Into the gray matter: construction and coupling of multiscale highly-detailed arterial networks in the human cerebral cortex

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Abstract. Strokes sum up to 11% of worldwide deaths. Imaging describes many aspects of cerebral circulation, but the limited resolution for smaller vessels hinders the study of hemodynamics, and computational models provide tools to characterize inaccessible scenarios. This work aims to build vascular networks in the human cerebral cortex across the gray matter. The method is based on the Constrained Constructive Optimization (CCO), called PDCCO, generating vascular networks following anatomical rules. A patient-specific geometry of the gray matter is partitioned into three territories, one for each main cerebral artery, which in turn were obtained from a generic cerebral vascular model. The pial surface is filled with blood vessels reaching 234000 vascular segments with diameters between 2100 µm and 26 µm, and terminal vessels ranging between 50 µm and 60 µm The network penetrates the gray matter, and deep vascularization is performed by appending prefabricated sub-trees to each terminal, yielding tens of millions of vascular segments for the entire left hemisphere. The resulting vascular network can be coupled with cardiovascular models for blood flow simulations, enabling the study of cerebral blood pressure in normal and pathological conditions. This approach proposes an automatic vascularization of the brain to understand microcirculation, the risk of stroke, and mechanisms involved in the onset and progress of degenerative diseases.

Keywords: cardiovascular system, automatic vascularization, human brain circulation, computational hemodynamics, numerical methods

1 Introduction

Stroke is the second leading cause of death worldwide according to Feigin et al. [1], being responsible for 11% of total deaths. Research in this field is of the utmost importance to improve early diagnosis and therapeutic strategies to reduce the healthcare burden caused by this disease. Computational modeling and numerical simulation are complementary tools that are exploited to leverage patient-specific data and provide estimates of the hemodynamic environment in the deepest regions of the brain (Blanco et al. [2]). These models permit to describe and simulate physiological systems and their evolution with a high degree of accuracy in diverse scenarios of interest. One of the obstacles in these studies, however, is the lack of information regarding smaller blood vessels, where pathologies commonly unfold. This is especially the case in patient-specific hemodynamic modeling, where limitations in the resolution of medical imaging data hinders vascular characterization. Given this problem, alternatives are used to model these networks and study pathophysiological phenomena at vascular spatial scales inaccesible to current medical imaging techniques.

Previous works have contributed to this area. In Hartung et al. [3] a complete vascular model of a rat brain was built, and in Józsa et al. [4] a porous media model of the human brain was proposed. Gould et al. [5] studied the pressure drop in smaller capillary networks, and Otani et al. [6] investigated the consequence of occlusions in collateral blood supply.

The present study aims to expand existing arterial models of the human cerebral cortex to vascularize the grey

matter. First, we use automatic vascularization algorithms derived from Constrained Constructive Optimization (CCO) (Karch et al. [7]) to generate a vascular network along the pial surface of the brain. This algorithm, named PDCCO (Cury et al. [8]), provides the proper tooling for the generation of highly detailed and dense vascular networks, allowing to extend existing blood vessel models. Next, we implement a method to generate cortical structures that penetrate the cortex and vascularize the gray matter. These penetrating arterioles continue from the terminals of the pial network, descending towards the gray matter, connecting to smaller sub-trees that supply blood to the regions surrounding each arteriole. This vastly increases the resolution of the vascular network into the order of millions of blood vessels and targets the same scale of vessels found in Schmid et al. [9] and Hartung et al. [3], reaching pre-capillary diameters just above 10 μm, and around 1% in fraction of vascular volume (Linninger et al. [10]).

The proposed approach can be used to model patient-specific cerebral vascular networks and to carry out blood flow simulations to characterize the hemodynamics over different regions of the brain, facilitating the investigation of the onset and progress of cerebrovascular disorders related to abnormal hemodynamic conditions. Potential areas of interest include the study of stroke, small vessel disease, hypertension, Alzheimer's, and Parkinson's disease, as well as the study of drug delivery and neurovascular coupling.

The human brain exerts the functions necessary to metabolism, sensory perception, movement, and cognition (Schünke et al. [11]). It comprises two hemispheres connected via the corpus callosum, while the brainstem connects the brain to the body via the spinal cord. The brain cortex is constituted of two tissues, the gray matter on the outer layer, and the white matter underneath (Schünke et al. [11]). These regions contain the nervous system's neuroglial cells, the fundamental substrate that enables proper neurological functions in the brain. The space between the dura matter, which is a thick membrane covering the inner side of the skull, and the brain, is filled with cerebrospinal fluid. The interface between this fluid and the gray matter is the pial surface and extends along the brain cortical structures called gyri, i.e. convex outwards loops, and sulci, i.e. concave inwards valleys.

