A cerebral circulation model for *in silico* clinical trials of ischaemic stroke

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1. Introduction

The INSIST consortium (www.insist-h2020.eu) set out to accelerate the advancement of stroke treatments by introducing *in silico* clinical trials which mitigate the need for resource-intensive experiments. The present work aims to contribute to INSIST by developing a cerebral circulation model that captures blood flow in the entire human brain. Progress in this field is complicated by the multi-scale nature of the flow, which stretches from small vessels with characteristic diameters of approximately 5 microns (capillaries) to large arteries with diameters of approximately 5 millimetres (e. g. internal carotid artery). Whereas it has become common practice to account for large arteries using one-dimensional network models, well-established methods are not available for a full description of the microcirculation. Therefore, this study focuses on the development of a cerebral microcirculation model and on bridging the gap between large arteries and the microcirculation.

Recently, cortical columns have been modelled by treating the capillary bed as a porous medium and representing the penetrating arterioles and venules as a one-dimensional vessel network [1]. This approach enables the resolution however of both blood flow in the capillary bed and the penetrating vessels in the entire human brain. On the other hand, connecting such models to large-scale artery networks is not trivial. In addition, capturing the flow in the corresponding large networks of arterioles and venules requires significant computational power. To overcome these difficulties, we propose a model environment relying on multiple scale separation and introduce a multi-scale, multi-compartment porous continuum model of the cerebral microcirculation.

2. Methods

A continuum model of the brain requires a sufficiently detailed geometrical description of the characteristic surface and volume regions. Here, a patient-specific volume mesh [2] is processed to obtain a tetrahedral mesh of the grey and white matters and to extract boundary regions. A slice of the volume regions is depicted in Figure 1(a). The bounding surface regions include (i) a transverse cut-plane of the brainstem (Γ^{BS}); (ii) surface of the ventricles bounding both grey and white matters (Γ^{V}); (iii) outer surface bounding the grey and white matters (Γ^{outer}) including cerebellum, brainstem and pial surfaces.

The governing equations describing multi-scale porous flow are derived using homogenisation [3]. The resulting partial differential equation system leads to a multi-compartment Darcy flow model which was previously employed for computer simulations of the coronary circulation [4]. In the case of three compartments, the Darcy pressure (p_i) of compartment i is governed by

$$\nabla \cdot (\boldsymbol{K}_i \cdot \nabla p_i) - \sum_{j=1}^{3} \beta_{i,j}(p_i - p_j) = 0 \text{ in } \Omega. \quad (1)$$

Here, $\boldsymbol{K}_i$ represents the permeability tensor of compartment i, $\beta_{i,j}$ are the elements of the coupling coefficient matrix, and Ω denotes the domain of interest. The arteriole, capillary, and venule compartments correspond to $i = 1, 2,$ and 3, respectively. Darcy velocities in each compartment can be computed as

$$\boldsymbol{u}_i = -\boldsymbol{K}_i \cdot \nabla p_i. \quad (2)$$

The permeability tensor of the capillaries in the cortex is isotropic and effectively diagonal [3]. The permeability tensors of the arteriole and venule compartments however are anisotropic because penetrating vessels in the cortex tend to be aligned normal to the pial surface. The permeability tensors of compartments 1 and 3 are determined for a cortical column using one-dimensional network models of statistically accurate penetrating trees coupled to a porous capillary compartment as described in [1]. In the associated coordinate system, the Cartesian coordinate direction x_1 is perpendicular to the pial surface. The permeability tensors of the grey matter in this reference coordinate system are estimated to be

$$\boldsymbol{K}_1^{\mathbf{ref}} = \begin{bmatrix} k_1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}; \qquad \boldsymbol{K}_2^{\mathbf{ref}} = \begin{bmatrix} k_2 & 0 & 0 \\ 0 & k_2 & 0 \\ 0 & 0 & k_2 \end{bmatrix}; \qquad \boldsymbol{K}_3^{\mathbf{ref}} = \begin{bmatrix} k_3 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

The necessary permeability values are $k_1 = 5 \times 10^{-3}$, $k_2 = 4.28 \times 10^{-4}$, and $k_3 = 1 \times 10^{-3}$ $\mathrm{mm^3\ s\ kg^{-1}}$. The structure of these tensors indicate that penetrating arterioles promote flow towards deeper cortical layers where blood is distributed by capillaries and then collected by penetrating venules.

