood flow with traumatic brain injury and hydrocephalus [18].	Intracranial arterial occlusion [27, 33, 34], anatomical variations of CoW [3, 38], the effect of distal flow resistance on flow patterns of CoW [35], pharmacokinetics [36].	Anatomical variation [45, 50, 52, 54], the intracranial stenosis [9, 54], and aneurysm [50, 55, 60], intracranial arterial occlusion [67], the carotid stenosis [48], the cerebral flow reserve [59], the Reversed Robin Hood Syndrome [49], the effects of internal carotid [58] and cardiopulmonary bypass surgeries [63] on intracranial blood flow, endovascular mechanical recanalization [62].

TABLE 2. Main innovative techniques in the modeling of the circle of Willis.

Innovative techniques	0D models	1D models	3D models	nontraditional models
specific	Complicated model with more elements [12], additional flow resistance at the bifurcation [16], addition of leptomeningeal anastomoses [2], patient-specific model based on Kalman filters [24].	The combination with the pharmacokinetic advection-diffusion model [36], arterial radius variation [32], viscoelastic arterial wall model [40].	The effects of turbulence [5], the adjusted exponent 2.67 in Murray's law [47], a new meshing method for intracranial arteries [51], the stratified combination of 1D-0D models as outlet [9].	The probability applied in the FSI analysis of embolism in CoW [75], material properties of the human CoW [69].
common	Inlet coupled with heart and pulmonary circulation.[10, 21, 38], vein models included at outlet [19, 26], various elements for different positions [26], inclusion of ICP effects [8, 18, 19, 31].			
	Distal fractal structures at the outlet [3, 8, 9, 44], the inclusion of autoregulation effects [17, 27, 31, 49], non-Newtonian fluid models to delineate the Fåhræus–Lindqvist effect [9, 19, 30, 32, 68], in-vivo boundary conditions or validation [9, 23, 28, 30, 45, 51, 55, 58].			

computational costs. But the calculation was based on the approximately unidirectional steady flow without sudden changes in the cross-sectional area. Therefore, 0D and 1D models require additional empirical laws to simulate some geometric structures such as vessel curvatures, stenoses, and aneurysms [31]. The local hemodynamic conditions around these geometric structures are necessary to investigate the pathological phenomena but could not be presented in 0D or 1D models.

Compared with 0D and 1D models, in the 3D models more non-Newtonian rheological models have been applied such as the Carreau model [45], [53], [54], the Carreau-Yasuda model [55], the power-law model [5], the Casson model [47], and more complicated models in which the viscosity was derived from the hematocrit value [9], [68].

Focusing on the pulse wave transmission, the 0D and 1D models were mainly transient. However, in the 3D CFD models, the transient simulation consists of the solutions of many

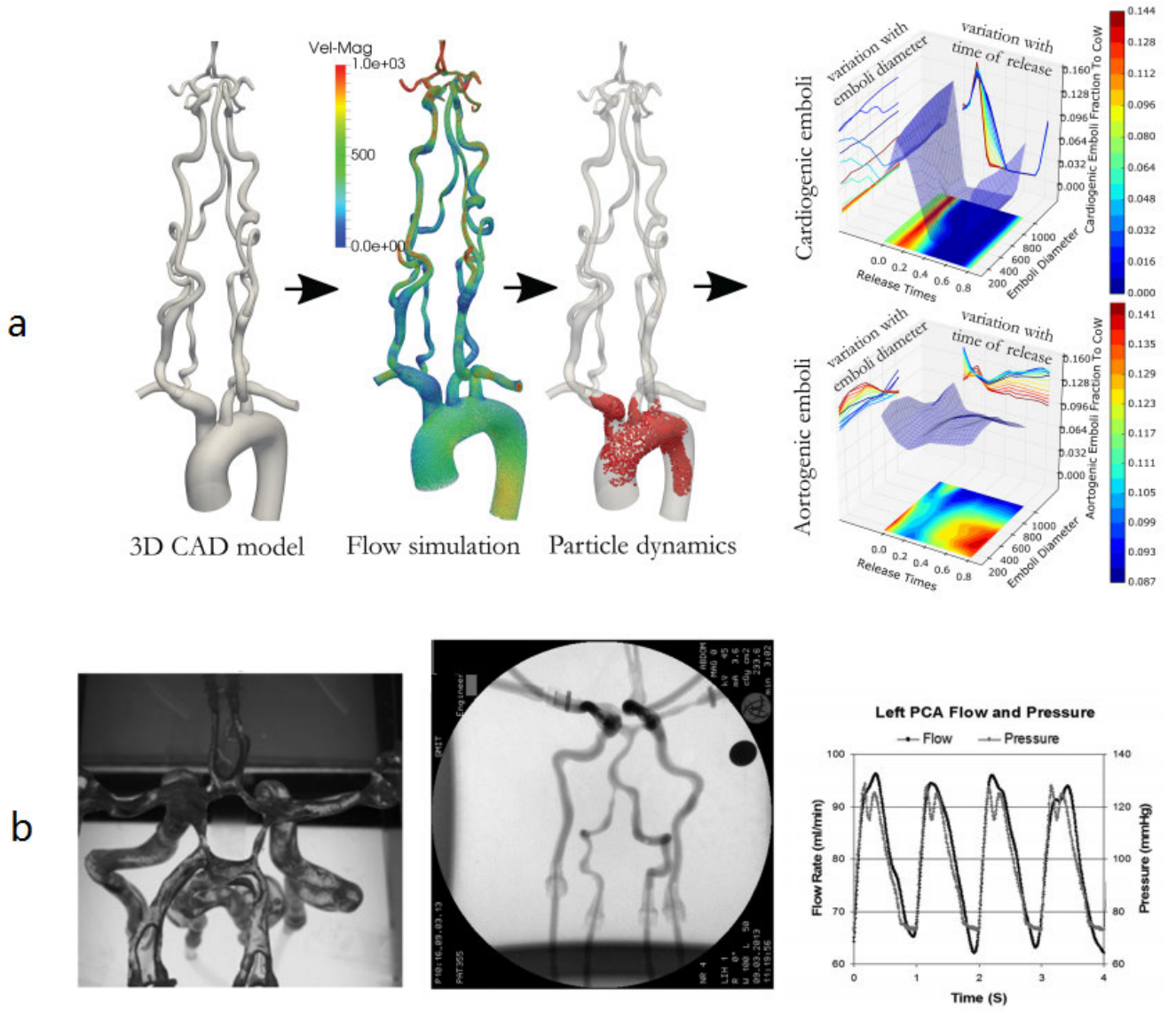


FIGURE 4. Some nontraditional CoW models. (a) A patient-specific FSI model for simulating embolism in the CoW. The probability of cardiac emboli reaching CoW was estimated based on emboli size and instance of release in a cardiac cycle [75]. (b) An in-vitro model. Firstly the flexible silicone model was built based on the geometry reconstructed from MRI imaging (left). The boundary conditions were imposed at the inlets and outlets of the model (middle) to derive the flow rate and pressure (right) [84].

independent time-steps, therefore needs more computational sources. When only time-averaged estimation of hemodynamic parameters is needed, the static 3D CFD simulation could be an appropriate option [49], [52]–[54], [56], [58], [62], [63].