Blood vessels vascularize these regions in the form of arterioles, capillaries and venules. Each hemispherical cortex is subdivided into three sub-regions, each of them perfused by one of the three major cerebral arteries and their branches (Schünke et al. [11]), the Anterior (ACA), Middle (MCA), and Posterior Cerebral Artery (PCA). They first run along the pial surface, yielding ramifications along its way towards the most distal parts of the brain. These ramifications continue to branch off into smaller vessels to homogeneously cover the maximum surface area available over the convexity of the cortex.

To supply the inner cortex with blood, smaller arterioles penetrate the gray and white matter downwards via cortical columns called descending arterioles (Lauwers et al. [12]), and bifurcate into massive networks of arterioles and capillaries (Reina-De La Torre et al. [13]). The vascular scales are such that the Farhaeus-Lindqvist effect (see Fåhræus and Lindqvist [14] and Pries et al. [15]) is not negligible, and so the variation of blood viscosity in these smaller blood vessels, which results in a non-Newtonian behavior, must be taken into consideration.

Current models of the human arterial system available permit the simulation of blood flow with a high degree of detail. This is the case of the Anatomically Detailed Arterial Model (ADAN) in Blanco et al. [16]. Although the cerebrovascular network in the ADAN model is highly descriptive and includes many branches of vessels over the pial surface, the blood flow phenomena in smaller arterioles, where pathologies unfold (Blanco et al. [2]), cannot be simulated due to a lack of vascular resolution. Thus, the present work proposes an anatomically consistent strategy to expand existing vascular networks such as that from ADAN model into massive networks of vessels that will enable organ-scale computational studies of brain perfusion, including up to pre-capillary arteriolar vessels.

2 Methods

2.1 Constrained constructive optimization

Constrained constructive optimization (CCO) is an optimization algorithm that automatically generates a vascular tree in a given domain, while following a set of physiological rules and anatomical constraints (Karch et al. [7]). This method allows the construction of networks of blood vessels via the minimization of a cost functional, generally associated with the total intravascular volume of blood in the territory. For a geometry of interest, the generation starts from an inlet or an existing base tree, from which the procedure is initiated. The algorithm sorts a terminal point in the domain and searches for nearby parent vessel candidates. For each bifurcation candidate, the blood volume functional cost $\mathcal{F}(T)$ for a tree T is calculated according to

$$\mathcal{F}(T) = \sum_{i=1}^{N} \pi l_i r_i^2, \tag{1}$$

where the sum spans all the N vessels in the network, and the cost for adding the new single vessel $\mathcal{J}(v)$ is

$$\mathcal{J}(v_i) = \mathcal{F}(T)(v_i) + c_p r_p + c_d l(v_i)^2. \tag{2}$$

Equations (1) and (2) depend on the vessel length l_i, radius r_i, parent vessel's radius r_p, and the coefficients c_p and c_d which characterize the predominance of proteolytic and diffusive mechanisms in the network. For the definition of these parameters please refer to Talou et al. [17]. The candidate with the lowest cost $\mathcal{J}(v_i)$ is chosen as the best vascular segment, and it is permanently appended to the tree. This procedure is repeated until the number of terminals reaches a target value.

One of the main physiological rules considered by the algorithm is the relation between vessel radii at a bifurcation. Every vascular segment, when connected to the existing network has to be such that vessel diameters must verify the following power law (see Murray [18])

$$r_p^\gamma = r_{c1}^\gamma + r_{c2}^\gamma, \tag{3}$$

where r_p is the radius of the parent blood vessel in the bifurcation, and r_{c1} and r_{c2} are the radii of the child vessels. The parameter γ is the power law's exponent, and its typical value surrounds $\gamma = 3.0$ (Cassot et al. [19]).

In addition, the network has to verify certain hemodynamics conditions. In particular, all terminal vessels have the same flow and the inlet pressure is fixed. These quantities are computed by the CCO algorithm assuming that vessels are rigid and that Poiseuille flow verifies, leading to a purely resistive steady-state model with non-linear viscosity in order to account for the Farhaeus-Lindqvist effect (Linninger et al. [10]).

Talou et al. [17] expanded the CCO algorithm to enable the generation of multi-stage generations, where parameters may vary stage-wisely. This work makes use of the PDCCO version presented in Cury et al. [8], where generation occurs independently in separate vascular domains which are then merged to form the entire cortical vasculature.

