An Analysis of Cerebral Arteriovenous Malformation Hemodynamics for Treatment Planning

Background and Rationale: Cerebral Arteriovenous Malformations (cAVMs) are congenital vascular lesions that affect 0.01-0.50% of the population. The annual risk of hemorrhage in the cAVM nidus is on average 3%, but the risk can be as low as 1% to as high as 33% depending on patient-specific anatomies. Since the cAVM nidus has low resistance, it allows blood to shunt directly from arterial feeders (AFs) to draining veins (DVs) at high flow rates. As a result, if the hemodynamic stresses exceed the elastic modulus of the vessel wall, then a rupture may form and cause a hemorrhage. Embolization – the intravascular injection of embolic materials to AFs, is one of the most common interventional therapies to prevent hemorrhages by diverting blood flow away from the nidus. However, current methods to visualize blood flow patterns for embolization treatment planning are limited. Using the standard-of-care – 2D superselective angiogram sequences (2D+τ) and 3D rotational angiography (3DRA) – is challenging because the contrast agent reaches multiple regions of the nidus simultaneously, which prevents the identification of cAVM compartments and fistulae. Therefore, there is an urgent need to elucidate blood flow patterns in the cAVM to improve on treatment planning for embolization.

One method to address this problem involves computational fluid dynamics (CFD) to simulate cAVM hemodynamics on patient-derived models. However, the length-scale of the nidus prevents CFD from being applied because the spatial resolution of 0.6mm in 3DRA is insufficient to capture the 0.1mm or smaller diameters of intranidal vessels. As an alternative, some studies have resorted to using electric network models, but these models are typically not based on clinical data. Instead of modeling every intranidal vessel in the nidus, I could model all the intranidal vessels collectively through a porous volume [1], which has been shown to be a good approximation of the nidus [2].

Simulating the density of intranidal vessels beyond the spatial resolution limitations of 3DRA is possible because voxel intensity is proportional to the amount of contrast agent in a vessel [1], which provides information on the internal geometry of the nidus. Based on Darcy's law and mass conservation, there are seven parameters that characterize blood flow through the porous volume: porosity, permeability, fluid viscosity, fluid density, quadratic drag factor, and the velocity and pressure boundary conditions [1]. These parameters can be inferred from 3DRA images. However, existing models [1], [3] lack validation with other paradigms, such as *in vitro* testing, and the models are limited to Types IIa, IIb, and IV in the Yakes classification of cAVMs, which are not representative of the population since there are a total of six types. My research objective is to investigate cAVM hemodynamics for embolization planning through generalized patient-specific CFD models for each angioarchitecture type in the Yakes classification, with a porous volume representing the nidus, and validate *in silico* results using an *in vitro* flow loop.

Specific Aim 1: *Develop simplified cAVM digital phantoms for validation with varying spatial porosity distributions.* I will design digital phantoms on SolidWorks (Dassault Systèmes, Vélizy-Villacoublay, FR) with one tubular AF and DV connected to a rectangular porous volume. The phantom will be meshed using a triangular grid of approximately 10^4-10^5 elements for a cell density of around 16 cells per voxel [1] using Gambit (Ansys, Canonsburg, PA). The velocity boundary condition at the AF inlet will be set according to phase-contrast magnetic resonance angiography (PC-MRA) images, while a zero-pressure boundary condition will be used at the DV outlet. Blood viscosity will be set to 4.00cP, density to 1060 kg/m^3, and *Re* to 265. Fluent (Ansys, Canonsburg, PA) will be used to run the CFD simulation. To **validate**, I will confirm that the fluid behaves according to expectations where flow paths will mostly circulate in nonporous regions and that flow through porous regions will obey theoretical expectations from Darcy's law.