IV. NONTRADITIONAL MODELS

In traditional models, the elasticity of artery wall was highly simplified (the capacitance in 0D models, the unified arterial wall in 1D models) or neglected (the assumption of rigid arterial in 3D models). It has been proven that rigid wall assumption could cause 8% - 50% overestimates of the maximum wall shear stress in some local regions [61, 66]. Considering the effect of arterial wall elasticity on the flow field, the FSI models have been proposed to simulate the interaction between blood flow and arterial wall deformation.

We found 8 FSI models of CoW. Ivanov *et al.* measured the material properties (Poisson's ratio, elastic modulus, etc.) from more than 100 human arterial samples of CoW for FSI modeling [69]. The FSI models could simulate the blood flow in CoW [70] and its fluctuations under cervical rotator manipulation [71]. With in-vivo measurement of blood flow velocity by transcranial Doppler as inlet condition, capillary blood pressure as outlet condition, and age-related elastic modulus of arterial wall, Jahed *et al.* investigated the effects of different hemodynamic and mechanical parameters (wall shear stress, blood pressure, mechanical stress, displacement) on the formation of aneurysms [72]. They found strong effects of these parameters on the size of aneurysm and the risk of aneurysm rupture at arterial bifurcations or the neck of aneurysm. Based on in-vivo measurement of cerebral blood flow velocity and clinical imaging (CT, MRI), Razaghi *et al.*

built a comprehensive FSI model including CoW, brain, skull, CSI, and neck to estimate the effect of traumatic brain injury on the risk of cerebral aneurysm rupture. They found the increase in the pressure and blood velocity in intracranial arteries after injury [73]. In estimating the risk of embolism in CoW, compared with the 3D CFD model [56], the FSI model more specifically reflected the effects of size and rigidity of the embolus on the occurrence of embolism [74]. Furthermore, Mukherjee *et al.* divided the embolism process into three independent steps, and estimated the risks of embolism from a probabilistic view using FSI simulation (Fig.4a) [75]. They applied the FSI model in 24 cases and concluded that anatomical variations of CoW significantly influenced embolus distribution to the six major cerebral arteries while MCA territory was least sensitive to the influence of anatomical variations [76].

Based on the ordinary differential equations abstracted from the 0D and 1D models, Sui *et al.* proposed a non-linear difference control model of CoW and used it to estimate the cerebral blood flow [77], [78]. Based on the models they investigated cerebral infarction [79] and the acupunctural treatment [11], [80]. This model is potential for clinical use but needs further validation using in-vivo data.

Finally, in-vitro experimental models of the CoW have been proposed. In 3D CFD models, there were geometric models reconstructed from in-vitro models [49], [50], [54] and experiments on in-vitro model for validation [60]. The CFD simulation could assist designing the in-vitro phantoms [57]. In in-vitro experimental models, the geometry was reconstructed from patient-specific imaging data. Specific fluid and elastic materials were used to simulate the blood and arterial walls. In-vitro experiment models have been applied in investigating the interaction between anterior and posterior cerebral circulations with serious ICA stenosis [81], validating patient-specific 1D models [82], explaining the liability of the CoW to aneurysms [83] , and estimating the effects of geometric variations on the formation of aneurysms in the CoW (Fig.4b) [84].

V. SUMMARY AND CONCLUSION

A. SUMMARY

Due to its significance in clinical and physiological studies, the modeling of CoW has attracted much attention. With simplified geometries, the 0D and 1D models (12 and 19 items) were mainly used to estimate the blood flow distribution or certain physiological parameters. In this review, the majority of the recent models are the 3D models (28 items). With the ability to simulate the local fluid field, the application background of 3D models expanded from estimating physiological parameters to simulating the diagnosis and treatment of specific diseases (Table 1). Compared with 3D CFD models, the FSI models (7 items) could simulate the flow field more accurately at a higher computational cost. Therefore FSI models were only applied in the situations where the elasticity of artery wall or embolus was indispensable. The models based on control theory (5 items) were innovative in simulating the CoW-oriented treatments but needed further validations. The in-vitro experimental models (9 items, 4 pure in-vitro studies) enabled the direct observation of blood flow in CoW, but the outlet resistance and capacitance are needed for more accurate simulation.

Compared with these earlier studies, recent traditional (0D, 1D, and 3D) models have been developed with more complex structure (3D-1D-0D coupling, Fig.3c), and more components added to simulate different physiological and pathological conditions. The non-traditional models provided novel perspectives of modeling CoW. The details of the innovations and their applications will be analyzed below.

B. TECHNICAL INNOVATIONS

Some state-of-the-art techniques in CoW modeling were summed up in Table 2. In the 0D and 1D models, major innovations included more advanced elements to simulate certain anatomical structure (veins, heart, cerebrospinal fluid, etc.) or physiological phenomena. In the 3D models, the innovations included more advanced models to describe the rheological and mechanical properties, the turbulence model, and other details related to local flow field. In all these models, in-vivo data were important towards providing patient-specific estimation of blood flow in the CoW.

C. APPLICATIONS: MODEL SELECTION

The selection of model depends on the application scenario. Static simulations are appropriate if the transient fluctuation is not the focus. The 0D and 1D models are acceptable for estimating the blood flow in the CoW. Existing 0D and 1D models have shown good accordance with clinical measurement in estimating blood flow [23], [24], [28], [30], [31]. However, 3D CFD models are necessary if the local flow field is focused. Though 0D and 1D models can reflect the physiology, it is important to calibrate these models to fit patient-specific 3D CFD or FSI models to achieve the reliability in estimating hemodynamic parameters. To investigate the interaction among blood flow, arterial wall, and embolus, FSI models should be applied at a higher computational cost.

