Assessment of Intracranial Dynamics Using MRI

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Für Maria und Walter, Sandra und Thomas und meine Freunde, die mit ihrer immerwährenden Unterstützung diese Dissertation ermöglicht haben.
Summary

The brain is one of the most integrated organs of the human body. Still there are plenty of secrets to be discovered.

With the advent of magnetic resonance imaging (MRI) a new era of brain research was heralded. Elucidating the insight of the skull noninvasively and thus under normal conditions became possible. First investigations concentrated on the high contrast between white and grey matter allowing detailed anatomic brain imaging. The unique property of MRI to sensitize the image to different functional contrasts has started to shed light on various brain functions. Next to the detection of active brain regions during different mental tasks, the detection of brain fibers and consequently of connections between different brain areas are prominent examples of functional imaging in the central nervous system. Additionally, perfusion, blood flow, and tissue motion detection with MRI show great potential to become prominent research and diagnostic tools applicable to central nervous system.

Dynamically the brain can be separated in four compartments: arterial blood, venous blood, brain tissue and the cerebrospinal fluid. The cerebrospinal fluid, which is also called liquor, is a water-like fluid that on one hand surrounds the brain hemispheres and on the other hand fills the ventricular system. The ventricular system consists of connected cavities in the brain. The entire liquor volume is replaced about five times a day. It is thought to be primarily produced in the ventricles and mainly absorbed in the subarachnoidal space and brain parenchyma. This hypothesis is built on the fact that a bulk flow between the ventricular system and the subarachnoidal space can be observed.

Hypotheses of the pathogenesis of diseases associated with abnormal cerebrospinal flow dynamics often concentrate only on the bulk flow of the cerebrospinal fluid. In recent years the superimposed pulsatile flow attracts more and more attention. Pulsatility which is found in all four compartments of the brain is mainly caused by cardiac pulsation. The blood pressure pulse wave enters the brain via the arterial blood flow. In the cranium the pulse wave is damped by the cerebrospinal fluid, venous blood and brain tissue.

In order to gain further knowledge about the dynamics in the ventricular system, detailed models of the ventricular system and flow simulations including pulsatile information are needed. Characterization of subject-specific flow patterns is highly desired. Therefore, accurate boundary conditions incorporating cerebrospinal pulsatile fluid flow and pulsatile brain motion at the geometric boundaries of the domain in question are necessary.

During this thesis magnetic resonance imaging methods allowing accurate acquisition of these boundary conditions were developed. The developed measurement protocols noninvasively assess intracranial dynamics under normal in-vivo conditions. The methods presented are designed for measuring pulsatile cerebrospinal fluid flow and pulsatile brain motion.

Velocity mapping in the aqueduct was successfully accomplished with an in-plane resolution of 0.6 x 0.6 mm² and a temporal resolution of 26 ms.

Two methods are introduced for brain motion measurements and both imaging methods were evaluated in healthy volunteers. The data reveal a decrease of feet-head displacement towards the periphery and a strong damping of caudal brain motion from the brain stem towards the skull.

Eventually, the MRI data were used to build up CSF flow simulations in the 3rd ventricle. These simulations can now serve as a tool, which can be used in manifold ways to improve existing treatments, like CSF shunting. This tool can play an important role in gaining basic knowledge on flow and transport phenomena of nutrients and drugs in the ventricular system. It can be used to develop new
treatments and new devices, e.g. devices reacting on time-dependent physiological variations. Thus, medical devices and mixing effects, important for drug delivery, can be checked subject-specifically before the actual application to the patient.

Zusammenfassung


Hypothesen über die Entstehung von Krankheiten, die mit veränderten dynamischen Eigenschaften des Liquorflusses zusammenhängen, betrachten meist nur den Nettofluss des Liquors.

Um mehr Wissen über diese Dynamik im Gehirn zu sammeln sind neue, detaillierte Modelle des Ventrikelsystems und Flussimulationen, welche auch die Pulsatilität miteinbeziehen, notwendig. Für genaue Aussagen ist aber auch die Charakterisierung von subjekt-spezifischem Flussverhalten erwünscht. Dies ist wiederum nur mit genauen Randbedingungen, die die Pulsatilität des Flusses und der Hirnbewegung integrieren, möglich.


Im Aquädukt wurden Geschwindigkeitsmessungen längs der Aquäduktachse mit einer räumlichen Auflösung von 0.6 x 0.6 mm² und einer zeitlichen Auflösung von 26 ms durchgeführt.

Für die Gehirnbewegung wurden zwei Methoden entwickelt und an gesunden Probanden evaluiert. Die Dämpfung der Pulswelle vom Hirnstamm zum Schädel hin wird vor allem in der kraniokaudalen Komponente der Hirnbewegung klar sichtbar.

Chapter 1

1 Introduction

The human skull contains brain parenchyma with its nerve cells and two different fluids, blood and the water-like cerebrospinal fluid (CSF), often simply called liquor (Figure 1.1). Manifold functions are attributed to the cerebrospinal fluid. ‘Chemical’ functions range from nutrition of the brain to absorption of brain metabolism waste products. ‘Mechanically’, liquor reduces the weight of the brain due to buoyancy, and serves as a pressure regulator. Additionally the CSF prevents the brain from mechanical damages by surrounding the brain and thereby serving as a cushion. Different pathologies like hydrocephalus occur, when any of these mechanisms break down. Detailed knowledge on intracranial dynamics is on demand to improve diagnostic and therapeutic tools.

Traditional descriptions of intracranial dynamics are limited to the net flow of blood and cerebrospinal fluid (CSF) in the cranium. Current magnetic resonance imaging (MRI) data from flow-studies stress that the flow of blood and CSF in the cranium is highly pulsatile. These pulsatile dynamics can be simulated on an analog electrical circuit. Such pulsation models can be used to investigate on global changes of intracranial dynamics. More detailed view on these dynamics is highly desired. Therefore, three-dimensional modeling of the intracranial dynamics using real geometries becomes necessary.

This thesis is part of an extended project on three-dimensional modeling of the ventricular system and the motion of CSF for gaining deeper insight and understanding of brain physiology and intracranial dynamics. In this work new methods based on MRI are developed for the assessment of boundary conditions for such a three-dimensional modeling. New physiological results are presented which may serve as the basis for experimental verification of the outcome of flow simulations in vitro and in vivo.

Figure 1.1: The ventricular system embedded in brain parenchyma (Based on Putz/Pabst: Sobotta, Atlas der Anatomie des Menschen, 20th ed. © Elsevier GmbH, Urban & Fischer Verlag.).
1.1 Background

First mention of CSF dates back to 2600 BC and is accredited to Imothes, an Egyptian architect, priest and physician. It took another 1600 years -until about 300 BC- the inner cavities were identified from Herophilus of Chalcedon. First geometric descriptions of the ventricular system are accounted to Galen (130-200 AD), a Roman physician (1.1). The human skull as a whole was finally described by Leonardo da Vinci in 1504 (Figure 1.2). The schemata contained detailed ventricular space descriptions as Leonardo da Vinci used wax casts to extract the ventricular geometries. These casts were sufficient for the big cavities but they were too soft for determining the connections and in- and outlets reliably.

In the 17th century Franciscus Sylvius could extract the cerebral aqueduct, also named aqueduct of Sylvius (1.3). Alexander Monroe II added the foramina between the lateral ventricles and the third ventricle (1.4). The anterior outflow at the fourth ventricle were identified from Francois Magendie and thus called foramina of Magendie (1.5). The two small lateral foramina were first identified by Albrecht von Haller, a Swiss anatomist and physiologist in 1749 (1.6), but detail description was published more then 100 years later, 1855, by Hubert von Luschka, after whom the outflows are named (1.7). In the early twentieth century air filled ventricular systems were imaged with x-rays to get a more precise anatomical view of the ventricles.

The advent of anatomical magnetic resonance imaging (MRI) brain scans revealed details of the actual in-vivo shape of the ventricular cavities and the subarachnoidal space. In the 20th century ventriculostomy, radionuclide cisternography and functional magnetic resonance imaging (MRI) revealed basic physiological knowledge on the flow dynamics of the ventricular system.

1.2 Physiology

The whole subarachnoidal space contains about 150 ml CSF, whereas about 1/6 of the liquor is within the ventricles and the major part surrounds the spinal cord and the two brain hemispheres. The CSF behaves like a Newtonian fluid with a viscosity of about 0.6 mPas (37°C). About 500-900ml are produced a day by the choroid plexus, mainly in the lateral and 4th ventricles. In the choroid plexus liquor is derived from blood plasma. CSF contains a few proteins, potassium sugar, chloride and sodium and sometimes blood cells.

Unlike the cardiovascular system, there is no dedicated pump, such as the heart, that directly drives the CSF flow. The cerebrospinal fluid is propelled in a pulsatile manner, primarily due to brain motion, which is
caused by the expansion and contraction of cerebral blood vessels due to the pulse pressure wave.

Superimposed on this motion is flow generated by the secretion of CSF by the choroid plexus in the ventricles at the center of the brain and cerebrospinal fluid absorption, predominantly at the arachnoid villi in the subarachnoid space that surrounds the brain (1.8). Additional drainage into the blood-stream is purported to occur through the cerebral extracellular space (1.9). In the healthy brain the same amount is reabsorbed and drained into the big brain veins. The detailed pathway from CSF to the big veins is still a question of ongoing research. During the 1990’s many studies focused on the nature of cerebrospinal fluid flow in the ventricles, as earlier studies indicated bulk and superpositioned pulsatile flow. Dan Greitz presented a comprehensive work (1.10) in 1993 where he had used MRI to measure temporally resolved CSF flow and blood flow in the brain feeding arteries and draining. Additionally, brain parenchyma displacement was detected and evaluated for several different brain regions.

However, there is also an internal, short term pressure regulating function attributed to the cerebrospinal fluid. With every heart beat the blood volume increases as the pulse pressure wave reaches the cranium. The arterial expansion during systole can bypass the brain via the CSF, as the arteries pass down their pressure wave directly to the intracranial CSF. From the intracranial CSF space the pressure wave moves on to the veins in the subarachnoidal space and to the compliant spinal canal through the foramen magnum. Consequently, the capillary bed is affected only very little from the pulse pressure wave (1.9, Figure 1.3).

1.3 Pathology

Due to the manifold functions of CSF in the central nervous system (CNS) there is hardly any pathology of the brain which is not somehow related to abnormalities in the chemical composition of the fluid itself and/or impaired fluid dynamics of the CSF system. Diseases like
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multiple sclerosis, Alzheimer’s disease and Parkinson’s disease are often associated with dilated ventricles. However, under these conditions the CSF system changes are supposed to be only a secondary effect. Examples for diseases in which changes of the ventricular system play a central role are meningitis, Chiari malformation syringomyelia and the most prominent, hydrocephalus. The latter is described more detailed in chapter 1.3.1. In meningitis the pathogen either of bacterial, viral, fungal or other any other origin invades the subarachnoidal space and multiplies in the CSF. As a consequence, the meninges swell due to the infection. The mortality rate of bacterial meningitis, the most dangerous type of meningitis, is 5% to 25% if adequate treatment is initiated immediately. Neurological impairment of varying degrees is common in the surviving patients. The pathology named Chiari malformation describes caudal parts of the cerebellum and/or the medulla oblongata reaching into the spinal canal. This wrongly located brain tissue on the one hand exerts pressure on the spinal cord and the affected brain tissue and on the other hand disrupts the cerebrospinal fluid flow. Patients usually suffer from severe headache and may have impairment of the senses as well as balance problems. In some patients Chiari malformation also progresses and develops syringomyelia. Syringomyelia describes the presence of pathological fluid-filled cavities (syringes) within the spinal cord (1.11).

