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BENG 501

11/2/18

## Literature Review on Methods of Modeling the Cerebral Network and the Circle of Willis

### **INTRODUCTION**

The Circle of Willis is a network of internal carotid arteries, basilar arteries, and vertebral arteries all coming together to perfuse the brain with blood. In the event that stenosis occludes part of the circle, the communicating arteries located at the posterior and anterior of the circle can compensate for the blood flow. However, if the communicating arteries themselves are occluded or entirely missing, the risk of ischemic stroke and subsequent death is possible. The literature surrounding the Circle of Willis is robust; the following review establishes historical context surrounding the development of mathematical models around the cerebral network and those specific to the circle of Willis, while also highlighting the applications and future for modeling.

#### **1. Comparative examination of cerebral circulation models**

*Clark et.al* first hints at the use of cerebral circulation models as a means of visualizing the circle of Willis in common experimental animals, such as rats, mice, or fish [1]. In this review, criteria for a model of cerebral circulation models is developed – an adequate description of the geometry, an estimate of total flow the circle, adequate representation of pressure gradients for all components/portions of the model, an estimate of division of flow in the afferent and efferent vessels [1]. The authors compare the use of an electrical model and a computer model, highlighting the

sophisticated technology that was available at the time to simulate complex arterial systems with varying degrees of elegance and accuracies [1]–[4].

Clark et al points to Avman and Bering as an important model for the reason that it was studied with actual fluids, as opposed to being a mathematical model[5]. Early on, Avman et al attempted to model a circle of Willis in a patient experiencing a cerebral aneurysm. The use of a blood flow model is extremely limited, as it does not allow for the assumptions or mathematical approximation that a computer could work with. However, the close agreement between anatomical literature published at the time of this study and the diameter and length measurements of the tubing used allowed the authors to closely mimic a circle of Willis in an adult male [2]. While the authors developed a model that agreed with the criteria set forth by Clark et al, certain questions regarding the methods are left unanswered by Avman and Bering – how was peripheral pressure imposed, and was it maintained throughout the experiments? By using rigid tubing, was there any real point to simulating flow as a pulse? These questions underline the limitations of a physical flow model and point to a need for computer models.

## **2. Mechanisms of cerebral blood flow regulation**

A different simulation examines the mathematical model of flow in the Circle of Willis based on one-dimensional equations for blood motion. In its first iteration it assumed a linear relationship in its equations, and its boundary conditions were generated with a prescribed periodic pressure and assumed mass balance, only taking into account a few segments of the CoW [6]. In its next iteration, however, it was more sophisticated, being able to correctly model ‘variations in the communicating arteries and physiological changes in the resistance of vertebral arteries.’ The literature surrounding the specific area of research that details insights into anatomical variations of the circle of Willis indicates

that the value of a model of the CoW is both in its relatively simple structure as well as its ability to model flow in the event of anatomic variations.

### **3. Neurovascular Flow Simulation Review**

Charbel et. al's review asserts that all accurate mathematical models that simulate the flow through the cerebral network up to the time of publishing in 1998 are one dimensional and therefore are governed by one dimensional Navier-Stokes (N-S) equations[7]. A set of criteria to derive N-S equations are set forth. They assert that the value of the CoW model lies in its ability to simulate flow and pressure distribution, and offer different methods of validation. In the review, the authors also address the limitations of using finite volume, finite-element and finite-difference tools in computational fluid dynamics (CFD), and hint at the future applications of the finite element method in regards to cerebral network simulation. The authors conclude the review by indicating that at the time of publication, little had been done in the way of applying models of the CoW as clinical tools for diagnosis, as opposed to use in research and theory.

Duros et al. attempted to model the CoW mathematically, using nonlinear equations to model cerebral aneurysms in a human brain [7]. Unlike Avman et al., the model took the different arteries that supplied blood to different organs into account in addition to being a purely theoretical model, as opposed to a sophisticated system of tubes and valves that simply modeled the cerebral network. Different parameters were adjusted to simulate an aneurysm rupture, such as terminal vessels' resistance, stenosis induced in the cerebral arteries and hypertension was simulated. This model was able to manipulate many factors that previous models had attempted but not completely succeeded; later models would follow its lead in taking a systemic approach to calculating pressure and flow.

### **4. Flows in Stenotic Vessels**

While not directly addressing the modeling practices in the Circle of Willis, a different study reviews the practices used when modeling flow through arteries assumed to be affected by severe conditions such as atherosclerosis. The review discusses work on Navier-Stokes equations pertaining to curvature and flow [8]. The use of linear equations, while allowing for a simple model, fail to adequately account for deformation, wall shear, and artery curvature that require more sophistication in the N-S equations. Berger et. al assert that using numerical solutions of the N-S equations are required to develop a 3-D model of the artery flow; however, they also argue that in order to understand artery curvature and wall shear, work must be done to understand the composition of atherosclerotic plaque.