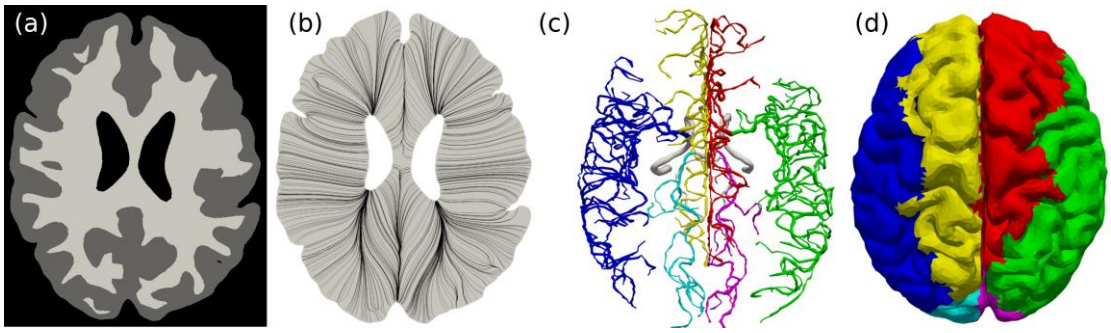

Figure 1 *Properties of the microcirculation model: (a) grey and white matter distribution along a sagittal plane; (b) visualisation of the projection of* $\boldsymbol{e}_{local}$ *based on lines tangential to the vector field; (c) large arteries of the one-dimensional arterial network model; (d) perfusion regions on the outer surface of the brain model mapped to the end-nodes of the arterial network model.*

Once the permeability tensors are determined in a reference coordinate system ($\boldsymbol{K}_i^{\mathrm{ref}}$) with a given reference direction ($\boldsymbol{e}_{\mathrm{ref}} = [1,0,0]$), the local permeability tensors are computed as $\boldsymbol{K}_i^{\mathrm{local}} = |\boldsymbol{R} \cdot \boldsymbol{K}_i^{\mathrm{ref}} \cdot \boldsymbol{R}^T|$. The transformation tensor $\boldsymbol{R}$ can be calculated from the local characteristic direction ($\boldsymbol{e}_{\mathrm{local}}$) and the reference direction ($\boldsymbol{e}_{\mathrm{ref}}$). The unit vector of the local characteristic direction is given as $\boldsymbol{e}_{\mathrm{local}} = |\nabla \mathrm{a}|$, where the a scalar field satisfies $\nabla^2 \mathrm{a} = 0$. The

boundary conditions are $\mathrm{a} = 1$ on Γ^{outer}, $\mathrm{a} = 0$ on Γ^{V}, and $\nabla \mathrm{a} \cdot \mathbf{n} = 0$ on Γ^{BS}, where $\mathbf{n}$ is the outward directed boundary normal. The $\boldsymbol{e}_{\mathrm{local}}$ vectors highlight the least resistant path from the outer surface to the ventricles as visualised in Figure 1(b). Beyond anisotropy, the permeability tensors are inhomogeneous because the domain of interest incorporates grey and white matters ($\Omega \in \Omega_G \cup \Omega_W$). It is estimated that the reference permeability in the white matter is one third of that in the grey matter ($\boldsymbol{K}_i^{\mathrm{white}} = \boldsymbol{K}_i^{\mathrm{ref}}/3$) because, on average, white matter has three times lower perfusion than grey matter.

Another key parameter of the model is the coupling coefficient matrix $\beta_{i,j}$. The developed model neglects anastomoses between arterioles and venules, therefore only the $\beta_{1,2} = \beta_{2,1}$ and $\beta_{2,3} = \beta_{3,2}$ elements are non-zero. In practice, this leads to a flow field which drives blood from the pial surface through the arterioles, then the capillaries and finally into the venules. Based on cortical column simulations [1], the coupling coefficients are estimated to be $\beta_{1,2} = 1.89 \times 10^{-3}$ and $\beta_{2,3} = 2.14 \times 10^{-3}$ mm s kg^{-1}.

Boundary conditions for the multi-compartment porous model are provided by a one-dimensional distributed parameter arterial network model. The large vessels of this arterial network model are shown in Figure 1(c). The end-nodes of the arterial network are mapped to the outer surface of the porous domain. Surface territories corresponding to the major cerebral arteries (XCA) are identified ($\Gamma^{\mathrm{outer}} \in \Gamma^{\mathrm{ACA}} \cup \Gamma^{\mathrm{MCA}} \cup \Gamma^{\mathrm{PCA}} \cup \ldots$) as shown in Figure 1(d). The volumetric flow rate of blood corresponding to each region is obtained from simulations with the one-dimensional arterial network model[1]. This method enables us to model occlusions of large vessels, and hence stroke events, by modifying the surface fluxes.