Calculations could be finished in seconds for 0D and 1D models, but in hours and days for CFD models, and even longer for FSI models. A parallel study on coronary arteries indicated that the time length for a FSI simulation could be more than 20 times of that for the corresponding CFD simulation [85]. It is computationally unaffordable to simulate the whole human circulatory system which consists of more than 50,000 miles of blood vessels. The seamless and reliable coupling among FSI, 3D CFD, 1D, and 0D models plays a key role in reducing the computational complexity.

D. LIMITATIONS

Firstly, the structure of arteries needs to be extended. Some 0D and 1D models started from the aorta, or included the whole cardiovascular system including heart, veins, and capillaries while the majority of 3D and FSI models included

only the CoW. It has been shown that compared with localized arterial model, the extended vessel structure could improve the accuracy of estimating wall shear stress in aneurysms [66].

Secondly, many physiological details are often neglected such as the non-Newtonian effect of blood, the viscoelasticity of artery wall, and the effect of ICP on cerebral blood flow.

Thirdly, the application of patient-specific imaging data and hemodynamic parameters is limited. Patient-specific arterial geometry was widely applied in 3D and FSI models. In the majority of 0D and 1D models, and all the control theory models, results were validated by comparing with the data in literature, or not validated. For in-vitro models, the bidirectional flow in a cardiac cycle was difficult to perform at outlet [82]. Currently, it is difficult to measure the flow velocity in intracranial arteries. Therefore, there are few patient-specific models of CoW that are fully validated by in-vivo measurement.

Finally, most of the existing studies have not been applied in clinical diagnosis and treatment. On the one hand, the number of patient-specific models did not exceed 30 in all the computational studies (in Ivanov *et al.*'s study, more than 100 cases were included but have not been simulated individually [69]). Large-scale validations are still needed before further clinical application. On the other hand, for 3D and FSI models, the computational complexity limited the real-time clinical application.

E. FUTURE DIRECTIONS

Considering the limitations of current CoW models, some improvements could be considered in future studies. Firstly, the extended arterial structure and other physiological effects (non-Newtonian blood model, viscoelastic artery wall model, and ICP) are needed to improve the accuracy of models in estimating hemodynamic parameters. Secondly, large-scale validation is need for the clinical application of the models. Thirdly, to achieve fast estimation of hemodynamic parameters in local flow field, the combination of low-dimensional (0D and 1D) and high-dimensional (3D, FSI) models deserves further investigation.

REFERENCES

[1] J. S. Kim and O. Y. Bang, "Medical treatment of intracranial atherosclerosis: An update," *J. Stroke*, vol. 19, no. 3, p. 261, 2017.
[2] T. G. Phan, J. Hilton, R. Beare, V. Srikanth, and M. Sinnott, "Computer modeling of anterior circulation stroke: Proof of concept in cerebrovascular occlusion," *Front. Neurol.*, vol. 5, p. 176, 2014, doi: 10.3389/fneur.2014.00176.
[3] X. Yu, C. Ji, Y. He, and J. Chen, "Numerical analysis of blood flow in the dysplastic circle of Willis using one-dimen-sional patient-specific model," in *Proc. 3rd Int. Conf. Comput. Math. Bio-Med. Eng.*, Hong Kong, 2014, vol. 20, no. 3, pp. 405–408.
[4] S. R. Naveen, V. Bhat, and G. A. Karthik, "Magnetic resonance angiographic evaluation of circle of Willis: A morphologic study in a tertiary hospital set up," *Ann. Indian Acad. Neurol.*, vol. 18, no. 4, p. 391, 2015.
[5] P. Reorowicz, D. Obidowski, P. Klosinski, W. Szubert, L. Stefanczyk, and K. Jozwik, "Numerical simulations of the blood flow in the patient-specific arterial cerebral circle region," *J. Biomech.*, vol. 47, no. 7, pp. 1642–1651, May 2014.
[6] N. P. Denswil, A. C. van der Wal, K. Ritz, O. J. de Boer, E. Aronica, D. Troost, and M. J. A. P. Daemen, "Atherosclerosis in the circle of Willis: Spatial differences in composition and in distribution of plaques," *Atherosclerosis*, vol. 251, pp. 78–84, Aug. 2016.
[7] L. Mu *et al.*, "Experimental studies on the contralateral regulation of cerebral blood flow using a patient-specific aneurysm model," in *Advances in Cognitive Neurodynamics (V)* (Advances in Cognitive Neurodynamics), R. Wang and X. Pan, Eds. Singapore: Springer, 2016, doi: 10.1007/978-981-10-0207-6_46.
[8] B. J. E. Misgeld, R. Mondal, and S. Leonhardt, "Hybride modellierung intrakranieller pulswellen unter berücksichtigung der kardiovaskulären kopplung," *at-Automatisierungstechnik*, vol. 64, no. 11, pp. 858–869, Jan. 2016.
[9] S. Yamada, M. Oshima, M. Kobayashi, Z. Hao, Y. Watanabe, H. Miyake, and K. Yamamoto, "Cerebral circulation simulation model for predicting hemodynamic cerebral infarction risk in cervical internal carotid artery stenosis," (in Japanese), *Stroke Surgery*, vol. 43, no. 2, pp. 91–97, 2015, doi: 10.2335/scs.43.91.
[10] S. H. Sadraie, M. Abdi, M. Navidbakhsh, K. Hassani, and G. R. Kaka, "Modeling the heart beat, circle of willis and related cerebral stenosis using an equivalent electronic circuit," *Biomed. Eng., Appl., Basis Commun.*, vol. 26, no. 5, Oct. 2014, Art. no. 1450052.
[11] J.-X. Sui, L. Yang, and H.-Z. Shi, "Hemodynamic assessment and computation on vertebral artery stenosis," *Technol. Health Care*, vol. 23, no. s1, pp. S83–S88, May 2015.
[12] I. Kokalari, T. Karaja, and M. Guerrisi, "Review on lumped parameter method for modeling the blood flow in systemic arteries," *J. Biomed. Sci. Eng.*, vol. 6, no. 1, p. 92, 2013.
[13] M. Soehle, "Fractal analysis of the cerebrovascular system physiopathology," in *The Fractal Geometry of the Brain* (Springer Series in Computational Neuroscience), A. Di Ieva, Ed. New York, NY, USA: Springer, 2016, doi: 10.1007/978-1-4939-3995-4_16.
[14] S. P. Nejad-Davarani, H. Bagher-Ebadian, J. R. Ewing, D. C. Noll, T. Mikkelsen, M. Chopp, and Q. Jiang, "A parametric model of the brain vascular system for estimation of the arterial input function (AIF) at the tissue level," *NMR Biomed.*, vol. 30, no. 5, p. e3695, May 2017.
[15] A. M. T. Rojas, A. M. Romero, I. Pagonabarraga, R. D. M. Travasso, and E. C. Poiré, "Obstructions in vascular networks: Relation between network morphology and blood supply," *PLoS ONE*, vol. 10, no. 6, 2015, Art. no. e0128111, doi: 10.1371/journal.pone.0128111.
[16] C. Chnafa, K. Valen-Sendstad, O. Brina, V. M. Pereira, and D. A. Steinman, "Improved reduced-order modelling of cerebrovascular flow distribution by accounting for arterial bifurcation pressure drops," *J. Biomech.*, vol. 51, pp. 83–88, Jan. 2017.
[17] F. K. McConnell and S. Payne, "The dual role of cerebral autoregulation and collateral flow in the circle of Willis after major vessel occlusion," *IEEE Trans. Biomed. Eng.*, vol. 64, no. 8, pp. 1793–1802, Aug. 2017.
[18] T. Sethaput, "Mathematical model for hemodynamic and intracranial Windkessel mechanism," M.S. thesis, Dept. Elect. Eng. Comput. Sci., Case Western Reserve Univ., Cleveland, OH, USA, 2013. [Online]. Available: http://rave.ohiolink.edu/etdc/view?acc_num=case1363149368
[19] T. Utsuki, "Development of a cerebral circulation model for the automatic control of brain physiology," in *Proc. 37th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC)*, Aug. 2015, pp. 1890–1893.
[20] C. Zhang, S. Li, F. Pu, Y. Fan, and D. Li, "The effect of anatomic variations of circle of Willis on cerebral blood distribution during posture change from supination to standing: A model study," *Bio-Med. Mater. Eng.*, vol. 24, no. 6, pp. 2371–2380, 2014.
[21] M. Abdi, A. Karimi, M. Navidbakhsh, M. Rahmati, K. Hassani, and A. Razmkon, "Modeling the circle of Willis using electrical analogy method under both normal and pathological circumstances," *J. Biomed. Phys. Eng.*, vol. 3, no. 2, p. 45, 2013.
[22] M. Abdi, A. Karimi, M. Navidbakhsh, K. Hassani, and S. Faghihi, "RETRACTED: Modeling of cerebral aneurysm using equivalent electrical circuit (lumped model)," *Perfusion*, vol. 29, no. 2, pp. 142–152, Mar. 2014.
[23] C. Zhang, L. Wang, X. Li, S. Li, F. Pu, Y. Fan, and D. Li, "Modeling the circle of Willis to assess the effect of anatomical variations on the development of unilateral internal carotid artery stenosis," *Bio-Med. Mater. Eng.*, vol. 24, no. 1, pp. 491–499, 2014.
[24] R. Lal, F. Nicoud, E. L. Bars, J. Deverdun, F. Molino, V. Costalat, and B. Mohammadi, "Non invasive blood flow features estimation in cerebral arteries from uncertain medical data," *Ann. Biomed. Eng.*, vol. 45, no. 11, pp. 2574–2591, Nov. 2017.