## **5. Current Progress in Patient Specific Modeling**

Charbel et al.'s predictions regarding the progression of modeling from theoretical research tools to effective diagnosis were correct[7]. Neal and Kerchkhoffs conducted a literature review of models which had been able to simulate patients' physiological systems with high accuracy. [9] The authors point to the use of magnetic resonance angiography/velocimetry (MR) and computed tomography (CT) as common techniques for collecting data for cerebral geometries, so as to predict the onset of cerebral aneurysms and other occlusions in the brain [10]–[15].

### **a. Patient Specific Modeling Using Finite Element Methods**

Oshima et al integrated three-dimensional imaging such as MRI and CT with Doppler ultrasound in order to construct a patient-specific model with the intent of studying cerebral aneurysms [16]. Using finite-element methods over a more complex mesh that resulted from the data pulled from the CT scans, flow dynamics were visualized. The authors chose finite-element schemes for calculating flow due to the accuracy and stability with which flow could be modeled through arteries [17], [18] The implications of combining numerical solutions with imagery were so such that measures such as WSS and curvature could be examined in greater detail in the future. Through modeling these attributes with

greater accuracy, a more sophisticated model of the CoW could be created. Furthermore, different measures such as surface traction and the use of a cardiac cycle in consideration when creating this model helped to understand the impact that the cardiovascular system has on the CoW.

In light of this review, Oshima's paper is limited in its ability to not only generate an accurate model using CT and MRI data, but also to calculate WSS. The literature published prior to Neal et al. indicated that the use of finite element calculation schemes presented anatomical simulations as 'undeformed', regardless of the patient data used. By failing to minimize the error in creating these patient specific simulations, the results of this study are brought into question. WSS, the main parameter of this study therefore has a danger of being overestimated and therefore inaccurate for the purpose of the study. Since Oshima's publication, different models have been proposed that can take on said 'deformities' in order to provide more accurate results [19], [20].

Cebral et al notes the difficulty associated with validating hemodynamics in patient specific models due to the lack of *in vivo* data available at the time of publication. [21] The authors' method of collecting data to generate an accurate model was consistent with Neal et al.'s established wisdom regarding the use of MR angiograms in patient data. Cebral et al. also note the limitations and possible inaccuracy of a nonlinear CFD model; relatively small changes to parameters can have a substantial influence on results. The authors note that the geometry of the patient model used plays a large role in the experiment and encourage that further steps are taken towards a process for automatically generating a 3D model of the CoW in order to minimize error and inaccuracies in later experiments.

#### **b. Partial Patient Specific Modeling Using 1-D Models**

Alastruey et. al modeled the CoW in further depth [22]. While opting out of using a patient-specific model using 3-D imaging due to computation costs, they were able to use a 1-D model that could accurately model occlusions in the internal carotid arteries. The authors go on to present different

modifications to their model, which contain (or more appropriately, leave out) different sections of the circle of Willis to detect the difference in inflow and outflow accordingly. Consequently, the different anatomies are compared for determining which CoW is the most likely to suffer from strokes and aneurysms. Charbel et. al noted that models of the circle of Willis were most useful as research tools; rarely had models been verified and validated against *in vivo* measurements. Alastruey et al.'s model, though relatively simple in construction was one of the first to be able to validate its findings against *in vivo* data collected from previous experiments. The impact that Alastruey et al.'s findings have on further research speaks to the validity of the results and sets the foundation for future 1D/0D models of the CoW[23]–[27].

Alnaes et al. attempted to model the CoW using a three dimensional CFD simulation [23]. The methods proposed by the authors focused on the effects of varying vessel radii, bifurcation in WSS and vessel wall pressure. While the study was successful in confirming that WSS is affected by branch angles and differences in vessel radii, the drawbacks of the model are in its inability to simulate more than a localized area of the circle of Willis. Alnaes et al also mentions the need to include simulations 'with flexible vessel walls.' However, it is later established as common wisdom in the literature surrounding CFD that attempting to accurately model flexibility and elasticity in vessel and arterial walls is too computationally expensive to justify.

Devault et al notes the difficulty of validating and verifying studies of the CoW, based on the lack of *in vivo* digital transcranial Doppler (TCD) available [24]. Most simulations of the CoW at the time of publishing had been verified qualitatively, rather than quantitatively. The model proposed by the authors, however, had been calibrated, verified and validated based off physiological data, lending it accuracy and viability. The authors intended to supplement their simulations with computational fluid dynamics, a practice that was not common at the time of publishing. In contrast to previous studies, however, Devault et al did not consider patient specific parameters in their approach.

