IN-VITRO MODEL OF INTRACRANIAL PRESSURE AND CEREBROSPINAL FLUID DYNAMICS

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Abstract

The intracranial cavity experiences complex biological as well as fluid-mechanical interactions. There, brain, blood and cerebrospinal fluid (CSF) cooperate to preserve the homeostasis of the central nervous system (CNS). The brain and spinal cord float within a bath of CSF that is pressurized with respect to the atmosphere. In healthy conditions, circulation of blood and CSF minister the optimal fluid-dynamic state for the CNS, in terms of mechanical stability, as well as transport of nutrients and waste products. Alterations of intracranial fluid dynamics associate with disorders, such as hydrocephalus and traumatic brain injuries, which might ultimately damage the CNS.

The present thesis addresses the demand of an in-vitro model of intracranial pressure (ICP) and CSF dynamics that would fill the gap between standard numerical or computational models (in-silico) and animal or patients studies (in-vivo).

A first-of-its-kind life-size phantom model is presented in this thesis. The intracranial domains including ventricular, cisternal and subarachnoid spaces (SAS) were derived via magnetic resonance imaging (MRI) and combined to a brain and skull with realistic anatomical shape and mechanical properties. Brain elasticity and cranio-spinal compliance were set based on published data. Bulk and pulsatile physiologic CSF flows as well as ICP were modeled for standard healthy conditions. Model validation was carried out by comparisons of flow and pressure measurements obtained in the phantom with published in-vivo data.

Major intracranial arteries were included in a second generation phantom, and their cardiovascular contribution to the modulation of ICP pulsation was evaluated. MRI was used to design the internal carotid arteries (ICAs), basilar artery (BA) and the circle of Willis (CoW). Arterial mechanical properties for healthy subjects were retrieved from published data, and a novel protocol was developed for the molding of a realistic cerebro-vascular domain. Our results show that cardiovascular blood pulsation in the major intracranial arteries
only partially contributes to induce ICP pulsation, and other vascular entities such as the choroid plexus, veins and smaller arteries are needed to yield the intricate ICP waveforms observed in-vivo.

A third study is presented, in which the development of a non-linear physiologic CSF compliance for in-vitro models is introduced. The state of the art is reviewed and tested experimentally. A novel feedback controlled device for the reproduction of physiologic and pathologic CSF pressure-volume relations is presented.

The active compliance device was used to design a novel generation phantom that accounts for independently tunable exponential CSF pressure-volume relation, physiologic outflow resistance as well as venous pressure. Three infusion tests methods, which represent the neurosurgical standards in the clinical settings for diagnosis of hydrocephalus, were performed on the phantom. The constant flow and constant pressure methods revealed a more accurate estimation of CSF outflow resistance in comparison to the bolus method.

A viscoelastic theory is introduced herein to explain the inaccuracy of the bolus infusion method. A numerical approach is adopted to explain the impact of brain viscoelasticity on the performances of infusion tests. The viscoelastic model is proposed to application in the clinical settings for a more accurate derivation of CSF outflow resistance and other physiological parameters.

The development of an actively controlled shunt for the treatment of hydrocephalus is finally proposed. The presented phantom is ultimately proposed as in-vitro model of ICP and CSF dynamics for the development of such a device, offering as ideal platform for its evaluation in the prototyping phase, next to numerical and animal tests.
Il sistema nervoso centrale (CNS) è protetto da complesse interazioni biologiche e fluido-mecaniche che ne mantengono l’omeostasi. Il cervello e la spina dorsale sono immersi in un bagno di fluido cerebrospinale (CSF) lievemente pressurizzato, che li sorregge evitando l’insorgere di picchi di carico localizzati. In condizioni fisiologiche, la circolazione sanguigna e quella di CSF amministrano una fluido-dinamica ottimale per il CNS, in termini di stabilità meccanica ma anche di trasporto di nutrienti e rimozione dei prodotti di scarto. Alterazioni della fluido-dinamica intracranica sono responsabili di disturbi, come l’idrocefalia e il trauma cranico, che possono in ultima sede danneggiare il sistema nervoso centrale.

Nel presente lavoro si descrivono il disegno e lo sviluppo di modelli anatomici funzionali per lo studio in-vitro delle dinamiche di pressione intracranica e fluido cerebrospinale. Tali modelli mirano a colmare la distanza tra gli studi computazionali (in-silico) e i test animali o gli studi clinici (in-vivo).

Un primo modello anatomico della cavità intracranica, unico nel suo genere, include la ricostruzione dei domini anatomici intracranici di CSF, tra cui i ventricoli cerebrali, le cisterne e lo spazio subaracnoideo (SAS), ottenuti tramite ricostruzione tridimensionale d’immagini in risonanza magnetica (MR) su soggetti sani. L’uso di tecniche di prototipazione rapida permette la fabbricazione dettagliata dei domini anatomici. Siliconi con proprietà meccaniche simili a quelle del tessuto cerebrale sono stati utilizzati per generare uno stampo del cervello umano da accoppiare alla circolazione di CSF, e la complianza fluido-mecanica della cavità intracranica è stata calibrata sulla base dei valori pubblicati in letteratura. Si dimostra come la risposta fluido-dinamica del modello in-vitro sottoposto sia a circolazione stazionaria che pulsatile rifletta quella di un soggetto sano standardizzato. Le misure di pressione intracranica e dei flussi di CSF sono comparative ai valori fisiologici riportati in letteratura e dimostrano l’accuratezza del modello.

In un modello di seconda generazione le principali arterie cerebrali sono incluse con l’intento di valutare l’impatto della pulsazione
sanguigna al loro interno sulla generazione di oscillazioni nella pressione intracranica. La ricostruzione delle arterie carotidee interne, l’arteria pontina e il circolo di Willis è realizzata attraverso un protocollo innovativo che permette di produrre le pareti di tale complesso arterioso a partire da immagini MR. Il poli-dimetilsilossano è un silicone a due componenti i cui parametri di polimerizzazione sono stati calibrati al fine di ottenere le stesse proprietà meccaniche delle pareti arteriose di soggetti sani per il modello in-vitro. L’imposizione di pulsazioni cardiovascolari fisiologiche nelle arterie modellizzate evidenzia una generazione di oscillazioni in pressione nel fluido cerebrospinale, ma si conclude che altre entità vascolari come i plessi coroidei, arterie minori e vasi venosi, siano indispensabili per la formazione delle complesse forme d’onda registrate per le pressioni intracraniche in-vivo.

La riproduzione in-vitro della complianza dello spazio craniospinale è il soggetto del terzo studio presentato in questa tesi. Tale complianza mostra caratteristiche non lineari in-vivo. Lo stato dell’arte è stato riprodotto con test in laboratorio ed un’analisi critica di vantaggi e svantaggi è riportata per ciascun metodo. Si presenta un modello innovativo, che utilizza un motore lineare controllato da un computer: tale modello permette il controllo attivo della complianza craniospinale e la riproduzione delle sue caratteristiche non lineari sia fisiologiche che patologiche.

Il sistema di complianza attiva è stato utilizzato infine per la costruzione di un modello in-vitro di ultima generazione. L’introduzione di una complianza non lineare, efficace in un vasto intervallo di variazioni volumetriche, in combinazione con una resistenza regolabile per l’assorbimento del CSF e un riferimento per la pressione venosa, è un pre-requisito per la modellizzazione in-vitro di test clinici, tra cui i test d’infusione e l’impianto di shunt cerebrali. Tre test d’infusione che rappresentano gli standard clinici eseguiti in neurochirurgia sono stati testati su questo modello di ultima generazione. Il metodo “bolus” ha mostrato la stessa inaccuratezza riportata in letteratura per studi clinici, quando comparato ai metodi a “pressione costante” e “portata costante”.

Una teoria viscoelastica è perciò introdotta per giustificare l’inaccuratezza del metodo bolus. Simulazioni numeriche dei test
d’infusione dimostrano che la viscoelasticità dei tessuti soffici, come il tessuto cerebrale, debba essere tenuta in considerazione nei test clinici di neurochirurgia per evitare errori di diagnosi e migliorare la cura dei pazienti.

Il modello in-vitro delle dinamiche intracraniche, e il suo accoppiamento a sistemi di simulazione numerica, è infine suggerito come piattaforma per lo sviluppo di prototipi di shunt cerebrale a controllo attivo.
I would like to express my sincere gratitude to Professor Poulikakos, for his supervision, his will in hosting this project and most of all his ability in creating such an extraordinary work environment. His outstanding leading skills, a balanced mixture of sharp speaking and pragmatic thinking, have been mirrors for the whole group through these years.

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A PhD thesis means a lot of things: a lot of work done, a lot of information learnt, a lot of hypothesis assumed, a lot of attempts failed, a lot of knowledge gained, a lot of persons to work with. Some
of these things will slowly dilute in the flow of time and be forgotten, but there is one person that I will never forget because he has shared every single piece of my “a-lot-of-things”: Sghi, you have been the best ALL-mate and you have changed my perspective of things. Thanks Daniele. I am proud to have changed your accent...

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1 Introduction

When Mary Shelley wrote her science-fiction novel “Frankenstein; or, the Modern Prometheus” in 1818, biomedical engineering was living its embryonic stage in the mind of French physician René Laennec, whose modesty in placing his ear next to a woman’s chest made him roll up “a quire of paper into a kind of cylinder” and listen through it, triggering the idea for the invention of today’s stethoscope (Laennec, 1819). Whereas science fiction was provokingly suggesting the full manipulation of technology towards the generation of laboratory life, it took the whole second industrial revolution to merely set the basis for modern biomedical engineering, and the rest of recent history to initiate the related ethical debates.

With a clear literal reference to the Judaism, addressing Dr. Frankenstein, Mary Shelley’s creature refers to himself as someone who "would have been the Adam of your labors", but is instead a "fallen angel", highlighting that only time can uncover the whole nature of an invention (Shelley, 1818). Despite the moral integrity of a scientist's intentions, the improper use of inventions might reveal a unpredictable negative side of the coin in future applications. In the Western tradition, Prometheus has become the icon of the human quest for scientific knowledge, and the responsibility of taking risks with unintended consequences.

Prometheus’ destiny has been shared by a number of scientific talents. As most representative, the work by Albert Einstein has manifested the two sides of the coin with setting the fundamentals for the development of both nuclear energy and the atomic bomb. Gifted with an extraordinary talent, Einstein investigated quantum physics with the objectives of finding answers to fundamental natural questions. Despite his findings sourced the potential of sustainably dispensing energy to the whole world, the first application of his theory was meant to military purposes, showing the disgraced consequences of an unethical use of science. Given the ultimate goal of improving health by interfacing medicine to technology, biomedical engineering must be accompanied by constructive ethical debate that prevents from unethical use of its innovation.
Ancient history is riddled with disconnected anecdotes that could be nowadays defined as pioneer biomedical engineering. First reported attempt of interfacing the human body to a cosmetic prosthesis can be tracked back to ancient Egyptians: In the 2000 A.D. a mummy of a woman was found in a tomb near the city of Thebes with a wood-leather artificial big toe on her the right foot implanted as religious ritual, and archaeologists dated it between 1550 and 700 B.C. (Nerlich et al., 2000). On the other hand, history of Middle West is marked by a long cultural dominium of Roman Catholic Church that curbed most of non-spiritual operation of the human body. It took till the end of Middle Age and the dawn of Renaissance, to initiate empirical investigation of human anatomy by the genius of Leonardo Da Vinci (O'Malley & Saunders, 1952). His, back then considered un-ethical, work paved the basis to modern anatomy and ergonomics.

It was only during the second half of the twentieth century that today’s concept of biomedical engineering was born. The advent of plastic synthetic materials and the invention of magnetic resonance imaging (MRI) (Lauterbur, 1973) can be acknowledged as the main boaster of a scientific development, whose highest peak is yet to come. Since industrial processing of synthetic polymers has boomed, medical milestones in the field of bio-fluid dynamics such as extracorporeal circulation and assisted dialysis have been reached; without accounting for the terrific impact on everyday life that has accompanied the commercialization of disposable equipment such as contact lenses, syringes and condoms. On the other hand, MRI has revolutionized the concepts of pre-interventional diagnosis and surgical planning, as well as given to engineers an unprecedented access to information for the design of implantable bio-device.

Since then, technology has drastically changed the health care system and improved the quality of life to points that not even novelists and science fiction had forecast. Outstanding minds such as Stephen Hawking wouldn’t have the chance of contributing to the ongoing debate on relativistic physics if it were not for a speech generating device. Next to improvements for disabled, life-assisting and life-sustaining devices are even capable of maintaining the basal body functioning in advanced stage dystrophic or tetraplegic patients, as well as in case of cerebral death: This has accompanied the latest ethical intellectual fight concerning biomedical engineering, related
to euthanasia, which has found in the Italian poet Piergiorgio Welby perhaps its most representative pro-activist.

The design of any biomedical device requires access to anatomical and physiological data. MRI provides engineers not only with two- and three-dimensional quantification of anatomical structures, but also with other important design specifications such as fluid velocimetry (Elkins & Alley, 2007). However, other quantitative assessments are not resolved by MRI techniques yet, such as intracorporeal pressure measurements, and remain to be performed invasively. With respect to the brain and its surrounding, cerebral blood perfusion and cerebrospinal fluid (CSF) flows have been precisely resolved by MRI velocimetry and computational fluid dynamic (CFD) approaches (Kurtcuoglu, 2011; Wagshul et al., 2011). Intracranial pressure (ICP) has on the other hand only been measured during animal and patient studies, providing in-accurate data with respect to a normal healthy human subject, next to rising ethical concerns on the use of animals and patients for research purposes. Progress in engineering allows nowadays for the development of novel alternative experimental models that would assist animal and patient studies, by promoting a fully ethical investigation of intracranial dynamics.

In the work presented herein we have designed and developed a phantom of the intracranial cavity to in-vitro model and investigate the dynamics of CSF and ICP. We have utilized the state-of-the-art literature, with respect to MRI studies, animal and patients recordings, as well as novel protocols for the shaping of synthetic polymers to manufacture an anatomical replica of the human brain where realistic fluid-mechanical conditions are reproduced for both the physiological and pathological cases.

A similar scientific approach has been adopted in many other biomedical engineering fields, of which the most representative and best known example is likely to be the design of an artificial heart. From an engineering standpoint, an artificial heart is nothing but a phantom model of cardiac pulsation with respect of blood flow and pressure, which is meant to be fully implanted in the human body as substitute of the biological heart. Aside from the implantation requirement, our phantom model aims for an analog objective: The
setup is conceived as substitute platform to animal and patient case studies. It represents a test-rig that aims to the testing of diagnostic tools, such as CSF infusion tests, and of implantable devices, such as cerebral shunts, in their prototyping phases.

Cerebral shunts are standard neurosurgical solutions for the relief of ICP and abnormal storage of CSF as consequence of e.g. traumatic brain injury or hydrocephalus. Hydrocephalus is a condition that manifests with an accumulation of CSF within the intracranial cavity. It is a disorder of CSF circulation that cannot be cured by medical therapy. However, it can be observed via MRI, assessed by infusion tests and reversed by shunt implant.

In different forms, hydrocephalus statistically affects infants and elderlies. According to “The Hydrocephalus Foundation” (910 Rear Broadway, Saugus, MA) and the “Hydrocephalus Association” (4340 East West Highway, Bethesda, MD), one to two of every one thousand babies are born with hydrocephalus in the US, making it as common as Down’s syndrome and more common than brain tumors, and by far the most common reason for brain surgery in children. On the contrary, idiopathic normal pressure hydrocephalus (NPH) is most common in adults over the age of 60 years (Black et al., 1985; Petersen et al., 1985). The occurrence of NPH has been reported to range between 2 to 20 per million per year (Krauss & Halve, 2004b; Tisell et al., 2005b; Klassen & Ahlskog, 2011a).

NPH as defined today is a neurological disorder that associates with the “Hakim triad” symptoms of dementia, gait disturbance, and urinary incontinence (Adams et al., 1965; Hakim & Adams, 1965). Dementia manifestations often lead to rushed misdiagnosis, confusing NPH for Alzheimer’s or Parkinson’s disease, by non-prepared physician. A recent review study (Siedlecki, 2008) has estimated that more than 750 thousands Americans are affected by NPH, but less than 20% receive an appropriate diagnosis and treatment; 5 to 10 % of all patients diagnosed with senile dementia in the United States might actually have NPH, with a total amount accounting to 375,000 people. NPH, unlike Parkinson’s and Alzheimer’s diseases, is a potentially reversible neurological condition: Patients affected by NPH might live in in the belief of being
affected by a degenerative irreversible syndrome, unaware that shunt treatment could instead recover them to a normal quality of life.

Misdiagnosis is associated with a broader socio-political concern. On the one hand, the necessity of rising awareness on NPH among population and non-specialized doctors is evident: Accompanied by the fact that population age is rising in most of the developed countries, and with it the occurrence of NPH, it is imperative that health care providers learn to recognize the symptoms of NPH. On the other hand, this also lead to a potential risk of health care systems being driven by un-ethical business practices: Insurances have to assist in the access to appropriate diagnostic tool, such as MRI facilities and infusion tests, in order to correctly diagnose NPH and selectively target patients who would effectively benefit from surgery, without neither over- or under-providing health care services.

This work was produced in this historical, technological, socio-political and ethical background. Although far from giving life to clay as the Titan Prometheus or the Jewish God, or even from assembling creatures such as Dr. Frankenstein, biomedical engineering possesses nowadays the technological background as well as covers the socio-political task of assisting medicine in improving health care and life quality in its widest sense. This thesis aims to humbly contribute to the long lasting path of this mission, with the hope that this work as well as all the past and upcoming medical research will be ethically used as “Adam of science” and won't give birth to “fallen angels”.

In this larger contest, the scope of this thesis is to address the demand for an in-vitro model of ICP and CSF dynamics that would fill the gap between standard numerical models (in-silico) and animal or patients studies (in-vivo).
Thesis Outline

The thesis is divided into seven main chapters including this introductory chapter (Chapter 1). The bulk of the authors PhD work is contained in Chapters 3 through 6.

