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Modelling cerebral blood flow and perfusion during acute ischaemic stroke

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Chapter 6

Conclusions and Outlook

The work in this thesis focuses on the modelling of cerebral blood flow and perfusion during acute ischaemic stroke. Chapter two introduced a model of cerebral blood flow and a one-way coupling algorithm to couple this pulsatile model to a tissue perfusion model. The pulsatility of blood flow, caused by the beating of the heart, is small at the point of coupling, i.e., at the pial surface. This justifies an approximation of the blood flow dynamics to the average flow rate and pressure across a heart beat.

The pulsatile blood flow model is replaced in chapter three with a steady state blood flow model. In addition, the coupling algorithm is updated to allow for bi-directional communication between the blood flow and tissue perfusion models. This two-way coupling captures the retro-grade flow distally of a thrombus, which significantly affects the pattern of hypoperfusion during a stroke, leading to smaller estimates of infarct volume.

One important aspect that has not been addressed in chapter two and three, is the collateral circulation. Chapter four therefore looks in detail at the effect of the leptomeningeal collateral circulation on cerebral blood flow. The steady state blood flow model, presented in chapter three, is extended with bifurcating trees that represent the missing vessels between the (previous) model outlets and the pial surface. In addition, the pial surface network is explicitly modelled including the variability of the collateral vessels. The model is able to reproduce the variability in collateral flow, in addition to two clinical measurements in

stroke patients: the time delay and pressure drop over the thrombus.

Chapter five builds on chapter four by including the modelling of permeable thrombi, model calibration and infarct volume estimations. The parameter that determines the variability of the collateral circulation is calibrated to clinical measurements of infarct volume. Based on the estimated thrombus permeability and the measured flow rates, the flow through a thrombus is unlikely to affect the infarcted tissue. In addition, the collateral circulation was concluded to be the most important aspect in determining infarct volume and its variability in the model. Approximating a thrombus as impermeable is therefore a valid approximation based on the amount of flow through it.

6.1 Outlook

The models developed in this thesis focus on modelling blood flow and tissue perfusion during acute ischaemic stroke. There are many other cerebral diseases that also result in altered cerebral blood flow, such as hypertension, haemorrhages, cerebral small vessel disease, intracranial artery calcification, Alzheimer's disease, and many others. It would be interesting to model these diseases using the same framework. Other organs than the brain can also be simulated using the same methods, especially if their tissue structure is similar to the brain. Organs with significantly different perfusion structures, e.g., not through a boundary layer or altogether different such as in the lungs, would require an update to the coupling algorithm to handle different source terms.

In the context of acute ischaemic stroke, there are several areas that can be explored in future work. The microcirculation, for instance, has been modelled as an anisotropic porous media with constant permeability in this thesis. Many important effects and behaviour of the tissue have been neglected. However, there are important effects to consider during and after a stroke. One such effect is cerebral oedema, a severe complication of acute ischaemic stroke [129]. Cerebral oedema is essentially the disruption of ion transport in the brain, which can cause (among other things) swelling of the brain [130]. Increased intracranial pressure due to swelling can cause, for instance, tissue to remain hypoperfused even after the thrombus is removed [131]. The toxic effects and

increased intracranial pressure caused by cerebral oedema are important effects to consider in modelling cerebral perfusion and tissue infarct formation.

Another effect is that of thrombus fragmentation. During thrombectomy, there is a chance that small fragments of the thrombus break off and occlude smaller downstream vessels [132]. These micro-emboli are small, tens of micrometers, but numerous [133]. There has been some work within INSIST on modelling the impact of these small emboli [134]. However, the combined effect of a few large emboli and a large number of micro-emboli on cerebral perfusion has not been investigated. Work is currently in progress on modelling micro-emboli and their effects on arterial blood flow and tissue perfusion.

One limitation that runs throughout this thesis is the lack of model validation. One reason for this is the difficulty of doing experiments on living humans. Some experimental animal data is available but such data raises questions of validity. In the future, this issue will be addressed with thorough validation using clinical data from AIS patients. Another issue is that of uncertainty quantification and sensitivity analysis. Understanding the uncertainty in the predictions of the model is critical to building confidence and a deeper understanding of the models. Sensitivity analysis helps to develop a better understanding of which model parameters are important for the uncertainty in the output. The models can then be refined by reducing the uncertainty of the most sensitive parameters. Uncertainty quantification and sensitivity analysis, as well as verification and validation, are necessary steps in building *in silico* trails. Capturing the variation in the patient population is an interesting next step in the development of computational (stroke) models.