### c. **Partial Patient Specific Modeling Using 0-D Models**

A 0D network model using RC circuits to simulate the circle of Willis was created by Almuhanha et al to investigate the factors that play an important role as biomarkers of vulnerable carotid plaque [25]. Instead of modeling the left internal carotid artery as a single RC circuit, the authors presented the artery as three segments – LICA 1, LICA 2 LICA 3, while modeling stenosis across the LICA 2. The values for resistance, capacitance and elastance used throughout the model were based on real patient data acquired from previous literature [22], [28]–[30]. Varying stenosis against mean flow and mean flow velocity in the LICA 2, it was found that mean flow decreased with an increase in stenosis across the internal carotid artery. However, mean flow velocity increased against an increase in stenosis, but tapered off after a certain velocity. In both instances, mean flow and mean flow velocity increased across the RICA to compensate for the stenosed internal carotid artery.

### d. **Partial Patient Specific Modeling To Examine Stenosis**

In a separate experiment, Almuhanha et al uses CFD to investigate flow dynamics in the internal carotid artery. Like previous patient specific models, the authors use MR data to develop realistic portraits of patient data in order to properly simulate hemodynamics. In addition, Almuhanha investigates the effect of increased stenosis against WSS of carotid arteries across three different subjects using Cebra et al.'s CFD technology. While contributing towards a greater understanding of the effects of atherosclerotic plaque in the internal carotid artery, there were a number of important limitations to consider with the development of this model. A small patient body implies that only a small range of plaque geometries were considered in the development of this study [9], [21]. In addition, Almuhanha et al also assume that stenosis increases uniformly and radially across the artery. The author notes the unlikelihood of such an event occurring in a realistic clinical setting.

While Almuhanha et al. used a circuit model, Zhu et al attempted to model the CoW using a three dimensional computational model, similar to Oshima et al [26]. The simulations were prepared by incompressible N-S equations, as opposed to Almuhanha et. al.'s model which only relied on the basic equations for flow, pressure, compliance, and resistance in fluid dynamics. Similar to Alastruey, Zhu et al. did not take into account the compliance and elastic properties of the arterial wall, in contrast to the specifications and physiological data given by the circuit model. Using CT images to reconstruct specific patients' CoW, varying degrees of stenosis were modeled in the right internal carotid artery (RICA) with this computational model in an approach similar to Oshima et al.

Perera et al. proposed a follow up approach to Almuhanha et al.'s model, integrating Zhu's modeling a segmented RICA with an existing network model. Working within the constraints of a network model, the authors were able to increase the specificity of Almuhanha et al's network model and simulate stenosis in different areas of both internal carotid arteries [31]. Because this effort was an extension of a pre-existing study, some extrapolation was required from the physiological data available to the authors in order to build the modules that would become the integrated RICA segments. The authors concluded that the model, while complex, did not take into account certain things like flow division and independence; these assumptions laid the groundwork for future research into this topic where rather than having a single aortic generator supply flow to the whole model, separate flow generators could be applied to each input. In addition, the authors proposed integrating cerebral autoregulation as a feedback mechanism within the model in order to improve both complexity and accuracy of the model[32]-[33].

## **6. Recent Applications of Circle of Willis Research**

Huang et al. asserts that 1D modeling has greater utility over the use of CFD, given that the latter method is generally localized and can easily produce inaccurate results [34] This assertion is in line



with Cebal et al.'s conclusions regarding the application and error-prone nature of the modeling techniques. The use of the Total Human Intravascular Network Simulation (THINKS) is shown to be a more accurate model for modeling cerebral flow than CFD. The authors note the intended future for THINKS as a method for predicting risk associated with vascular lesions in addition to guiding surgical treatments. Given the nature of this model, we can assume that it is a partially patient specific model; while providing a model that may accurately model data in a typical adult male or female, it is not practical to gear the model to simulate specific patients, similar to Almuhanha's network model.

Most recently, Mukherjee et al attempted to study the links between the circle of Willis and the risk of cardio-embolic stroke. Using MR, CT, and TCD data to generate patient specific models, the authors were able to model flow through different anatomical variations of the CoW. Using N-S equations and a finite element method to calculate flow and pressure, Mukherjee modeled emboli as particles flowing through the CoW. The authors concluded that the shape of the CoW played a large role in determining the risk of cardio-embolic stroke[35]. While acknowledging the model's limitations which were consistent with literature discussing patient specific models, Mukherjee et al asserted that the imaging-based procedure used was detailed and flexible such that any modification to the CoW geometry could be taken into account. The model used here is less of a research tool than it is a blueprint for a model for the purpose of planning stroke treatment.

## **Conclusion**

The current literature discussing the circle of Willis discusses the growing sophistication and accuracy of network models that couple with imaging from TCD, MRI, and CT to produce powerful tools for patient-specific prediction. The future of the CoW model is rooted in our ability to model the cardiovascular network as a factor behind flow, and map out more cause-and-effect relationships in the circulatory systems. Based on the models put forth in this review, using a 1-D network model is most conducive to building a computationally inexpensive yet precise simulation of the CoW. Cerebral

autoregulation has been identified multiple times throughout this literature review as an extremely important feedback mechanism in cerebral networks; therefore, it is necessary that future research and development of models of the CoW take steps towards modeling cerebral autoregulation in order to build a more complex, yet more accurate model to improve research and diagnostic tools[36].

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