1.3.1 Hydrocephalus

Hydrocephalus is a pathologic condition with an imbalance between CSF production and absorption. Mostly, this impairment is caused by reduced absorption. New theories suggest this reduced absorption to be caused by decreased intracranial compliance (1.9). This type of hydrocephalus is called ‘obstructive’ as an obstruction in the CSF pathways hinders the cerebrospinal fluid from being absorbed. Two subclasses, the communicating and non-communicating hydrocephalus are defined. The latter one shows a blockage of the CSF pathway from the ventricles to the subarachnoidal space (SAS), often by a stenosis of the aqueduct of Sylvius, which can be caused by a tumor. Communicating hydrocephalus shows no blockage of flow between ventricular space and SAS, but still suffers from reduced absorption.

An increasing number of elderly people suffers from normal pressure hydrocephalus (NPH), a subtype of communicating hydrocephalus, where the cerebrospinal fluid pressure stays close to the normal values (1.12), although the ventricles are dilated. To date there is no common sense on the cause of the imbalance between production and absorption in NPH.

Some theoretical models try to explain how NPH occurs (1.13-1.18). Levine gives a possible explanation by suggesting that due to dilation, the ventricle walls allow for passage of cerebrospinal fluid into the parenchyma where the CSF is efficiently absorbed (1.18).

1.4 Motivation

In 2006 Bergsneider M, Egnor M, et al phrase ten basic questions on ‘What we don’t (but should) know about hydrocephalus’ (1.19). Amongst those questions are basic ones like ‘How do we define hydrocephalus?’, ‘How is CSF absorbed normally and what are the causes of CSF malabsorption in hydrocephalus?’, or ‘What causes NPH?’. The article illustrates very clearly, that, to date, there is no well-defined view on the pathologic dynamics of CSF in hydrocephalus patients at all. Studying brain dynamics in detail not only becomes helpful for a better understanding of brain physiology in diseases directly or indirectly related to these dynamics (chapter 1.3) but is needed to build up detailed knowledge on intracranial dynamics in the healthy brain.

Even for healthy subjects it is not known, to date, how much of the pulsatility of the blood pressure wave is transferred from the big
arteries via CSF to the veins and how much is transferred via brain tissue itself by pulsatile brain motion expansion (chapter 1.2).

In the 18th century, Monro published the first mathematical description of the CSF system (1.4). His single compartment lumped parameter model was extended throughout the years by other researchers in order to better capture the pressure dynamics of the CSF and the volume dynamics of its cerebral compartments. Sivaloganathan et al. give a detailed review of such lumped parameter models (1.20). The desire to better understand and treat disorders of the CSF space, such as hydrocephalus, has introduced novel models based on computational fluid dynamics (CFD) simulations and numerical structural mechanics.

The advent of magnetic resonance imaging of dynamic processes accomplishes developments in simulations. It is a powerful tool to provide accurate dynamic models describing intracranial dynamics, as presented in this thesis.

1.5. Combining MRI and Computational Fluid Dynamics (CFD)

Although significant research effort has been undertaken (1.8-1.10, 1.21-1.30) on assessing brain dynamics, there is relatively little information available on the actual dynamics of brain tissue itself and the adjacent ventricular space containing cerebrospinal fluid. With the tremendous growth of computational power the three-dimensional simulation of the CSF system becomes feasible (1.31-1.32).

1.5.1 Modeling Approach

The sharp rise of computer power and the fall of hardware costs over the last decade, allows building these models on real, albeit simplified anatomical geometries (1.20, 1.34-1.35). As opposed to lumped parameter models, these novel representations yield the spatial distribution of CSF pressure and velocity.

In order to accurately capture the widest possible range of effects of the domain geometry on the CSF flow, in-vivo brain anatomy data is indispensable. This data can be acquired using MRI. Fin et al. are currently, to the best of our knowledge, the only group to have published a three-dimensional CFD model of a part of the intracranial CSF system (the aqueduct of Sylvius) based on MRI anatomy scans. They showed that a domain generated from anatomic MRI scans which capture the geometry of ventricular cavities, can serve as a base for CFD calculations (1.36). Using the methods introduced above, CSF flow and the ventricular wall motion can be determined and then additionally introduced to such simulations as boundary conditions. A combination of CFD and magnetic resonance imaging (MRI) applied on brain dynamics might give further insight into the dynamics not directly accessible with any imaging modality (Figure 1.4).

Assessing the real, subject-specific geometry of a cerebral ventricular system by anatomic MRI scans allows the creation of a three-dimensional grid for individual subjects. The boundaries of such a grid are the openings of the ventricular space and the ventricular walls. These walls are simply formed by the pulsating brain tissue in the proximity of the ventricular spaces. Thus, the necessary dynamic boundary conditions for three-dimensional simulations of the flow characteristics within the ventricular space are CSF flow at the open domain boundaries and spatiotemporally well resolved ventricular wall motion at the remaining domain boarders.
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With improved boundary conditions the combination of MRI data with computational fluid dynamics becomes a promising strategy for investigations on brain dynamics in healthy and diseased subjects. Ideally, such simulations can then serve as a tool, which can on one hand be used to improve existing treatments, like CSF shunting. On the other hand, such a tool facilitates investigations of new treatments and new devices, e.g. devices reacting on time-dependent physiological variations. Additionally, general dynamic effects, such as mixing effects, important for drug delivery, can be investigated before the actual drug administration to the patient.

As the accuracy of CFD results highly depends on the quality of the boundary conditions it’s based on, the measured data have to be as accurate as possible in order to gain valuable information from the simulations run on the models constructed from anatomical magnetic resonance images.

**1.5.2 Available Techniques**

CSF flow can be examined with ventriculostomy, radionuclide cisternography or functional magnetic resonance imaging. Ventriculostomy is an invasive method, where a catheter is introduced through the scull and brain parenchyma to the ventricular system, mostly entering through the third ventricle. The inside of the ventricles can then be imaged with micro cameras. For radionuclide cisternography radioactive tracers are injected into the CSF and the radioactive particles can be followed throughout the ventricular system.

Nowadays MRI is often used for measuring CSF flow. During the last two decades motion sensitive MRI methods have become a very useful tool for measuring CSF flow noninvasively (1.37). Fast Spin-Echo T2-weighted imaging, tagging and cine phase contrast are the most prominent sequences used for CSF flow measurements.

Mass flow of the ventricular space can be assessed in the aqueduct of Sylvius, where laminar flow is expected. Connor et al (1.37) found cine phase contrast to be the method of choice for aqueductal flow measurements.

For investigating brain motion, ultra-sound can only be used after opening the skull during examination. To our knowledge there is only MRI capable to capture detailed pulsatile brain motion under normal in-vivo conditions. Brain tissue velocities have already been investigated with two dimensional phase-contrast methods (1.8, 1.22,
1.25, 1.26, 1.28, 1.39-1.40), which is similar to measuring CSF flow. Tagging was recently published for two dimensional caudal brain motion measurements (1.41) and is presented in chapter 3 of this thesis. Displacement-encoded imaging with stimulated echoes (DENSE) (1.42) is a method similar to tagging, but the acquisition scheme limitations of displacement sensitivity and spatial resolution are better adaptable to small motions compared to tagging. Therefore, DENSE suits very well for three dimensional brain motion detection, as presented in chapter 4.

1.6 Outline

It is the aim of this thesis to develop and optimize MRI sequences enabling the three-dimensional in-vivo determination of dynamic boundary conditions for the proposed model. The boundary conditions needed are namely the cerebrospinal fluid flow at the cerebral aqueduct and the pulsatile motion of the ventricular wall. These data shall then allow simulations of fluid dynamics and mass transport phenomena within the ventricular system as schematically described in Figure 1.4. The developed methods are presented in the following chapters. Results of CFD simulations of the 3rd ventricle are presented in chapter 5.

Chapter 2

Specific aspects on the accuracy of phase contrast methods for measuring slow velocities like in the cerebral aqueduct are discussed in section 2.1. An appropriate measurement protocol and correction methods are proposed in 2.2 and finally spatio-temporally resolved velocity data of CSF in the aqueduct are presented.

Chapter 3

In Chapter 3 measurements of pulsatile brain motion using CSPAMM in combination with HARP are described. The properties of the presented MR technique and the postprocessing tool are assessed with respect to reproducibility and periodicity of the acquired data and the received physiological information.

Chapter 4

Investigations on an optimized cine phase-contrast displacement encoding method (DENSE) (23, 27) combined with a three dimensional EPI readout scheme are presented. Three subsequent stacks, with each encoding displacement in one direction, are acquired to obtain cine displacement data of the whole central brain regions in twelve healthy volunteers. Thirteen selected brain regions are evaluated in detail. The reproducibility as well as the accuracy of the obtained displacement results is assessed.

Chapter 5

In Chapter 5 the use of MRI CSF-flow data acquired at the cerebral aqueduct and caudal brain motion data as boundary conditions for flow calculations over the whole 3rd ventricle are explained and results are presented for one specific subject. Anatomic MRI scans are used to capture the geometry of the third ventricle and the aqueduct of Sylvius of a healthy volunteer. This domain serves as the base for the subsequent CFD calculations. MRI is also used to measure brain motion, from which the displacement in feet-head direction is calculated. A third set of MRI scans provides the CSF flow velocity at the inferior end of the aqueduct of Sylvius. These data serve as boundary conditions for the CFD calculations.

Chapter 6

Some conclusions can be drawn from the results presented and an outlook for future work which might improve the assessment of brain dynamics is given.
2 On the Assessment of Cerebrospinal Fluid Velocities

2.1 Introduction

The approach for assessing velocities chosen for this thesis is the most widely used MRI velocity mapping method. Velocities directed into the main flow direction are measured using phase-contrast MRI. The area with non-zero velocities can then be quantified in the reconstructed phase information of the MRI signal.

In the following, details on the specific demands for measuring aqueductal CSF flow are discussed.

Flow measurements in the ventricular system

Circulation, production and absorption of the CSF are important parameters describing the dynamic properties of the liquor space. In the ventricular system CSF flow has been commonly assessed at the cerebral aqueduct, as it is the only connection between the third and fourth ventricle. Due to its almost tube like shape, laminar flow is expected, which is beneficial regarding flow modeling. Previously published values for stroke volume, the volume which is transferred caudally during systole, caudal and cranial peak velocity show wide range variations (2.1). These variations are mainly attributed to the limited spatial resolution of the different MRI measurements and the different choice of sections in the aqueduct to be imaged.

Theoretical considerations allow for a correction of errors caused by...
resolution with adequate signal-to-noise ratio is inherently limited by the scan time available in an in vivo/clinical setup. Note that measurement accuracy is furthermore comprised by imperfections of the point spread functions (PSF), such that peak velocities are underestimated for low resolution acquisitions (typically having broadened PSFs). (Figure 2.1, 2.2).

