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Modelling cerebral blood flow and perfusion during acute ischaemic stroke

Padmos, R.M.

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Chapter 1

Introduction

The cardiovascular system is a complex network of vessels, responsible for, among other things, supplying tissue with blood containing oxygen, glucose, and other nutrients. However, the transport of blood through a vessel can become blocked, e.g. due to thrombus embolisation. This reduces blood flow and can lead to tissue damage and ultimately tissue death. The blockages can happen gradually, for example, by the buildup of plaques (atherosclerosis), but they can also occur suddenly. Blood clots can form anywhere in the body, for instance, in the veins, and produce no symptoms [1]. A clot can become dislodged, travel through the cardiovascular system, and block flow in a major organ. These blockages cause tissue death when there is no redundant blood supply. For instance, a blockage in the coronary arteries could lead to a heart attack, in the lungs to an pulmonary embolism, and in the brain to an acute ischaemic stroke (AIS).

Every year, millions of people suffer a stroke, often resulting in disability or death [2, 3]. Stroke is currently the second leading cause of death worldwide [4]. Stroke survivors are often chronically disabled and may require lifelong care. Understanding how a stroke affects the brain and (long term) patient outcome can help develop and improve treatments for stroke. Time is one of the most important factors in patient outcome [5, 6]. As long as the vessel is blocked, blood flow cannot reach the cerebral tissue, thereby leading to cell death. The quicker blood flow is restored, the less severe the tissue damage.

This thesis addresses modelling (arterial) blood flow to the brain and perfusion of brain tissue during AIS. Understanding how blood flow and tissue perfusion are affected by a clot will contribute to the development and improvement of treatment for AIS. The models proposed in this thesis are put to use in the context of *in silico* trials for AIS, and can thus contribute to improving treatment options for stroke patients.

1.1 In Silico Trials

The work presented in this thesis is part of "In silico clinical trials for the treatment of acute ischaemic stroke", INSIST, a collaborative multidisciplinary effort (Appendix A: INSIST Investigators, insist-h2020.eu). The aim of the INSIST consortium is to develop computational tools that can aid in the development and improvement of treatment for AIS. Medical tools and treatments are often tested in large clinical trials. However, these trials are time-consuming, expensive, prone to failure, and other issues [7]. The INSIST consortium aims to reduce, refine, and (partially) replace these traditional clinical trials with *in silico* trials, using computational modelling and simulations. Many of the modelling choices made in this thesis are made with the idea of setting up *in silico* stroke trials. The models presented in this thesis play an important role in setting up an *in silico* stroke trial by estimating arterial blood flow and tissue perfusion during an acute ischaemic stroke.

In silico trials (IST) are patient-specific simulations on cohorts of virtual patients to improve the development and evaluation of medical devices, drugs and treatment. The patient in this context is generally a set of parameters and other data that is used in a computational model. *In silico* trials can overcome some of the limitations and lower the cost of clinical trials. IST are closely related to computational biomedicine and similar to personalised medicine. Personalised medicine looks at a real patient and tries to predict treatment or outcome. IST try to do the same but rather on a population level, similar to traditional (clinical) trials. The goal is to predict the efficacy and efficiency of a treatment, drug or device. As such, they are similar to traditional clinical trials where the testing happens on animals or humans. The models presented

here are incorporated into the INSIST framework to simulate tissue perfusion in populations of virtual AIS patients [8].

1.2 Cardiovascular Anatomy

The human circulatory system is a closed-loop system, blood is confined to the vessels and pumped around by the heart. We can regard the heart as the start of the circulatory system. The vessels originating from the heart, up to and including the brain are covered here. The heart pumps oxygenated blood into the systemic circulation through the aorta. From there, the aorta bifurcates and distributes blood throughout the human body. Blood reaches the brain through the internal carotid and vertebral arteries. The vertebral arteries merge into the basilar artery. The basilar artery and the internal carotid arteries connect to the circle of Willis. Figure 1.1 shows the major cerebral vessels. Arguably the most important part of the cerebral vasculature is the circle of Willis (CoW). This is an arrangement of vessels, located below the brain at around eye-level, forming a circle and distributing incoming blood flow from the heart to the rest of the brain.