Chapter 2 presents the anatomical, as well as the physiological and theoretical background of cerebrospinal fluid and intracranial pressure required to understand the following chapters and critically interpret results and conclusions.

Chapter 3 describes a novel phantom model of physiologic CSF and ICP dynamics. MRI techniques, as well as rapid prototyping and molding protocols to develop the phantom are reported and explained. Literature of both continuous and cardiovascular CSF dynamics is reviewed, and a standardized healthy subject is defined with physiological parameters to model with the phantom. The physics and technology of the components designed to in-vitro reproduce CSF dynamics are described. ICP and CSF flow patterns in the cerebral aqueduct as well as subarachnoid space are analyzed.

In chapter 4 the question on the cardiovascular origin of ICP pulse is addressed. The physiological background of ICP waveform is introduced, together with the un-resolved debate regarding its actuation from heart pulsation. A unique phantom model of major intracranial arteries and CSF domains is described. The role of the arterial complex consisting of internal carotid arteries, basilar artery and circle of Willis, in generating ICP pulse waveforms is investigated, and the contribution by the remainder blood vessels is deducted.

Chapter 5 reviews the state-of-the art in phantom modeling of physiopathological CSF pressure-volume relations. A detailed physical description of those methods is reported, and a novel actively controlled system is presented, to reproduce subject specific non-linear CSF compliance.

Chapter 6 describes the implementation of this actively controlled compliance on the phantom reported in chapter 2. The phantom
response to neurological infusion tests is reported, and the accuracy of each test is investigated. A viscoelastic theory is developed that explains the error reported by clinical studies in the literature, when the bolus infusion method is adopted. A theoretical description of this concept is reported as well as proven with a numerical model.

Chapter 7 concludes this thesis by summarizing the main achievements and outcomes of the current work, as well as proposing an outlook for suggested future research.
Nomenclature

*Abbreviation*

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<th>Abbreviation</th>
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<tbody>
<tr>
<td>CBV</td>
<td>Cerebral Blood Volume</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<td>ICP</td>
<td>Intracranial Pressure</td>
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<td>ICV</td>
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<td>Interstitial Fluid</td>
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<td>SAS</td>
<td>Subarachnoid Space</td>
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<td>Sagittal Sinus</td>
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*Symbols*

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<td>k</td>
<td>Brain Elastance</td>
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<tr>
<td>P</td>
<td>Intracranial Pressure</td>
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<tr>
<td>PVI</td>
<td>Pressure-Volume Index</td>
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<td>R&lt;sub&gt;CSF&lt;/sub&gt;</td>
<td>CSF Outflow Resistance</td>
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<td>V</td>
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2 Fundamentals of Intracranial Pressure and Cerebrospinal fluid Dynamics

2.1 Anatomy and Physiology of the Intracranial Cavity

The intracranial cavity is pressurized with respect to the atmosphere. Intracranial pressure (ICP) results from the equilibrium between blood vessels, brain tissue and cerebrospinal fluid (CSF). According to the Monro-Kellie doctrine (Mokri, 2001), the intracranial cavity is regarded as an open system with rigid boundaries and 100% filled by incompressible materials*. In other words, the rigid skull encloses a heterogeneous domain consisting of cerebral matter, blood and CSF: These three elements are 1) at different physical states, 2) with specific physiological as well as 3) fluid-mechanical properties, but can all be considered to be macroscopically incompressible. Given the nature of such a system, any perturbation (i.e. mass change of one of the three main components) has to be compensated by an equal adjustment of mass and energy transfer within the system, defining the rules for flow and pressure dynamics of the intracranial cavity, as they will be described herein.

The modeling of intracranial pressure and fluid dynamics ultimately associates to the understanding of its anatomical compartments.

Brain

The brain is the center of the nervous system. The physiological function of the brain is to exert centralized control over the other organs of the body. The brain communicates with the rest of the body, and vice-versa, by mean of electrical (e.g. sensing and muscle stimulation) and chemical (i.e. secretion of hormones) signaling.

The size of an adult human brain ranges averagely between 1.2 and 1.5 liters. Despite differences between white and grey matters as well

* Monro-Kellie doctrine assumes closed fontanels, i.e. adulthood, whereas infants are characterized by different intracranial dynamics, which are briefly described in Section 2.2.
as among anatomical regions, the overall cerebrum is slightly less dense than water and with the same consistency as jelly. As a first approximation, its elastic modulus is in the kPa range, however a viscoelastic theory has to be introduced in order to fully grasp the mechanical behavior of brain tissue: this is described in details in Chapter 1.

Brain floats within CSF and is penetrated by a fine network of blood vessels.

**Cerebral Blood**

Blood is essential to the homeostasis of any organ of the human body as it delivers oxygen and nutrients. In the intracranial cavity blood and cerebral matters interface via the blood-brain barrier that regulates the exchange of substances. Blood volume takes up 3-4% of the intracranial system, and approximately 80% of the blood is supplied to the cerebrum through the internal carotid arteries (ICA),
whereas the rest of the blood is delivered by the basilar artery (BA). These arteries converge into a circularly shaped vascular structure located at the base of the brain and known as the Circle of Willis (CoW), from which the arterial tree branches into smaller arteries and arterioles, turning eventually into capillaries. Continuing along the perfusion stream, cerebral blood collects into venules and veins to finally leave the intracranial cavity via the jugular veins.

Thickness and mechanical properties of blood vessels vary depending on their cellular composition, which depends on their position along the blood tree. The most comprehensive review of geometrical and mechanical properties of intracranial arteries has been performed by (Alastruey et al., 2007), who have reported elastic moduli in the order of the MPa.

Intracranial arteries and their fluid-mechanic behavior represent the main subject of Chapter 1 in this thesis.
After departing from the circle of Willis, blood vessels undergo a branching-refinement that ultimately reduces them into capillaries. One of the most important capillary-structure of the intracranial cavity is represented by the choroid plexi (CP). The choroid plexi are clusters of capillaries made of modified ependymal cells, which are
responsible for CSF production via ultrafiltration of plasma (blood-
CSF barrier).

**Cerebrospinal Fluid (CSF)**

The French physiologist Magendie is credited for giving the
cerebrospinal fluid its name (Fishman, 1992). Cerebrospinal fluid is a
colorless liquid consisting of water (99%), plasma proteins (0.3%)
and electrolytes (Felgenhauer, 1974). CSF is contained within the
cerebral ventricles, as well as in the cranial and spinal subarachnoid
space (SAS). The ventricles are four interconnected chambers at the
center of the brain. The two lateral ventricles, each confined to one of
the two cerebral hemispheres, are connected to the third ventricle via
the foramina of Monro. The third ventricle is centered about the mid-
sagittal plane between the lateral ventricles and the fourth ventricle,
to which it connects via the aqueduct of Sylvius. The fourth ventricle
accesses the intracranial cisterns via the foramina of Luschka and
Magendie; The CSF cisterns are located at the base of the neck, and
the SAS departs from there. The cortical (or cranial) SAS is the room
between the pia-matter and the arachnoid matter, two of the three
meninges‡, while the spinal SAS lays in between the spinal cord and
the vertebrae, or the intra-vertebral discs.

Although marked by a large inter-subject variability, the average
volume of CSF is in the range of 30 to 40 ml in the ventricles, 130 to
140 ml in the cortical SAS and around 30 ml in the spinal SAS
(Kurtcuoglu, 2007).

Physiologically, CSF serves three primary purposes: (i) it supports
and stabilizes central nervous system (CNS) by buoyancy; (ii) it
protects the same CNS from impacts; (iii) it preserves the chemical
equilibrium of the CNS by removing the metabolic waste.

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† The site of CSF production is only conceptually limited to the choroid plexi of
the ventricular system. Extrachoroidal production of CSF is most likely
responsible for a reasonable amount of the total fluid formation in humans.
‡ The remaining meninges, the dura matter, is a fibrous membrane that
adheres to the walls of the cranium.
From a fluid-mechanical standpoint, the action of ventricles and cisterns is analogous to an inflatable mattress on which the brain stands. In addition to that, the whole CNS floats in a liquid bath (the CSF in the SASs) and experiences buoyancy. As a result, despite the fact that the actual mass of the human brain is about 1.5 kg, the net weight of the brain suspended in the CSF is equivalent to a mass of about 25 grams, due to the density difference between CSF and brain tissue. This ultimately prevents the brain from being impaired by its own weight, i.e. from harming neurons and hampering blood supply. Next to buoyancy at steady-state, CSF dynamically protects the CNS from impacting with the cortical and vertebral bones when large accelerations occur, such as during traumatic (e.g. car accidents and sport impacts), but also physiologic events (e.g. walking and coughing). Finally, next to its fluid-mechanical action, CSF also regulates the chemical homeostasis of the CNS, by acting as a vector for the transport of metabolic waste products towards absorption sites where these are displaced into the blood streaming and ultimately handled by the liver and kidneys. For example, high glycine concentration in the CSF disrupts temperature and blood pressure control within the intracranial cavity, and high CSF pH causes symptoms of dizziness and syncope (Saladin, 2007).

In order to fully understand the physiological functions of CSF, from both a fluid-mechanical and chemical standpoint, the concepts of CSF...
circulation and intracranial pressure have to be introduced and explained in details.

**Physiologic Intracranial Dynamics**

At physiologic conditions CSF is characterized by two main dynamics: a steady-state and a pulsatile circulation.

CSF is derived by active secretion from cerebral arterial blood (Davson, 1984) through the choroid plexi in the ventricular domains and absorbed into the venous blood stream at SASs levels, through structures called arachnoid villi or granulations. The rate of CSF production has been reported to be constant under healthy conditions, around an approximate average rate of 500 ml/day (Ekstedt, 1978). At normal conditions CSF absorption equilibrates production, in order to maintain the volume of CSF constant, making the whole CSF to be renewed from 4 to 5 times a day at standard rate. The arachnoid granulations are part of the blood-brain barrier and act as a mono-directional proportional valves draining CSF from the SASs into the venous blood. The largest intracranial absorption site is identified as the sagittal sinus (SS).

From a fluid-dynamic standpoint, the arachnoid villi represent a macroscopic resistance to the passage of CSF. As a result, CSF is pressurized with respect of the downstream venous pressure level. The nominal equilibrium ICP is defined as the pressure value that drives absorption of CSF at equal rates as production, and ultimately allows for compensation of the secreted CSF in normal conditions.

Pulsatile CSF dynamics result from physiologic cardiovascular, respiratory and vasogenic activities and superimpose to the steady-state dynamics in terms of both CSF circulation and ICP. Pulsating CSF flows have been quantified in humans by mean of magnetic resonance velocimetry measurements (Schroth & Klose, 1992a; b; c; Baledent et al., 2004; Stoquart-ElSankari et al., 2007). ICP pulsation is observed in the neuro-clinical settings via standard ICP monitoring, and has been characterized with respect of its frequency components (Lundberg, 1960; Lundberg et al., 1965; Takizawa et al., 1986; Czosnyka et al., 2004; Wagshul et al., 2011). In simple terms, the
pulsatile nature of CSF and ICP dynamics generates from volumetric changes acting on the CSF system and will be thoroughly described throughout the entire thesis. For examples, the cardiovascular pulsation induces transient oscillatory changes in cerebral blood volume (CBV), respiration acts by squeezing the spinal SAS and blood vessels at the thoracic level, and intracranial as well as spinal vaso- genesis and -constriction alters the overall CBV. At any such volumetric change, CSF compensates with an equal displacement of fluid according to the Monro-Kellie doctrine, and with dynamic changes in ICP.

Pathological conditions of the CNS often associate with disorders of intracranial dynamics, both steady and pulsatile. In traumatic brain injuries (TBIs), hydrocephalus, Chiari malformation and syringomyelia, anatomical modifications of the CNS domains are related to altered CSF and ICP dynamics (Hakim, 1971; Koyanagi & Houkin, 2010; Noble, 2010; Di Rocco et al., 2011). Next to these, several other diseases such as Alzheimer’s, cerebral malaria and multiple scleroses have recently been suggested to associate with alterations of blood or CSF dynamics in the intracranial cavity (Newton et al., 1991; Silverberg et al., 2006; Zamboni et al., 2009).

This thesis particularly focuses and finds its motivation in the clinical assessment of hydrocephalus and its treatments.
Figure 2.4: The cardiovascular blood and cerebrospinal fluid circulation. CSF production occurs via microfiltration of arterial blood in the choroid plexus. CSF flows through the ventricular and subarachnoid spaces, to finally get resorbed into the venous blood stream (adapted from Rekate et al., 2012)
2.2 Clinical Assessment of Hydrocephalus

Hydrocephalus (Greek: *hydros* water and *cephalus* head) is defined as “a condition characterized by a dynamic imbalance between the formation (production) and absorption of cerebrospinal fluid resulting in an increase in the size of the fluid cavities within the brain” (Rekate et al., 2012).

Hydrocephalus often associates with increased intracranial pressure and related symptoms, such as headache and nausea, however this is not always the case. Idiopathic normal pressure hydrocephalus (iNPH) is associated with ventriculomegaly in the absence of elevated ICP. INPH is characterized by a triad of symptoms, namely gait impairment, cognitive decline and urinary incontinence (Adams et al., 1965; Hakim & Adams, 1965; Gallia et al., 2006).

According to the “Hydrocephalus Association” (4340 East West Highway, Bethesda, MD) the medical costs of treating hydrocephalus in the US are over $1 billion per year. Although the epidemiology of iNPH is largely unknown, its incidence has been reported to vary in different studies from 2 to 20 per million per year (Krauss & Halve, 2004a; Tisell et al., 2005a; Klassen & Ahlskog, 2011b). iNPH can occur in all age groups, however it is most common in adults over the age of 60 years (Black et al., 1985; Petersen et al., 1985). It is equally common in both sexes (Marmarou et al., 2005c).

Contrary to other common CNS disorders, such as Parkinson’s and Alzheimer’s diseases as well as multiple sclerosis, for which there exist no scientific diagnostic test as well as neither pharmaceutical nor surgical treatment yet, hydrocephalus can be diagnosed with magnetic resonance imaging and treated with surgical intervention. However, the pathophysiology of iNPH is still not fully understood, and without additional diagnostic testing only between 46% and 61% of probable and possible iNPH patients will improve with surgical treatment (Marmarou et al., 2005a).

Infusion tests are clinical assays designed for (i) the diagnosis of iNPH patients, (ii) the prediction of shunt responders and (iii) the evaluation of shunts functioning. Although several types of infusion test have been reported in the literature, mainly three protocols are
commonly used in the standard clinical practice nowadays: the constant flow, constant pressure and bolus infusion tests (Eklund et al., 2007; Sundstrom et al., 2010). Mathematical models of the respective infusion methods have been derived, and are used in the clinical settings to derive patient-specific clinically-relevant parameters (Ekstedt, 1977; Marmarou et al., 1978; Eklund et al., 2007). The analytical assessment of intracranial dynamics under infusion tests is described in details in Section 2.3.

The treatment for iNPH consists of the surgical diversion of CSF. This is accomplished by implanting a shunt to drain CSF from either the intracranial ventricular system or the lumbar subarachnoid space to a distal site, such as the peritoneal cavity or the venous system, where the CSF can be re absorbed. Standard shunts consist of three assembling parts, namely a proximal catheter, a passive monodirectional valve and a distal catheter. The most common shunts utilized today are ventriculo peritoneal (VP) and ventriculo atrial (VA) shunts. Several factors are considered when evaluating patients for placement of a shunt, including the risk-to-benefit ratio of the procedure, sites of the proximal and distal catheter, valve specifics, and shunt-related complications (Bergsneider et al., 2005). Placement of a shunt is a neurosurgical procedure performed under general anesthesia, which takes less than an hour to complete.

Although CSF shunting is a relatively straightforward neurosurgical procedure, it is associated with numerous potential complications. Commercially available shunts show a significance incidence of complications after surgery, and secondary operations are often needed. The Hydrocephalus Association estimates that of the over 40,000 hydrocephalus operations performed annually in the US (one every 15 minutes), only 30% are the patient’s first surgery. Complications can be categorized into three main groups: (i) those related to the operative procedure (e.g. intracerebral hematoma, catheter malposition, shunt infection); (ii) those related to the shunt system (e.g. valve malfunction, proximal or distal catheter obstruction); and (iii) those attributable to the flow characteristics of the shunt system (e.g. overdrainage-associated headaches, or subdural hematoma) (Gallia et al., 2006). Recent reviews have reported the occurrence of these complications based on previously published patients studies (Bergsneider et al., 2005): shunt
malfunction (20%), subdural hematoma (2–17%), seizure (3–11%), shunt infection (3–6%) and intracerebral hematoma (3%).

The significant incidence of failures and complications in the commercially available shunts calls for the design and development of innovative shunt solutions, such as intelligent actively-controlled devices. This thesis presents the design and development of a platform that reproduces human intracranial dynamics. Such a platform offers as a laboratory bench for the testing of novel shunt prototypes prior and next to animal investigations.
2.3 Theoretical Background

The theoretical modeling of cerebrospinal fluid circulation and intracranial pressure dynamics has been first introduced by Marmarou (Marmarou et al., 1978). According to this model, the intracranial dynamics are described by a constant CSF outflow resistance ($R_{CSF}$) and an exponential pressure volume relation. Although minor variations exist (Ursino & Lodi, 1997; Stevens & Lakin, 2000; Eklund et al., 2007), Maramrou’s model still represents the most accepted mathematical description of the intracranial cavity. An electrical analogy consisting of an R-C (resistor and capacitor) circuit has been suggested by Marmarou to describe CSF and ICP dynamics, which is presented in Figure 2.5.

\[
I_{CP} = R_{CSF} \dot{Q}_{CSF} + P_{SS}, \quad (2.1)
\]

where venous pressure in the intracranial cavity is assumed to be uniform and equal to the pressure in the dural sagittal sinus ($P_{SS}$),

\[\text{§ In this chapter, and in the rest of this thesis, Monro-Kellie hypothesis are assumed, i.e. adult intracranial dynamics are described and investigated. When dealing with infants (prior to fontanels closure), different theoretical models have to be adopted.}\]
and the CSF absorption flow rate $Q_{CSF}$ to equal the production rate. These assumptions are valid for healthy subjects.