For phase contrast methods velocity sensitivity highly depends on the proper choice of the encoding velocity, the highest velocity to be measured without any phase wraps. Ideally, the encoding velocity should be as close as possible to the peak velocity of the flow measured, such that the whole phase range can be used for velocity encoding without any occurrence of phase wraps. According to literature (2.3) available on CSF flow within the cranium, peak velocities of 2 to 15 cm/s are to be expected. These low peak velocities demand very strong encoding gradients. As described in detail in 2.2 2.4, 2.5, phase errors are induced by such strong gradients. Hence, concomitant field effects and eddy current effects need to be minimized and/or corrected to get accurate velocity measurements for the velocity range under investigation.

In this work an optimized phase contrast imaging protocol for velocity mapping combined with phase correction postprocessing is presented. The proposed imaging protocol is evaluated on healthy volunteers. The methods used and the results are discussed in the following. First physiological observations are presented.

### 2.2 Methods

#### 2.2.1 Measurements

Standard cine phase contrast (PC) MRI was applied for velocity mapping with high spatial and temporal resolution of cerebrospinal fluid flow in the aqueduct. All measurements were performed on a 3T whole body MR system (Achieva, Philips Medical Systems, Best, The Netherlands). For excitation the body coil was used, while the MR signal was detected using a 6-element head coil, driven in quadrature mode. ECG triggering was employed.

The sequence parameters used for high resolution velocity data acquisition in the aqueduct are: in-plane resolution: 0.5 x 0.5 mm², slice thickness: 5 mm, temporal resolution: 26 ms, encoding velocity: 7 cm/s, number of signal averages: 3. Turbo field echo with a turbo factor of 3 was used for read-out. For evaluation and comparison of peak velocity values with literature the experiments were repeated on three healthy volunteers with the parameters mentioned above but a temporal resolution of 40 to 50 ms.

#### 2.2.2 Postprocessing

Phase contrast sequences are based on the use of a bipolar gradient. The phase introduced by such a bipolar gradient is zero for any static tissue as the zeroth moment of a bipolar magnetic gradient field is zero. The phase induced is mainly proportional to the mean flow velocity of the fluid represented in one voxel during the application of a bipolar gradient pair. Flow velocities in the aqueduct with peak velocities around 7 cm/s are small compared to most other flow velocities measured with cine phase contrast, like blood flow in the aorta or the carotid arteries. As mentioned in section 2.1 the accurate assessment of the expected low velocity values of CSF flow requires very high velocity encoding gradients. The accuracy of phase velocity mapping methods, however, can be compromised by phase errors (2.1) arising from eddy-currents (2.2), concomitant gradient fields (2.4) and gradient inhomogeneities (2.5). Fortunately, gradient inhomogeneities cancel out due to the phase subtraction employed when using phase contrast methods.
Concomitant field errors result from transversal magnetic fields which are concomitantly activated longitudinal field gradients. They are very small compared to the longitudinal field gradients but have to be taken into account when measuring very small velocities as CSF-velocities in the aqueduct. As these phase errors directly result from Maxwell’s laws, the lowest order concomitant fields can be approximated, which is nicely presented in Bernstein, et al (2.4). The phase maps are then corrected by subtraction of these quadratic field terms (Figure 2.2). The influence of higher order concomitant fields is negligible.

Eddy currents are induced in any surrounding conductive material by high gradient switching rates. If these eddy currents are not fully blocked or if pre-emphasis currents are not adjusted appropriately magnetic field distortions occur. Errors are readily apparent as velocity offsets in image regions known to be stationary, which can still be found after concomitant field error correction. Additionally, the induced phase errors are mainly linear, thus a ‘background phase subtraction’ correction method can be applied to minimize the eddy currents (Figure 2.2). For the measurements of aqueductal CSF flow the background phase was calculated as the mean phase from a region of interest chosen around the aqueduct.

All visualization and postprocessing was performed on an in-house developed tool based on IDL (Interactive Data Language, RSI). The phase correction methods described were implemented.

*Figure 2.2: Phase correction in PC velocity mapping. Cranio-caudal velocities acquired along the midsagittal plane with an encoding velocity of 1 cm/s. a) Velocity map without any postprocessing except noise clipping, b) after concomitant field correction, and c) after subsequent background phase correction for eddy currents corrections. Before any correction (a)) there is almost no flow in the fourth ventricle (ellipse) but high phase values in the periphery of the brain. The parabolic phase distributions correspond to the concomitant field induced phases and thus vanish in b). An offset phase over the whole image indicates residual phase errors. Background phase correction with the mean phase calculated from brain tissue around the aqueduct and 4th ventricle removes this offset and reveals flow in the 4th ventricle.*
2.3 Results

Accurate CSF velocity measurements were successfully accomplished in the cerebral aqueduct. Three healthy subjects were measured with the presented sequence. In Figure 2.3 the mean periodicity (P), the ratio between peak velocity difference and time of peak difference for 1.0 x 1.0 mm\(^2\) and 0.6 x 0.6 mm\(^2\) spatial resolution are compared. P is highly increased for the higher resolution and the standard deviation decreases. The corresponding peak velocities over time are presented in Figure 2.4. The results are in good agreement with literature (2.1), which mainly range from 2 to 15 cm/s for caudal flow.

![Figure 2.3: The Periodicity P of peak velocity for two different in-plane resolutions. The standard deviation decreases for 0.6x0.6 mm\(^2\) in-plane resolution (n=3).](image)

Using these results, the sequence was adjusted and subsequently used for acquisition of ventricular velocity data (Figure 2.5) for computational fluid dynamics. Subject-specific simulations of ventricular flow resulted in very plausible flow patterns within the third ventricle using these data. Therefore, aqueductal flow data were calculated from the velocity profiles (Figure 2.6) and were used as boundary conditions for the simulation of flow in parts of the ventricular system.

![Figure 2.4: Peak velocities as a function of measured heart phases for three different healthy volunteers. Spatial resolution: 0.6x0.6 mm\(^2\).](image)

![Figure 2.5: Phase map from through-plane velocity measurement in the inferior part of the aqueduct. The pictures are encoded such, that black depicts cranial and white caudal flow. In a) the time frame 26 ms after the R-wave is presented. The aqueductal region of three selected time frames of the same dataset is shown in b). The pulsatility of the flow is clearly visible. The flow in the prepontine region can also be observed on these data.](image)
The first time frames in Figure 2.6, 26 ms to 181 ms after the R-wave, represent CSF flowing caudally towards the spinal canal. Then directional changes and the pulsatile flow drives CSF back into the third ventricle. Cranial peak velocities were found 400 ms after the R-wave. At the end of the cardiac cycle the initial situation is reached again and CSF flows caudally out of the cranium.

Simulation results for the flow in the aqueduct and the third ventricle are presented in chapter 5.

### 2.4 Discussion

Acquisition of flow boundary conditions for computational fluid dynamics demands accurate velocity measurements. The accuracy of MRI phase contrast velocity mapping highly depends on the spatial resolution, optimal velocity sensitivity, i.e. choice of encoding velocity and accurate MRI phase mapping methods.

The dimensions of the cerebral aqueduct (chapter 1) demand in-plane resolution below 1 mm to not only detect mean velocities but two dimensional flow profiles (Figure 2.6), (2.6, 2.7). For the dataset presented in detail the imaging plane was chosen rather inferior, hence the number of pixel within the area of interest could be increased further.

Peak velocities determine the encoding velocities and thus the gradient strength to be applied during measurements. Compared to blood flow, mainly measured with phase contrast MRI, aqueductal CSF flow is very slow, it is expected to be around 5 cm/s, whereas peak blood velocities in the carotid arteries are usually around 100 cm/s. Thus, the gradients applied in CSF flow measurements cause strong concomitant field errors, and eddy currents deteriorate the quality of the velocity phase maps. The significance of this influence highly depends on the vendor’s hard- and software and can also differ from scanner to scanner. As demonstrated in the methods, the velocity data acquired in
Assessment of CSF Velocities

demand correction of gradient induced phase errors. Using background phase correction in combination with first order concomitant field correction resulted in accurate two dimensional flow profiles as presented in Figure 2.6.

A main limitation of the protocol proposed is the restriction to one velocity direction only. In order to further increase the accuracy of the flow profiles the use of a three-dimensional flow measurement method is suggested. This allows accounting for through-plane velocity components which are not perpendicular to the main aqueduct axis. The use of higher static field strengths may also provide means to further increase the spatial resolution without a significant increase in scan-time or loss in signal-to-noise ratio.
Chapter 3

3 Assessment of Human Brain Motion Using CSPAMM

3.1 Introduction

Brain motion has already been investigated with phase-contrast methods (3.1-3.5). The accuracy of phase velocity mapping methods, however, can be compromised by phase errors (3.6) arising from eddy-currents (3.7), concomitant gradient fields (3.8) and gradient non-linearities (3.9), which are pronounced when measuring small velocities (3.7). As an alternative to phase contrast velocity mapping, tagging methods may be used. Motion analysis based on tagging data has been successfully demonstrated in the heart (3.10).

In tagging methods, the magnetization established within the body is modulated with a cosine prior to image acquisition and these saturation lines can be used as landmarks for distinct areas as the magnetization is fixed to the object. These landmarks can then be tracked throughout the cardiac cycle by acquiring subsequent images, whereas their contrast decreases with T1. The relatively long T1 values of brain tissue at 1.5T (gray matter: 950 ms, white matter: 700 ms) potentially allow coverage of the whole cardiac cycle. The maximal displacement of the brain due to pulsation is expected in the range of 0.3 mm (3.2) and thus demands on the one hand a very fine tagging grid and on the other hand refined tracking algorithms finding these very small deformations of the grid between subsequent cardiac phases. Applying a very dense tagging grid requires high scan resolution resulting in a low signal-to-noise ratio (SNR). In addition, the tagging information decays with time and thus the contrast-to-noise ratio (CNR) decreases as a result of T1 relaxation becoming prominent in the later heart phases (3.11). This can be significantly improved by using complementary spatial modulation of magnetization (CSPAMM) (3.12). In CSPAMM, two measurements with a relative phase shift of $\pi$ in the tagging modulation are subtracted. The improved CNR in the images as well as the fact that the signal has zero mean makes CSPAMM preferred in conjunction with the harmonic phase (HARP) (3.13,3.14) post-processing method. After filtering the tagged images in k-space, information of motion of any point within the selected slice becomes available by its phase.

Chapter 3 describes measuring pulsatile brain motion with CSPAMM in combination with HARP. The properties of the presented MR technique and the post-processing tool are assessed with respect to reproducibility and periodicity of the acquired data and the received physiological information. Additionally, this chapter shows that direct quantification of periodic caudal brain tissue displacement is feasible with the proposed method, and several brain regions can be distinguished through peak displacement and time-to-peak values.

3.2 Materials and Methods

Ten healthy volunteers (mean age 27 years, range: 22 – 61 years; 7 male, 3 female) were examined on a Philips 1.5T system (Philips Medical Systems, Best, The Netherlands) using the CSPAMM (3.12) method. The displacement data were then derived using HARP post-processing (3.14). In order to assess reproducibility eight subjects were measured two times subsequently on the same occasion.
3.2.1 Tagging Measurements

For tagging preparation a CSPAMM sequence with separate tag-line preparation in two orthogonal directions was used. The tag distance was 2 mm, with a scan resolution of 0.5 mm (scan matrix: 512 x 128) in three volunteers, whereas in all other examinations the scan resolution was set to 1 mm with a scan matrix of 256 x 64. For data acquisition a TFE (Transient Field Echo) sequence was used (turbo factor: 3, $T_R/T_E$: 8.3/4.0 ms). The number of cardiac phases was chosen such that at least 125 % of the average R-R interval were covered and the heart rate. One mid-sagittal slice with a slice thickness of 4 mm was obtained twice in each volunteer. With four signal averages the scans took approximately 5-10 minutes, again depending on the heart rate.