[25] P. Garcia-Canadilla, P. A. Rudenick, F. Crispi, M. Cruz-Lemini, G. Palau, O. Camara, E. Gratacos, and B. H. Bijens, "A computational model of the fetal circulation to quantify blood redistribution in intrauterine growth restriction," *PLoS Comput. Biol.*, vol. 10, no. 6, Jun. 2014, Art. no. e1003667.

[26] S. Manini, L. Antiga, L. Botti, and A. Remuzzi, "PyNS: An open-source framework for 0D haemodynamic modelling," *Ann. Biomed. Eng.*, vol. 43, no. 6, pp. 1461–1473, Jun. 2015.

[27] J. Ryu, X. Hu, and S. C. Shadden, "A coupled lumped-parameter and distributed network model for cerebral pulse-wave hemodynamics," *J. Biomech. Eng.*, vol. 137, no. 10, Oct. 2015, Art. no. 101009.

[28] H. Zhang, N. Fujiwara, M. Kobayashi, S. Yamada, F. Liang, S. Takagi, and M. Oshima, "Development of a numerical method for patient-specific cerebral circulation using 1D–0D simulation of the entire cardiovascular system with SPECT data," *Ann. Biomed. Eng.*, vol. 44, no. 8, pp. 2351–2363, Aug. 2016.

[29] S. R. Ghodsi, V. Esfahanian, and S. M. Ghodsi, "Modeling requirements for computer simulation of cerebral aneurysm," *J. Comput. Med.*, vol. 2014, pp. 1–9, Feb. 2014.

[30] P. Perdikaris, L. Grinberg, and G. E. Karniadakis, "An effective fractal-tree closure model for simulating blood flow in large arterial networks," *Ann. Biomed. Eng.*, vol. 43, no. 6, pp. 1432–1442, Jun. 2015.

[31] M. Connolly, X. He, N. Gonzalez, P. Vespa, J. DiStefano, and X. Hu, "Reproduction of consistent pulse-waveform changes using a computational model of the cerebral circulatory system," *Med. Eng. Phys.*, vol. 36, no. 3, pp. 354–363, Mar. 2014.

[32] J. Fillenwarth, "Improved one-dimensional model of blood flow in the human arterial network, with application to cerebral flow," Ph.D. dissertation, Dept. Chem. Biomolecular Eng., Univ. Delaware, Newark, DE, USA, 2016. [Online]. Available: http://udspace.udel.edu/handle/19716/19592

[33] M. Majka, G. Gadda, A. Taibi, M. Gałązka, and P. Zieliński, "Earliest effects of sudden occlusions on pressure profiles in selected locations of the human systemic arterial system," *Phys. Rev. E, Stat. Phys. Plasmas Fluids Relat. Interdiscip. Top.*, vol. 95, no. 3, Mar. 2017, Art. no. 032414.

[34] A. Piechna and M. Pieniak, "Numerical simulation of the effect of supplying arteries occlusion on cerebral blood flow," in *Advanced Mechatronics Solutions* (Advances in Intelligent Systems and Computing), vol. 393, R. Jabłoński and T. Brezina, Eds. Cham, Switzerland: Springer, 2016, doi: 10.1007/978-3-319-23923-1_27.