2.2 Brain geometry and initial network registration

The process of network generation starts with the definition of cerebral territories from a 3D geometrical image dataset made available for this study. The provided geometry is split in Blender 3D into three larger sections as defined by Schünke et al. [11], and each region comprehends the presence of one of the larger cerebral arteries (ACA, MCA, PCA), as shown in Figure 1. After that, the cerebral vessels of the ADAN model (Blanco et al. [16]) were registered onto the pial surface. The registration is done by a linear map towards the brain geometry, followed by projection of the coordinates onto a surface outwardly extruded by 1 mm from the pial surface, as illustrated in Fig. 1.

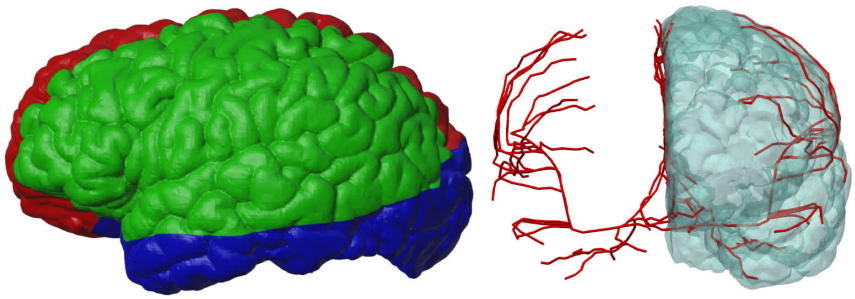

Figure 1. Left panel: Regions of the brain. Geometrical division of the three regions of the brain associated with each main cerebral artery (ACA: red, MCA: green, PCA: blue), coronal view. Right panel: Registration of the ADAN cerebral vessels (red vessels) to the geometrical brain model, sagittal view.

2.3 Generation of pial vessels

The generation is initiated from the larger arteries, which are used as the initial stage of the network in the left hemispherical cortex, i.e. the vascularization domain. The region where the pial network is to be created, hereafter called pial domain, is defined by the pial surface and by an external boundary obtained from a 2 mm-outward extrusion of the pial surface. The PDCCO algorithm from Cury et al. [8] is used to vascularize the pial domain corresponding to each one of the three territories (ACA, MCA, PCA), while the vertical structures that penetrate the gray matter are generated from the terminal vessels of the pial network. As previosuly anticipated, the

vascularization algorithm considers the Fahraeus-Lindqvist effect and the blood flow rate for each major territory. These flow rates are gathered from simulation data obtained with the ADAN model (Blanco et al. [16]).

For the pial network, the first generation stage uses a sprouting-like functional combining volumetric, proteolytic, and diffusive cost (see eq. (2)), while the second stage uses a purely-volumetric cost functional. The third stage generates a parallel network, using 7 (ACA), 8 (MCA), and 6 (ACA) subdomain partitions, and the resulting networks are merged for each region according to Cury et al. [8]. The number of terminal vessels targeted for generation in the pial surface is based on the density of the descending arterioles (DA). According to Schmid et al. [9], we consider 1 DA per mm^2, calculated for the surface area of the pial boundary.

2.4 Generation of penetrating arterioles

This stage regards the bifurcation of penetrating vessels from the pial network downwards into the gray matter domain. For each terminal vessel in the pial network, the algorithm bifurcates from the endpoint and from the midpoint towards the closest point lying on the pial surface. At the end of these newly created vessels, additional segments continue penetrating the gray matter in the inward normal direction to the pial surface at that point. The endpoint of these vessels reach either the inner boundary of the gray matter (i.e. the boundary separating grey and white matter regions) or, if its length reached a maximum value of 2.5 mm following Schmid et al. [9], completely into the gray matter.

A population of 100 different small-scale arborizations (also called sub-trees) is generated separately, in a hexagonal prism of 2.5 mm of height and 1 mm of diameter of the circumscribed cylinder. Each sub-tree contains 100 vessels. These sub-trees are appended to the penetrating vessels by random sampling out of the 100-arborizations population, and the vessels' diameters are updated according to eq. (3).