3.2.2 HARP Post-processing

The harmonic phase method was implemented as described in (3.13). A circular Gaussian band pass filter was used for extracting harmonic peaks in k-space. As a trade-off between contrast-to-noise ratio (CNR) and tracking resolution, the optimal shutter width was found to be 24 pixels resulting, with the aforementioned CSPAMM acquisition parameters, in a HARP image resolution of about 5.3 mm

Figure 3.1: Tagging image of the brain. Example of an image acquired at 50 ms after the R-wave a). The six regions evaluated in this paper are indicated. In b) the region around the fourth ventricle as indicated in a) acquired 150 ms and 850 ms after the R-wave is shown with identical intensity scaling. The decreasing contrast-to-noise-ratio due to tag fading is evident.
Assessment of Brain Motion Using CSPAMM

(3.11,3.14). Furthermore the algorithm was improved by combining motion information of both spectral peaks as introduced in (3.16).

3.2.3 Evaluation

In order to evaluate CSPAMM, periodicity and reproducibility of displacement data from CSPAMM measurements acquired across 125% of the average R-R cycle were evaluated. For eight healthy volunteers, two out of ten had a too low heart rate, thus tag fading did not allow tracking over 125% of the cardiac cycle. The difference in peak caudal displacement of two serial measurements was determined in several brain regions. Additionally the mean of difference over all subjects relative to the peak displacement was determined across 125% of the cardiac cycle. In the same regions periodicity was quantified by assessing the relative root mean square of differences between the time frames within 0%-25% and 100%-125% of the average cardiac cycle

\[ E_{\text{Period.}} = \frac{\sum_{t=0}^{0.25\times RR} |d_t - d_{t+RR}|^2}{\sum_{t=0}^{0.25\times RR} |d_t|^2} \]

Eq. 3.1

where \(d\) denotes displacement, index \(t\) cardiac phase and \(RR\) the average duration of the cardiac cycle.

To complete the proof of feasibility, physiological properties of brain motion, such as peak displacement and time-to-peak values were extracted for all subjects in six different regions of the brain (Figure 3.1).

3.3 Results

In the following, results on caudal displacement data evaluated in six mid-sagittal regions of the brain – as indicated in Figure 3.1 - are presented. Displacement values as a function of cardiac phase in one exemplary volunteer for the six evaluated regions are shown in Figure 3.2. In all volunteers the peak displacements was determined for all regions under consideration as presented in Figure 3.3. The peak caudal displacement was found to be \(0.184 \pm 0.021\) mm in the pons decreasing cranially to \(0.052 \pm 0.010\) mm in the corpus callosum (trunk) and to \(0.041 \pm 0.011\) mm in the frontal lobe. Thus the peak caudal displacement decreases with the distance from the brain stem, and the pulse wave travels from the pons occipitally and finally towards the frontal lobe. Figure 3.4 depicts the mean ratios of peak displacement to time-to-peak value, which pronounces the decrease of the peak displacement with increasing time-to-peak values.

**Figure 3.2:** Example of displacements as a function of the cardiac cycle of one volunteer in the six regions of the brain indicated in Figure 3.1.
Assessment of Brain Motion Using CSPAMM

**Figure 3.3:** Mean ± standard deviation of the peak displacement and its time-to-peak value of eight volunteers in the regions indicated in Figure 3.1. The peak displacement is the maximum amplitude of the pulse wave. Its temporal behavior is described by the time-to-peak value reflecting the delay of the peak amplitude with respect to the R-wave of the cardiac cycle.

Assessment of Brain Motion Using CSPAMM

**Figure 3.4:** Mean ± standard deviation of the ratio between peak displacement and the time-to-peak value in the regions indicated in Figure 3.1 in eight volunteers. The ratio is decreasing from the brain stem towards the periphery.

The relative difference of displacement values as a function of cardiac phase derived from two subsequent measurements in each volunteer is shown in Figure 3.5 for the six regions investigated. As observed in all volunteers, good reproducibility can be found for the first 500 ms of the cardiac cycle in all regions except for the splenium of the corpus callosum. The relative mean differences of peak displacement calculated from the two subsequent measurements in all volunteers amounted to (mean ± SD) of 9.1 ± 8.5 %, 6.9 ± 15.2 %, 2.7 ± 34.8 % and 17.7 ± 18.0 % in the pons, cerebellum, corpus callosum (splenium) and corpus callosum (trunk), respectively (Figure 3.6). For areas with the peak displacement appearing later within the cardiac
cycle, reproducibility decreased to 14.7 ± 29.3 % in the corpus callosum (genu) and 12.1 ± 43.8 % in the frontal lobe. The standard deviation is increasing towards the later cardiac phases, as the contrast-to-noise ratio decreases due to the tag fading caused by the T1 decay of the tagged signal (3.10). The statistical significance of differences of the peak displacements between the six regions is listed in Table 3.2. Periodicity given as the root-mean-square error as described in Equation (1) were: 0.43 ± 0.20, 0.53 ± 0.24, 1.18 ± 0.85, 0.99 ± 0.52, 1.03 ± 0.56, 1.38 ± 0.81 for the pons, cerebellum, corpus callosum (splenium), corpus callosum (trunk), corpus callosum (genu), frontal lobe, respectively.

Figure 3.5: Reproducibility. Mean of relative differences of displacement values from two subsequent measurements performed in each subject across 125% of the average cardiac cycle.

Figure 3.6: Mean difference of peak displacement from two subsequent measurements (#1 and #2) in the eight healthy volunteers. The displacement values are presented for the six different areas indicated in Figure 3.1.
### Table 3.1: Peak displacements and time-to-peak values for the six evaluated regions.

<table>
<thead>
<tr>
<th>Region</th>
<th>Peak displacement (mean in mm)</th>
<th>SD in mm</th>
<th>Time-to-peak (mean in % ES)</th>
<th>SD in % ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pons</td>
<td>0.184</td>
<td>0.021</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.104</td>
<td>0.008</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Corpus callosum (splenium)</td>
<td>0.092</td>
<td>0.019</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Corpus callosum (trunk)</td>
<td>0.052</td>
<td>0.010</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>Corpus callosum (genu)</td>
<td>0.081</td>
<td>0.019</td>
<td>58</td>
<td>10</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>0.041</td>
<td>0.011</td>
<td>73</td>
<td>10</td>
</tr>
</tbody>
</table>

SD: standard deviation; ES: end-systole

### Table 3.2: Significance of the differences of peak displacement and time-to-peak values as assessed by student-t-test.

<table>
<thead>
<tr>
<th>Displacement</th>
<th>1st measurement</th>
<th>2nd measurement</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pons</td>
<td>0.184</td>
<td>0.104</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.104</td>
<td>0.092</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Corpus callosum (splenium)</td>
<td>0.092</td>
<td>0.052</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Corpus callosum (trunk)</td>
<td>0.052</td>
<td>0.010</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Corpus callosum (genu)</td>
<td>0.081</td>
<td>0.019</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>0.041</td>
<td>0.019</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### 3.4 Discussion

It has been demonstrated that CSPAMM with HARP post-processing is a technique which can be used for the assessment of brain motion in cranio-caudal direction. The physiological data as illustrated in Figure 3.3 are in good agreement with values from literature (3.4) and indicate the pathway of the pulse wave through the brain moving from caudal to cranial as well as its attenuation towards the periphery.

The comparison of two subsequent CSPAMM measurements in the same subject reveals small differences in peak displacements, especially in the pons (Figure 3.6). The variance, however, increases towards areas further cranially. As depicted in Figure 3.3 the time-to-peak of the pulse wave, i.e. the time of appearance of the peak displacement in the cardiac cycle also increases towards the caudocranial direction. Thus the variance increase can possibly be explained by the decrease of CNR towards the later heart phase due to the fading of the tags (3.10). Very high variation is also found in the splenium of the corpus callosum where the signal might suffer from the proximity to cavities containing CSF (see Figure 3.1) and major blood vessels, as further discussed below.

As described above HARP post processing uses a filter in k-space in order to extract the harmonic peak containing all motion information. As the reduction of the filter width in k-space equals a decrease of spatial resolution in the final image, the HARP method suffers a loss in spatial information. In this study, scan resolution was 0.5 and 1 mm and the best HARP tracking results were achieved with a filter which reduced the actual spatial resolution to 5.3 mm. This implies spatial blurring of the displacement data and therefore edges of structures moving independently can not be clearly discriminated. A further disadvantage related to the reduced spatial resolution is the influence of cerebrospinal fluid (CSF) showing very slow flow. In regions close to CSF-filled cavities the CSF motion contributes to the
brain displacement signal. This influence is observable in the reduced reproducibility and periodicity of displacement data in the splenium of the corpus callosum. Lower periodicity is also found in the frontal brain regions with very small displacement.

In conclusion tagging allows the measurement of periodic caudal motion caused by the pulsatile blood flow in several regions of the brain. The proposed method is relatively insensitive to phase-related image artifacts and displacement data are directly obtained without requiring numerical integration steps as used in phase-contrast based methods. The accuracy, which is of particular interest for work simulating CSF flow behavior, is sufficient to simulate CSF flow with good consistency in the cavities incorporating brain motion data (3.17). Further improvements of the proposed approach are expected from translating the method to higher static field strengths. Besides the SNR gain, T1 increases and thus tag fading is reduced.
Chapter 4

4 Three-dimensional Assessment of Brain Motion Using DENSE

4.1 Introduction

In Chapter 3 a two dimensional imaging method based on tagging was introduced for the assessment of caudal pulsatile brain motion. The CSPAMM approach suffered from limited displacement sensitivity and spatial resolution, if measuring very small displacements (4.1).

In this chapter a three-dimensional approach allowing not only caudal, but also anterior-posterior and right-left motion is presented. The method is similar to CSPAMM tagging and uses a stimulated echo acquisition mode (STEAM) for motion detection. A cine phase-contrast displacement encoding using stimulated echoes (DENSE) (4.2, 4.3) sequence combined with a three-dimensional EPI readout scheme is proposed for measuring the small pulsatile displacements.

DENSE has already been successfully used for measuring pulsatile tissue motion in humans, mainly in the heart, where peak displacements are in the range of one to two centimeters. Usually, single slices are examined. For assessing general displacement information of the entire brain or motion patterns of large structures (e.g. the ventricular system or tumors) three-dimensional measurements are required.

By applying DENSE, the longitudinal magnetization established within the body is cosine-modulated prior to image acquisition. The resulting signal consists of three harmonic peaks in k-space, the DC-peak due to T1 relaxation, the displacement-encoded echo signal and its complex conjugate one, as recently discussed in detail (4.3-4.5). For displacement imaging only the echo signals containing motion information, namely the displacement-encoded echo signal and its complex conjugate one, are of interest. With DENSE one of the displacement-encoded echo signals is shifted to the center of k-space. The separation of the peaks is proportional to the displacement encoding frequency (ke). The choice of ke is determined by the peak displacement, as the resulting displacement encoded phase is proportional to ke and the actual displacement value. In order to ‘cut out’ only the central motion encoded echo by the acquisition window, ke has to be greater than half of the spatial encoding frequency (kmax) (ke>kmax/2). For larger displacements, as for example in the heart, this would lead to very low spatial resolutions and thus a band pass filter (4.3) and/or sophisticated echo-elimination schemes (4.4, 4.5) have to be applied for the separation of the signals of the different echoes. For small motions, as in the brain, where peak displacements are expected in the range of tens of micrometers, high motion encoding frequencies are needed. Thus, the relationship ke> kmax/2 is easily fulfilled for the spatial resolutions desired and neither filtering nor echo cancelling acquisition schemes have to be applied.