Cerebrospinal fluid compliance represents the storing properties of the cranio-spinal system and is accepted to be described by an exponential pressure volume relation (Avezaat & van Eijndhoven, 1984; Czosnyka et al., 2004), according to Eq. (2.2)

$$ICP = P_0 e^{k\Delta V} + P_1,$$

where $P_0 + P_1 = P_r$ represents the resting (also called baseline) ICP level for unaltered CSF volumes ($\Delta V$), $k$ is the brain elastance, and $P_1$ accounts for offset induced by changes in body position and venous pressure levels (Lofgren et al., 1973; Avezaat & van Eijndhoven, 1984; Raabe et al., 1999). Mathematically, CSF compliance is defined as the derivative of CSF volume with respect of pressure, according to Eq. (2.3)

$$C = \frac{dV}{dICP} = \frac{1}{k(ICP-P_1)} = \frac{e^{-k\Delta V}}{kP_0}$$

Figure 2.6: The exponential CSF pressure-volume relation. Assuming unaltered volumetric oscillations during the pulsatile dynamics
described in session 2.1, ICP pulsation are larger for increased mean ICP levels.

In the clinical settings, CSF compliance is often referred in terms of pressure-volume index (PVI)

\[
PVI = \frac{\Delta V}{\log_{10} \left( \frac{I CP - P_1}{P_0 - P_1} \right)} \approx \frac{1}{0.434k} ,
\]

defined as the volume added to the craniospinal system in order to produce a tenfold increase in the ICP (Marmarou, 1973).

Following the electrical representation of CSF circulation (Figure 2.5), a state equation can be written following Kirchhoff law as

\[
I_{pr} + I_{inf} = I_{ab} + I_{st} ,
\]

where current “I” in the electrical analogy stands for flow rate in the fluid dynamic circuit. In particular I_{pr} and I_{ab} are the CSF production and absorption rates, respectively, I_{st} is the stored CSF flow due to compliance and I_{inf} represents any additional external infusion, such as during infusion tests.

Solution to Eq. (2.5) can be derived by mean of Eq. (2.1), (2.2) and (2.3) resulting in the generic Marmarou’s equation (Marmarou et al., 1978; Eklund et al., 2007)

\[
\frac{1}{k \cdot (I CP(t) - P_1)} \frac{d I CP(t)}{dt} + \frac{(I CP(t) - P_0)}{R_{CSF}} = I_{inf} .
\]

Eq. (2.6) allows calculation of the patient-specific parameters k and R_{CSF}, when controlled infusion tests are performed in the clinics and ICP is monitored.

When a constant flow infusion test is performed, a constant flow rate perturbation is induced to the CSF system by infusion and ICP response over time t (after infusion has started) can be derived as
\[ ICP(t) = \frac{\left( l_{inf} + \frac{p_0 - p_1}{R_{CSF}} \right) (p_0 - p_i)}{\frac{p_0 - p_1}{R_{CSF}} l_{inf} \exp\left(-k \left( l_{inf} + \frac{p_0 - p_1}{R_{CSF}} \right) t \right)} + P_1 , \]  

(2.7)

and for sufficiently long elapsed time, a new steady state pressure condition \( ICP_{end} \)

\[ ICP_{end} = R_{CSF} l_{inf} + P_r \]  

(2.8)

is reached, from which the unknown parameter \( R_{CSF} \) can be estimated.

During constant pressure infusions, several steady state \( ICP_{end} \) levels are reached for consecutive constant flow infusion steps. \( R_{CSF} \) is calculated by linear regression of the flow-pressure operating points measured during the test (Ekstedt, 1978; Andersson et al., 2005): The outflow resistance of the system is the slope of the regression line.

In bolus tests a given volume of fluid (usually between 4 at 10 ml) is infused instantaneously with a syringe into the CSF space, and ICP is recorded. When processing bolus test measurements, the volumetric step variation is assumed as Heaviside function \( \Delta V \cdot H(t-t_0) \) and the ICP response is derived as (given \( t_0=0 \))

\[ ICP(t) = \frac{P_{peak} \cdot \exp\left( k \frac{p_r}{R_{CSF}} t \right)}{1 + \frac{P_{peak}}{P_r} \exp\left( k \frac{p_r}{R_{CSF}} t \right) - 1} , \]  

(2.9)

where \( P_{peak} \) is the maximum ICP reached at the full delivery of the bolus. In the clinical settings the so called visual method (Sundstrom et al., 2010) is adopted to estimate the patient specific \( k \) and CSF outflow resistance \( R_{CSF} \). The brain elastance coefficient \( k \) is calculated during the infusion phase as

\[ k = \frac{\ln\left( \frac{P_{peak}}{P_r} \right)}{\Delta V} , \]  

(2.10)

being \( \Delta V \) the given bolus volume.
On the other hand the CSF outflow resistance $R_{CSF}$ is calculated during the recovery phase, after the bolus infusion has terminated**, as

$$
R_{CSF} = \frac{k \cdot t \cdot P_r}{\ln \left( \frac{I(CP(t)/P_{peak})(P_{peak} - P_r)}{I(CP(t) - P_r)} \right)}.
$$

(2.11)

The clinical importance of infusion tests stands in the calculation of the patient-specific CSF outflow resistance. In fact, identification of abnormally elevated $R_{CSF}$ has been shown to increase the likelihood of a favorable response to shunt placement (Marmarou et al., 2005a). Clinical infusion tests are ultimately a decision-making tool for neurosurgeons, who need to select candidate patients for surgery.

In this work, anatomical data of the human cranio-spinal domain and the mathematical description of CSF and ICP dynamics under physiological and pathological conditions, as well as infusion tests and shunting, were adopted to design an in-vitro anatomical model of the intracranial dynamics.

** For exact delivery of the bolus as analytical Heaviside function the infusion phase is instantaneous and the recovery phase begins immediately. However this condition is not realistic in the experimental settings, as a finite time is needed to deliver the bolus with a pump.
3 Phantom Model of Physiologic ICP and CSF Dynamics

Parts of This chapter are published in:


Abstract

We describe herein a novel life-size phantom model of the intracranial cavity and its validation. The cerebrospinal fluid (CSF) domains including ventricular, cysternal and subarachnoid spaces were derived via magnetic resonance imaging (MRI). Brain mechanical properties and cranio-spinal compliance were set based on published data. Both bulk and pulsatile physiologic CSF flow were modeled.

Model validation was carried out by comparisons of flow and pressure measurements in the phantom with published in-vivo data of healthy subjects. Physiologic intracranial pressure (ICP) with 10 mmHg mean and 0.4 mmHg peak pulse amplitude was recorded in the ventricles. Peak CSF flow rates of 0.2 ml/s and 2 ml/s were measured in the cerebral aqueduct and subarachnoid space (SAS), respectively.

The phantom constitutes a first-of-its-kind approach to modeling physiologic intracranial dynamics in-vitro. Herein, we describe the phantom design and manufacturing, definition and implementation of its operating parameters, as well as the validation of the modeled dynamics.
3.1 Introduction

The cerebrospinal fluid (CSF) contributes to the homeostasis of the central nervous system (CNS). Within the intracranial cavity, CSF is confined in the ventricular and subarachnoid spaces (SAS) pressurized with respect to atmospheric reference. CSF supports the brain by buoyancy, protects it from impact, transports nutrients as well as neuroendocrine substances, and removes metabolic waste products.

Alteration in CSF dynamics relates to several disorders. Hydrocephalus and syringomyelia, for example, have been linked to disturbances in CSF bulk flow as well as pulsation (Hakim et al., 1976; Di Rocco et al., 1978; Heiss et al., 1999). However, the specifics of these relations are not yet understood.

Models of intracranial dynamics can improve the understanding of CNS patho-physiology. Both lumped parameter and computational fluid dynamics (CFD) models have been used to characterize dynamics within the CSF spaces (Ursino & Lodi, 1997; Stevens & Lakin, 2000; Loth et al., 2001; Kurtcuoglu et al., 2005; Linninger et al., 2005; Ambarki et al., 2007; Gupta et al., 2009; Gupta et al., 2010; Howden et al., 2011), as well as in major intracranial arteries (Chatziprodromou et al., 2007; Zuleger et al., 2010; Ho et al., 2011). The lumped parameter approach is particularly well suited for a global, empirical description of intracranial dynamics (Ursino & Lodi, 1997; Stevens & Lakin, 2000; Ambarki et al., 2007). Corresponding model parameters such as CSF outflow resistance and pressure-volume index have become standards in the clinical practice during the last decade (Czosnyka et al., 2004). In contrast, CFD models can be employed to access spatially resolved flow information that cannot be obtained through measurement (Gupta et al., 2010; Kurtcuoglu, 2011).

However, neither lumped parameter nor CFD models of the intracranial cavity have proven to be optimal for the development of medical devices that alter intracranial dynamics. For example, CSF shunts used to treat hydrocephalus are tested experimentally according to the ISO 7197 standard to assess hydraulic resistance (ISO/DIS, 2009). To analyze the full dynamic behavior of a specific
shunt rather than just measuring hydraulic resistance, animal models have to be employed. However, besides ethical concerns, these are expensive, especially when larger animals such as dogs, goats or monkeys are used, whose intracranial dynamics are closer to those of humans compared to those of mice, rats or rabbits.

In-vitro phantoms represent a fourth model type that may aid in the investigation of CNS pathophysiology. Both anatomically detailed and simplified phantoms have been used to validate MRI sequences (Fahrig et al., 1999; Salm et al., 2007; Driscoll et al., 2011), computational models of brain mechanics (Ma et al., 2010) as well as CSF flow in the third ventricle (Schibli et al., 2008). In brain injury research, phantom models have been employed to study tissue response to impact (Ivarsson et al., 2001; Ivarsson et al., 2002). To our knowledge, only one phantom model of fluid and pressure dynamics in the spinal CSF space has been reported; it was employed to gain understanding of syringomyelia (Martin & Loth, 2009; Martin et al., 2010).

Phantom models of the intracranial space have the potential to reduce, refine and to a smaller extent replace animal models for the testing of shunts and other neurosurgical devices. An important step towards such application is the replication of healthy state intracranial dynamics. We present herein a first-of-its-kind phantom model of the intracranial cavity that can reproduce physiologic cerebrospinal fluid and pressure dynamics. We report on the phantom design, development and validation with in-vivo data described in the literature, showing that this modeling approach can contribute to the understanding of intracranial dynamics.

### 3.2 Materials and Methods

**CSF and Ventricular System**

We formed a ventricular system in a silicone brain using the following approach: A three-dimensional reconstruction of MRI data acquired on a 27 year old healthy male volunteer [5] provided the anatomical
reference to design the ventricular domain of the phantom. The ventricular system was simplified to obtain a sagittal symmetry suitable for casting: The lateral ventricles were merged to a single ventricle representation using computer aided design (CAD) software (NX 7.5, Siemens PLM Software, Plano, TX, USA); the foramina of Monro were unified into a single connector to the third ventricle; the foramina of Luschka and Magendie were also merged into a single channel. A negative of this simplified ventricular domain was manufactured in two sagittal symmetric halves by 3D printing on an Eden350V photopolymer printer (Objet Geometries Inc., Billerica, MA, USA).

After obtaining a positive of the ventricle space (see Section II.B), a 2 mm inner diameter silicone tube was inserted into the cerebral aqueduct to avoid its deformation during the phantom construction. For simulation of CSF production in the ventricles (Wolburg & Paulus, 2010), an access port was established at the top of the ventricular system. The same access port was also used for the initial filling of the CSF space. Two access points for pressure sensing were established at the top and bottom of the cerebral aqueduct. The adapted ventricular system is shown in Figure 3.1, and the effects of the simplifications are discussed in the discussions section.

**Brain and Skull**

A life-sized silicone brain was made using Sylgard 527, A&B Dielectric Silicone Gel (Dow Corning, Midland, MI, USA). Previous investigations have shown this material to have similar mechanical behavior as brain under static deformation (Ma et al., 2010) and dynamic loading up to 10 Hz (Brands et al., 1999). The silicone was cast around each of the two ventricle negative halves. After curing, the negatives were removed and the left and right brain parts were glued together with the same silicone. A thin layer of a standard casting silicone (Ecoflex, Smooth-on Inc., Pennsylvania, USA) was applied onto the ventricle walls to prevent adhesion when collapsed.

The completed brain was placed in a plastic human skull model (3B Scientific, Hamburg, Germany) of which the upper part had been removed (Figure 3.1).
Cisterns and Subarachnoid Space

CSF bulk flow originates in the ventricles, continues to the cisterns at the base of the skull, and reaches the spinal and cortical SAS where it is to a large part reabsorbed into venous blood. The SAS microstructure influences CSF dynamics (Gupta et al., 2010). The effect of the microstructure can be spatially averaged and expressed through its hydraulic resistance, which is related to permeability. Subarachnoid space permeability has been reported to range in the orders $10^{-9}-10^{-7}$ m$^2$ (Gupta et al., 2010). We used a homogenous pillar structure between parallel plates (Figure 3.2) to account for the hydraulic resistance of the SAS. In such a structure, the permeability $k$ is a function of the pillar radius $r$ and the void fraction $\varepsilon$ of the representative unit cell (Westhuizen & Du Plessis, 1994):

$$\frac{k}{r^2} = \frac{\pi \varepsilon (1-\sqrt{1-\varepsilon})^2}{24(1-\varepsilon)^{3/2}}$$  (3.1)
and

\[ \varepsilon = \frac{V_{\text{fluid}}}{V_{\text{tot}}} = \frac{L^2 - \pi r^2}{L^2}, \]

(3.2)

where L is the center-to-center distance between two neighboring representative unit cells. We chose a configuration with r=0.5mm and L=1.5mm, with a resulting permeability value of $1.7 \times 10^{-8}$ m² according to Eq. (3.1) and (3.2). This pillar configuration was manufactured by 3D printing (Eden350V, Objet Geometries Inc.) and placed in a PMMA case outside the phantom brain to represent its SAS with 123.7 mL volume according to in-vivo MRI data (Fig. 2) (Kurtcuoglu et al., 2005; Gupta et al., 2010). The SAS compartment is connected to the ventricular space via a cylindrical cavity of 24 mL volume representing the cysternal space (Fig. 1). This modular approach allows for an uncomplicated change of the SAS resistance to address the effects of pathologic conditions, such as hemorrhage, that can lead to SAS obstruction.

Figure 3.2: Design of SAS compartment. A uniform modular pillar structure was used to achieve in-vivo values of hydraulic resistance. a) SAS macro anatomy; b) idealized pillar structure to represent SAS microanatomy; c) top view of the representative unit cell. d) CAD design of the SAS compartment. e) 3D printed SAS representation and connection to the phantom’s cistern (Figure 3.3 and Figure 3.4).
With exception of the SAS representation and compliance modules (see Section Compliance p.35), all intracranial elements including skull, silicone brain, cistern and ventricular lumen are enclosed in a water filled, hermetically sealed PMMA box (Figure 3.4). The water replicates the buoyancy effect on the brain observed in-vivo and serves as a transmission medium for the pressure pulses from the pulsatile pump (see Section Actuation System p.36) to the intracranial compartments, simulating the effects of arterial pulsation.

**Compliance**

Compliance $C$ of the cranio-spinal system is defined as the change of its volume $V$ in response to a variation in its pressure $P$:

$$ C = \frac{dV}{dP} \quad (3.3) $$

Compliance can be measured by infusion testing (Eide & Brean, 2010). The physiologic pressure-volume relation from which compliance can be derived follows approximately

$$ ICP = P_0 e^{kV} + P_1 \quad (3.4) $$

where $P_r=P_0+P_1$ is the resting ICP level prior to infusion and $K$ the brain elastance coefficient. $K$ has been reported to range between 0.0886 and 0.177 ml$^{-1}$ in healthy humans (Czosnyka et al., 2004), with a corresponding physiological compliance between 0.56 and 1.13 ml/mmHg for undisturbed ventricular volume and healthy resting pressure of $P_r=10$ mmHg.

Two compliance boxes filled with water and air are used to reproduce physiologic compliance values. Their overall design is based on the assumption of ideal gas behavior with adiabatic compression and expansion according to

$$ PV^{1.4} = const \quad (3.5) $$
The boxes were calibrated experimentally to yield overall compliance of 1 ml/mmHg at the phantom’s operating conditions. They connect to the cisternal and SAS compartments, respectively. The former represents spinal compliance (35% of the overall compliance), and the latter cranial compliance (Marmarou et al., 1975; Wahlin et al., 2010).

While compliance follows an exponential trend during infusions tests, it can be considered constant under physiologic conditions (Eide & Brean, 2010): Cranial blood volume changes during the cardiac cycle are two orders of magnitude smaller than volumes injected during infusion (Baledent et al., 2004).

**Actuation System**

Both bulk and pulsatile CSF flow can be reproduced by the phantom. Deionized water at room temperature is used to represent CSF (Bloomfield et al., 1998). A peristaltic pump (Peristaltic Pump 66 & 77, Harvard Apparatus, Massachusetts, USA) imposes CSF production in the ventricles and absorption in the cortical subarachnoid space. CSF bulk flow was set to 0.35 ml/min (500ml/day) at both production and absorption sites to model healthy conditions. A programmable pump (CompuFlow 1000MR, Shelley Medical Imaging Technologies, Ontario, Canada) is used to pressurize the water surrounding the cranial compartment in the PMMA box, as well as the CSF space, transiently with 1 Hz: This induces CSF and ICP pulsation similar to healthy in-vivo conditions (Table 3.I). The pulsatile pump is controlled through a LabVIEW interface (National Instruments, Texas, USA). Two fine-regulating valves (Serto AG, Aadorf, Switzerland) divide the pump output into two parts: The first induces transient changes in ventricular CSF volume through ventricular wall displacement, while the second displaces CSF in the SAS compartment.