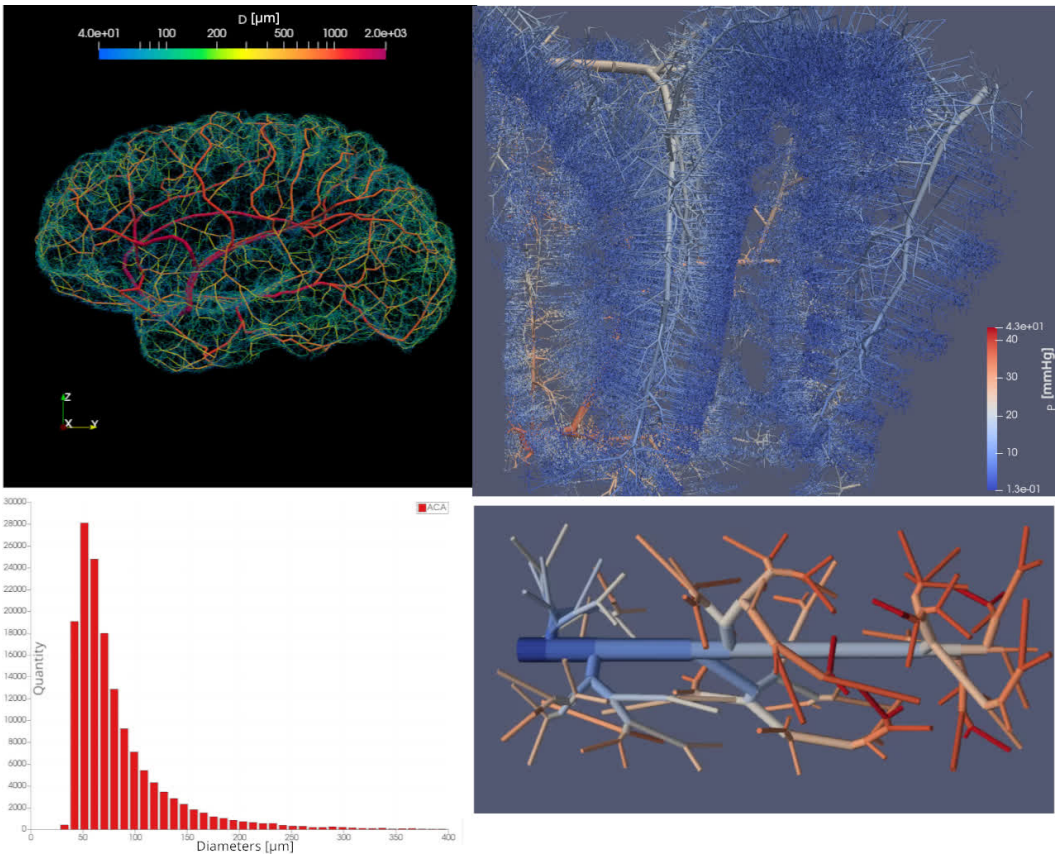

Figure 2. Top left panel: Full pial vascular network generated with the proposed PDCCO approach, colored by vessel diameter (log scale in μm, sagittal view). Top right panel: Vascular network with sub-trees generated for a section of the ACA territory, between the frontal and parietal lobes, sagittal view. Bottom left panel: The distribution of vessel diameters for the pial network of the ACA territory, in μm. The maximum diameter in the scale is 400 μm, and the other territories present similar distributions. Bottom right panel: Zoomed-in sample of a penetrating sub-tree, to be appended to each terminal vessel, blue colors denote segments closer to the surface, and red colors are segments deeper in the gray matter.

3 Results

Figure 2 illustrates the resulting vascular network for different regions and scales. The pial network is shown in the top left panel, where the color scale shows the variation of the vessel diameters along the pial surface. The top right panel shows the vascularization of the grey matter for a region between the frontal and parietal lobes, within the ACA territory. An example of a penetrating arteriole and its ramifications is shown in the bottom right panel, and the distribution of vessel diameters in the ACA territory for the pial network is displayed in the bottom left panel.

For the pial network, the first stage of generation reaches 4 000 terminals for all territories, and the second stage extends the network to 20 000 terminals. The parallel stage results in 116 977 terminal vessels distributed as follows: 32% ACA, 44% MCA, 24% PCA, and giving rise to over 230 000 penetrating vessels. Sub-tree networks, each featuring 100 segments, are appended to each penetrating arteriole, resulting in a network with over 23 million vascular segments. This vascularization procedure yields a network architecture which resembles the morphology results presented in Reina-De La Torre et al. [13] and Cassot et al. [20]. The number of segments reaches the proposed target of descending arterioles in the human brain and allows the generation of long and short penetrating vessels, as mentioned in Hartung et al. [3], by using different sub-tree lengths.