Taking advantage of this characteristic specific to DENSE, The method was optimized for the measurement of human brain parenchyma displacements. Three subsequent stacks with displacement encoding in all three directions allow accurate cine displacement data acquisition of the whole central brain region. These data can then be used as boundary conditions for simulations of the ventricular system.

For validation a study was performed on twelve healthy volunteers. Thirteen selected brain regions were evaluated in detail. Time series of these regions were extracted and used to validate the
proposed method. Reproducibility and periodicity were assessed and the obtained displacement values themselves were intrinsically validated, meaning that intra- and inter-subject comparison of different brain regions was used for a plausibility check of the displacement results.

4.2 Methods

4.2.1 Data Acquisition and Post-processing

Cine DENSE (4.6,4.7) was implemented on a 3T Achieva MRI system (Philips Medical Systems, Best, The Netherlands). For signal reception an 8-coil element head coil array was utilized. The sequence was modified to allow inversion of the displacement encoding/decoding gradients. In two consecutive measurements the gradients were applied with opposite gradient strength values, yielding two fully acquired data sets with inverted displacement encoded phases. Additional sequence parameters were: spatial resolution = 2x2x3 mm³, temporal resolution = 35 ms, EPI factor = 7, TE = 9.5 ms. To obtain constant SNR throughout the whole cardiac cycle, ramped flip angles (4.8) were employed. The maximum flip angle values ranged between 6° and 10°, depending on cardiac frequency. A total of three axial, orthogonally motion encoded stacks was acquired. The first stack was motion encoded in measurement direction, oriented in right-left direction. A 90° rotation of the measurement direction about the slice encoding direction yielded anterior-posterior motion in the second stack. For motion encoding in through-plane direction (feet-head direction) a third stack with encoding and decoding gradients in slice selection direction was added. Motion encoding frequencies were adapted to the peak displacements expected in the three directions. Anterior-posterior and right-left motion encoding sensitivity was set to 0.18mm/pi and feet-head motion was encoded with 0.35mm/pi. In Figure 1 the schematic of the preparation sequence is given. It is followed by a three-dimensional readout scheme with two-dimensional echo-planar sampling.

In post-processing, the data sets from the two subsequent measurements were combined by complex division similar to the peak-combination method (4.6) thereby eliminating phase errors from EPI readout imperfections and B₀ offsets. Automated unwrapping was applied to data sets where high peak displacements introduced phase wraps. To allow inter-scan comparison of different data sets the extracted time series were temporally resampled and normalized to the RR-interval (100%, starting with the ECG R-wave).

Measurement reproducibility was assessed by repeated acquisition in each volunteer. In addition, periodicity was determined by triggering the sequence to every other heart beat thereby allowing coverage of more than 100% of a nominal cardiac cycle. Coverage of more than 125% of the cardiac cycle could be achieved in ten out of the total of twelve volunteers. Two male volunteers could not fulfill this criterion, as their heart rate was too low and thus, they were excluded from further analysis.

Finally, an additional three-dimensional cine DENSE data set was acquired with reduced cycle coverage of 770 ms facilitating triggering on each heart beat. In those scans, displacement sensitivities were adapted to the peak displacement of the specific volunteer based on the measurement used to test reproducibility and periodicity. With an encoding frequency of 0.15 mm/pi in all three directions a volume of 15 axial slices covering the whole ventricular system of the brain was encoded. The following imaging parameters were used: spatial resolution = 2x2x4 mm³, temporal resolution = 30 ms, EPI-factor = 5.
Figure 4.1: a) Basic STEAM experiment. b) Preparation and acquisition scheme of the proposed method. For the first stack (x-direction) a cine-DENSE acquisition scheme with a positive encoding gradient (G) in measurement direction and a spoiling gradient (S) in slice selection direction is applied after the cardiac trigger. For each cardiac phase the same gradient (G) is applied before the readout. For the second stack (y-direction) the sequence coordinate system is rotated by 90 degrees and repeated to encode the second in-plane direction. For the through plane direction in the third stack (z-direction) the gradients (G) are switched to slice encoding direction. The measurement of the three stacks is then repeated with inverted gradients (-G).

4.2.2 Study Population

Twelve healthy volunteers (5 male / 7 female, 26.3 ± 3.8 years old) were examined. Detailed written informed consent from all study participants and institutional review board approval was obtained.
3D Assessment of Brain Motion Using DENSE

4.2.3 Data Analysis

For basic motion visualization and analysis a software tool (FlowTrack, GyroTools Ltd., Zurich, Switzerland) was adapted. Brain motion time series for 13 different anatomical areas (Figure 2; left (sin) and right (dx) putamen, occipital lobe, left and right thalamus, left and right caudate nucleus (head and body evaluated separately), frontal lobe, corpus callosum trunk and regions in the upper right and left hemispheres) were extracted by averaging four adjacent pixels within the anatomic structure.

The three-dimensional data set allowed verification of displacement results i) with phase-contrast data reported in the literature, ii) and, intrinsically, based on the symmetry of the brain assuming brain pulsation to be symmetric along the AP axis in healthy subjects. Mean of peak displacement ± standard deviation of all three directions is reported separately for the 13 regions evaluated.

Reproducibility was calculated as the mean difference of the absolute displacement between two subsequent measurements. The Error of Periodicity (EPeriod) was determined according to:

$$ E_{Period.} = \sqrt{\frac{\sum_{t=0}^{NoT} (d_t - d_{t+1 \cdot RR})^2}{\sum_{t=0}^{NoT} |d_t|^2}} $$

with $d$ being absolute displacement, index $t$ cardiac phase, NoT number of temporally overlapping cardiac phases between two subsequent RR intervals and $t_{RR}$ the average duration of the cardiac cycle.

Statistical values were derived with ‘InStat’ (3.01, Graph-Pad Software Inc., San Diego, USA). Analysis of variance (ANOVA) for repeated measurements followed by Bonferroni post-hoc testing was applied. P-values < 0.05 were considered statistically significant.

4.3 Results

Three-dimensional DENSE measurements were successfully accomplished in all twelve healthy volunteers. For ten subjects at least 125% of the cardiac cycle could be covered. The results discussed in the following were conducted from those ten data sets. Figure 3 depicts two-dimensional phase maps after phase unwrapping for the three encoding directions at different heart phases from a healthy volunteer. The phase maps acquired at 10-25 % of a nominal cardiac cycle.
cycle show the onset of brain tissue expansion. Combination of the three phase maps allows the visualization of three-dimensional displacement maps, depicting dynamics of various brain regions (Figure 4). As an example the motion around the 3rd ventricle is shown in Figure 5.

The time series from the selected regions (Figure 2) reveal good agreement between the average cardiac frequency and the periodicity of the data (Figure 6), i.e. the temporal frequency of the measured data reflects the average cardiac frequency of the volunteer. Quantitative results based on Equation 1 are collected in Table 1, which verify the periodicity of the data. The regions in the central brain areas show a periodicity of approximately 0.3±0.1 on average. In the occipital lobe the periodicity is deteriorated (1.02±0.43). Reproducibility, given as the mean of absolute difference expressed in % of the peak displacement (Figure 7) stays within 25% in all regions except for the frontal and occipital lobe. In these areas displacement values are very small on the order of 0.02 to 0.04 mm.

The mean of peak displacements in Figure 8a reflects the general brain motion pattern. The data reveal a decrease of feet-head displacement towards the periphery which is in good agreement with the results presented in (4.1). In Figure 8b) and c) the mean peak displacements for anterior-posterior and right-left motion are presented. The results of identical anatomical structures in the right and left hemisphere generally correlate very well (Figure 8), except for the regions in the upper left and right brain hemispheres.

Comparing the occipital lobe with the cerebral hemisphere and the head of the caudate nucleus with its body revealed non-significant differences in mean peak displacement. The frontal lobe and corpus callosum (trunk) compared to the cerebral hemispheres differed significantly with p<0.01. For all other evaluated areas highly significant differences (p<0.001) of the mean peak displacements were found in at least one encoding direction.

Figure 4.4: Selected slices of a 3-dimensional brain motion data set covering the volume of the ventricular system. Slice 1 depicts the lower parts with the brain stem and the fourth ventricle. 1 the fourth ventricle is non-uniformly ‘torn’ caudally like 2 the pons, which is also strongly compressed in the proximity of the basilar artery. Slice 10 contains information on central brain regions and the ventricular wall of the third ventricle. 3 the corpus callosum strongly delineates the expansion of central brain tissue, which results in compression of the third ventricle, from the cerebral hemispheres. Slice 13 represents brain motion just above the lateral ventricles. The residual pulsation of brain tissue at position 4 might origin from the strong pulsation of the plexi choroidei of the lateral ventricles and the corresponding arteries. 5 pulsation in the proximity of the anterior cerebral artery. The colors
and the length (scaled by a factor of 100) of the bars represent the motion amplitude of the brain and the bar orientation indicates the displacement direction. Seed density: 0.2 of original voxel density (i.e. bar for every 5th pixel is shown).

An example for the results of pixel-wise comparison is depicted in Figure 9. The motion of two neighboring anatomical units shows that close brain areas can still be distinguished by the characteristics of the displacement curves.
Figure 4.6: Example for the time series of selected regions from the left hemisphere. Feet-head (fh), anterior-posterior (ap) and right-left (rl) displacements for the first (meas#1) and second measurement (meas#2) are compared.

Figure 4.7: Reproducibility. The mean ± standard deviation of relative difference, the difference between two subsequent measurements in percentage of the mean peak displacement of those two measurements, of ten healthy volunteers for 110% of the cardiac cycle is shown for six different regions (each of the 13 regions only for one brain hemisphere).
Table 4.1: Periodicity of the absolute displacements in all 13 selected regions evaluated using Equation 4.1.

<table>
<thead>
<tr>
<th>Periodicity</th>
<th>putamen</th>
<th>putamen</th>
<th>occipital</th>
<th>thalamus</th>
<th>thalamus</th>
<th>caudate</th>
<th>caudate</th>
<th>nucleus</th>
<th>nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(sin)</td>
<td>(dx)</td>
<td>(sin)</td>
<td>(dx)</td>
<td>(sin)</td>
<td>(dx)</td>
<td>(head.sin)</td>
<td>(head.dx)</td>
<td></td>
</tr>
<tr>
<td><strong>mean</strong></td>
<td>0.30</td>
<td>0.33</td>
<td>1.02</td>
<td>0.26</td>
<td>0.29</td>
<td>0.31</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>stdev</strong></td>
<td>0.10</td>
<td>0.13</td>
<td>0.43</td>
<td>0.11</td>
<td>0.10</td>
<td>0.11</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Periodicity</th>
<th>caudate</th>
<th>nucleus</th>
<th>frontal</th>
<th>corpus</th>
<th>cerebral</th>
<th>cerebral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(body.sin)</td>
<td>(body.dx)</td>
<td>lobe</td>
<td>callosum</td>
<td>hemisph.</td>
<td>hemisph.</td>
</tr>
<tr>
<td><strong>mean</strong></td>
<td>0.32</td>
<td>0.34</td>
<td>0.62</td>
<td>0.42</td>
<td>0.58</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>stdev</strong></td>
<td>0.18</td>
<td>0.13</td>
<td>0.23</td>
<td>0.14</td>
<td>0.23</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Figure 4.8: Comparison of mean peak displacements in the two hemispheres (right: dx and left: sin) of 10 subjects. The mean peak displacement ± standard deviation from the a) right-left (rl), b) feet-head (fh) and c) anterior-posterior (ap) motion are compared.