[35] C. L. de Lancea, T. David, J. Alastruey, and R. G. Brown, "Recruitment pattern in a complete cerebral arterial circle," *J. Biomech. Eng.*, vol. 137, no. 11, Nov. 2015, Art. no. 111004.

[36] S. Safaei, "Simulating blood flow in an anatomical arterial network," M.S. thesis, Auckland Bioeng. Inst., ResearchSpace Auckland, Auckland, New Zealand, 2015. [Online]. Available: http://hdl.handle.net/2292/25552

[37] H. Yu, G. P. Huang, Z. Yang, F. Liang, and B. Ludwig, "The influence of normal and early vascular aging on hemodynamic characteristics in cardio- and cerebrovascular systems," *J. Biomech. Eng.*, vol. 138, no. 6, Jun. 2016, Art. no. 061002.

[38] P. G. Huang and L. O. Muller, "Simulation of one-dimensional blood flow in networks of human vessels using a novel TVD scheme," *Int. J. Numer. Methods Biomed. Eng.*, vol. 31, no. 5, May 2015, Art. no. e02701.

[39] G. P. Huang, H. Yu, Z. Yang, R. Schwieterman, and B. Ludwig, "1D simulation of blood flow characteristics in the circle of Willis using THINkS," *Comput. Methods Biomech. Biomed. Eng.*, vol. 21, no. 4, pp. 389–397, Mar. 2018.

[40] C. S. Park, A. Alaraj, X. Du, F. T. Charbel, and A. A. Linninger, "An efficient full space-time discretization method for subject-specific hemodynamic simulations of cerebral arterial blood flow with distensible wall mechanics," *J. Biomech.*, vol. 87, pp. 37–47, Apr. 2019.

[41] J.-X. Wang, X. Hu, and S. C. Shadden, "Data-augmented modeling of intracranial pressure," *Ann. Biomed. Eng.*, vol. 47, no. 3, pp. 714–730, Mar. 2019.

[42] T. Gamilov, S. Simakov, and P. Kopylov, "Computational modeling of multiple stenoses in carotid and vertebral arteries," in *Trends in Biomathematics: Modeling, Optimization and Computational Problems: Selected Works From the BIOMAT Consortium Lectures, Moscow 2017*, R. P. Mondaini, Ed. Cham, Switzerland: Springer, 2018, pp. 301–312.

[43] A. Melis, F. Moura, I. Larrabide, K. Janot, R. H. Clayton, A. P. Narata, and A. Marzo, "Improved biomechanical metrics of cerebral vasospasm identified via sensitivity analysis of a 1D cerebral circulation model," *J. Biomech.*, vol. 90, pp. 24–32, Jun. 2019.

[44] B. J. E. Misgeld, R. Mondal, and S. Leonhardt, "Cardiovascular to intracranial transmission characteristics for hydrocephalus," in *Advances in Cognitive Neurodynamics (V)* (Advances in Cognitive Neurodynamics), R. Wang and X. Pan, Eds. Singapore: Springer, 2016, doi: 10.1007/978-981-10-0207-6_65.

[45] X. Liu, Z. Gao, H. Xiong, D. Ghista, L. Ren, H. Zhang, W. Wu, W. Huang, and W. K. Hau, "Three-dimensional hemodynamics analysis of the circle of Willis in the patient-specific nonintegral arterial structures," *Biomech. Model. Mechanobiol.*, vol. 15, no. 6, pp. 1439–1456, Dec. 2016.

[46] S. N. Wright, P. Kochunov, F. Mut, M. Bergamino, K. M. Brown, J. C. Mazziotta, A. W. Toga, J. R. Cebral, and G. A. Ascoli, "Digital reconstruction and morphometric analysis of human brain arterial vasculature from magnetic resonance angiography," *NeuroImage*, vol. 82, pp. 170–181, Nov. 2013.

[47] I. D. Šutalo, A. V. Bui, S. Ahmed, K. Liffman, and R. Manasseh, "Modeling of flow through the circle of Willis and cerebral vasculature to assess the effects of changes in the peripheral small cerebral vasculature on the inflows," *Eng. Appl. Comput. Fluid Mech.*, vol. 8, no. 4, pp. 609–622, Jan. 2014.

[48] A. Kashefi, M. Mahdinia, B. Firoozabadi, M. Amirkhosravi, G. Ahmadi, and M. S. Saidi, "Multidimensional modeling of the stenosed carotid artery: A novel CAD approach accompanied by an extensive lumped model," *Acta Mechanica Sinica*, vol. 30, no. 2, pp. 259–273, Apr. 2014.

[49] A. Piechna and K. Cieslicki, "Reversed robin hood syndrome in the light of nonlinear model of cerebral circulation," *Int. J. Appl. Mech. Eng.*, vol. 22, no. 2, pp. 459–464, May 2017.

[50] S.-W. Nam, S. Choi, Y. Cheong, Y.-H. Kim, and H.-K. Park, "Evaluation of aneurysm-associated wall shear stress related to morphological variations of circle of Willis using a microfluidic device," *J. Biomech.*, vol. 48, no. 2, pp. 348–353, Jan. 2015.

[51] M. Ghaffari, K. Tangen, A. Alaraj, X. Du, F. T. Charbel, and A. A. Linninger, "Large-scale subject-specific cerebral arterial tree modeling using automated parametric mesh generation for blood flow simulation," *Comput. Biol. Med.*, vol. 91, pp. 353–365, Dec. 2017.

[52] Y. Ren, Q. Chen, and Z.-Y. Li, "A 3D numerical study of the collateral capacity of the circle of Willis with anatomical variation in the posterior circulation," *Biomed. Eng. OnLine*, vol. 14, no. 1, p. S11, 2015.

[53] S. E. Razavi and R. Sahebjam, "Numerical simulation of the blood flow behavior in the circle of Willis," *BioImpacts, BI*, vol. 4, no. 2, p. 89, 2014.

[54] G. Zhu, Q. Yuan, J. Yang, and J. H. Yeo, "The role of the circle of Willis in internal carotid artery stenosis and anatomical variations: A computational study based on a patient-specific three-dimensional model," *Biomed. Eng. OnLine*, vol. 14, no. 1, p. 107, Dec. 2015.

