Unboxing the brain

Summary

EARLY diagnosis and monitoring of brain function is crucial to provide adequate healthcare to patients suffering from cerebral pathologies and injuries. Unfortunately, most existing monitoring methods are either invasive, not accurate enough, or limited by the restricted accessibility of the brain and, hence, need to be improved. Moreover, there are still many cerebral pathologies that cannot be monitored because the relevant metrics can simply not be measured. Technologies such as computer algorithms might be used to improve the accuracy of non-invasive assessments methods, whereas computational models that mimic physiological processes of the human body might be used to estimate clinical metrics by using and combining information that can be measured at other more accessible locations in the body.

In this thesis we have developed two new technologies to improve the non-invasive assessment of two different cerebral pathologies. In **Part I** of this thesis (Chapters 2 and 3) we address the non-invasive assessment of elevated intracranial pressure (ICP) by means of the optic nerve sheath diameter (ONSD) and develop an automated algorithm to obtain operator-independent metrics, whereas in **Part II** (Chapters 4 and 5) we focus on improving the estimation of *patient-specific* boundary conditions for cerebral aneurysm rupture risk models by using a 1D pulse wave propagation model (PWPM) to simulate pressure and flow waveforms that can often not be measured.

Non-invasive ICP assessment using the ONSD

Intracranial pressure assessment plays a crucial role in monitoring patients suffering from traumatic brain injury. Since existing ICP measurement techniques are very invasive, other ways to estimate ICP have been explored. The diameter of the optic nerve sheath (ONS) has proven to be a promising surrogate marker for ICP because the optic nerve sheath expands when ICP increases[1, 2] and its diameter can be measured from B-mode ultrasound images obtained by means of transorbital insonation. However, ONSD cut-off values for the detection of elevated ICP vary between studies[3–5], which hampers its clinical applicability.

In **Chapter 2** we performed a review of the current literature on manual ONSD assessment methodologies to identify differences in ONSD assessment methodologies that could potentially cause the discrepancies in ONSD threshold values. Our review not only showed differences in the characteristic appearances of the B-mode ultrasound images, but also in the placement of the ultrasound markers used to denote the ONSD. Most importantly, the differences in ultrasound marker

placement resulted in different ONSD values that also had varying sensitivities to changes in ICP. The chapter is concluded with a set of guidelines as a first step towards standardization of manual ONSD assessment to reduce the variations in ONSD values due to methodological differences

In **Chapter 3** we took the standardization of ONSD assessment a step further by developing a fully automatic algorithm that is capable of segmenting the ONSD from B-mode ultrasound images. We demonstrated that the algorithm not only removed the intra- and interobserver variability associated with manual ONSD assessment, but also resulted in ONSD values that were comparable to the manual ONSD assessment performed by two experts. Using the presented algorithm, the variation within ONSD values decreases, which in turn, reduces the discrepancies within the ONSD threshold values and might lead to an improved stratification between patients with normal and elevated ICP.

Estimation of cerebral boundary conditions

The risk of aneurysm rupture has to be carefully balanced against the risk of complications associated with interventions. Computational fluid dynamics (CFD) models have proven to be capable of simulating rupture risk indices that can aid in clinical decision-making[6]. However, the accuracy of rupture risk indices is highly dependent on the boundary conditions (BCs) applied to the CFD simulations. Unfortunately, it is often not possible to measure *patient-specific* BCs within the clinical setting. As an alternative, BCs can be simulated using 1D pulse wave propagation models[7]. However, simulated BCs and corresponding rupture risk indices most likely depend on the input parameters and model assumptions of the PWPM. Therefore, the effects of the model input parameters and model assumptions on the BCs and rupture risk indices have to be investigated.

In **Chapter 4** we investigated the influence of inter-subject variations in our PWPM input parameters on simulated BCs and corresponding rupture risk indices that were derived from 3D cerebral aneurysm simulations. Our results showed that the inter-subject variations of the input parameters can lead to uncertainties within the rupture risk indices that are of the same order as the difference between ruptured and non-ruptured aneurysms and might therefore lead to misdiagnoses. These results highlight the importance of accurate and *patient-specific* BCs and the development of frameworks that can simulate these *patient-specific* BCs.

In **Chapter 5** we investigated the effect of the often discussed static pressure-coupling assumption at bifurcations[8] on our pressure and flow waveforms simulated with the PWPM. Although our results showed that changing the pressure-coupling hardly altered the 1D pressure and flow waveforms, it might be that pressure-coupling becomes important when the PWPM is adjusted to match *patient-specific* hemodynamic situations. Using the framework presented in Chapters 4 and 5 the effects of model assumptions and model input parameters on (possible) clinical metrics can be evaluated and used to optimize and individualize computer models that mimic physiological processes of the human body.

This thesis is concluded with a General Discussion (**Chapter 6**) where the results and main findings of the different chapters are put into a broader perspective. Moreover, the limitations of our research are discussed and we elaborate on how new technologies can contribute to the future of *patient-specific* clinical monitoring and decision-making.