Figure 4.9: Comparison of right-left displacement time series of two regions within the thalamic nucleus in one subject. The lateral dorsal (lat. dor.) tissue of the nucleus shows higher displacement (difference about 20 µm) towards the midsagittal plane than the anterior part.

4.4 Discussion

A phase contrast based three-dimensional cine DENSE method, which is sensitive to very small displacements, has been proposed for measuring pulsatile brain motion. The method allows the assessment of spatiotemporal highly resolved brain tissue displacement data with sufficient accuracy to be used as boundary conditions for three-dimensional simulations of brain dynamics.

A validation study was performed to assess periodicity and reproducibility. The comparison of displacement in the right and left hemisphere in healthy volunteers and group analysis of peak
displacements allowed a physiological verification of the proposed method.

The high periodicity of pulsatile brain motion in the central brain areas decreases towards the periphery due to the smaller displacement amplitudes in these regions (Table 1). Brain tissue displacements are mostly pronounced in the vicinity of pulsating vessels and damped with increasing distance to those pulsation sources. In the brain regions under consideration the brain arteries, which are located in the center, serve as pulsation source. Consequently, the drop of periodicity in peripheral areas is in accordance with the physiological conditions of the brain. In general, the mean values for periodicity suffer from varying cardiac frequencies during the examination. The rather long duration of the scans makes the method susceptible to cardiac frequency variations, resulting in misregistration of displacement echoes in the later heart phases. In segmented EPI these frequency changes can lead to relative shifts of k-space lines which can cause ghosting. The problem was pronounced in the frontal and occipital lobe where residual ghosting appeared in the later heart phases. Reproducibility was found to be excellent except in regions with very low peak displacements such as the frontal lobe. Increasing the gradient strength and thus the motion encoding sensitivity would improve the reproducibility significantly. However, errors induced by variations of the cardiac frequencies would potentially increase simultaneously.

In general, the peak displacements determined (Figure 8) are consistent with well established theories on brain motion (4.10). Figure 8 also allows a physiological validation of the measured data. The mean peak displacements of the different anatomical regions, which are measured in the right and left hemisphere, show good agreement for identical anatomical structures, except for the regions examined in the upper cerebral hemispheres. Two effects may be attributed to the observation for these regions: i) the limited sensitivity to very small displacement values and ii) observer variability in defining the region-of-interest for the ‘upper cerebral hemisphere’.

A closer look at the group analysis proofs that the proposed method is sensitive enough to reveal physiological features, as most anatomically separated regions can be clearly distinguished by their motion patterns, which might change in certain diseases. Highly significant differences of the peak displacements between almost all selected regions, except for the occipital lobe, frontal lobe and corpus callosum (trunk) were found. These regions are separated from the central brain region by the corpus callosum, which might act as a motion barrier. The head and body of the caudate nucleus were found to not show any significant difference in peak displacement. The non-significance in the difference of displacements between the head and body of the caudate nucleus indicates that the proposed method allows the detection of tissue connections between different locations in central brain regions, where higher peak displacements and thus higher SNR than in the periphery can be achieved.

To improve the SNR in the data when comparing different brain regions, four image pixels were averaged, as described in the methods. This reduces the spatial resolution of the displacement data presented. But this is not a general limitation of the method. The acquisition scheme used for the validation covered 125-150% of the cardiac cycle with about 35 cardiac phases. Thus, the SNR became very low. For ‘normal’ brain motion examinations usually less than 35 cardiac phases are needed and therefore the SNR of the displacement maps can be improved significantly and pixel-averaging is no longer necessary, as shown by an example data-series in Figure 9. In contrast to tagging methods (4.1), no band-pass filtering was applied in k-space when using the DENSE approach.

Main limitations of the method proposed relate to the long measurement times. Varying heart rates were found to cause ghosting
3D Assessment of Brain Motion Using DENSE artifacts. The use of higher static field strengths and/or optimized receive coil arrays may provide means to reduce the number of RR-intervals needed and thereby shortening the measurement duration in future work.

4.5 Conclusion

A three-dimensional cine DENSE acquisition method has been proposed enabling the assessment of pulsatile brain motion down to displacement amplitudes of 0.01 mm. A validation study was conducted to assess the accuracy of three-dimensional and temporally resolved pulsatile brain motion measurements. Observation of the 3-dimensional pulse pressure wave throughout the brain was possible. Additionally, wall motion of the whole cerebral ventricular system could be assessed with the potential to provide new insights into brain dynamics, specifically in combination with computational fluid dynamics.
Chapter 5

5 Combining MRI and CFD: Investigation of Flow in the Third Cerebral Ventricle and the Aqueduct of Sylvius¹


5.1 Introduction

Chapter 5 presents investigations on the fluid dynamics of the human brain resulting from the combination of computational fluid dynamics (CFD) and magnetic resonance imaging (MRI). The observations on functions from Monroe date back to the 18th century (5.1). At the second half of the 20th century new mathematical (5.2) and computational models (5.3) describing pressure gradients fluid flow along the cerebral ventricles and the spinal cavities (5.4) approached. Detailed investigations focused on the aqueduct of Sylvius (5.5, 5.6) describe the pulsatile flow overlaid by a net flow. First physiological considerations of the cerebrospinal fluid dynamics as a whole and their dependence on production and absorption are described in 5.7 and 5.8.

In this work, the cerebrospinal fluid flow in the third ventricle of the brain and the aqueduct of Sylvius was studied using CFD based on subject-specific boundary conditions derived from static and dynamic MRI scans. The flow domain geometry was reconstructed from anatomical MRI scans by manual image segmentation. The movement of the domain boundary was derived from MRI brain motion scans.

Velocimetric MRI scans were used to reconstruct the velocity field at the inferior end of the aqueduct of Sylvius based on the theory of pulsatile flow in pipes. A constant pressure boundary condition was assigned at the foramina of Monro. Three main flow features were observed: a fluid jet emerging from the aqueduct of Sylvius, a moderately mobile recirculation zone above the jet and a mobile recirculation below the jet. The flow in the entire domain was laminar with a maximum Reynolds number of 340 in the aqueduct. The findings demonstrate that by combining MRI scans and CFD simulations, subject-specific detailed quantitative information of the flow field in the third ventricle and the aqueduct of Sylvius can be obtained.

5.2 Methods

5.2.1 MRI Anatomy Data Acquisition and Processing

Structural MR imaging to define the ventricle and aqueduct boundaries consisted of a strongly T2-weighted, 3D, turbo spin-echo sequence (5.9) performed on a 27 year old healthy male volunteer, on a high-field clinical imaging system (Philips Achieva 3T, Philips Medical Systems, Best, The Netherlands). The imaging parameters were: repetition time (TR) = 2325 ms, echo time (TE) = 160 ms, number of signal averages = 1 and echo train length of 36 echoes, covering a field-of-view of 23 x 18.23 x 11.36 cm with an acquisition matrix of 512 x 178 - 213 x 142 interpolated to 1024 x 1024 x 284, giving a reconstructed image resolution of 0.22 x 0.22 x 0.4 mm, which is higher than the physical resolution.

To accommodate for the slight anisotropy in the spatial resolution of imaging data and to diminish partial volume effects due to the relatively large true voxel size, the sequence was performed three
times, each acquisition in a different cardinal orientation. These three data sets were aligned by minimizing the Euclidean distance between similar gray values. The registration was further enhanced using a quasi-Newton optimizer (5.10) and the datasets were merged using Lanczos interpolation (5.11).

The third ventricle and the aqueduct of Sylvius were manually segmented and the voxel-based 3D representation obtained was converted to NURBS surfaces (nonuniform rational B-spline). This approach ensured adequate smoothing of the domain surface which is necessary for the generation of a high-quality computational grid.

![Figure 5.1](image1.png)

**Figure 5.1:** a Drawing of the ventricular space in a human brain. Thr: third ventricle, Aq: aqueduct of Sylvius. (Based on Putz/Pabst: Sobotta, Atlas der Anatomie des Menschen, 20th ed. © Elsevier GmbH, Urban & Fischer Verlag.) b CSF mass flow rate in grams per second through the aqueduct of Sylvius during one cardiac cycle based on velocimetric MRI measurements. Positive values indicate cranial flow direction. R1: first flow reversal, R2: second flow reversal.

![Figure 5.2](image2.png)

**Figure 5.2:** Left: Rendering of the treated domain – third ventricle and aqueduct of Sylvius – with lines indicating the position of the section planes S1, S2 and S3. Right: Cross-sections of the third ventricle within the section planes. The arrows indicate the data sampling direction for the grid, time-step and period independence studies. Orientation of the cross-sections designated by a: anterior, p: posterior, l: left, r: right, f: feet, h: head.

### 5.2.2 MRI Brain Motion Data Acquisition and Processing

For measurement of the brain tissue displacement, the aforementioned volunteer was scanned with a complementary spatial magnetization modulation (CSPAMM) prepared sequence (5.12). In such tagging studies, the magnetization established within the body is sinusoidally modulated along one (or more) of the image axes prior to image acquisition. This produces a regularly spaced series of saturated lines in the image which serve as landmarks. The spacing and position of the lines in images made at different delays after tagging follow the displacement of tissue during the delay. Thus, tracking the lines
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throughout the cardiac cycle using a series of images reveals the brain motion information.

Figure 5.3: Reproducibility of feet-head brain motion data in the mid-sagittal plane obtained using CSPAMM and HARP. The MRI image (top left) shows the measurement locations. I: corpus callosum, frontal, II: frontal lobe, III: cerebellum, a: corpus callosum, central, b: corpus callosum, occipital, c: brain stem. The brain displacement at the last three locations are shown in the graphs a, b and c for two consecutive measurements in order to assess reproducibility. The beginning of the cardiac cycle, $t = 0$, where $T$ is the cycle length, is defined to coincide with the R-peak of the electrocardiogram (ECG).

The data were collected in a mid-sagittal slice using a tag distance of 2 mm (see Fig. 3). The scans were performed on a whole body MRI system (Intera 1.5T, Philips Medical Systems, Best, The Netherlands). Separate tag line preparation was performed in two orthogonal in-plane directions (cranio-caudal and anterior-posterior). The number of cardiac phases was chosen such that at least 120% of the R-R interval could be covered to allow indirect validation of the tracking error. Reproducibility of the measurements was assessed by two subsequent measurements on the same volunteer.

After tag preparation, the data were acquired with a turbo field echo (5.9) sequence with a turbo factor of three, $TR = 8.13$ ms and $TE = 3.8$ ms. A scan matrix of 256 x 256 pixels covering a field of 240 x 240 x 4 mm resulted in a spatial resolution of about 1 mm. The temporal resolution was 60 ms. Cranio-caudal displacement was finally quantified using harmonic phase (HARP) (5.13) post-processing, which allows the quantification of displacement values in the order of one tenth of the spatial resolution. A circular Gaussian band pass filter was used to extract the harmonic peaks in k-space containing the displacement information. A shutter width of 24 pixels yielded a HARP tracking resolution of about 5.3 mm (5.14).