[55] P. Berg, D. Stucht, G. Janiga, O. Beuing, O. Speck, and D. Thévenin, "Cerebral blood flow in a healthy circle of Willis and two intracranial aneurysms: Computational fluid dynamics versus four-dimensional phase-contrast magnetic resonance imaging," *J. Biomech. Eng.*, vol. 136, no. 4, Apr. 2014, Art. no. 041003.

[56] D. Fabbri, Q. Long, S. Das, and M. Pinelli, "Computational modelling of emboli travel trajectories in cerebral arteries: Influence of microembolic particle size and density," *Biomech. Model. Mechanobiol.*, vol. 13, no. 2, pp. 289–302, Apr. 2014.

[57] G. Pattyn, "Creating *in-vitro* phantoms of blood vessels to support the testing and validation of new ultrasonic blood flow imaging techniques," M.S. thesis, Dept. Electron. Inf. Syst., Ghent Univ., Ghent, Belgium, 2015. [Online]. Available: https://lib.ugent.be/fulltxt/RUG01/002/300/755/RUG01-002300755_2016_0001_AC.pdf

[58] F. Zhu, Y. Qian, B. Xu, Y. Gu, K. Karunanithi, W. Zhu, L. Chen, Y. Mao, and M. K. Morgan, "Quantitative assessment of changes in hemodynamics of the internal carotid artery after bypass surgery for moyamoya disease," *J. Neurosurg.*, vol. 129, no. 3, pp. 677–683, 2017.

[59] K. E. Lee, A.-J. Ryu, E.-S. Shin, and E. B. Shim, "Physiome approach for the analysis of vascular flow reserve in the heart and brain," *Pflügers Arch.-Eur. J. Physiol.*, vol. 469, nos. 5–6, pp. 613–628, Jun. 2017.

[60] F. Liang, X. Liu, R. Yamaguchi, and H. Liu, "Sensitivity of flow patterns in aneurysms on the anterior communicating artery to anatomic variations of the cerebral arterial network," *J. Biomech.*, vol. 49, no. 15, pp. 3731–3740, Nov. 2016.

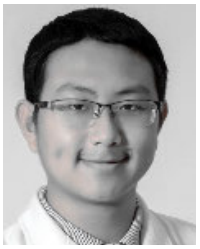
[61] D. Sekhane, "Image-based computational fluid dynamics (CFD) modeling cerebral blood flow in the circle of Willis," *J. Adv. Res. Phys.*, vol. 6, no. 2, pp. 1–6, 2016.

[62] M. Neidlin, M. Büsen, C. Brockmann, M. Wiesmann, S. J. Sonntag, U. Steinseifer, and T. A. S. Kaufmann, "A numerical framework to investigate hemodynamics during endovascular mechanical recanalization in acute stroke," *Int. J. Numer. Methods Biomed. Eng.*, vol. 32, no. 4, Apr. 2016, Art. no. e02748.

[63] S. Piskin, A. Ündar, and K. Pekkan, "Computational modeling of neonatal cardiopulmonary bypass hemodynamics with full circle of Willis Anatomy," *Artif. Organs*, vol. 39, no. 10, pp. E164–E175, Oct. 2015.

[64] C. Karmonik, "Toward improving fidelity of computational fluid dynamics simulations: Boundary conditions matter," *Amer. J. Neuroradiol.*, vol. 35, no. 8, pp. 1549–1550, Aug. 2014.