**Acquisition System**

Pressure and flow are monitored at selected locations in the phantom. Intracranial pressure is recorded in the ventricles, cisterns and SAS.
Following the gold standard for clinical ICP monitoring, microtip pressure transducers and a corresponding control unit are used to acquire ICP (Microsensor™ and ICP Express™, Codman&Shurtleff, Raynham, MA, USA). Measured data are transferred to a datalogger (Beckhoff Automation GmbH, Verl, Germany), processed in LabVIEW and recorded on a desktop computer. Pressure sensors (Series 41X, Keller AG, Winterthur, Switzerland) are connected to the access points of the cerebral aqueduct (Figure 3.1). A coriolis flow transducer (Cubemass, Endress+Hauser Metso AG, Reinach, Switzerland) is used to measure oscillatory flow rates between the pulsatile pump and the SAS.

Figure 3.3: Schematic of the phantom setup. Ventricles are enclosed in a silicone brain and connected to the cisternal and subarachnoid spaces. CSF production and absorption rates can be controlled. Spinal and Cranial compliance units are connected to the cisternal and subarachnoid spaces, respectively. Pulsatile flow and ICP are monitored at the indicated locations. Black triangles indicate water-air interfaces.
Figure 3.4: The phantom setup. Top: Frontal view; Bottom: View from above. The cranial domain of the phantom is placed in a PMMA box and is therein surrounded by water. Components of the actuation and acquisition systems, as well as compliances and SAS compartments are shown.
3.3 Results

The results given in here demonstrate the validation of the phantom model with physiologic in-vivo literature data on intracranial dynamics. Concretely, mean ICP, pulsatile ICP amplitude as well as CSF flow rates in the aqueduct and the cortical SAS were analyzed.

Phase contrast MRI is used routinely to measure CSF flow in the aqueduct of Sylvius and the cervical spinal SAS, yielding in healthy subjects amplitudes of up to 0.3 ml/s and 1.18 to 3.97 ml/s, respectively (Luetmer et al., 2002; Baledent et al., 2004; Stoquart-ElSankari et al., 2007). In the phantom, the operating parameters described in Section Actuation System (p.36) were adjusted to obtain flow rates within the above range in the corresponding sections, i.e. in the aqueduct and the entrance to SAS compartment.

ICP is not measured routinely in healthy subjects due to the invasive nature of the procedure, but data have been reported for animals as well as for humans. Physiologic mean ICP has been shown to be of the order of 10 mmHg (Ghajar, 2000), but there is no agreement on the range of ICP pulsation amplitude that can be considered healthy: Only few quantitative measurements of amplitudes have been published with peak values of the order of 0.1 mmHg in cats (Takizawa et al., 1986) and of approximately 4 mmHg in patients with neurologic disorders (Ekstedt, 1978).

Concurrent measurements of flow rates and ICP are not carried out routinely on patients because standard ICP monitoring equipment is incompatible with MRI scanners. In the phantom, on the other hand, such measurements are possible: We recorded simultaneously pulsatile ICP and CSF flows in the cerebral aqueduct and the SAS. An overview of the operating parameters used to reproduce physiologic ICP and CSF flow patterns is given in Table 3.I.
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Phantom Values</th>
<th>Physiologic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Phi$</td>
<td>CSF bulk flow</td>
<td>0.35 ml/min</td>
<td>0.27-0.45 (Czosnyka et al., 2004)</td>
</tr>
<tr>
<td>$C_{tot}$</td>
<td>Total compliance</td>
<td>1 ml/mmHg</td>
<td>0.56-1.12 (Czosnyka et al., 2004)</td>
</tr>
<tr>
<td>$k$</td>
<td>SAS permeability</td>
<td>$1.7 \times 10^{-8}$ m²</td>
<td>9.05 $\times 10^{-9}$-1.45 $\times 10^{-7}$ (Gupta et al., 2009; Gupta et al., 2010)</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Basal heart rate</td>
<td>60 bpm</td>
<td>50-100 (Berne &amp; Levy, 1990; Camm et al., 1996)</td>
</tr>
<tr>
<td>$A_{ventricles}$</td>
<td>Amplitude of ventricular flow rate</td>
<td>0.2 ml/s</td>
<td>&lt;0.3 (Luetmer et al., 2002; Baledent et al., 2004; Stoquart-ElSankari et al., 2007)</td>
</tr>
<tr>
<td>$A_{SAS}$</td>
<td>Amplitude of SAS flow rate</td>
<td>2 ml/s</td>
<td>1.18-3.97 (Baledent et al., 2004; Stoquart-ElSankari et al., 2007)</td>
</tr>
<tr>
<td>$V_{ventricles}$</td>
<td>Ventricular volume</td>
<td>29.6 ml</td>
<td>17.6-34 (Tsunoda et al., 2002)</td>
</tr>
<tr>
<td>$V_{ic}$</td>
<td>Intracranial CSF volume</td>
<td>177.3 ml</td>
<td>143.1-246.3 (Tsunoda et al., 2002)</td>
</tr>
</tbody>
</table>

Table 3.1: List of operating parameters used to define the phantom working condition for the healthy state. Values reported in the literature, which define the physiologic range for a healthy subject, are also reported.
Figure 3.5 shows intraventricular pressure recording in the phantom over several cardiac cycles, demonstrating the stability of the setup. A mean physiologic ICP of 10 mmHg was reproduced and pulsations with approximately 0.4 mmHg amplitude were observed. Both are in agreement with values reported in the literature for in-vivo healthy conditions (Ekstedt, 1978; Takizawa et al., 1986; Ghajar, 2000).

![Graph showing intraventricular ICP oscillation](image)

Figure 3.5: Intraventricular ICP oscillation measured in the phantom over several cardiac cycles. Intracranial pressure oscillates around a mean value of 10 mmHg with a frequency of 1 Hz.

Transient ICP and corresponding CSF flow rate curves of one representative cardiac cycle are shown in Figure 3.6. CSF oscillations showed peaks of 0.2 ml/s in the aqueduct and 2 ml/s in the SAS, thus matching in-vivo values (Luetmer et al., 2002; Baledent et al., 2004; Stoquart-ElSankari et al., 2007). This was achieved with the proper choice of the pulsatile pump output and fine regulating valve settings as described in Actuation System (p.36).

To analyze the effect of change in CSF pulsation origin, the entire pulsatile pump output was applied to the brain surface, resulting in ventricular pulsation without contribution from the SAS. This reduced ICP amplitude from 0.4 mmHg to 0.15 mmHg, where the latter value corresponds to the expected peak aqueductal pressure.
drop (Kurtcuoglu et al., 2007). Physiologic ICP amplitude of 0.4 mmHg was restored when CSF pulsation originated again in both the ventricles and the SAS.

Figure 3.6: ICP (top) and CSF flow rate (bottom) measured in the phantom during one cardiac cycle. Top: triangular markers show ICP when CSF pulsation originates in both ventricles and the SAS; circular markers indicate ICP under ventricular pulsation only. Middle: CSF flow rate in the aqueduct. Bottom: CSF flow rate in the SAS.

To investigate the phantom’s flexibility in reproducing potential pathologic conditions by alterations of its operating parameters, we set the cranial compliance to zero. Figure 3.7 shows ICP measurements under physiologic conditions compared to ones made without cranial compliance. More than a factor of two increase in ICP pulse amplitude was observed in the pathologic case.
Figure 3.7: ICP pulsation measured intraventricularly in the phantom. Comparison of healthy condition with normal compliance (Table 3.I) and pathologic condition without cranial compliance.
3.5 Discussions

The phantom described herein represents a novel approach for the modeling of intracranial dynamics. Based on MRI data and the results of detailed CFD simulations, a model of the intracranial space including brain, ventricular and subarachnoid spaces was realized that allows for the reproduction and monitoring of bulk and pulsatile CSF flows, as well as ICP dynamics. The phantom was validated by comparison to physiologic CSF flow and pressure values reported in the literature.

The phantom features a set of operating parameters whose physiologic values cannot be readily obtained in-vivo. Specifically, these are the output wave form of the pulsatile pump and the division of this output for actuation in the ventricular and subarachnoid CSF spaces. In-vivo, the expansion and contraction of blood vessels propels CSF either directly or through transient brain tissue motion. As this complex interaction has not been fully quantified to date, our approach of directly displacing the ventricle walls and SAS volume is justified. More importantly, by treating the pulsatile pump output and the output division ratio as variables, we have obtained indication that in-vivo CSF oscillation is likely the result of transient changes in both SAS and ventricular volume of similar magnitude, rather than the result of a single compartment volume variation. In the phantom, the relative contribution is 2:3 in favor of the subarachnoid space.

While in its current state the phantom has not been validated for the reproduction of pathologic conditions, we have nevertheless simulated a hypothetical disorder in which cranial compliance was reduced. This was done to demonstrate that the phantom’s operating parameters can be easily adapted to study pathologic intracranial dynamics.

As all models, the phantom at hand is a simplified representation of the very complex real system. In particular, simplifications were introduced to handle the anatomic complexity of the intracranial space. The cerebral vasculature and its contribution to intracranial dynamics were included implicitly in the volume variation of the ventricular and SAS compartments. As a consequence, local effects of
blood flow are not taken into account. Similarly, the simplification of the ventricular and subarachnoid spaces precludes the acquisition of local flow information. The phantom nevertheless produces realistic pressure dynamics within the modeled CSF spaces: The aqueduct of Sylvius and SAS are responsible for the main CSF pressure drop under physiologic conditions (Kurtcuoglu et al., 2007; Gupta et al., 2009; Gupta et al., 2010), and both of these compartments are accurately modeled in our setup. Due to the short length of the foramina of Monro, Luschka and Magendie, and the large cross-section of the lateral ventricles, their simplified representations have negligible impact on global pressure dynamics and flow rates.

While the bandwidth of physiologic intracranial dynamics is limited to a few Hertz, taking into account only their first harmonic at 1 Hz as done here constitutes nevertheless a clear simplification. As a result, the shape of the measured flow profiles does not fully match those obtained on healthy subjects, even though amplitudes, mean flow rates and stroke volumes do. Reproducing in-vivo flow profiles in detail would require a more sophisticated actuation system with a bandwidth of at least 10 Hz. This would introduce a large new set of variables to be calibrated, while providing only very limited added value.

The phantom is operated in an air-conditioned room at 22 °C rather than at body temperature of 37 °C. Consequently, the density and viscosity of the working fluid (water) are higher than that of in-vivo CSF (Bloomfield et al., 1998). This results in an overestimation of peak pressure gradients of the order of 10%. For applications that require a more accurate representation of CSF, active heating of the setup could be implemented, or a different working fluid could be used.

The phantom features constant compliance, which represents a valid assumption for healthy conditions. Under pathologic conditions, however, cranio-spinal compliance variations may become important. To study these, the employed constant compliance elements can be replaced by exponential compliance modules as reported in (Andersson et al., 2005; Sundstrom et al., 2010).
4 The Role of Major Intracranial Arteries in ICP Dynamics

Parts of this chapter have been submitted for publication in *Intensive Care Medicine* (Submitted: August 2012).

4.1 Abstract

Changes in intracranial pressure (ICP) pulse waveform occur under pathologic conditions such as traumatic brain injury and hydrocephalus. In order to interpret ICP waveforms thoroughly, understanding of the pulse origin is necessary. While several mechanisms have been proposed for pulse transmission from the cardiovascular system to ICP, their relative contributions remain unknown. Here we aim to elucidate whether the pulsation of major intracranial arteries is sufficient to generate physiologic ICP waveforms.

We developed an anatomically accurate phantom of the intracranial cavity to investigate ICP dynamics under healthy conditions. Magnetic resonance imaging was used to acquire the in-vivo geometry of a volunteer’s cerebral ventricles, internal carotid arteries (ICAs), basilar artery (BA) and the circle of Willis (CoW). The artery walls and brain were then manufactured using silicones to reproduce realistic mechanical properties. The compliance of the intracranial space was set to 1 ml/mmHg. Physiologic blood pressure waveforms were imposed, and pressure was recorded simultaneously in the arterial and the ventricular space.

Our results show that pulsation of the ICAs, BA and CoW can generate ICP oscillations with amplitudes in the range reported for healthy subjects. However, waveforms obtained in this manner do not contain the percussion, tidal and dicrotic peaks observed *in vivo*.

Major intracranial arteries cannot by themselves produce physiologic ICP pulsation. Other vascular entities such as the choroid plexus,
veins and smaller arteries modulate their contribution to yield the intricate ICP waveform observed in vivo.

4.2 Introduction

Increased intracranial pressure (ICP) pulse amplitudes as well as altered waveforms generally indicate pathologic conditions (Citerio & Andrews, 2004). Severe brain injuries are often associated with a reduction of cranio-spinal compliance and subsequent alteration of ICP pulsation. Persistent changes in ICP dynamics have also been hypothesized as potential causes of disorders related to the flow of cerebrospinal fluid (CSF) such as hydrocephalus (Di Rocco et al., 1978).

Once an emerging diagnostic tool (Lundberg, 1960), ICP waveform analysis may see a renaissance with progress in the understanding of intracranial dynamics and advances in pressure signal acquisition and processing. For example, Eide and Kerty (Eide & Kerty, 2011) have reported recently that ICP pulsation may be more relevant than static ICP in diagnosing idiopathic intracranial hypertension.

In order to interpret ICP waveforms thoroughly, understanding of the pulse origin is necessary. It is accepted that the pulsatile CSF motion and ICP oscillations are driven by the cardiovascular system and modulated by respiration (Czosnyka et al., 2004). Phase-contrast MRI measurements have shown the pulsatile nature of cerebral blood flow in the carotid and basilar arteries, jugular and epidural veins, as well as resulting CSF flows in the cerebral aqueduct and the spinal canal (Baledent et al., 2004; Schmid Daners et al., 2012). Computational models have demonstrated the complexity of cerebrospinal fluid and pressure dynamics (Gupta et al., 2010; Kurtcuoglu, 2011). However, it remains unclear how cardiovascular action is transferred to produce the observed intracranial dynamics. Two main hypotheses have been proposed over the years to explain this transfer, namely cyclic brain tissue displacement due to the expansion and contraction of major arterial vessels (Lee & Yoon, 2009), and CSF displacement as a result of choroid plexus pulsation with the cardiac cycle (Bering, 1955; Schibli et al., 2009).
While it is probable that both major arteries and choroid plexus contribute to intracranial dynamics, it has not been demonstrated whether the one or the other is the main driving mechanism. Here we hypothesize that the pulsation of major intracranial arteries is the primary origin of ICP pulsation. To test this hypothesis, we have designed a unique cranial space phantom that allows for the isolation of major arteries for studying pressure pulse transmission to the brain.

4.3 Materials and Methods

The internal carotid (ICA) and basilar (BA) arteries, the circle of Willis (CoW) and the cerebral ventricles of healthy volunteers were segmented from MRI images following the protocols described in (Zuleger et al., 2010; Bottan et al., 2012a) (Figure 4.2). The lumina of ICAs, BA and CoW were rapid prototyped with wax and re-cast with Wood’s metal, a low melting point alloy. Silicone was applied to the surface of this negative to model the vessel wall. The material (Sylgard 184, Dow Corning, Midland, MI, USA) and the applied layer thickness were chosen to match physiologic mechanical properties of the vessels (see Table 4.1).

Following (Bottan et al., 2012a), the ventricular space was modeled within a soft silicone gel (Sylgard 527, Dow Corning) that mimics the mechanical properties of the brain. The brain section containing the ventricles and the modeled vasculature were placed in proper anatomic position in a transparent plastic skull (3B Scientific, Hamburg, Germany) (Figure 4.3). Silicone gel (Sylgard 527) was poured into the skull to represent the remainder of the brain, and the Wood’s metal was washed out with water at 80°C to access the vessel lumen.

The subarachnoid space (SAS) was modeled as an external compartment, and the intracranial compliance was set to 1 ml/mmHg, as described in (Bottan et al., 2012a) for healthy subjects (Figure 4.1).
Deionized water at room temperature was used to model both blood and CSF. The arteries were filled with water and connected to a programmable piston pump (CompuFlow 1000MR, Shelley Medical Imaging Technologies, Ontario, Canada). The CSF spaces were filled and connected to a roller pump (Figure 4.1).

The arteries were pressurized with the pulsatile pump to reproduce the textbook arterial blood pressure (ABP) waveform shown in (Guyton & Hall, 2000). Blood pressure was recorded in the left ICA with a capacitive transducer (Series 41X, Keller AG, Winterthur, Switzerland). The induced ICP response was measured in the ventricles using a clinical bedside monitoring system (Microsensor and ICP Express, Codman & Shurtleff, Raynham, MA, USA) as well as a second capacitive industrial transducer (Series 41X, Keller AG) for cross-validation.

<table>
<thead>
<tr>
<th>Description</th>
<th>Phantom Values</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial wall thickness</td>
<td>0.3 mm</td>
<td>(Alastruey et al., 2007)</td>
</tr>
<tr>
<td>Arterial wall elasticity</td>
<td>1.6 mPa</td>
<td>(Alastruey et al., 2007)</td>
</tr>
<tr>
<td>(Young’s modulus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial compliance</td>
<td>1 ml/mmHg</td>
<td>(Bottan et al., 2012a)</td>
</tr>
<tr>
<td>Mean nominal ICP</td>
<td>10 mmHg</td>
<td>(Bottan et al., 2012a)</td>
</tr>
<tr>
<td>Basal heart rate</td>
<td>54 bpm</td>
<td>(Camm et al., 1996)</td>
</tr>
</tbody>
</table>

Table 4.I: List of the phantom operating parameters used to reproduce physiologic conditions. Intracranial compliance was calculated for a subject with mean ICP of 10 mmHg and brain elastance coefficient of 0.1 ml¹ as in (Czosnyka et al., 2004; Bottan et al., 2012a).
Figure 4.1: Schematic of the phantom model. Anatomically accurate silicone representations of ICAs, BA and circle of Willis, as well as cerebral ventricles are located in a silicone brain within a plastic skull. A piston pump is used in conjunction with a restriction valve to apply physiologic pulsatile blood flow to the vessels. The corresponding pulse pressure is transmitted through the brain to the ventricular space where ICP is acquired and recorded on a desktop computer. Blood pressure is acquired in the left ICA. A roller pump infuses water from the reservoir into the system and is used to pressurize CSF to the mean nominal value (Table 4.1). The SAS is included in the model as an external porous compartment, accounting for hydrostatic loading as well as dynamic pressure loss during pulsation (Bottan et al., 2012a). Compliance boxes as described in (Bottan et al., 2012a) are connected to the SAS and cisterns, modeling spinal as well as cranial space compliance, respectively.
Figure 4.2: Rapid prototyped negative of vascular domain showing the positions of the connectors c1 to c8 to the pulsatile pump circuit.
Figure 4.3: Photograph of the main part of the phantom showing plastic skull, cistern, silicone tube connectors to the vascular and ventricular spaces and attachment location of the SAS model. ICP monitoring access is also shown.