Using least-squares error minimization, a 4th order Fourier series was fit to the timedependent displacement data of each measured brain location. This approach allowed to access displacement values at any point in time. Using MATLAB version 7 and the function tpaps of the SPLINE TOOLBOX version 3.1.1 (The MathWorks Inc., Natick, MA), the spatial distribution of displacement was approximated by fitting thin-plate smoothing splines through the measured locations. The thin-plate smoothing spline $f(x,y)$ is the unique minimizer of the weighted sum $S$, where

$$S = p \sum_i (d_i(x_i,y_i) - f(x_i,y_i))^2 + (1-p) \iint_{\mathbb{R}^2} \left( \frac{\partial^2 f(x,y)}{\partial x^2} + 2 \frac{\partial^2 f(x,y)}{\partial x \partial y} + \frac{\partial^2 f(x,y)}{\partial y^2} \right) \partial x \partial y, \ 0 \leq p \leq 1,$$

Equation 5.1
xi and yi are coordinates of the measured locations and di the corresponding displacement. The weight parameter p determines the contributions of the error measure of Eq. 1 (summation of displacement differences) and the roughness measure. With a p value of 0.9999, the maximum relative deviation between the measured displacement and the value approximated by the smoothing spline was less than 1‰. The displacement of the third ventricle and aqueduct boundaries was obtained by evaluating the function f(x,y) for every time-step at the location of projection of each surface grid node on the mid-sagittal plane.

5.2.3 MRI Flow Velocity Data Acquisition and Processing

A standard phase contrast velocity mapping sequence (5.9) was used on the same volunteer to acquire CSF velocity data in the aqueduct of Sylvius3. The measured slices were chosen perpendicular to the aqueduct in its caudal part. Due to the larger cross-section compared to the cranial part, the flow velocity of the cerebrospinal fluid is lower and more voxels that do not suffer partial volume effects can be obtained (5.15).

Figure 5.4. Phase contrast images of the inferior part of the aqueduct and its vicinity at a 26ms, b 207ms, c 337ms and d 1011ms of the cardiac cycle, where 0ms correspond to the R-peak of the ECG. The adjacent graphs show the CSF flow profile obtained from the phase contrast images.

The data were acquired with a turbo field echo read-out (turbo factor = 3), spatial scan resolution set to 288 x 216 and reconstructed to 512 x 512, covering a field of view of 250 x 211 x 5 mm, resulting in an in-plane resolution of 0.5 x 0.5 mm. The inferior part of the aqueduct was covered with 77 voxels. Since maximum velocity values in the range of 5 cm/s were expected (5.16), the encoding velocity was set to 7 cm/s in order to avoid phase wraps. A total of 40 cardiac phases were generated with a temporal resolution of 26 ms. Three signal averages were used to improve the signal-to-noise ratio.

Figure 5.4 shows phase contrast maps of the lower section of the aqueduct and its vicinity. As both the spatial and temporal resolution of the velocimetric MR data are lower than what is needed for accurate
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CFD calculations, the algebraic solution of the flow field at the inferior end of the aqueduct was reconstructed from the measured data using the theory of pulsatile flow in a pipe (5.17, 5.18). For this purpose, the aqueduct was regarded as a circular cylinder and the flow at its outlet section was assumed to be fully developed. The former is a plausible simplification, as the shape of the aqueduct is indeed approximately cylindrical, albeit with variable radius. The plausibility of the latter assumption can be verified as follows: The maximum Reynolds number (Re) and minimum Womersley parameter ($\alpha$) for the flow in the aqueduct can be calculated from the velocimetric MR data,

$$Re_{\text{max}} = \frac{u_{\text{max}} D}{\nu}, \quad \alpha_{\text{min}} = \frac{D}{2\nu} \sqrt{\frac{2\pi f_{\text{min}}}{\nu}},$$

Equation 5.2

where $u_{\text{max}}$ is the highest axial velocity – both locally and temporally – at the inferior end of the aqueduct of Sylvius, $D$ is the diameter of the aforementioned cylinder, $\nu$ is kinematic viscosity and $f_{\text{min}}$ is the cardiac cycle base frequency. In the case at hand, $Re_{\text{max}}$ is 70.9 and $\alpha_{\text{min}}$ is 2.9, which results in a hydrodynamic entrance length acceptably shorter than the length of the aqueduct (5.19-5.21). Consequently, the flow field at the inferior end of the aqueduct can be regarded as being fully developed. Assuming a harmonic driving pressure gradient, the velocity field can be calculated as

$$u(r,t) = \frac{ikR^3}{\mu \alpha^2} \left[ 1 - J_0 \left( \frac{A}{R} \right) J_0 (A) \right]^{-1} e^{i \omega t}, \quad A = \left( \frac{i-1}{\sqrt{2}} \right) \alpha,$$

Equation 5.3

(5.22), where $u$ is the axial velocity, $r$ is the radial location in the cylinder cross-section, $t$ is time, $i$ is $\sqrt{-1}$, $k$ is the amplitude of the driving pressure gradient, $R$ is the pipe radius, $\mu$ is dynamic viscosity, $\alpha$

is the Womersley parameter, $J_0$ is the Bessel function of first kind and order zero and $\omega$ is the angular frequency of the pressure gradient. By integrating Eq. (3), the mass flow rate is obtained,

$$m(t) = \frac{k B}{\alpha^2} e^{i \omega t}, \quad B = \frac{i \pi R^4}{\nu} \left[ 1 - \frac{2J_1(A)}{AJ_0(A)} \right],$$

Equation 5.4

where $J_1$ is the Bessel function of first kind and order. As the pressure gradient driving the flow in the aqueduct of Sylvius is periodic, it can be described using a Fourier series, so that from Eqs. (2, 4) and Poiseuille’s law (5.23) the mass flow rate can be expressed as

$$m(t) = \frac{k_0 \pi R^4}{8\nu} + \frac{1}{\alpha^2} \sum_{n=1}^{\infty} \left( k_{2n-1} Re\left( Be^{i \omega t} \right) + k_{2n} Im\left( Be^{i \omega t} \right) \right),$$

Equation 5.5

where Re and Im designate real and imaginary parts, respectively. This mass flow rate has to be equal to the one obtained by integrating the velocity field measured with velocimetric MR. Using weighted least-squares error minimization, the coefficients $k$ were calculated and, hence, the velocity profile at the inferior end of the aqueduct was determined.

5.2.4 CFD Calculations

For the computational fluid dynamics calculations, the CSF was regarded as an incompressible Newtonian fluid with the same material properties as water at 37°Celsius (5.5, 5.24). A non-uniform, unstructured computational grid consisting of about 558,000 tetrahedral elements was used in conjunction with the finite-volume code FLUENT (Fluent Inc., Lebanon, NH). The time step size was chosen to be $t = 1/1,000 T$, where $T$ is the length of one cardiac cycle. Second order of accuracy in space and first order of accuracy in time along with an
Implicit Algebraic Multigrid scheme and the PISO (5.25) pressure correction method constitute elements of the solution methodology. No-slip boundary conditions (BC) were specified at the ventricle and aqueduct walls. A zero pressure BC was assumed at the foramina of Monro. A transient velocity BC based on MRI data as described above was prescribed at the inferior end of the aqueduct of Sylvius. The domain wall motion was taken into account by specifying the position of each boundary grid node at each time step based on brain motion scans. Zero velocity and zero pressure throughout the domain were chosen as initial conditions. Grid independence, time-step independence and period independence studies were carried out successfully (see appendix).

5.3 Results

At the beginning of the cardiac cycle, the cerebrospinal fluid flows in cranial direction, as seen in Figure 5.1b (positive mass flow rate). A jet directed towards the foramina of Monro exits the aqueduct of Sylvius with a peak velocity of slightly less than 12 cm/s. Both superior and inferior of the jet, areas of recirculation form (hereinafter referred to as the first and second recirculation respectively, see Figures 5.5 and 5.6).

A third area of recirculation centered between the recessus opticus and the commissural anterior, caudal of the foramina of Monro, dissipates by the first flow reversal.

Initially, the first recirculation is centered at the height of the recessus pinealis. By the time the first flow reversal occurs 19% through the cardiac cycle, Fig. 1b, the recirculation center has traveled cranially along the jet and is positioned midway between the recessus pinealis and the adhesio interthalamica (Fig. 6). The second recirculation is initially clearly smaller than the first one, as it is restricted by the inferior wall of the third ventricle. The center of this recirculation also travels in cranial direction, reaching a position ventral to the adhesio interthalamica at the center of the third ventricle. Part of the CSF streaming back after the flow reversal is deflected caudally by this second recirculation, flowing along the inferior wall of the third ventricle into the aqueduct of Sylvius. A smaller part is deflected in cranial direction by the first recirculation, flowing along the superior wall of the ventricle and then in caudal direction towards the aqueduct, without entering the recessus suprapinealis and recessus pinealis.

Figure 5.5: Streamlines in the mid-sagittal plane of the third ventricle at 0, 25%, 50% and 75% of the cardiac cycle with period T. I, II and III: 1st, 2nd and 3rd area of recirculation as referred to in the results section. Ro: recessus opticus, Co: commissura anterior, Ad: adhesio interthalamica, Rp: recessus pinealis, Rsp: recessus suprapinealis. As the brain motion amplitude is two orders of magnitude smaller than the length scale of the domain, the deformation of the third ventricle cannot be discerned from this figure.
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Halfway through the cycle, the second recirculation has become the dominating flow feature, deflecting virtually all of the fluid in caudal direction and feeding the first recirculation, whose center has returned close to its original location. This recirculation causes the CSF to first flow in cranial direction and again along the superior ventricle wall in caudal direction into the aqueduct. The second flow reversal through the cycle weakens the now dominating second recirculation and transports its center towards the recessus opticus.

Figure 5.6. Paths of the centers of the main recirculations during one cardiac cycle projected onto the mid-sagittal plane. I: path of the first recirculation as referred to in the results section, II: path of the second recirculation, III: path of the third recirculation. The Arabic numerals along the paths indicate temporal position of the centers relative to the cardiac cycle (0, 19%, 25%, 50%, 75% and 90%).

At the end of the cycle, the second recirculation corresponds to the one referred to as third recirculation at the beginning of the cycle. The first recirculation, which was being fed by the second recirculation until the second flow reversal occurred, is also weakened and carried towards the recessus suprapinealis. By the time the cycle is 90%

through, the jet emerging from the aqueduct has become the driving force for the first recirculation. The recirculation is strengthened and moves back down to its initial position at the beginning of the cycle.

The highest velocities in the treated domain are observed in the narrowest cross-sections of the aqueduct of Sylvius, reaching peak values of 16.7 cm/s in caudal direction and 14.7 cm/s in cranial direction. Velocities up to approximately 12 cm/s in caudal direction are observed in the inferior section of the third ventricle within the region of the jet emerging from the aqueduct. Outside the jet, maximum absolute velocities in the third ventricle are generally below 1 cm/s. Maximum velocities in the foramina of Monro are 2.6 cm/s in caudal direction and 2.2 cm/s in cranial direction. The velocities in all of the recessi are below 0.1 cm/s. Figures 5.7 to 5.9 show velocity contour plots at selected cross-sections of the third ventricle, whose locations are depicted in Figure 5.2.