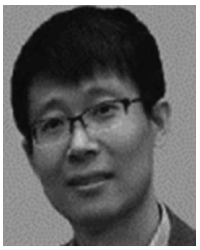
[65] M. Mamatyukov, I. Mikheev, D. Parshin, A. Khe, A. Cherevko, K. Orlov, and A. Chupakhin, "Comprehensive research of human brain hemodynamics: Clinical monitoring and computer simulations," in *Proc. AIP Conf.*, 2018, vol. 2027, no. 1, Art. no. 020009.
[66] Z.-Q. Zhang, L.-J. Xu, R. Liu, X.-S. Liu, B. Zhao, and F.-Y. Liang, "Importance of incorporating systemic cerebroarterial hemodynamics into computational modeling of blood flow in intracranial aneurysm," *J. Hydrodynamics*, vol. 32, no. 3, pp. 510–522, Apr. 2019.
[67] A. Chien and F. Viñuela, "Analyzing circle of Willis blood flow in ischemic stroke patients through 3D stroke arterial flow estimation," *Interventional Neuroradiol.*, vol. 23, no. 4, pp. 427–432, 2017.
[68] M. Oshima, R. Torii, S. Tokuda, S. Yamada, and A. Koizumi, "Patient-specific modeling and multi-scale blood simulation for computational hemodynamic study on the human cerebrovascular system," *Current Pharmaceutical Biotechnol.*, vol. 13, no. 11, pp. 2153–2165, Aug. 2012.
[69] D. Ivanov, A. Dol, O. Pavlova, and A. Aristambekova, "Modeling of human circle of Willis with and without aneurisms," *Acta Bioeng. Biomech.*, vol. 16, no. 2, pp. 121–129, 2014.
[70] H. Rezaie, A. Ashrafizadeh, and A. Mojra, "A patient-specific three-dimensional hemodynamic model of the circle of Willis," *Cardiovascular Eng. Technol.*, vol. 8, pp. 495–504, Sep. 2017.
[71] W. Lin, X. Ma, D. Deng, and Y. Li, "Hemodynamics in the circle of Willis with internal carotid artery stenosis under cervical rotatory manipulation: A finite element analysis," *Med. Sci. Monit.*, vol. 21, pp. 1820–1826, Jun. 2015, doi: 10.12659/MSM.892822.
[72] M. Jahed, F. Ghalichi, and M. Farhoudi, "Fluid-structure interaction of patient-specific circle of Willis with aneurysm: Investigation of hemodynamic parameters," *Bio-Med. Mater. Eng.*, vol. 29, no. 3, pp. 357–368, Mar. 2018.
[73] R. Razaghi, H. Biglari, and A. Karimi, "Risk of rupture of the cerebral aneurysm in relation to traumatic brain injury using a patient-specific fluid-structure interaction model," *Comput. Methods Programs Biomed.*, vol. 176, pp. 9–16, Jul. 2019.
[74] F. Khodaee, B. Vahidi, and N. Fatouraee, "Analysis of mechanical parameters on the thromboembolism using a patient-specific computational model," *Biomech. Model. Mechanobiol.*, vol. 15, no. 5, pp. 1295–1305, Oct. 2016.
[75] D. Mukherjee, N. D. Jani, K. Selvaganesan, C. L. Weng, and S. C. Shadden, "Computational assessment of the relation between embolism source and embolus distribution to the circle of Willis for improved understanding of stroke etiology," *J. Biomech. Eng.*, vol. 138, no. 8, Aug. 2016, Art. no. 081008.
[76] D. Mukherjee, N. D. Jani, J. Narvid, and S. C. Shadden, "The role of circle of Willis anatomy variations in cardio-embolic stroke: A patient-specific simulation based study," *Ann. Biomed. Eng.*, vol. 46, no. 8, pp. 1128–1145, Aug. 2018.
[77] J. Sui, L. Yang, S. Li, and H. Shi, "Blood circulation diseases treatment based on decentralized adaptive control," *J. Intell. Fuzzy Syst.*, vol. 33, no. 5, pp. 2851–2860, Oct. 2017.
[78] L. Yang, J. Sui, S. Li, and H. Shi, "Nonlinear hemodynamic difference equation control modelling with constraints and medication of cerebrovascular disease," *J. Difference Equ. Appl.*, vol. 23, nos. 1–2, pp. 42–54, Feb. 2017.
[79] J. Sui, L. Yang, X. Zhang, H. Shi, and Y. Hu, "Hemodynamic solution computation and pathological analysis in the circle of Willis," *J. Med. Syst.*, vol. 42, no. 10, p. 178, Aug. 2018.
[80] L. Yang, J. Sui, and H. Shi, "Control modeling and Chinese acupuncture treatment on cerebral circulation," *Technol. Health Care*, vol. 23, no. 1, pp. S77–S82, May 2015.
[81] G. Zhu, Q. Yuan, J. Yang, and J. Yeo, "Experimental study of hemodynamics in the circle of Willis," *Biomed. Eng. OnLine*, vol. 14, no. 1, p. S10, 2015.
[82] H. Yu, G. P. Huang, B. R. Ludwig, and Z. Yang, "An in-vitro flow study using an artificial circle of Willis model for validation of an existing one-dimensional numerical model," *Ann. Biomed. Eng.*, vol. 47, no. 4, pp. 1023–1037, Apr. 2019.
[83] P. Fahy, P. McCarthy, S. Sultan, N. Hynes, P. Delassus, and L. Morris, "An experimental investigation of the hemodynamic variations due to aplastic vessels within three-dimensional phantom models of the circle of Willis," *Ann. Biomed. Eng.*, vol. 42, no. 1, pp. 123–138, Jan. 2014.
[84] P. Fahy, P. Delassus, P. McCarthy, S. Sultan, N. Hynes, and L. Morris, "An *in vitro* assessment of the cerebral hemodynamics through three patient specific circle of Willis geometries," *J. Biomech. Eng.*, vol. 136, no. 1, Jan. 2014, Art. no. 011007.
[85] P. D. Morris, A. Narracott, H. von Tengg-Kobligk, D. A. Soto, S. Hsiao, A. Lungu, P. Evans, N. W. Bressloff, P. V. Lawford, D. R. Hose, and J. P. Gunn, "Computational fluid dynamics modelling in cardiovascular medicine," *Heart*, vol. 102, no. 1, pp. 18–28, 2016.



HAIPENG LIU received the B.S. and M.S. degrees in electrical engineering and biomedical engineering from Zhejiang University, Hangzhou, China, in 2012 and 2015, respectively, and the Ph.D. degree in medical sciences from The Chinese University of Hong Kong, Hong Kong, in 2018.

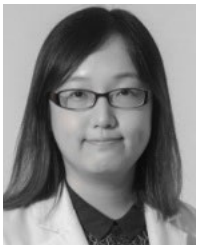
From 2019 to 2020, he was a Research Fellow with the Medical Technology and Research Center, Anglia Ruskin University. Since 2020, he has been a Research Fellow with Coventry University, Coventry, U.K. He is the author of 24 journal articles and four IEEE conference papers. He had an invited talk in the 41st IEEE International Engineering in Medicine and Biology Conference (EMBC 2019). His research interests include biomechanics, physiological measurement, and simulation of cardiovascular diseases.

Dr. Liu was a recipient of the Travel Award of British Heart Foundation in the 14th International Symposium on Biomechanics in Vascular Biology and Cardiovascular Disease, and the Research and Innovation Support Fund of Anglia Ruskin University.



DEFENG WANG received the B.Sc. degree from the Department of Computer Science, Jilin University, and the Ph.D. degree from the Department of Computing, The Hong Kong Polytechnic University.

He is currently a Professor with the School of Instrumentation Science and Optoelectronics Engineering, Beihang University, and the Beijing Advanced Innovation Center for Big Data-Based Precision Medicine. He has authored or coauthored more than 60 journal articles, more than 110 conference papers, and four U.S. patents. His research interests include medical imaging, statistical morphometry analysis, fMRI paradigm design and post-processing, quantitative medical image analysis, and computational life science. He won best scientific oral presentation award in annual meeting of the Korean Society of Magnetic Resonance in Medicine, in 2012, and the IFMBE Best Paper Award in EMBC 2005.



XINYI LENG received the M.B. and M.C.M. degrees from Capital Medical University, China, in 2009 and 2011, respectively, and the Ph.D. degree from The Chinese University of Hong Kong (CUHK), in 2014.

She worked as a Faculty Postdoctoral Fellow with CUHK, from 2015 to 2017. She is currently a Research Assistant Professor with the Department of Medicine & Therapeutics, CUHK. Her research interests include stroke and intracranial atherosclerotic disease (ICAD). Using multimodal neuroimaging and computational methods, she has been studying cerebral hemodynamics and plaque characteristics in ICAD and its clinical implications. She also works on the efficacy and safety of medical and interventional treatment regimens in ischemic stroke, and investigates mechanisms of collateral circulation recruitment and its clinical relevance in stroke patients. She was awarded the Lee Hysan Postdoctoral Fellowship in Clinical Neurosciences. In the last few years, she has also been funded by the Hong Kong Research Grants Council, the National Natural Science Foundation of China, the China Association for Science and Technology, and the World Heart Federation (The Emerging Leaders Programme), for her research in the area of stroke.

DINGCHANG ZHENG (Member, IEEE) received the B.Sc. degree in biomedical engineering from Zhejiang University, China, and the Ph.D. degree in medical physics from Newcastle University, U.K.