There are multiple configurations of the CoW throughout the population. Estimates of the CoW put the complete variant at about 50% of the population [9, 10]. There are seven vessels of the CoW that can be absent, or display hypoplasia. These are the posterior communicating arteries (PcoA), anterior communicating artery (AcoA), precommunicating segment of the posterior cerebral arteries (P1 PCA), and the precommunicating segment of anterior cerebral arteries (A1 ACA). These can occur in many combinations, with as many as 47 unique variants found [11]. The most common variants are (labelled by missing vessels) are left PCoA (30%), left PCoA and ACoA (5%), Left P1 PCA (8%), and right A1 ACA (5%) [9, 10]. In general, having a different CoW variant does not affect blood circulation to the brain. The CoW variant plays an important role when a blood vessel becomes blocked.

During an AIS, the collateral circulation becomes important. The collateral circulation are alternative pathways for blood that are used when the primary circulatory pathway is blocked [12–14]. The primary collateral circu-

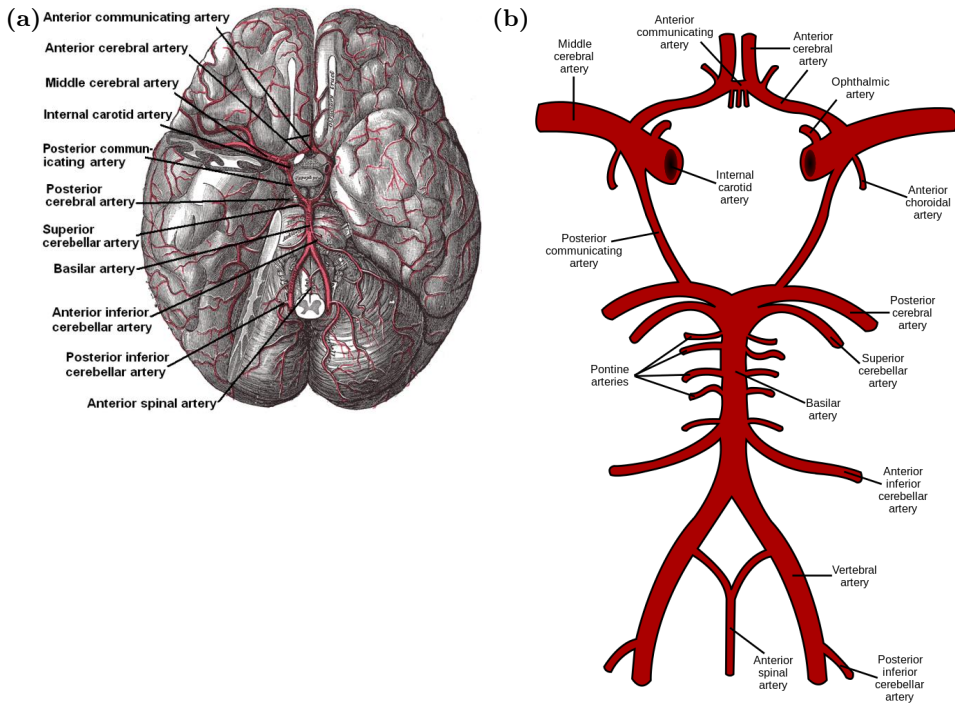


Figure 1.1: (a) Vasculature of the brain, overlaid on the brain. View point from below. The circle of Willis is the central ring structure in the middle of the image. (b) Schematic drawing of the main arteries of the brain. Blood enters the brain through the internal carotid and vertebral arteries. The vertebral arteries merge into the basilar artery which merges with the internal carotid arteries into the circle of Willis. Copyright: public domain, source: Wikipedia.

lation for the brain is the CoW. Secondary collateral pathways include the leptomeningeal collateral vessels, the external cerebral vessels, and the venous collateral circulation [13]. The collateral circulation is highly variable between individuals [15, 16]. Having better collateral circulation is associated with improved outcome after AIS [16–19]. The collateral circulation supplies blood to the tissue at risk of death, thereby extending the time until infarction. In essence, the collateral circulation extends the treatment window sufficiently long that treatment has a higher chance of being successful [6, 18]. Without some remaining flow to the tissue, cell death would occur within minutes and treatment would have no effect [20, 21].