### 4.4 Results

The phantom rendered the targeted ABP waveforms accurately (Figure 4.4, top panels), reproducing systole (116.3±0.8 mmHg peak in the left ICA), diastole (77.8±0.7 mmHg peak) and dicrotic notch. Heart rate was stable at 54 beats per minute.

The blood pressure oscillations in the ICAs, BA and CoW are transferred through the vessel walls and brain into the ventricular CSF space. The amplitude of the transferred pressure wave is
attenuated by compliance. Intra-ventricular pressure recorded concurrently with ABP is shown in the bottom panels of Figure 4.4: Mean ICP was 9.9 mmHg. Peak values of ICP were 9.3±0.1 (minimum) and 10.6±0.1 mmHg (maximum), with the same frequency as ABP pulsation. Peak-to-peak values of ICP (also referred to as ICP pulse amplitude) were 1.3±0.1 mmHg, which is well within the expected physiologic range (Czosnyka et al., 2004). However, the ICP waveform lacks the percussion, tidal and dicrotic waves observed in-vivo (Gega et al., 1980; Cardoso et al., 1983; Citerio & Andrews, 2004).

![Figure 4.4: Simultaneous recording of arterial blood pressure (ABP) in the ICA (top) and ICP in the ventricular space (bottom). Left: Data acquired over several cardiac cycles to demonstrate the long-term stability of the pulsation. Blood pressure is between 77.8±0.7 mmHg diastolic and 116.3±0.8 mmHg systolic. Right: Data acquired over a single cardiac cycle. The imposed ABP waveform (top right) shows the common physiologic characteristics such as dicrotic notch. The induced ICP waveform (bottom right) does not contain the percussion, tidal and dicrotic peaks observed in-vivo (Citerio & Andrews, 2004).](image)
4.6 Discussions

Bering (Bering, 1955) wrote in 1955 based on the results of an in vivo animal model that “[the] pulsation of the CSF is generated by the filling and draining of the choroid plexuses”. After performing his own animal trial, Dunbar (Dunbar et al., 1966) declared in 1966 “[...] the hypothesis that the CSF pulse wave originates from choroid plexus untenable”. To date, these contradictory statements on the origin of intracranial pulsation have not been resolved. This is at least in part due to the fact that a total isolation of vascular structures cannot be carried out in vivo without changing intracranial dynamics.

The phantom model presented herein allows for the complete isolation of major intracranial arteries from all other potential sources of pressure wave transfer to the brain. It enables thereby the investigation of the relative contribution of these vessels to the production of physiologic ICP oscillations.

Our results show that physiologic blood pressure pulsation in the ICAs, BA and CoW is sufficient to obtain ICP amplitudes in the range of those observed in vivo (Bottan et al., 2012a). However, the shape of the ICP waveform produced in the phantom does not contain the full detail seen in vivo (Gega et al., 1980; Cardoso et al., 1983; Citerio & Andrews, 2004), which implies that other pathways of pulse transmission from the cardiovascular system to the intracranial space must play a role.

Three comparably consistent components of physiologic ICP waveform are the percussion, tidal and dicrotic waves. It has been suggested that the percussion wave is caused by the pulsation of the choroid plexus and of the major cranial arteries, that the tidal wave may reflect variations in cerebrospinal compliance, and that the dicrotic wave derives from the dicrotic notch of the arterial pulse waveform (Gega et al., 1980; Citerio & Andrews, 2004).

The lack of pronounced percussion waves in the phantom model indicates that the major arteries can only play a secondary role in their definition. We thus conclude that primarily the choroid plexus must be responsible for the occurrence of percussion waves.
According to Cardoso et al. (Cardoso et al., 1983), the amplitude of the tidal wave relative to those of the percussion and dicrotic waves depends on vasoconstriction of arterioles. This finding is supported by the phantom model, where the absence of tidal waves indicates that modulation of the ICP waveform by blood vessels downstream of the major arteries must be responsible for their occurrence.

Transfer of the comparably small arterial dicrotic notch to the dicrotic wave of the ICP must occur through a pathway that provides little attenuation, which is either through major intracranial arteries or the choroid plexus. Other pathways with more damping would not preserve this small arterial pressure waveform segment. The absence of dicrotic waves in the phantom model suggests that their occurrence in vivo can be attributed to the pulsation of the choroid plexus rather than that of major arteries.

We conclude that major intracranial arteries cannot by themselves produce the complete ICP waveform. While their expansion and contraction yields ICP amplitudes within normal physiologic range, action of the choroid plexus and pressure modulation by the remainder of the vascular tree are necessary to yield the full ICP waveform.
5 Craniospinal Pressure-Volume Dynamics in Phantom Models

Parts of this chapter have been accepted for publication in IEEE Transactions on Biomedical Engineering (August 2012).

5.1 Abstract

Regulation of intracranial pressure (ICP) is vital to proper brain function. Pathologic conditions such as traumatic brain injury and hydrocephalus can cause lethal changes in ICP through an imbalance of fluid passage into and out of the craniospinal space. The relationship between craniospinal volume and pressure determines to a large extent whether such imbalance can be compensated or if it will lead to neuronal damage.

Phantom models are predisposed for the evaluation of medical procedures and devices that alter volume in the spinal or cranial space. However, current phantoms have substantial limitations in the reproduction of craniospinal pressure-volume relationships, which need to be overcome prior to their deployment outside the basic research setting.

We present herein a novel feedback controlled phantom for the reproduction of any physiologic or pathologic pressure-volume relation. We compare its performance to those of existing passive methods, showing that it follows reference curves more precisely during both infusion of large volumes and fast oscillatory volume changes.

5.2 Introduction

The central nervous system (CNS) is pressurized relative to both normal atmospheric and venous pressures. Cerebrospinal fluid (CSF) that surrounds brain and spinal cord equalizes spatial pressure differences to a large extent. By flowing from the cranial to the spinal
subarachnoid space (SAS) in systole and back in diastole, CSF also dampens temporal peaks of intracranial pressure (ICP) caused by the cardiovascular system.

Maintenance of pressure within physiological range is of utmost importance to proper brain function. Increased ICP as a possible result of traumatic brain injury (TBI) (Ghajar, 2000; Marmarou et al., 2005b), spina bifida (Edwards et al., 2003), hydrocephalus (Hakim, 1971; Hakim et al., 1976) and other pathologic conditions can lead to life-threatening neuronal damage (Gallia et al., 2006). ICP regulation is established primarily by balancing fluid transport into and out of the cranial space, which includes control of CSF production and absorption rates (Hakim et al., 1976; Rekate et al., 2008), interstitial fluid volume (Iencean, 2003) and vascular tone adaptation (Cipolla, 2009).

Malfunction of ICP regulation can result from failure of pressure sensing and processing, from a pathologic reduction of the ability to transport fluid (e.g. blockage of CSF absorption pathways), or from operation outside the viable parameter range (e.g. cerebral hemorrhage with high inflow rate). Since such differentiation is often not possible in the clinical setting, assessment of ICP regulation is commonly carried out via a phenomenological analysis of the relationship between craniospinal volume change and intracranial pressure.

A simplified empirical form (Avezaat & van Eijndhoven, 1986) of this relationship valid for a slow increase in volume is

\[
P = P_0 e^{kV} + P_1
\]  

(5.1)

where \( P \) is intracranial pressure, \( P_0 + P_1 \) is nominal intracranial pressure, \( V \) is added craniospinal volume relative to nominal and \( k \) is the brain elastance coefficient (Table 5.I).

Dysfunction of intracranial pressure regulation will eventually cause, through change in ICP, an alteration of craniospinal compliance \( C \) that is defined as
\[
\frac{1}{C} = \frac{dP}{dV}
\]

(5.2)

As we recently reported, phantom models are a promising platform for the evaluation and development of medical devices that influence ICP (Martin et al., 2010; Bottan et al., 2012a). In contrast to computational approaches (Kurteuoglu et al., 2007; Gupta et al., 2010), they allow for the inclusion of existing medical devices and prototypes in hardware. Compared to animal models, they are more flexible, less expensive and do not raise ethical concerns. They provide full control over pathophysiologic parameters as well as excellent reproducibility of experiments. Phantom models could be used, for example, to evaluate existing CSF shunts under dynamic conditions, or for the assessment of novel shunt system prototypes. They could be employed to gain a deeper understanding of infusion tests, and to unify conflicting results that are today reported through different infusion methods (Sundstrom et al., 2010).

However, current phantoms are limited by incomplete reproduction of in-vivo pressure-volume relations that are realized through pneumatic chambers (Bottan et al., 2012a) or fixed hydrostatic columns (Schuhmann et al., 2000; Taylor et al., 2002; Andersson et al., 2005) to reproduce Eq. (5.1) or similar empirical relations (Sainte-Rose et al., 1987). Eq. (5.1) was originally derived via controlled lumbar saline injection and concurrent ICP recording in animals (Marmarou et al., 1975) and patients (Katzman & Hussey, 1970). While it is commonly used in the literature, it does not represent the complete craniospinal pressure-volume relationship which depends on the time history (Kasprowicz et al., 2003) and rate of volume change (Galford & McElhaney, 1970).

Here we present a novel approach based on feedback control for the complete and accurate reproduction of any prescribed physiologic or pathologic pressure-volume relation. We compare its performance to those of existing methods, showing that it follows reference curves more precisely. Finally, we juxtapose and evaluate the advantages and limitations of the analyzed approaches.
5.3 Materials and Methods

We implemented five distinct designs for the reproduction of the craniospinal pressure-volume relation given in Eq. (5.1) using the parameter values shown in Table 5.I. The respective phantoms are described in the following subsections. The performance metrics according to which the individual designs were evaluated are given in the last subsection. The test rig within which the pressure-volume phantoms were evaluated is shown schematically in Figure 5.1 and described here below.

| Table 5.I: List of operating parameters used to define the phantoms working condition for the healthy state. Values reported in the literature, which define the physiologic range for a healthy subject, are also reported. Legend: nominal intracranial pressure (Nom. ICP), nominal compliance (nom. C) and nominal peak-to-peak (nom. PP). *P_1 is set to zero without loss of generality. **Computed from data given in the referenced work. |
A syringe pump (PHD Ultra, Harvard Apparatus, Holliston, MA, USA) was used to infuse the phantoms with deionized water at 23.5±0.5 °C and a constant flow rate of 1.5mL/min (Berne & Levy, 1990; Sundstrom et al., 2010). A second pump setup consisting of a LinMot/MagSpring linear motor assembly (NTI AG, Spreitenbach, Switzerland) and a custom-made polytetrafluorethylene (PTFE) fold bellows (ElringKlinger Kunststofftechnik GmbH, Bietigheim-Bissingen, Germany) provided oscillatory volume changes to mimic the effect of cardiac pulsation. A piezoresistive sensor PR-41X (Keller AG, Winterthur, Switzerland) with acquisition range of 0 to 100mbar was used to measure pressure in the phantoms.

MATLAB/Simulink R2011a and Real-Time Windows Target (The MathWorks, Inc., Natick, MA, USA) running on a Windows XP personal computer (PC) equipped with a MF624 I/O card (Humusoft s.r.o., Prague, Czech Republic) were used to acquire analog data at a sampling rate of 1 kHz. Digital data were recorded at 100Hz with a CANboardXL interface (Vector CANtech, Inc., Novi, MI, USA) on the same PC.

![Figure 5.1: Schematic of the test rig used to investigate craniospinal pressure-volume phantoms. Constant infusion of volume $V_{sp}$ and oscillatory volume variation $V_{op}$ yield the total volume change $V$ in the phantom, whose pressure-volume characteristic then determines the measured pressure $P_m$.](image)

**Pneumatic Chamber**

The first craniospinal pressure-volume phantom model, shown schematically in Figure 5.2, relies on the compressibility of air in a
hermetically sealed PMMA chamber as briefly described in (Bottan et al., 2012a).

Under the assumption of ideal gas behavior and adiabatic conditions, the pressure-volume relation of the air in the chamber is given by

\[ P_a V_a^\lambda = P_{ao} V_{ao}^\lambda \]  

(5.3)

where \( \lambda = 1.4 \) for air, and \( P_{ao} \) and \( V_{ao} \) are the initial air pressure and volume, respectively.

Combining Eq. (5.2) and (5.3), the compliance of the pneumatic chamber is given by

\[ C = -\frac{1}{\lambda} \sqrt{P_{ao} V_{ao}^\lambda} P_a^{-\frac{1+\lambda}{\lambda}}. \]  

(5.4)

This relation was used to dimension the chamber. To compensate for possible errors introduced by the assumption of ideal gas undergoing an adiabatic process, a calibration was performed by adjusting the initial air volume \( V_{ao} \) required to obtain the targeted compliance value.
Figure 5.2: Sketch of the pneumatic chamber phantom. A sealed PMMA chamber with cross-sectional area $A$ contains water to level $h$ and air of volume $V_a$ at pressure $P_a$. Added volume of water $V$ causes a change in measured pressure $P_m$. The triangle indicates air-water interface.

**Hydrostatic Column**

The second and third phantom rely on the hydrostatic pressure generated by a column of water in an upright channel (Andersson *et al.*, 2005) and a tube (Taylor *et al.*, 2002), respectively.

The channel features a cross-sectional area that is a function of the position along the channel’s vertical axis Figure 5.3. The function is chosen such that Eq. (5.1) is reproduced when fluid is injected at the base of the channel.

The hydrostatic pressure at the base is given by
\[ P = \rho gh , \quad (5.5) \]

where \( \rho \) is the density of water in the channel, \( g \) the gravitational acceleration and \( h \) the height of the water column. The corresponding water volume is

\[ V(h) = d \int_0^h w(h) \, dh , \quad (5.6) \]

where \( d \) is the constant depth of the channel and \( w \) the variable width. It can be obtained by substituting \( P \) and \( V \) in Eq. (5.1) with Eq. (5.5) and (5.6), respectively, and then solving for \( w \), yielding

\[ w(h) = \frac{1}{kdh} , \quad (5.7) \]

We designed a channel with corresponding width function starting at an initial height of 9.5 cm (7mmHg starting pressure), 90 cm total height and 3mm depth, and had it precision milled via CNC in an aluminum plate based on our CAD design. The channel was closed off using a PMMA plate and sealed with an O-ring.
Figure 5.3: Sketch of hydrostatic column (channel). A channel of width \( w \), which is a function of height has given by Eq. (5.7), is milled into an aluminum plate, closed by a transparent PMMA plate and sealed with an O-ring. Added volume of water \( V \) causes a change in measured pressure \( P_m \) as defined by the function \( w(h) \) and the constant depth of the channel.

In the third phantom, a hydrostatic column is established via water in a tube deflected horizontally in a vertical plane (Figure 5.4). Water pressure and volume in the tube are given by
\[ P(x) = \rho gh(x) \] and \( V(x) = AI(x) \), respectively, where \( h \) is the height of the water column, \( x \) the horizontal deflection of the tube centerline at \( h \), \( A \) the tube constant cross-sectional area, and \( l \) the length of the water column along the centerline. The function \( h(x) \) is then described implicitly by substituting Eq. (5.8) and (5.9) in (5.1) to yield the ordinary differential equation

\[ \frac{h'}{h} = kA\sqrt{1 + h'^2}, \] (5.10)

Where \( h' \) is the derivative of \( h \) with respect to \( x \).

We solved Eq. (5.10) numerically in MATLAB to obtain the centerline profile of the tube. We then printed this profile to scale on a poster, fixed the poster on a vertical whiteboard, and attached a PVC tube with 4mm inner diameter (VWR International AG, Dietikon, Switzerland) along the printed profile using neodymium permanent magnets.
Figure 5.4: Sketch of hydrostatic column (tube). A tube fixed onto a whiteboard by magnets (inset) follows a curve (blue) defined by Eq. (5.10). Added volume of water V increases the height of the water level (inset), which in dependence of the curve shape causes a change in measured pressure \( P_m \). Different pressure-volume relations can be set by moving the tube to different curves such as the red and yellow ones shown in the inset.

**Active Control**

The fourth and fifth, novel, phantoms follow prescribed pressure-volume curves by feedback control. As shown in Figure 5.5, a linear actuator pressurizes a water tank that, as a variant, may also contain air, Figure 5.6. Both approaches without and with air are investigated herein. In both cases the pressure \( P \) is the process variable. In the first case, the actuator force \( F \) is the manipulated variable, in the second it is the actuator position \( z \). The actual value of the process variable \( P \) is measured \( (P_m) \) with a piezo-resistive transducer (PR-41X, Keller).

The control system is implemented in MATLAB/Simulink Real-Time Windows Target to follow Eq. (5.1) and to interact with the hardware setup in real-time over an RS-232 serial port.
This includes acquisition of the linear actuator’s slider position \( z \) and transmission of the slider position set point \( z_w \) in the case of position control, or the actuator force set point \( F_w \) in case of force control to the actuator controller (E1200-GP, NTI AG) at 100 Hz. The actuator itself consists of a LinMot/MagSpring linear motor assembly (NTI AG) attached to a custom-made PTFE bellow with a displacement to volume relation described with good approximation by

\[
V_B = V_{B0} - zA_B, \quad (5.11)
\]

where \( V_{B0} \) is the bellow volume at initial position \( z_0 \), \( z \) is the actual slider position and \( A_B \) is the effective cross-sectional area of the bellow. \( A_B \) was determined with continuous water infusion from \( z_0 \) to \( z_{\text{max}} \).