He is currently a Professor of Healthcare Technology and Research Theme Leader with Coventry University. He is also leading research in medical device and technology development with physiological measurements and bio-signal processing, working across multidisciplinary areas with electronic engineers, medical physicists, computer scientists, clinical consultants, industrial partners, guideline makers, and allied professionals at different stages along the pathway of medical device development and commercialization. He is the winner of the IPEM Martin Black Annual Prize, in 2011, and the Institution of Engineering and Technology (IET) JA Lodge Award 2009 for Recognising and Promoting Outstanding Work in the Field of Research and Development in Medical Engineering.

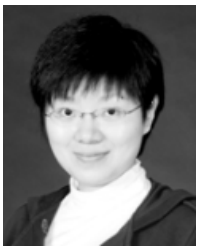
FEI CHEN (Senior Member, IEEE) received the B.Sc. and M.Phil. degrees in electronic engineering from Nanjing University, and the Ph.D. degree in electronic engineering from The Chinese University of Hong Kong, in 2005.

He continued his research as a Postdoctoral/Research Assistant Professor in The University of Texas at Dallas and The University of Hong Kong, and moved to the Southern University of Science and Technology (SUSTech) as an Associate Professor in the Department of Electronic Engineering, in 2014. He has published over 80 journal articles and over 60 conference papers. His research interests include speech perception and assistive hearing technology, brain–computer interface, and biomedical signal processing. He received the best presentation award in the 9th Asia Pacific Conference of Speech, Language and Hearing, and 2011 National Organization for Hearing Research Foundation Research Awards in States. He is also serving as an Associate Editor for *Frontiers in Psychology*, and an Editorial member for *Biomedical Signal Processing and Control* and *Physiological Measurement*.

LAWRENCE KA SING WONG received the M.B.B.S. and M.D. degrees from the University of New South Wales, Sydney, NSW, Australia, in 1985 and 1998, respectively.

He completed a Neurology Residency Program at the Prince of Wales Hospital, Hong Kong. He has published more than 400 full scientific articles in indexed international journals, such as *The New England Journal of Medicine*, *Nature*, *The Lancet Neurology*, *Circulation*, *Annals of Neurology*, *Stroke*, and *Neurology*. His research interests include various aspects of cerebrovascular disease, such as intracranial atherosclerosis, neurosonology, epidemiology, cerebral blood flow, atrial fibrillation, and clinical trials for treatment and prevention of stroke in Asians. He co-ordinates many international clinical trials in Asia. He first established that intracranial atherosclerosis is the major cause of stroke in Chinese stroke patients. He led the FISS-TRIS and CLAIR studies which provided the scientific basis for early aggressive use antithrombotic treatment for ischemic stroke and TIA.

Prof. Wong is currently the Secretary of the World Stroke Organization and the Asian Oceanian Association of Neurology, and an Associate Editor of the journal *Stroke* (American Heart Association). He also serves or had served as member of the editorial board for the *Journal of Neurology, Neurosurgery and Psychiatry* (JNNP), the *European Journal of Neurology*, the *Journal of the Neurological Sciences*, *Chinese Medical Journal*, and the *Journal of Neuroimaging*. He was the Chairman of the organizing committee of the 1st International Conference on Intracranial Atherosclerosis, in 2004, the 9th International Symposium on Thrombolysis and Acute Stroke Therapy, in 2006, and the Co-Chair of the Scientific Committee of Asian Oceanian Congress of Neurology, Macau, in 2014, and the World Stroke Congress, Seoul, in 2010.



LIN SHI (Member, IEEE) received the Ph.D. degree in computer science from The Chinese University of Hong Kong (CUHK), in 2008.

She worked as a Postdoctoral Research Fellow and a Research Assistant Professor with CUHK for six years. She is currently an Assistant Professor with the Department of Imaging and Interventional Radiology (DIIR), CUHK. She is also the Director and the Co-Founder of the Division of Imaging Informatics, DIIR. She has published more than 120 articles in peer-reviewed journals. She is the inventor of seven patents related to medical imaging and quantification techniques, and founded a startup company, BrainNow Ltd., in 2015, to promote the clinical applications of neuroimage analysis technology. Her research interests include multimodal image quantification of brain and orthopedic images to support clinical research and practice. She has been awarded the Best Young Engineer's Paper Award, by the Biomedical Division, The Hong Kong Institution of Engineers.

THOMAS WAI HONG LEUNG received the M.B. Ch.B. degree from The Chinese University of Hong Kong (CUHK), in 1995.

He is currently a Professor with the Department of Medicine & Therapeutics, CUHK, and the National Coordinator for Safe Implementation of Treatment in Stroke (SITS). He has published more than 150 full articles in peer-reviewed journals and book chapters. He serves as a Regular Reviewer for *The Lancet*, *Stroke*, the *Journal of Neurology, Neurosurgery and Psychiatry* (JNNP), the *American Journal of Neuroradiology* (AJNR), *Cerebrovascular Diseases*, the *International Journal of Stroke*, and the *International Journal of Cardiology*. His research interests include stroke mechanism, outcome, and cerebral revascularization as treatment for intracranial atherosclerotic disease. He also serves as an Editor/Editorial Board member of *Stroke*, the *Journal of Neurology and Neurosurgery*, *Interventional Neurology*, and *International Scholarly Research Network (ISRN) Radiology*, and *Hong Kong Medical Journal*. Over the years, he has delivered more than 100 lectures worldwide for The World Federation of Neurology, Food and Drug Administration (the United States), the World Stroke Organization, the European Stroke Organization, the American Stroke Association, the International Stroke Genetics Consortium, the Society of Vascular Interventional Neurology, the Asia Pacific Stroke Organization, and the Ministry of Health, China. He was awarded the prestigious First Class Award of the 2011 Higher Education Outstanding Scientific Research Output Award (Science and Technology) in the category of Natural Sciences by the Ministry of Health, China, for the studies in Intracranial Large Artery Atherosclerotic Stroke: Epidemiology, Diagnosis, Pathogenesis, Imaging, and Treatment. For his research in endovascular neuro-intervention, he received the Second Prize in Medical Technology by the Chinese Medical Association, in 2011, for Angioplasty and stenting for intracranial stenosis in Chinese; and Second Prize in the State of Scientific and Technological Progress Award, China, in 2014, for Strategies in cerebral revascularization. He was a recipient of HIMSS-Elsevier Digital Health Award (Asia-Pacific Region) 2013 for his contribution in developing telemedicine to enhance stroke care of the underserved regions.