On the outer surface of the brain, between the grey matter and the cerebrospinal fluid, lies the pial surface vessel network containing the leptomeningeal collateral vessels. This network is interconnected and provides redundancy, similar to the CoW [12, 14, 22]. The pial vessel network distributes blood to the penetrating arteries. These arteries penetrate the cerebral tissue at close to perpendicular angles to the surface [23]. The penetrating arteries connect to the capillary bed, where the transfer of oxygen and other nutrients to cells generally occurs. Blood flows from the capillary bed back to the heart through the veins, completing the loop of the systemic circulation. Most of the vessels of the circulation are part of the capillary bed. These vessels are tiny, about the size of a single blood cell, around $10\ \mu\text{m}$ in diameter.

1.3 Thesis Outline

Modelling cerebral blood flow and perfusion after AIS requires the coupling of models on multiple scales. Large vessels can be modelled as simple elastic tubes while the microcirculation is often modelled as a porous medium. Various effects that affect patient outcome also have to be included to accurately make predictions of patient outcome. This thesis focuses on the development of cerebral blood flow models, their coupling, and the modelling of various effects that affect patient outcome after an AIS.

Chapter two presents a one-dimensional pulsatile blood flow model for the cerebral circulation, and a method to couple this model to a three-dimensional

cerebral tissue perfusion model. The coupling occurs at the surface boundary of the tissue perfusion model by estimating perfusion territories. The coupling is one-directional; both models are separate systems with the surface boundary conditions of the tissue perfusion model set by the one-dimensional blood flow model. This coupling method is able to accurately estimate perfusion territories. However, the tissue perfusion model cannot affect the blood flow model in this setup. Finally, blood flow can be approximated as steady state flow to reduce the cost of organ-scale simulations.

This one-directional coupling does not accurately capture the perfusion pattern during a stroke and overestimates the perfusion drop. Chapter three presents a method for two-way coupling of a one-dimensional steady state blood flow model and a three-dimensional cerebral tissue perfusion model. The two-way coupling occurs through the pial surface, where the pressure drop between the models is captured by a coupling resistance. The models are allowed to communicate directly. Two-way coupling enables the model to capture changes in cerebral tissue perfusion, caused by retro-grade flow between the models during an AIS. The two-way coupled model is used to simulate arterial blood flow and tissue perfusion during an AIS. Infarct volume is estimated by setting a threshold on the perfusion change.

Chapter four extends the one-dimensional blood flow model by adding an explicit model of the leptomeningeal collaterals. The collateral circulation provides residual blood flow to tissue at risk during a stroke and significantly affects infarct volume. The extent of the collateral circulation is varied by defining a collateral vessel probability. Blood flow and pressure are simulated using a one-dimensional steady state blood flow model. Contrast advection is modelled and the effect of collateral flow during an AIS is investigated. Model results are compared to dynamic computed tomography angiography (CTA) measurements performed in AIS patients. The model is able to reproduce the measurements in these patients. The leptomeningeal collateral vessels are able to provide significant blood flow to cerebral tissue at risk of infarction during AIS.

Chapter five investigates the effect of permeable clots on blood flow during

AIS. Permeable clots are modeled using Darcy's law for porous media. The effect of a porous clot on cerebral flow were investigated. In addition, the collateral circulation is calibrated to match the collateral flow grading used in the assessment of AIS patients.

Finally, chapter six concludes the thesis, covers some of the applications, and discusses possible future directions of the work presented in the previous chapters.