In the case with air, Figure 5.6, the position set point \( z_w \) is the output of the pressure controller implemented in MATLAB/Simulink. In the approach without air, Figure 5.5, pressure control is performed by the actuator controller E1200-GP. Here the force set point \( F_w \) (Eq. (5.12)) and actual value \( F_m \) (Eq. (5.13)) are implemented using appropriate scaling factors to reflect the following relations:

\[
F_w = P_w A_B \quad \text{and} \quad (5.12)
\]

\[
F_m = P_m A_B. \quad (5.13)
\]

The pressure set point \( P_w \) is calculated according to the desired craniospinal pressure-volume relation, e.g. Eq. (5.1). For the case without air, the actual volume change in the phantom equals the volume change in the bellow \( V_B \). In the case with air in the water tank, assuming ideal gas behavior and isothermal conditions, the actual volume change in the phantom is estimated to be

\[
\tilde{V}(P_a, z) = V_{a0} - \frac{P_{a0} V_{a0}}{P_a} + V_B, \quad (5.14)
\]
where $P_{ao}$ and $V_{ao}$ are the initial air pressure and volume, respectively, and

$$P_a = P_m + P_{amb} - \rho gh$$

(5.15)

is the current air pressure. $P_{amb}$ is the absolute ambient pressure, $\rho$ the water density and $h$ the water level above the pressure sensor.

For oscillatory volume changes, the active control phantoms do not have to rely on physical volume inflow from the test rig. Instead, nominal oscillatory volume curves can be prescribed that are then integrated on the software side to a corresponding control signal for the actuator as indicated by $V_{op}$ in Figure 5.5 and Figure 5.6.
Figure 5.5: Control scheme of the active control phantom without air in the water tank. An actuator consisting of a linear motor and a bellow with effective displacement area $A_B$ pressurizes the sealed water tank of cross-sectional area $A$. Pressure $P$ is the process variable, recorded as $P_m$ by a pressure sensor. The actuator force $F$ is the manipulated variable. The pressure set point $P_w$ is calculated according to the desired craniospinal pressure-volume relation (Eq. (5.1)). The actual volume change in the phantom equals the volume change in the bellow $V_B$. Here, $h$ is the water level. In contrast to the first three phantom models, the oscillatory pump is implemented in software and the oscillatory pulse $V_{op}$ is applied virtually to the setup. The continuous volume $V_{sp}$ is infused physically into the tank.
Figure 5.6: Control scheme of the active control phantom with air in the water tank. An actuator consisting of a linear motor and a bellow with effective displacement area $A_B$ pressurizes the sealed water tank of cross-sectional area $A$. Pressure $P$ is the process variable, recorded as $P_m$ by a pressure sensor. The actuator position $z$ is the manipulated variable: The position set point $z_w$ is the output of the pressure controller implemented in MATLAB/Simulink. The pressure set point $P_w$ is calculated according to the desired craniospinal pressure-volume relation (Eq. (5.1)). The actual volume change in the phantom is estimated according to the air compression model from Eq. (5.14) as $V$. Here, $h$ is the water level, $V_a$ and $P_a$ the air volume and pressure, respectively. In contrast to the first three phantom models, the oscillatory pump is implemented in software and the oscillatory pulse $V_{op}$ is applied virtually to the setup. The continuous volume $V_{sp}$ is infused physically into the tank.
**Performance Metrics**

We assessed each method’s accuracy in following the pressure-volume relation (Eq. (5.1)) under physiologic conditions as given in Table 5.I. This approximates a clinical infusion test. We further evaluated the reproduction of ICP oscillation due to mimicked cerebral blood pulsation with frequency of 1Hz and amplitude of 0.5 mmHg at a mean intracranial pressure of 10 mmHg (Wagshul et al., 2011). The performance metrics used for these assessments are given below.

The accuracy with which Eq. (5.1) was reproduced within the range of 10 to 60mmHg was evaluated via the mean square error (MSE) of the measured versus targeted pressure curve.

For sinusoidal volume input, the deviation of the measured oscillatory pressure response from the targeted curve was quantified using the metrics of total harmonic distortion (THD) and amplitude of the first harmonic (AFH). While the former includes measured components beyond the expected targeted oscillation, the latter allows for an evaluation of the measured signal amplitude independent of noise. THD is defined according to (IEEE, 1993) as

$$THD = \sqrt{\frac{\sum_{n=2}^{\infty} P_n^2}{P_1^2}},$$  \hspace{1cm} (5.16)

where $P_n$ are the amplitudes of the second to the $n^{th}$ harmonics, and $P_1$ is the amplitude of the fundamental frequency. Given the finite bandwidth of the test rig, we filtered the measured ICP signals using a digital 30-point two-pass moving average filter with 1ms sampling time, resulting in a cut-off frequency of 10 Hz, and approximated THD by considering up to and including the 10th harmonic component. Due to the nonlinear pressure-volume relation, the target pressure response to the sinusoidal volume modulation does not correspond to a sinusoidal wave and, therefore, its THD is 1.25% rather than 0. We designate this as reference THD$_{ref}$ and define the increase in a phantom’s total harmonic distortion THD relative to THD$_{ref}$ as
\[ D = \frac{THD - THD_{\text{ref}}}{THD_{\text{ref}}}, \]  

with \( D=0 \) denoting optimal reproduction of the reference oscillation without additional distortion.

We further define the amplitude of a phantom’s first harmonic component AFH relative to the reference amplitude AFH_{\text{ref}} as

\[ A_1 = \frac{AFH}{AFH_{\text{ref}}}, \]  

with \( A_1=1 \) denoting optimal reproduction of the reference amplitude. \( A_1<1 \) and \( A_1>1 \) indicate amplitudes below and above the reference, respectively.
5.4 Results

To test the five phantom implementations, we defined a representative physiologic state as reported in Table 5.I based on literature data. For some of the implementations, additional pressure-volume relations were followed, in which case the corresponding parameters are given in the respective figure.

### Table 5.II
**Accuracy of Oscillatory Pressure-Volume Dynamics Reproduction**

<table>
<thead>
<tr>
<th>( P_{\text{mean}} ) (mmHg)</th>
<th>THDref</th>
<th>Pneumatic Chamber (Channel)</th>
<th>Hydrost. Column (Channel)</th>
<th>Hydrost. Column (Tube)</th>
<th>Active Control (Air)</th>
<th>Active Control (No Air)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.22</td>
<td>24.05</td>
<td>3.94</td>
<td>1.40</td>
<td>11.94</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.14</td>
<td>13.41</td>
<td>5.29</td>
<td>0.35</td>
<td>17.26</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.17</td>
<td>6.49</td>
<td>6.24</td>
<td>0.53</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>n/a</td>
<td>3.59</td>
<td>n/a</td>
<td>1.01</td>
<td>1.07</td>
<td></td>
</tr>
</tbody>
</table>

| Mean ± SD | 0.18± 0.04 | 11.89± 9.10 | 5.16± 1.16 | 0.82± 0.48 | 8.02± 7.91 |

<table>
<thead>
<tr>
<th>( P_{\text{mean}} ) (mmHg)</th>
<th>AFHref</th>
<th>Pneumatic Chamber (Channel)</th>
<th>Hydrost. Column (Channel)</th>
<th>Hydrost. Column (Tube)</th>
<th>Active Control (Air)</th>
<th>Active Control (No Air)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.5</td>
<td>1.38</td>
<td>0.60</td>
<td>16.33</td>
<td>0.92</td>
<td>1.26</td>
</tr>
<tr>
<td>25</td>
<td>1.25</td>
<td>1.24</td>
<td>0.54</td>
<td>14.18</td>
<td>0.96</td>
<td>1.17</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>1.4</td>
<td>0.81</td>
<td>11.22</td>
<td>1.01</td>
<td>0.95</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
<td>n/a</td>
<td>1.4</td>
<td>n/a</td>
<td>1.06</td>
<td>0.88</td>
</tr>
</tbody>
</table>

| Mean ± SD | 1.34± 0.09 | 0.84± 0.39 | 13.91± 2.57 | 0.99± 0.06 | 1.07± 0.18 |

Table 5.II: \(*D = 0\) corresponds to optimal reproduction of the reference oscillation without additional distortion. THD\(_{\text{ref}}\) is the total harmonic distortion reference value.
**A1 = 1 corresponds to optimal reproduction of the reference amplitude. A1 <1 and A1 >1 indicate amplitudes below and above the reference, respectively. AFH_ref is the first harmonic reference amplitude.

The pressure-volume relationship of the phantom based on the pneumatic chamber approach is shown in Figure 5.7. It is evident that its behavior does not follow the target curve given by Eq. (5.1). However, by switching among operating points, an approximation of the target curve is possible. The pneumatic chamber phantom shows good reproduction of ICP oscillation in response to mimicked cerebral blood pulsations as illustrated in Figure 5.8. It features very low distortion and acceptable amplitude replication (see D and A1 values in Table 5.II).

Figure 5.7: Pressure-volume measurements in the pneumatic chamber phantom. Three initial settings of the phantom were tested at operating points of 10, 25 and 40mmHg with compliance values of 1, 0.4 and 0.25ml/mmHg, respectively. The pressure-volume recordings show that the target curve (dashed black line) is only reproduced acceptably at and in the vicinity of the operating points.
Figure 5.8: Accuracy of phantoms in following target exponential pressure-volume curves with 10mmHg initial pressure and elastance k as indicated. Channel and tube refer to the corresponding hydrostatic column phantom implementations. Air and no air refer to active control phantoms. The shown mean square error values are calculated for a pressure range of 10 - 60mmHg during steady infusion.

The channel implementation of the hydrostatic column approach shows good fit at the beginning and end of the pressure-volume curve, Figure 5.9(a). However, in the vicinity of 10 mL of added volume, pressure deviates from its target value. This is due to the limits of manufacturing accuracy.

As a result, the mean square error (MSE) is high (Figure 5.8). Furthermore, reproducible pressures are limited to a range of 7 to 71mmHg in this particular implementation due to practical considerations regarding the physical size of the phantom. The oscillation response to the sinusoidal volume input is highly distorted with the highest D-values among all phantoms (Table 5.II). A₁ values are in a reasonable range.
Figure 5.9: Pressure-volume recordings of the hydrostatic column phantoms in the channel (a) and tube (b) implementations, as well as of active control phantoms with (c) and without (d) air. In all plots, solid lines represent measurements within the respective phantoms, while dashed lines indicate the target curves. Only a single pressure-volume relation is shown in (a) with $k=0.1$ ml$^{-1}$ due to the limited flexibility of this method. Elastance values of up to 0.13 ml$^{-1}$ are reported in (b) to show the higher flexibility of this approach, although compliance below a limit value cannot be reproduced as is visible at $k=0.13$ ml$^{-1}$ for volumes larger than 12.5 ml. Both (c) and (d) show accurate representation of all curves with elastances in the entire physiologic range of 0.0886<$k<$0.177 ml$^{-1}$.

Unlike the channel phantom, the tube implementation of the hydrostatic column approach allows for quick adaptation of pressure-volume curves. Figure 5.9-b shows three such curves that are well reproduced down to a minimum compliance value of 0.182mL/mmHg, below which a linear trend can be discerned. The reproducible pressure range is 8 to 67 mmHg over the three configurations (see Discussions). Pressure oscillations are replicated with small harmonic distortion, but large overshoot of the first harmonic amplitude (Figure 5.10).
Figure 5.10: Comparison of the phantom models’ pressure response to oscillatory volume changes. Pulsation at mean pressure values of 10, 25, 40 and 60 mmHg (horizontal dash-dotted lines) are shown in panel (a). Panel (b) shows a magnified view of pulsation at 10mmHg. The black dashed line represents the nominal pressure-volume curve (corresponding unit on the horizontal axis: ml). The grey line is the target pressure pulse wave (horizontal axis unit: seconds). The colored curves are the pressure waveforms measured in the active control phantom with (blue) and without air (cyan), the hydrostatic column implemented as channel (purple) and tube (green) and the pneumatic chamber (red).

The novel craniospinal pressure-volume phantom based on active feedback control reproduces ICP oscillations (Figure 5.10) and target curves well in both of its implementations, i.e. with air in the pressurized water tank, Figure 5.9(c), and without air, Figure 5.9(d). In both cases, pressure is mapped well over the entire studied volume range of −10 to 20 mL. With the exception of k=0.177 mL⁻¹ in the configuration with air, the MSE is low for all elastance values (Table
5.II). The setup with air renders ICP oscillations more accurately 
(D=0.82±0.48 versus 8.02±7.91 and A1=0.99±0.06 versus 1.07±0.18, 
mean±SD), while the phantom without air follows the prescribed 
curves with higher precision (MSE=0.06±0.02 versus 0.1±0.09).
5.6 Discussions

We have introduced herein a novel, feedback controlled phantom model of craniospinal pressure-volume relations, and compared two implementations of this model to three approaches that had been reported previously. Each of these phantoms is characterized by certain advantages and shortcomings that we will describe further below, distinguishing between inherent disadvantages and technical limitations (Table 5.III). Inherent disadvantages are due to the governing physics. They can only be remedied by using a different implementation of the respective model. Technical limitations can be removed or at least relaxed by improving the respective implementation, for example by increasing manufacturing or measuring accuracy.

<table>
<thead>
<tr>
<th></th>
<th>Pneum. Chamber</th>
<th>Hydrost. Column (Channel)</th>
<th>Hydrost. Column (Tube)</th>
<th>Active Control (Air)</th>
<th>Active Control (No Air)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow infusion</td>
<td>- - (i)</td>
<td>- (t)</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Oscillatory volume change</td>
<td>+ +</td>
<td>- (i)</td>
<td>- - (i)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Calibration</td>
<td>- (t)</td>
<td>+ +</td>
<td>- - (i)</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>Flexibility</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cost Efficiency</td>
<td>+ +</td>
<td>- (t)</td>
<td>+ +</td>
<td>- - (i)</td>
<td>- - (i)</td>
</tr>
</tbody>
</table>

Table 5.III: “+” and “++” indicate positive and very positive evaluations, respectively. Negative and very negative evaluations (“–”, “––”) indicate limitations of the respective phantom model, with (i) designating inherent and (t) technical limitations. Inherent limitations are governed by the underlying physics and cannot be solved unless the phantom model is changed. Technical limitations can be removed or reduced by improving the respective implementation.

**Pneumatic Chamber**

The pneumatic chamber phantom is easy to fabricate and can be set to approximate pressure-volume curves at different operating points.
Switching among operating points requires interruption of the experiment and recalibration of the air volume. Consequently, this phantom is not suited for infusion tests or other situations with large volume increase. This is an inherent limitation. However, it can accommodate small volume changes around a given operating point very well (Figure 5.7). Such small volume oscillations can be used to emulate the effect of vascular pulsation (Bottan et al., 2012a). Calibration represents the main technical disadvantage of this phantom model. Eq. (5.3) for the design of the initial air volume $V_{ao}$ assumes ideal gas behavior and adiabatic condition. The real system differs from this assumption and $V_{ao}$ needs to be calibrated experimentally.

**Hydrostatic Column**

Both tube and channel implementations of the hydrostatic column model can reproduce prescribed exponential pressure-volume relations of the Eq. (5.1) type. While the tube approach can be used to replicate various such relations, the channel implementation can only follow a single curve. Each new pressure-volume relation requires the manufacture of a dedicated phantom, which is expensive and time consuming. The precision of curve reproduction depends on the accuracy of the channel fabrication. In contrast to the pneumatic chamber, no calibration was needed in the current implementation of the channel phantom. Yet this approach shows clear limitations in the replication of oscillatory volume changes (Figure 5.10 and Table 5.II). Surface tension at the channel walls generates noise in the pressure measurements when rapid oscillations of fluid are applied.

The tube phantom offers higher flexibility than the channel model. The pressure-volume relation to be reproduced can be adjusted by simply shifting the tube to the desired printed curve. However, the constant cross-sectional area of the tube is an inherent limiting factor: With the tube in vertical position, the lowest achievable compliance is $A/(\rho g)$ according to Eq. (5.2), (5.8) and (5.9). As the desired elastance $k$ in Eq. (5.1) is increased, the minimum compliance is reached at lower infused volume, and the MSE increases consequently (Figure 5.8). Thus a small inner diameter tube is required to reach low compliance values, which not only leads to a
longer phantom, but also to poor reproduction of dynamic pressure-volume changes as can be seen in Figure 5.10. This is due to the fact that Eq. (5.8) is only valid for quasi-steady conditions, i.e. for slow changes of the water level in the tube. The faster the volume change and the smaller the tube diameter, the more important inertial and viscous forces will become. In addition, capillary forces will increase with decreasing diameter. In the tube implementation used here, their contribution is estimated to be below 0.7 mmHg (below 0.5 mmHg for the channel implementation).

**Active Control**

The active control phantom in both of its implementations is more flexible and, over the investigated range of elastance values, more accurate than the passive phantoms in the steady infusion tests. The remaining small deviation from the target curve is caused by nonlinearities in the displacement-to-volume relation of the bellow. This is a technical limitation that can be addressed by calibration and fitting of the bellow output to a function with higher order than the linear one used here. A piston would give a simpler output function, but would also increase friction.

When reproducing oscillatory dynamics at low pressure levels, the active control phantom implementations are inferior to the pneumatic chamber with respect to total harmonic distortion, but they map the amplitude more precisely. The distortions are caused largely by friction in the linear motor. This is again a technical limitation that can be addressed by changing the actuator.

Friction has a smaller effect in the implementation with air, where a feed-forward control component can be used, since actuator position rather than force is controlled. Nevertheless, we see the active control implementation without air as the more advantageous approach due to the simpler setup and higher accuracy in following steady infusion curves.