Firstly, Neumann boundary conditions $(\boldsymbol{K}_i \cdot \nabla p_i) \cdot \boldsymbol{n} = 0$ are prescribed representing no flow through the following boundaries: (i) brainstem section and on the ventricle surface of the arteriole and venule compartments (Γ_1^{BS}, Γ_1^{V} and Γ_3^{BS}, Γ_3^{V}); (ii) every boundary of the capillary compartment (Γ_2). Secondly, Neumann boundary conditions $(\boldsymbol{K}_i \cdot \nabla p_i) \cdot \boldsymbol{n} = Q_{XCA}/A_{XCA}$ representing prescribed volumetric flow rate through the surface are given on the outer surface of the arteriole compartment, where Q_{XCA} and A_{XCA} are the corresponding volumetric flow rates and surface region areas, respectively. Dirichlet boundary conditions are defined on the outer surface regions of the venule compartment representing venous pressure: $p_3 = 15$ mmHg on $\Gamma_3^{\mathrm{outer}}$.

3. Results and Discussion

The governing equations are discretised and solved numerically employing FEniCS [5], an open-source finite element platform. It was found that the piecewise polynomial trial function representing the pressure field should be at least second order to avoid unphysical oscillations on the baseline mesh including approximately 1 million elements. With a piecewise constant permeability tensor field, the velocity field is approximated as a piecewise linear function. For a state-of-the-art desktop with 6 cores (Intel Xeon E-2146G CPU) and the baseline mesh, the model can predict the velocity and the pressure fields in a few minutes.

[1] The details of the arterial network model are provided in another CompBioMed conference contribution by Padmos et al. (2019)

Figures 2(a) and (b) show the computed pressure and velocity fields in the capillary compartment for a healthy and an occluded scenario. The model provides sufficient information to estimate infarcted regions, for instance, based on a comparison of the healthy and occluded cases relying on the capillary velocity magnitude (u_2). The location and volume of the infarcted region estimated this way shows encouraging qualitative agreement with clinical data.

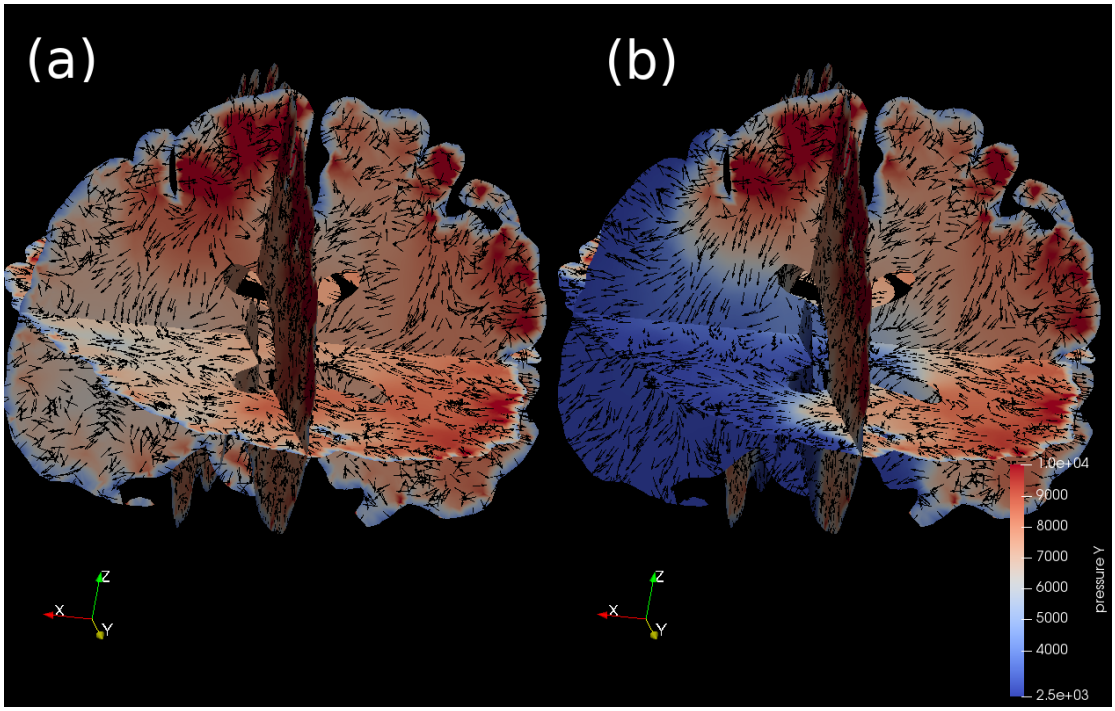

Figure 2 *Pressure [Pa] and velocity fields in the capillary compartment: (a) healthy scenario; (b) right middle cerebral artery occlusion.*

4. Conclusions

A computational framework is introduced to capture the effect of vessel occlusion on cerebral blood flow in the entire human brain. The model captures cerebral blood flow through three orders of magnitude of vessel diameter and provides suitable output for the development of an oxygen-based metabolism model that can predict the tissue response to vessel occlusion. Future development of the blood flow model will target (i) generalisation by introducing two-way coupling between the arterial network model and the microcirculation model, and (ii) addition of porous compartments for superficial vessels. Validation of the model against a large clinical database is in progress.

5. References

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