The vascularization was conducted for the power law exponent $\gamma = 3.0$, and the resulting penetrating arterioles's diameters range between 50 and 60 µm, in agreement with Duvernoy et al. [21]. The gray matter network, extending from the penetrating vessels, perfuses the deep human cortex regions with a static pressure distribution along vessels as shown in Fig. 3, following Gould et al. [5]. Median pressure in the gray matter drops from around 45 mmHg, (over the pial surface), down to 25 mmHg, at the end of the penetrating arborizations.

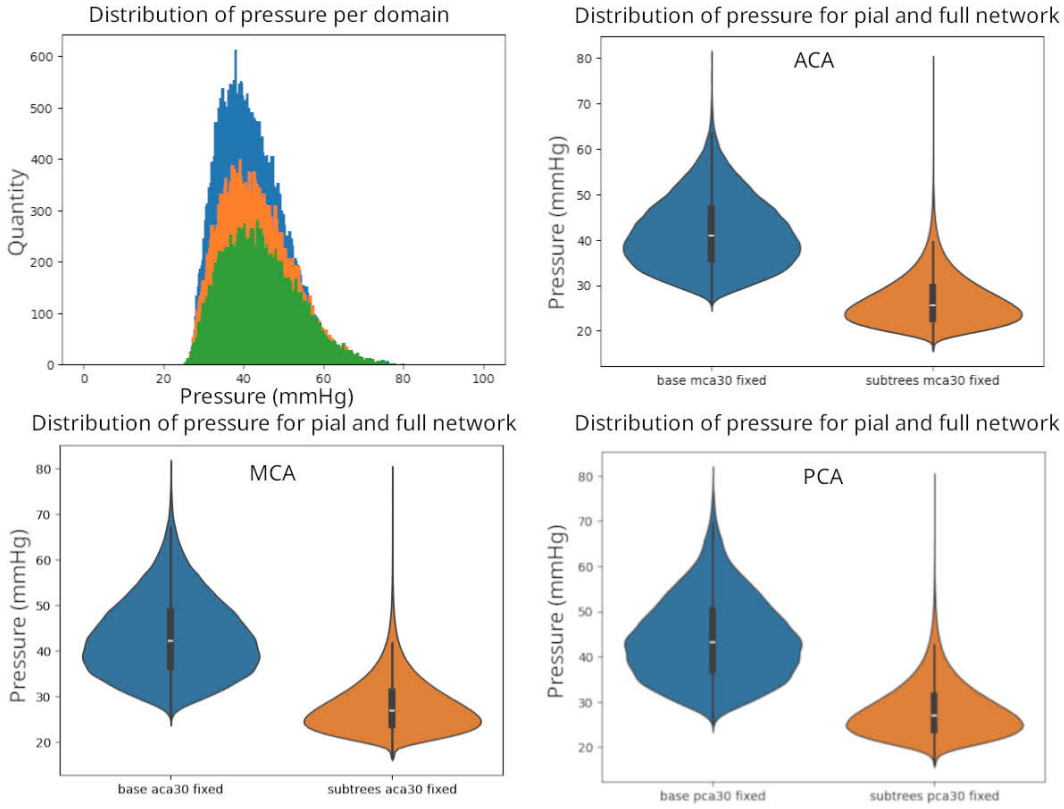

Figure 3. Top left panel: Distribution of pressure in the pial network before appending the penetrating arterioles, for the ACA (orange), MCA (blue) and PCA (green) territories. Top right panel: Distribution of pressure in vessels between pial (blue) and complete (orange) networks, for the ACA territory. Bottom left panel: For the MCA territory. Bottom right panel: For the PCA territory.

4 Conclusions

This work presented a novel strategy that enables the modeling of the cerebrovascular network in the human brain with an unprecedented level of detail and described a prototypical vascular network in the left hemisphere

down to the gray matter vascularization. One of the applications is the simulation of blood flow phenomena. For instance, by coupling these networks to the ADAN model, it is possible to simulate the blood flow in the entire cerebral hemisphere and assess the behavior of the blood pressure and flow rate across the cortical regions of the brain and deep into the grey matter.

This novel approach lays the foundation for the investigation of cerebrovascular hemodynamics and the connection with neural activity in both normal and abnormal conditions. In this regard, it also presents a novel tool to investigate blood flow phenomena and the relation to the onset and progress of neurodegenerative diseases, among other applications. Importantly, the proposed methodology can be applied to patient-specific settings, with data extracted from MRI, taking into account the inter-individual variability.

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