The active control phantom is not limited to pressure-volume relations of the Eq. (5.1) form. Instead, it can be used to replicate subject-specific or pathologic curves by simple adjustments in the
controller software. As an example, Fig. 10 shows hysteresis behavior of craniospinal pressure-volume relation in hydrocephalic patients reported in (Kasprowicz et al., 2003) and its replication with the active control phantom (air). No physical changes to the phantom were necessary for this. Similarly, any dynamic change in ICP, intracranial volume or compliance can be reproduced. This includes B-waves (Lundberg, 1960; Lundberg et al., 1965), the effects of respiration, hemorrhage, trauma and surgical intervention.

![Graph showing hysteresis of craniospinal pressure-volume relation](Figure 5.11)

Figure 5.11: Reproduction of hysteresis of craniospinal pressure-volume relation as observed during infusion tests on hydrocephalic patients (black dashed and black dash-dotted line) by the active control phantom with air (red line). Averaged patient data were taken from (Kasprowicz et al., 2003), where the pressure-volume relation was shown to follow two different trends during ($k_1=0.24 \text{ ml}^{-1}$) and following ($k_2=0.11 \text{ ml}^{-1}$) constant infusion.
5.7 Conclusions

The active control model offers the highest overall accuracy among the discussed phantoms. Despite the higher cost and complexity, it is our method of choice due to its flexibility in replicating any physiologic and pathologic craniospinal pressure-volume dynamics.
6 Underestimation of Cerebrospinal Fluid Outflow Resistance in Bolus Infusion Test is caused by Viscoelasticity

Parts of this chapter are due to be submitted for publication in *Journal of Neurosurgery*.

6.1 Introduction

Infusion tests are powerful diagnostic tools for the quantification of patients’ CSF outflow resistance $R_{CSF}$ (Marmarou et al., 1978; Marmarou et al., 2005a). Although its clinical relevance is still debated, $R_{CSF}$ is used by some neurosurgeons as parameter for the selection of shunt candidates and as a technique to check CSF shunt function (Marmarou et al., 2005a; Eklund et al., 2007; Sundstrom et al., 2010). Standard infusion tests consist of three principal methods, called constant flow infusion, constant pressure infusion and bolus infusion methods, respectively. Standard clinical protocols as well as the mathematical rationale for post-process analysis of each method have been established (Marmarou et al., 1978; Eklund et al., 2007).

It has been stated that for unknown reasons $R_{CSF}$ as determined by the bolus infusion methods is lower than those determined by steady-state methods, such as constant flow and constant pressure infusions (Marmarou et al., 2005a), and this dilemma still remains unsolved nowadays. In a recent study by Sundstrom et al (Sundstrom et al., 2010) this has been observed in a large population of patients: In-vivo data have shown significant underestimation when $R_{CSF}$ was measured by bolus infusion, with respect to constant flow and pressure methods performed on the same population. On the other hand, Sundstrom et al (Sundstrom et al., 2010) have also compared their in-vivo results to an in-vitro phantom setup, showing that ICP cardiovascular pulsatility hampers post-processing of bolus infusion measurements. Other authors have suggested that other physiologic changes might alter patients’ response, such as transient vasogenic effects (Friden & Ekstedt, 1983).
Calculation of $R_{CSF}$ from infusion test measurements are based on the mathematical model proposed by Marmarou et al. (Marmarou et al., 1978) which describes the response of the intracranial cavity to external infusions using an electrical analogous (R-C circuit) with exponential CSF compliance $C$ and a constant $R_{CSF}$.

Marmarou’s model is widely accepted as robust as well as intuitive representation of CSF and ICP dynamics under infusion tests. However, the exponential pressure-volume relation defined by Marmarou does not account for the viscoelastic behavior of biological tissues. Viscoelasticity would imply the dependency of such a relation on the rate or velocity at which the volumetric and pressure loading is applied. If viscoelasticity significantly affects the biomechanics of intracranial tissues, then calculation of $R_{CSF}$ according to Marmarou’s model after infusion tests might lead to wrong estimations.

Viscoelasticity has been assessed in-vivo human brains by magnetic resonance elastography (MRE) (Green et al., 2008; Kruse et al., 2008; Sack et al., 2008). Miller and Chinzei (Miller & Chinzei, 2002) have proposed a hyper-viscoelastic constitutive model for the brain tissue. Hysteresis of the CSF pressure-volume curve was first reported by Marmarou et al. (Marmarou et al., 1978) during their experiments on cats, and later by Kasprowicz et al. (Kasprowicz et al., 2003), who have reported it in hydrocephalic patients. Hysteresis after imposition and withdrawal of a load is linked to viscous dissipation and ultimately to the viscoelasticity of the intracranial cavity. Viscoelasticity of brain tissue has been recently characterized and quantified in animal experiments (Elkin et al., 2011; Laksari et al., 2012; Streitberger et al., 2012), and alteration of viscoelastic properties have been reported in hydrocephalic patients before and after shunting (Freimann et al., 2012).

We hypothesize that viscoelastic properties of cerebral matter may contribute to the underestimation of $R_{CSF}$ during bolus infusion test. This work aims to prove this hypothesis. We adopted an anatomical phantom model of realistic ICP dynamics to evaluate the effects of brain viscoelasticity on infusion tests, and we coupled it with a mathematical and computer model that expands Marmarou’s solution with viscoelastic relaxation. Our work shows and explains the effect of viscoelasticity on clinical infusion tests.
6.2 Materials and Methods

Phantom Model

The in-vivo CSF and ICP dynamics were reproduced in-vitro, by a phantom of the intracranial domain that was designed according to Marmarou’s model. The phantom consists of CSF ventricular domain included in a silicone brain within a human size plastic skull; cisternal as well as subarachnoid space (SAS) compartments were also included following the protocol by Bottan et al. (Bottan et al., 2012a). The phantom is connected to a roller pump (Peristaltic Pump 66 & 77, Harvard Apparatus, Holliston, MA) that imposes a constant production rate of de-ionized water of 0.35 ml/min (Eklund et al., 2007) to the lateral ventricles (Q_{CSF}). The SAS compartment of the phantom terminates in a reservoir that is hydrostatically set to nominal sagittal sinus pressure P_{ss} of 7 mmHg (Czosnyka et al., 2004). SAS and venous reservoir are connected through a fine regulating valve (SS-SS6MM-VH, Swagelok, Solon, OH, USA) that was set to 8.57 mmHg/(ml/min) as representative R_{CSF} for the healthy subject (Czosnyka et al., 2004). When the phantom is operated at the above described conditions, ICP reaches the steady-state level of 10 mmHg. A standard microtip pressure transducer was used to monitor ICP within the phantom (Microsensor and ICP Express, Codman&Shurtleff, Raynham, MA, USA) as well as an industrial pressure sensor for cross-reference (PR-41X, Keller AG, Winterthur, Switzerland).

Exponential CSF pressure-volume relation was implemented on the phantom by an active compliance device (Bottan et al., 2012b) consisting of a linear motor connected to a bellow and controlled by a computer: an exponential pressure-volume curve was used to govern the computer control loop, and a PVI of 23 ml (k=0.1 ml⁻¹) was chosen for the phantom as representative for the healthy subject. A schematic and a picture of the phantom model are shown in Figure 6.1, and the phantom operating conditions are summarized in Table 6.I.
Figure 6.1: Description of the phantom used to test our viscoelastic theory. On the top panel (a) a schematic shows the main structure and functioning units of the setup, whereas on the bottom panel (b) a picture of the experimental workspace is reported. A human anatomical phantom of the intracranial cavity, including ventricular, cisternal and subarachnoid spaces (Bottan et al., 2012a) is connected to a fluid dynamic circuit that models the same intracranial pressure and CSF dynamics as reported in-vivo. The setup is an experimental representation of Marmarou’s model. CSF production rate is generated with a peristaltic pump; CSF is modeled with de-ionized water, which flows through the intracranial pathways, passes a fine tunable resistance valve ($R_{CSF}$) and is dispensed to a reservoir at the sagittal sinus pressure level ($P_{SS}$). Resting ICP ($P_r=P_0+P_1$) is generated via this circulation, and any alteration of it is controlled by an active compliance device system (Bottan et al., 2012b) that regulates the CSF pressure-volume relationship, according to the exponential curve defined by Marmarou (Marmarou et al., 1978). Infusion tests are modeled on the phantom by mean of a syringe pump that controllably infuses additional fluid within the CSF domains.

Viscoelastic mechanical properties of the intracranial cavity were accounted in the model by mean of a soft silicone gel. Sylgard 527 (Sylgard 527, A&B Dielectric Silicone Gel, Dow Corning, Midland, MI) has been shown to have similar mechanical behavior as brain under static (Ma et al., 2010) as well as rapid dynamic loading up to 10 Hz (Brands et al., 1999). In addition to that, during characterization the silicone gel showed a viscoelastic relaxation when a step deformation is applied: this is reported in details in the Results Section (Figure 6.2). A viscoelastic exponential pressure volume relation is ultimately obtained within the phantom.
Table 6.I: List of operating parameters used to define the phantoms working conditions for the healthy state. Values reported in the literature, for in-vivo healthy subjects are listed with the respective references.

<table>
<thead>
<tr>
<th>Name</th>
<th>Symbol</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Pressure</td>
<td>P₀</td>
<td>10 mmHg</td>
<td>(Bottan et al., 2012a)</td>
</tr>
<tr>
<td>Offset Pressure</td>
<td>P₁</td>
<td>0 mmHg</td>
<td>(Avezaat &amp; van Eijndhoven, 1984; Czosnyka et al., 2004)</td>
</tr>
<tr>
<td>Venous (Sagittal Sinus) Pressure</td>
<td>PSS</td>
<td>7 mmHg</td>
<td>(Czosnyka et al., 2004)</td>
</tr>
<tr>
<td>Brain Elastance</td>
<td>k</td>
<td>0.1 ml⁻¹</td>
<td>(Czosnyka et al., 2004)</td>
</tr>
<tr>
<td>Compliance at P₀</td>
<td>C</td>
<td>1 ml/mmHg</td>
<td>(Bottan et al., 2012a)</td>
</tr>
<tr>
<td>Production Rate</td>
<td>Q̇_{CSF}</td>
<td>0.35 ml/min</td>
<td>(Czosnyka et al., 2004)</td>
</tr>
<tr>
<td>Outflow Resistance</td>
<td>R_{CSF}</td>
<td>8.57 mmHg/ (ml/min)</td>
<td>(Czosnyka et al., 2004)</td>
</tr>
</tbody>
</table>

Infusion Tests

The protocols of clinical infusion tests have been recently reviewed by (Sundstrom et al., 2010). These protocols were applied on our phantom model. A syringe pump (PHD 4400, Harvard Apparatus, Holliston, MA, USA) was used to perform the infusions.
Constant flow as well as constant pressure infusion, and bolus tests were performed on the phantom. Infusion tests were defined based on the clinical settings reported in literature (Takeuchi et al., 2000; Sundstrom et al., 2010). The adopted infusion tests parameters are summarized in Table 2 for each infusion method.

ICP was recorded on a computer platform and processed with Matlab (The MathWorks, Inc., Natick, MA, USA) to compare the phantom response to Marmarou’s analytical model.

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant Flow Infusion</td>
<td>Infusion Rate</td>
<td>1.5 ml/min</td>
</tr>
<tr>
<td></td>
<td>Infusion Time</td>
<td>30 min</td>
</tr>
<tr>
<td>Constant Pressure Infusion</td>
<td>Step Pressure</td>
<td>3 mmHg</td>
</tr>
<tr>
<td></td>
<td>Step Time</td>
<td>4 min</td>
</tr>
<tr>
<td></td>
<td>Number of Steps</td>
<td>6</td>
</tr>
<tr>
<td>Bolus Infusion</td>
<td>Infused Volume</td>
<td>10 ml</td>
</tr>
<tr>
<td></td>
<td>Infusion Rate</td>
<td>104 ml/min</td>
</tr>
<tr>
<td></td>
<td>Recovery Time</td>
<td>30 min</td>
</tr>
</tbody>
</table>

Table 6.II: Phantom operating parameters for the investigated infusion tests (Takeuchi et al., 2000; Sundstrom et al., 2010).
Analytical model

A quasi-linear viscoelastic (QLV) constitutive theory (Fung, 1993) was adapted to adjust Marmarou’s exponential pressure-volume relation and define the time dependent response of the intracranial cavity, as

\[
ICP(t) = \int_{-\infty}^{t} G(t - \tau) \frac{\partial ICP_{\text{Marmorou}}}{\partial \tau} d\tau 
\]

(6.1)

where \( ICP_{\text{Marmorou}} \) is the volume dependent exponential ICP described by Marmarou (Eq. (2.2)) and \( G(t) \) is the reduced relaxation function, which expresses the viscous content and can be experimentally determined (Fung, 1993). According to this approach, ICP follows Marmarou’s model, however it is adjusted of a quantity that depends on the history of loading that the system has experienced, according to the function \( G(t) \). The reduced relaxation function has been experimentally quantified for bovine (Laksari et al., 2012), as well as rat (Elkin et al., 2011) brain tissues.

We implemented a computer model that simulates Marmarou’s response under infusion tests (MATLAB/Simulink R2011a and Real-Time Windows Target, The MathWorks, Inc., Natick, MA, USA). Constant flow as well as pressure and bolus infusion tests simulations were numerically carried out. The QLV theory was included in the numerical models by means of the reduced relaxation functions characterized by Laksari and Elkin (Elkin et al., 2011; Laksari et al., 2012), and the impact of viscoelasticity on the different infusion test methods was investigated.

6.3 Results

Constant flow, constant pressure and bolus infusion experiments were performed on the phantom as well as the simulink model. RCSF was calculated for each recordings and simulations, according to the methods reported in the literature: A differential method for the constant flow infusion (Marmarou et al., 1978), a linear regression method (Ekstedt, 1977) for the constant pressure infusions, and a
visual method (Marmarou et al., 1978) for the bolus infusion experiments (Eklund et al., 2007; Sundstrom et al., 2010). Underestimation of $R_{CSF}$ by bolus infusion method with respect to constant flow and pressure tests was observed in the phantom and explained with the numerical simulation.

Initial calibration performed on the phantom showed agreement with the physiologic intracranial exponential pressure-volume relation (Figure 6.2-a). In addition to that a viscoelastic relaxation was observed: when the volumetric load was kept constant, ICP relaxed to a lower value (Figure 6.2-b).

![Figure 6.2: Phantom viscoelastic relaxation. The top panel (a) reports the phantom to follow Marmarou’s exponential pressure-volume relation: ICP recordings in the phantom (dotted blue line) show to follow the analytical solution (red dashed line) with respect to CSF volumetric variations. The bottom panel (b) plots ICP response in time within the phantom after a peak in ICP is reached and the CSF volume is kept constant (i.e. CSF absorption is prevented by full blockage of $R_{CSF}$). A relaxation phase is observed (transparent green) which brings to a drop in ICP over time (green arrows). This behavior cannot be observed in vivo, unless $R_{CSF}$ is fully blocked and CSF absorption completely prevented.](image-url)
Infusion tests on the phantom were compared with Marmarou’s models, by plotting ICP recordings as well as analytical solutions for the respective parameter settings reported in Table 6.I and Table 6.II (Figure 6.3-a, b, and c). While good agreement was found in the constant flow and pressure infusion methods, a mismatch was observed for the bolus infusion test. Computation of $R_{CSF}$ for the respective recordings showed an underestimation by bolus method of approximately 14% compared to constant flow and pressure methods (Figure 6.3-d).
Figure 6.3: Infusion tests performed on phantom: constant flow infusion (a), constant pressure infusion (b), bolus infusion (c) and calculation of $R_0$ for the three methods (d). A total number of tests $n=3$ was performed for each method. Green lines show the imposed flow patterns to simulate the respective infusion test; blue lines represent ICP recordings in the phantom whereas red line are the computed analytical solution of Marmarou’s model at the phantom’s operating conditions (Table 6.I and Table 6.II). Although all experiments were carried out at the same operating conditions, a lower outflow resistance was calculated when bolus infusion tests were performed (d: bar plot, average with standard errors), showing an overall underestimation of $R_{CSF}$ for this method.
Simulations of infusion tests were performed on the Simulink model for the elastic as well as viscoelastic brain, in order to investigate the contribution of viscoelasticity on each respective infusion methods (Figure 6.4). Constant flow infusion test showed a reduction of the initial ICP slope and longer transitory for increased viscoelasticity when compared to the elastic brain model. However the equilibrium pressures at the end of infusion phases were found to be independent on the viscoelasticity. Constant pressure infusion test showed overshooting peaks in the viscoelastic models when pressure steps were applied; similarly to constant flow simulations, the pressure plateaus at each steps were found to be unaffected by the viscoelastic component. Finally bolus infusion tests were observed to be affected the most when accounting for viscoelasticity: both a reduction of peak pressure at the end of bolus, as well as slower recovery phase was found when viscoelasticity was included in the simulations.
Figure 6.4: Simulation of infusion tests including the elastic and viscoelastic brain. Marmarou’s model is shown in red (solid line) that assumes a purely elastic behavior of brain tissue, whereas the results of simulations accounting for brain viscoelasticity as reported in Laksari’s and Elkins’ works are shown in green (squared markers) and blue (rhomboid markers), respectively. Top panel (a): Constant flow infusion (CFI) test simulation. The higher the viscoelastic component, the slower ICP rises during infusion as well as recovers after infusion is stopped. However, viscoelasticity only affects the transient behavior during CFI, whereas equilibria ICPs, i.e. steady states after long enough infusion and recovery times, only depend on $R_{CSF}$. Middle panel (b): Constant pressure infusion (CPI) test simulation. Viscoelasticity affects the initial part of each step by introducing rapid peaks that are promptly recovered. On the other end, the steady ICP at each step is not affected by viscoelasticity. Bottom panel (c): bolus infusion (BI) test simulation.
Viscoelasticity affects both the ICP peak during bolus as well as the transient trend during recovery to resting ICP. For increasing viscoelasticity, the ICP peaks after bolus becomes lower and the recovery phase smoother.