CSF flow throughout the domain is laminar. The maximum Reynolds number (Re_{aq}) observed in the aqueduct is 340. Re_{aq} is defined as

$$Re_{aq} = \frac{\rho \cdot V_{max} \cdot D_{min}}{\mu}$$

Equation 5.6

where \(\rho\) is density, \(D_{min}\) is the diameter of the smallest cross-section of the aqueduct, \(V_{max}\) is the maximum flow velocity at that location and \(\mu\) is dynamic viscosity. The Reynolds numbers in the rest of the domain are clearly lower, owing to the fact that as the flow area increases, the velocity has to, as a first approximation, decrease inversely proportional to that increase of area due to mass conservation. Since the flow area is
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proportional to the square of its diameter, the Reynolds number will decrease. The pressure difference between the inferior end of the aqueduct and the foramina of Monro reaches maximum values of approximately 20 Pa. Approximately three quarters of the pressure loss occurs in the aqueduct of Sylvius. Figure 5.10 shows pressure iso-surfaces in the third ventricle at different times.

**Figure 5.7**: Contour plot of normal velocities in the cross-section $S_1$ (see Figure 5.2) at 0, 25%, 50% and 75% of the cardiac cycle with period $T$. Values are given in cm/s.

**Figure 5.8**: Contour plot of normal velocities in the cross-section $S_2$ (see Figure 5.2) at 0, 25%, 50% and 75% of the cardiac cycle. Values are given in cm/s.
The volume change of the third ventricle due to the motion of its walls in feet-head direction is shown in 5.11. Two features stand out: first, the volume displaced by the third ventricle due to feet-head brain motion is significantly smaller than the volume passing through the aqueduct of Sylvius during one cardiac cycle. Second, as CSF flows in cranial direction, the combined volumes of the third ventricle and aqueduct decrease. The volumes increase again during caudal flow. The former observation indicates that the feet-head motion of the third ventricle walls is only marginally responsible for the pulsatile motion of CSF. The latter appears to be counterintuitive at first, but can be explained if one bears in mind that only feet-head motion has been taken into account: As the brain moves upwards during diastole (5.26), its caudal parts are displaced farther than the cranial ones, causing the third ventricle to be compressed in feet-head direction. At the same time, however, the brain also moves outwards, causing the third ventricle walls to bulge out. It can be assumed that the contraction of the third ventricle due to feet-head brain motion is overcompensated by expansion due to motion in the remaining directions. Therefore, the overall volume of the third ventricle and aqueduct is expected to increase during cranial CSF flow and decrease during caudal flow. As the lateral and fronto-occipital motion of the third ventricle walls portray smaller amplitudes than the feet-head movement, they are unlikely to be the main driving force of CSF pulsation.
Figure 5.11. Plots of volume and volume flow rates during one cardiac cycle. The solid curve represents the volume of the third ventricle and aqueduct throughout the cycle relative to their volume at $t = 0$. The dashed curves represent the volume flow rates through the inferior end of the aqueduct of Sylvius and through the foramina of Monro.

5.4 Discussion

The basis of the simulation of cerebrospinal fluid flow in the third ventricle and the aqueduct of Sylvius as presented above are MRI scans of an individual. Therefore, the accuracy of the simulation is first and foremost governed by the accuracy of the MRI data acquisition. Velocimetric MRI acquisition can be performed reliably, if partial volume effects are minimized, if concomitant fields are avoided and eddy currents are corrected (5.27, 5.28). Due to the large size of the inferior part of the aqueduct, partial volume effects are indeed negligible. By positioning the region of interest in the isocenter of the magnet, concomitant fields are avoided. Eddy current correction is performed based on parts of the brain tissue that portray negligible displacement amplitudes.

Anatomic MRI scans cannot resolve the detailed surface structures of the choroid plexus, which are on the scale of microns. We believe that neglecting these structures in the third ventricle will have limited influence on the flow field, as they are located predominantly at the ventricle’s top wall, where flow velocities are low. The quality of the segmentation performed to isolate the flow domain, on the other hand, has a large influence on the accuracy of the simulations and must, therefore, be carried out with great care.

MRI tagging can be used to capture the brain motion in feet-head direction (maximum amplitude 0.25 mm). However, it will not capture the motion in the remaining directions, which generally portray amplitudes less than 0.15 mm, with sufficient accuracy (5.29) with currently available techniques. The volume change of the treated domain due to feet-head motion of its walls constitutes roughly 1% of the CSF stroke volume (see Figure 5.11). It has only a marginal effect on the cerebrospinal fluid flow. The effect of the wall motion of the remaining ventricular structures is accounted for by the velocity field specified at the inferior end of the aqueduct of Sylvius. This velocity boundary condition also takes into account the overall mass flow caused by the lateral and fronto-occipital motion of the third ventricle and aqueduct walls.

However, as the lateral and fronto-occipital motion of the third ventricle walls will (to a yet unknown extent) also influence the local flow field, more advanced MRI techniques should be applied to capture the wall motion in every direction (5.30).
The narrow and twisted shape of the foramina of Monro renders the accurate acquisition of velocimetric MRI data difficult. By using a constant pressure boundary condition instead, the introduction of virtual flow features due to MRI noise is avoided. At the same time, some real flow features may be suppressed as well. Incorporating the lateral ventricles into the computational domain would render this boundary condition obsolete. However, it would also significantly increase the needed computer resources.

The resolution of current MRI scanners is not high enough for a direct validation of the results presented here. Validation of the methods used could be performed using a transparent phantom of the third ventricle and aqueduct of Sylvius and non-intrusive optical techniques for velocity measurements. This would signify a major experimental effort, as the wall motion of the phantom would have to be taken into account.

5.5 Conclusion

We have shown that it is possible to combine anatomic, velocimetric and magnetization modulated MRI scans with CFD simulations to reconstruct the CSF flow field in the third brain ventricle and the aqueduct of Sylvius. The feet-head motion of the domain walls has only a marginal effect on the cerebrospinal fluid flow.

The significance of third ventricle wall motion in the remaining directions for the local CSF flow field remains unknown, as the motion was accounted for only indirectly by a velocity boundary condition at the inferior end of the aqueduct of Sylvius. The methods described herein can be used without significant modifications to calculate the flow in the entire ventricular system.

Interventions that seek to influence the CSF flow, such as the placement of a shunt for the treatment of hydrocephalus, will profit from the detailed knowledge of cerebrospinal fluid flow. Current shunts drain CSF when the static pressure of the cerebrospinal fluid exceeds the opening pressure of the shunt valve. The use of CSF pressure as the sole valve control parameter is suboptimal (5.31). Ideally, the amount of cerebrospinal fluid to be drained would be determined in real time based on a model of the patient’s CSF space that is embedded in an intelligent shunt’s control system. The calculations presented here represent a first step towards such a model.

Intracerebroventricular administration of morphine is an example of the use of CSF as a pathway to the brain (5.32). Knowledge of the transient distribution of morphine concentration in the binding sites may help determine the optimal amount to be administered. To this end, the characteristics of morphine transfer from CSF into the brain tissue and the fluid dynamics of cerebrospinal fluid have to be known. The model shown in this paper constitutes a part of the latter requirement.

5.6 Appendix

5.6.1 Independence Studies

The grid independence study was carried out using three different grids, where the coarsest one consisted of roughly 257,000 tetrahedral elements, the medium one of 558,000 and the finest grid of 811,000. Pressure and velocity contours at several cross-sections of the domain were compared at different simulation times. It could be shown that the medium grid is sufficient to capture all of the important flow features accurately. Figure 5.12 shows plots of normalized pressure at selected cross-sections for each grid.

Time-step independence was assessed by carrying out the computations for the first period using time step sizes of \( T/100 \), \( T/1,000 \) and \( T/10,000 \). The choice of the first period to carry out this study is a
conservative one, as at this point high-frequency flow features are present due to the initial conditions. A time-step size of T/1,000 proved to be sufficient.

Period independence was evaluated by carrying out the calculations over six periods and comparing velocity and pressure contours of the last three periods. Table 5.1 summarizes the results of this and the other independence studies. The relative error listed in the table is defined as

$$e = \left| \frac{P_{\text{fine}}(t,x) - P_{\text{medium}}(t,x)}{P_{\text{fine}}(t,x)} \right|,$$

Equation 5.7

where e is relative error, p is pressure, t is time within the cardiac cycle and x is spatial position within the calculated domain. The subscripts “fine” and “medium” refer to calculations carried out with the fine and medium grid, respectively, for the grid independence study. For the remaining independence studies, they refer to the corresponding time-step size and number of calculated periods.

Figure 5.12: Plots of normalized pressure along vectors through the third ventricle as calculated with three grids of different density: coarse: 257,000, medium: 558,000 and fine: 811,000 tetrahedra. a Normalized pressure along the vector shown in Figure 5.2 at the cross-section S1 34% through the cardiac cycle, b S2, $t = 0.34T$, c S3, $t = 0.34T$. 
Chapter 6

6 Outlook

To date research on mechanics of the brain mainly concentrates on investigations of brain tissue ex-vivo or under surgery, i.e. on the open skull. In this dissertation MRI was used to investigate the dynamic behavior of the central nervous system under ‘normal’ conditions. Therefore, the pulsatility of the cerebrospinal fluid and brain tissue were investigated in detail. MR sequences were adapted to the needs of measuring very small displacements within the skull. Thus, boundary conditions for computational fluid dynamics simulating the flow in the cerebral ventricles could be provided. First simulation results of the 3rd ventricle were presented. Additionally, the three dimensional brain parenchyma motion measurements themselves directly allowed studies on the spatiotemporal behavior of brain tissue. The method introduced for three-dimensional tissue displacement can potentially serve in different fields of medical research. In general any pulsatile small motions in the body, such as vessel wall motions or small contractions of muscles may be detected with the proposed method.

Even for the brain itself, there is a variety of applications in medical research to be explored. As already stated above only very little is known about the elastic behavior of brain tissue under normal in-vivo conditions, even for healthy subjects. In principle, the method for brain motion determination described in Chapter 4 allows an estimation of these elastic properties. Therefore, temporal and spatial derivations have to be calculated from the measured displacement data. These numerical operations are very prone to errors arising from noisy data. Consequently, higher signal-to-noise ratio than achieved today is desired.

Higher field strengths potentially increase the signal-to-noise ratio. Going from the static field strength of 3T to 7T therefore promises a significant improvement in SNR. However, some technical issues arising with the new equipment like B1 and B0 inhomogeneities need to be overcome. Combination with new motion correction schemes and/or less motion sensitive readout schemes may further improve motion sensitivity. Hence, the capture of the pulse shear wave propagation throughout the brain will be facilitated.

Next to getting better knowledge on the mechanical properties of brain tissue, the application of brain tissue displacement measurements may then offer a new contrast mechanism for different diseases changing the mechanical properties of brain tissue, (e.g. tumors).

Combining the derived knowledge on brain elasticity again with the cerebrospinal fluid flow and with computational fluid dynamics based on subject specific geometries of the brain opens the possibility to investigate case specific dynamics on a computer model even more accurately.

There are plenty of applications for an elastic and dynamic model of the brain, drug delivery processes through CSF, brain pressure regulations, etc. Such a tool might for example help in developments of new devices or improved shunts in hydrocephalus. The simulations might allow checking on the effects of shunting in dependence of its location in the individual patient’s brain before implantation, and potentially teach intelligent shunts the special in-vivo condition of the specific patient before surgery. The risk of non-effective surgeries or non-optimally distribution of drugs delivered via the CSF can thus be reduced.
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