Specific Aim 2: *Construct generalized patient-specific cAVM models.* I will construct the boundaries of the cAVM and the AFs and DVs from 3DRA images. This will be done through segmentation (3D Slicer, Boston, MA), and I will obtain morphometric measurements using Analyze 12.0 (AnalyzeDirect, Overland Park, KS). Based on the segmented anatomies and patient-specific measurements, I will create generalized models for each cAVM angioarchitecture type on SolidWorks. Afterwards, I will mesh the models using a tetrahedral grid on Gambit. The porous volume parameters will be inferred from 3DRA images and then averaged. As before, I will set the fluid properties of blood based on nominal values. I will **validate** mesh convergence through a mesh independence study on Fluent by comparing coarse vs. medium, medium vs. fine, and coarse vs. fine meshes. Moreover, I will compare porosity distributions through CFD between the generalized models and five different patient-specific anatomies for each angioarchitecture type.

Specific Aim 3: *Develop a flow loop for in vitro validation.* I plan to modify an existing flow loop in **Prof. Ajit Yoganathan's lab** to simulate cAVM hemodynamics. For example, the flow loop has two pressure measurement probes, which is insufficient for cAVM simulation. I will make modifications to incorporate more probes to accommodate for all the AFs and DVs. From the models used in the *in silico* study, I will manufacture transparent rigid physical phantoms using an MR-compatible resin (Watershed 11122, DSM Somos, Elgin, IL). I will then implement the same inflow conditions from the computational study to the flow loop and compare flow field data through PC-MRA and digital particle image velocimetry for **validation**. Furthermore, I will also manufacture the five patient-specific anatomies for each angioarchitecture type in the Yakes classification from **Specific Aim 2** and compare *in vitro* flow field results to *in silico* results.

Timeline and proposed laboratory: I would like to work with **Prof. Ajit Yoganathan** (Georgia Tech) because of the close alignment of research interests. I anticipate that this study will take five years: one for **Specific Aim 1**, and two each for **Specific Aim 2** and **Specific Aim 3**.

Intellectual Merit: Currently, only Orlowski et al. [1], [3] have used a porous volume to simulate the cAVM nidus. **My project expands on this model, in that there have been no published papers that uses a generalized CFD model based on patient-averaged data, an *in vitro* flow loop to validate and compare with *in silico* findings, and a porous model to simulate the cAVM nidus.** As post-embolization complications are a major concern, my computational model can serve as the first step to a surgical planning software that meets this need.

Broader Impact: With further exploration, the computational model proposed can be expanded to a two-fluid model for simulating the propagation and solidification of embolic therapies, which can provide pre-operative outcome prediction, potential increase in embolization session efficiency, and optimize interventional strategies. My project may also be scaled-up for interventional planning in other AVMs situated in the lung, muscle or bone, prognosis evaluation, and optimization of therapies. Finally, I will collaborate with clinicians at Emory University and University College London to ensure clinical utility and present my work at conferences.

Feasibility: From my master's thesis, I will be supported by University College London, University College Hospital, and Kings College London to obtain 3DRA and PC-MRA patient data. I will seek Institutional Review Board approval under **Prof. Yoganathan's** support.

[1] P. Orlowski, F. Al-Senani, P. Summers, J. Byrne, J. A. Noble, and Y. Ventikos, "Towards Treatment Planning for the Embolization of Arteriovenous Malformations of the Brain: Intranidal Hemodynamics Modeling," IEEE Trans. Biomed. Eng., vol. 58, no. 7, pp. 1994–2001, Jul. 2011. [2] C. W. Kerber, S. T. Hecht, and K. Knox, "Arteriovenous malformation model for training and research," AJNR Am. J. Neuroradiol., vol. 18, no. 7, pp. 1229–1232, Aug. 1997. [3] P. Orlowski, P. Summers, J. A. Noble, J. Byrne, and Y. Ventikos, "Computational modelling for the embolization of brain arteriovenous malformations," Med. Eng. Phys., vol. 34, no. 7, pp. 873–881, Sep. 2012.