Calculation of $R_{CSF}$ was performed on the three simulated infusion tests for each viscoelastic model based on the methods used in the clinical settings and reported in the literature (Marmarou et al., 1978; Eklund et al., 2007; Sundstrom et al., 2010). For the constant flow test the pressure drop at the end of the infusion phase was used together with the infusion rate as parameters to calculate $R_{CSF}$. Outflow resistance was assessed in the constant pressure tests by linear regression of the observed pressure steps (Ekstedt, 1977; Eklund et al., 2007). For the bolus infusion simulation the visual method was used (Eklund et al., 2007; Sundstrom et al., 2010) that accounts for both the bolus and recovery phases to compute $R_{CSF}$, according to

$$k = \frac{\ln\left(\frac{P_{peak}}{P_r}\right)}{\Delta V} \text{ or } PV1 = \frac{\Delta V}{\log\left(\frac{P_{peak}}{P_r}\right)} \approx 0.4343 k$$  \hspace{1cm} (6.2)

and

$$R_{CSF} = \frac{k \cdot t \cdot P_r}{\ln\left[\frac{(P_{peak})}{(P_{peak}-P_r)}\frac{P_r}{ICP(t)-P_r}\right]}$$ \hspace{1cm} (6.3)

being $P_{peak}$ the peak ICP reached after the bolus phase, and $P_r$ the resting ICP prior to infusion. Calculation of $R_0$ by visual method is highly sensitive to physiological ICP pulsations during in-vivo, and the use of Eq. (6.3) has been recommended in the initial part of recovery (Marmarou et al., 1978; Sundstrom et al., 2010). Marmarou et al. have suggested 1 minute after recovery has begun as the optimal time point to compute $R_0$ (Marmarou et al., 1978), other authors have used the initial 3 minutes of the recovery (Sundstrom et al., 2010).
Our results showed that whereas the constant flow and pressure infusion methods are not affected by viscoelasticity and compute \( R_{CSF} \) within good approximation to the nominal value, a significant underestimation was observed when viscoelasticity is introduced in bolus infusion tests (Figure 6.5).

![Calculation of \( R_0 \) by standard method](image)

Figure 6.5: Calculation of CSF outflow resistance \( (R_{CSF}) \) for the simulated infusion tests. Results from the simulations shown in Figure 6.4 are processed according to the standards adopted in the clinical settings (Marmarou et al., 2005a; Sundstrom et al., 2010). The accuracy of each infusion test approach is shown in terms of \( R_{CSF} \) estimation. The red dashed-line represents the nominal setting of \( R_{CSF} \) in the simulations (Table 6.1). Whereas the steady methods, constant flow and pressure infusions, are only minimally affected by viscoelasticity and show good prediction of \( R_{CSF} \), the bolus infusion method significantly underestimates \( R_{CSF} \). \( R_{CSF} \) is calculated following Eq. (6.2) and (6.3) for the initial 3 minutes after recovery (Sundstrom et al., 2010).
6.4 Discussions

The phantom model of ICP dynamics was designed based on Marmarou’s definition of CSF circulation, outflow resistance and cerebrospinal compliance. Artificial viscoelasticity was included in the model by mean of a silicone gel. Good agreement between the phantom response and Marmarou’s model was shown when infusion tests were performed. The steady state infusion methods at constant flow and pressure showed accurate prediction of $R_{CSF}$. However, in agreement with what reported in the literature (Sundstrom et al., 2010), bolus infusion method underestimated $R_{CSF}$ in our phantom tests. Bolus method has the advantage of keeping the patients at increased ICP for only a limited time, therefore can be recommended as method of choice in the clinical settings in comparison with the steady state methods with constant pressure and constant flow rate (Eklund et al., 2007).

Viscoelasticity of the brain tissue has been assessed by several authors (Miller & Chinzei, 2002; Green et al., 2008; Sack et al., 2008; Elkin et al., 2011; Freimann et al., 2012; Laksari et al., 2012; Streitberger et al., 2012) but its effects on Marmarou’s formulation of CSF circulation and ICP dynamics have not been assessed so far. We have expanded Marmarou’s model to account for brain viscoelasticity and developed a numerical tool for evaluating the effects on $R_{CSF}$ calculation following to infusion tests. We have qualitatively shown that viscoelasticity significantly affects calculation of $R_{CSF}$ in the bolus method if standard solutions are used, whereas $R_{CSF}$ estimation following constant flow and pressure infusion tests is only minimally influenced.

Among the three infusion methods, bolus infusion is the only one that combines a fast stimulation of the system to a slow recovery phase. Viscoelasticity expresses the dependency of mechanical response on the rate at which the load or deformation are applied. The bolus method is by its own nature affected the most by viscoelasticity. In fact, the first rapid phase is employed to calculate PVI, which is then used to compute $R_{CSF}$ during the slow recovery phase (equations (6.2) (6.3)), leading to underestimation of $R_{CSF}$ itself if viscoelasticity is not accounted for in the calculation. A mathematical adjustment of
standard solutions is needed in order to account for viscoelasticity of
the intracranial cavity, and derive $R_{\text{CSF}}$ more accurately.

Next to viscoelasticity other sources of error can affect $R_{\text{CSF}}$
estimation by bolus infusion. A bolus as defined by Marmarou
(Marmarou et al., 1978) is an instantaneous volumetric variation.
This is described mathematically by a step function, by which the
analytical solution in Eq. (6.3) is derived (Marmarou et al., 1978).
However, a perfect bolus or a volumetric step function is
experimentally impossible to obtain and can only be approximated by
mean of a pump in the clinical and experimental settings: The higher
the infusion flow rate the better the bolus is approximated. If the
infusion rate is of the same order as CSF absorption, then
Marmarou’s assumption of perfect bolus does not hold, as the
volumetric variation is reduced by CSF absorption itself and only
partially delivered. An error in the calculation of $R_{\text{CSF}}$ is eventually
introduced (Figure 6.6). This underlines the importance of proper
pump settings during clinical studies, to reduce additional error
sources. However, such an error is lower than the one introduced by
viscoelastic effects and quantitatively does not justify the
underestimation of $R_{\text{CSF}}$ in the patient clinical studies reported in the
literature.

Figure 6.6: Calculation of $R_{\text{CSF}}$ for different bolus rates, simulation results for
the perfectly elastic brain, when viscoelasticity is not accounted for. The
red dashed line represents the exact nominal $R_{CSF}$ imposed within the computer model. When a perfect bolus is applied, calculation of $R_{CSF}$ following Marmarou's solution (Eq. (6.2) and (6.3)) perfectly estimates the nominal value in the elastic brain. If the bolus speed is reduced, underestimation of $R_{CSF}$ is observed. However, the effect of bolus rate is smaller than the underestimations reported in previous in vivo studies: Sundstrom et al. have measured underestimations between 27 and 42% during BI compared to CFI and CPI tests in patients, whereas the largest underestimation in our simulations is 5.3% for the lowest flow rate, indicating that other causes for underestimation must be more significant. The maximum flow rate of our pump was tested (104 ml/min) to validate results from our phantom, as well as two other infusion rates reported in the literature for clinical studies: 60 ml/min (Marmarou et al., 2005a) and 15 ml/min (Sundstrom et al., 2010), respectively, and a perfect bolus represented by an exact step function.

Sundstrom et al. (Sundstrom et al., 2010) have investigated the three infusion tests methods by mean of a rigid phantom and in comparison with patients study. However, they have not been able to capture the reason for a consistent $R_{CSF}$ underestimation during bolus tests. They have hypothesized that the effects of physiologic ICP pulsations might affect calculation of $R_{CSF}$, however in the respective phantom they could not correlate these effects to a consistent underestimation. In our experiments as well as simulations, physiological ICP pulsation were not implemented, with the intent to avoid bias effects described by Sunstrom et al. (Sundstrom et al., 2010).

Nevertheless, we acknowledge that calculation of $R_{CSF}$ by visual method is highly sensitive to physiological ICP pulsations (Sundstrom et al., 2010). In the final part of the recovery curve, cardiac and respiratory ICP oscillation may become dominant during in-vivo studies and significantly affect the calculation of $R_{CSF}$ (Eq. (6.3)). Therefore, $R_{CSF}$ computation has been recommended in the initial part of recovery, and 1 minute from begin of recovery has been suggested as optimal time point (Marmarou et al., 1978; Sundstrom et al., 2010). However, in terms of viscoelastic effects, the initial part of recovery phase is where the viscoelastic contribution is highest, and calculation of $R_{CSF}$ would lead to an even larger underestimation.
We performed simulations that included physiologic ICP pulsation in bolus infusion tests for the viscoelastic brain as well as for the idealized case, where a pure elastic brain tissue was assumed. Our results showed that ICP pulsatility alone does not justified underestimation of $R_{CSF}$, and viscoelasticity remains the most significant source for error in computing $R_{CSF}$ in bolus infusion tests (Figure 6.7).

![Figure 6.7: Bolus simulation with pulsating intracranial dynamics. Cardiovascular as well as respiratory and slow waves were included in the simulations. In the top panel (a) two simulations of response to bolus infusion tests are reported for the elastic (blue) and viscoelastic brain (green); a solid line for the respective model without pulsation is superimposed. In the bottom panel (b) computations of outflow resistance are shown in a bar plot. The red dashed line represents the value of the nominal $R_{CSF}$ set in the simulations, and error bars indicates standard deviations due to pulsation. Four different sets of simulations were performed with different phase shifts of pulsations with respect to the start of the bolus. Although pulsation introduces variability (error bars) a consistent underestimation of $R_{CSF}$ is observed for the viscoelastic brain.]

Our results showed that brain tissue viscoelasticity of brain tissue affects infusion tests. However other tissues are within the
intracranial cavity and might lead to a final overall different viscoelastic function. In fact the effects of blood and vessel wall tissues have not been accounted for in these study. Furthermore, physiologic active phenomena such as autoregulation and vasoconstriction, have not been included in our model but might ultimately play a significant role in-vivo (Friden & Ekstedt, 1983). Finally, viscoelasticity alterations have been observed in pathologic states such as NPH and multiple sclerosis (Freimann et al., 2012; Streitberger et al., 2012). As infusion tests are performed in the clinical settings to evaluate the outcome of shunt surgery, accounting for viscoelasticity in infusion becomes recommended. In order to define a quantitative model that allows for accurate prediction of all this effects, more in-vivo tests need to be designed and performed, that would quantify the overall relaxation function of the entire intracranial cavity.

6.5 Conclusions

Despite other source of error are acknowledged to trigger underestimation of $R_{CSF}$ in bolus with respect to constant flow and pressure infusion tests, viscoelastic mechanical properties of cerebral matter as reported in the literature introduce an additional and significant underestimation of $R_{CSF}$ in bolus tests. Viscoelasticity is neglected when standard approach is used for calculation of $R_{CSF}$. Bolus infusion tests are used in the clinical settings as methods to precisely quantify subject specific $R_{CSF}$ and ultimately decide on shunt surgery and draw conclusion on shunts performances. We recommend that more detailed assessment of viscoelastic relaxation in the intracranial cavity is investigated in order to define a quantitative corrective model for the computation of CSF outflow resistance in bolus infusion tests.
7 Epilogue

This thesis presents the design and development of today’s most comprehensive in-vitro model of ICP and CSF dynamics.

In-vivo human MRI data were employed to define anatomical intracranial domains within the model. Three-dimensional ventricular CSF spaces were obtained by photolithography, and a molding protocol was developed to cast an anatomical synthetic brain around the ventricles. A silicone gel was employed to mimic the cerebral mechanical properties in terms of density and elastic modulus. Cisternal and subarachnoid spaces were connected as external compartments to account for their physiologic fluid dynamic contributions, derived from computational and MR velocimetry data. ICP was monitored by mean of clinical as well as industrial sensor units and recorded via data acquisition systems.

Physiologic CSF dynamics were obtained by circulation of water at standard production and absorption rates (500 ml/day). The thermodynamic response of an air box was calibrated to match cerebrospinal compliance for the healthy subject. Healthy conditions are defined for a standard subject and modeled with nominal* values of 10 mmHg and 1 ml/mmHg, for ICP and compliance, respectively. CSF pulsatility is applied with a pulsatile pump and physiologic flow rates are achieved in the cerebral aqueduct as well as the cortical SAS.

An expanded phantom model that includes the major intracranial arteries was then introduced to address the open question on the anatomical origins of CSF pulsatility. The circle of Willis, internal carotid and basilar arteries are designed from MRI data, and a protocol to combine wax rapid prototyping, molding with silicone and low melting point alloys was developed to manufacture the intracranial arteries. PDMS was used as synthetic compound for arterial walls: mixing ratio and curing conditions were tuned to match

* The term “nominal,” indicates the values adopted in the model to define a standard healthy subject. Despite large variability has been reported in the literature for these physiologic parameters, we have chosen values that are representative for the respective ranges based on discussions with clinical consultants and our own experience.
the arterial mechanical properties, which were tested by uniaxial indentation tests.

Using this model, the transmission of cardiovascular pressure to the ventricular CSF was evaluated. Application of physiologic cerebral blood pulse within the intracranial arteries revealed ICP waves to be transferred in the CSF, however shaping and modulation of high frequency features were not observed. These tests allowed to conclude that a higher degree of complexity needs to be accounted for in terms of anatomical details of the vascular tree: smaller arteries as well as the choroid plexus and veins have to be included in the phantom model to achieve a realistic physiologic generation of the ICP cardiovascular pulse in-vitro.

Given the large volumetric alterations of CSF during hydrocephalus and in clinical infusion tests, the technical challenge of modeling Marmarou’s exponential ICP characteristics in-vitro was tackled in this thesis. Four devices are designed and experimentally tested, leading to the conclusion that an active compliance system is recommended, which allows for combined application of complex non-linear pressure-volume relations as well as CSF pulsations.

A numerical model of ICP response was also introduced in this thesis based on Marmarou’s definition of CSF circulation. The model allows for efficient experimental planning as it predicts the in-vitro response in the phantom. Comparisons between numerical and experimental results also allows for validations of the phantom response to specific boundary conditions such as during infusion tests.

Finally, a novel phantom was developed and the in-vitro modeling of clinical infusion tests was performed. An active compliance system as well as a fine tunable restriction valve that models CSF outflow resistance \( (R_{CSF}) \) were connected to the phantom. Intracranial venous pressure was accounted for with an adjustable reservoir, whose height was set to the nominal value for sagittal sinus pressure of 7 mmHg \( (P_{SS}) \). Calibration of RCSF to the nominal value of 8.57 mmHg/(ml/min) allowed for the establishment of a steady nominal ICP of 10 mmHg.
The in-vitro modeling of standard infusion tests showed agreement with the numerical solutions, and revealed the same inaccuracy for bolus infusion tests as reported in clinical patient studies. A quasi-linear viscoelastic theory for soft biological tissues is introduced in this thesis to explain the physical source of such inaccuracy. The numerical model was expanded to account for the viscoelasticity of human brain tissue, which was demonstrated to generate inaccuracy in the bolus tests.

Although Marmarou’s model remains an accurate, intuitive and simple-to-implement representation of ICP and CSF dynamics, this work has shown that more complex approaches, such as the inclusion of viscoelastic characteristics, might be important to understand the response of the intracranial cavity under specific conditions. In this respect, the described viscoelastic model can be proposed for clinical applications. In fact, the inverse fitting of in-vivo data during bolus infusion tests would serve the double purpose of (i) quantifying the lumped viscoelasticity of the intracranial cavity and (ii) estimating $R_{CSF}$ more accurately.

Although the brain tissue is by far the largest tissue of the intracranial cavity and most likely represents the largest viscous contributor, the effect of other intracranial players might become relevant in different clinical conditions. For example, localized contribution by arterial and venous vessels have been lumped in this work within compartmental units such as the active compliance device, outflow resistance, CSF production site and source of ICP pulsation. However, a more detailed anatomical design could be needed if local effects such as autoregulation or traumatic injuries were to be investigated, underlining the necessity to design ad-hoc phantom features for specifically targeted investigation.

Next to inherent limitations deriving from the design of phantom’s features, in-vitro modeling is often hampered by limited access to reference in-vivo data. The definition of nominal parameters always requires either large infrastructures or broad literature surveys of clinical studies, on animal and/or human patients. In both cases, given the wide inter-subject variability, standard conditions representative for healthy humans are difficult to define. Although non-invasive ICP measurements have been suggested by several
authors, none of them has shown a reliable accuracy, and invasive recording remains the clinical gold standard for acquiring ICP data. The insertion of transducer probes, stimulates the meningeal nervous response, generates neuronal shock and subsequent cardiovascular excitation, which ultimately alters ICP. On the other hand, far from other anatomical sectors and research branches (such as cardiac or orthopedic prosthesis, or neuroscience), where rodents, dogs, goat and pigs still represent accessible resources for animal studies, only monkeys and baboons have brain-to-body ratios comparable to humans.

The presented phantom model is a powerful laboratory bench for the investigation of CSF dynamics prior and next to animal tests and patients studies. In this thesis the coupling of in-vitro infusion protocols to numerical simulation has led to develop a novel theory that addresses the open clinical question of bolus tests inaccuracy. Although the presented phantom model is far from explaining the physical origins of NPH, it can nevertheless be adopted to in-vitro model the pressure dynamics of hydrocephalic brains and to ultimately support the development of innovative shunt solutions.

Hydrocephalus can be reproduced in-vitro by inducing enlargement of the CSF space, ICP increase, reduction of CSF compliance or outflow resistance, or any combination of these. On the other hand, the ultimate goal of a shunt is the re-establishment of healthy intracranial dynamics, namely ICP, CSF compliance and $R_{CSF}$, which can be evaluated within the phantom. The market demand for solutions that would reduce the failure rate of commercial shunts endorses the development of alternative platforms where the performances of innovative shunts are evaluated. The high incidence of secondary corrective surgeries as well as of mechanical failures indicates that commercial shunts are subjected to long term transient alterations of their operating conditions which significantly affect their performances. The phantom presented herein is a recommended in-vitro model for the development of innovative shunt devices that actively respond to anatomical and physical alterations of its surroundings and ultimately trigger the re-establishment of optimal healthy ICP and CSF dynamics.
Bibliography


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