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# Functional modeling of the craniospinal system for in-vitro parameter studies on the pathogenesis of NPH

**Abstract:** Normal Pressure Hydrocephalus (NPH) has become a common disease in the elderly coming along with typical symptoms of dementia, gait ataxia and urinary incontinence, which make the differential diagnosis with other forms of dementia difficult. Furthermore the pathogenesis of NPH is still not understood. About 10% of all demented patients might be suffering from NPH [1]. Many hypotheses suggest that modified biomechanical boundary conditions affect the craniospinal dynamics inducing the pathogenesis of NPH. We present a novel approach for an in-vitro model of the craniospinal system to investigate important hydrodynamic influences on the system such as (dynamic) compliance of the vascular system and especially the spinal subarachnoid space (SAS) as well as reabsorption and hydrostatics. The experimental set-up enables the individual adjustment of relevant parameters for sensitivity analyses regarding the impact of resulting CSF dynamics on the pathogenesis of NPH.

**Keywords:** in-vitro modeling, NPH, CSF dynamics, pathogenesis, aging

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## 1 Background

The craniospinal compartment consists of the brain, cranial

and spinal subarachnoid space (SAS), the cerebrospinal fluid (CSF) and the vasculature. The cerebrospinal fluid is an aqueous fluid containing small concentrations of various proteins, glucose and anions that surrounds the central nervous system and in this way serves as a lymphatic system and mechanical shock absorber [2].

Its production of approximately 35 ml/min occurring mainly inside the ventricles and absorption in the cranial and spinal subarachnoid system are usually in a fragile equilibrium [2]. However, the CSF dynamics are mainly determined by the rapid in- and outflow of blood, forcing the fluid to move to the more compliant spinal compartment in systole and returning in diastole.

### 1.1 Hydrocephalus and NPH

In case of hydrocephalus the lateral and third ventricles of the patients are enlarged pathologically often accompanied with a rise of intracranial pressure (ICP).

Although the Normal Pressure Hydrocephalus (NPH) has an intracranial pressure within physiological limits, the ventricles dilate. The Hakim Trias – dementia, gait ataxia and urinary incontinence – are good indicators for an existing NPH indisposition. However, the cause for these symptoms is mainly unknown, despite many hypotheses regarding the onset. The most common and accepted hypothesis for the onset of NPH is a reduction of a craniospinal compliance [3]. Moreover, the energy transfer of the vasculature to the CSF system alters with increasing age; the pulse pressure amplitude is elevated [4] and simultaneously the regional blood flow is reduced [5, 2]. Furthermore, modified reabsorption sites and resistances to outflow (ROF) [2] as well as altered biomechanical properties [6] are reported for NPH patients [7].

Altogether it is clear that the dynamics of the craniospinal system are disturbed. However, it is currently still unclear which parameters are disturbed initially and set off in the causal chain of disturbances. So far none of the suggested parameters seem to be able to cause NPH on its own, but

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rather a combination and mutual amplification of their effects appear to be likely.

## 2 State of the art – anatomical models

To our knowledge two in-vitro modeling approaches exist, that represent the craniospinal hydrodynamics.

The first model is focusing on the anatomically correct representation of the brain as well as CSF flow and pressure of the physiological state [8]. It consists of the brain, a cistern and a connected flat box, containing a pillar structure, reproducing the cranial subarachnoid space [8]. However, a spinal canal is not provided. Therefore, hydrostatic effects cannot be investigated and absorption only takes place at the cranial SAS.

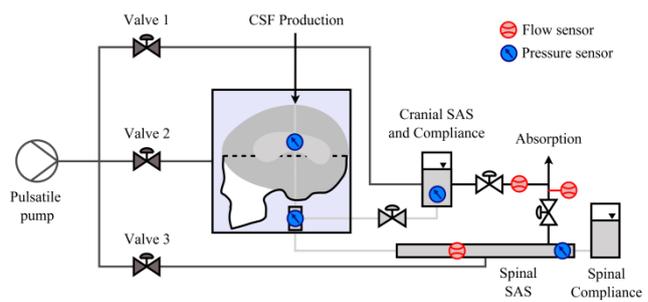
The second model addresses the pressure transmission from the arterial to the CSF compartment and back to the venous blood vessels as well as the resulting aqueductal and cervical flows [9]. Its special feature is on the one hand MRI compatibility and on the other hand the actual representation of the spinal canal, enabling the assessment of the hydrostatical influence and the spinal contribution to the CSF dynamics [9]. Nevertheless, production and absorption of CSF are not reproduced in the model and flow resistances are not taken into consideration.

## 3 Objective

It is our goal to investigate the impact factors of NPH regarding parameters that have been suggested in literature. Therefore, a hydrodynamic craniospinal model of the physiological state is needed in order to assess the physiological behaviour. The experimental lab-model should be used to examine the impact of single parameters such as absorption magnitude, mechanism and distribution as well as compliance magnitude and distribution, altered vascular pressure transmission and CSF pathway modifications due to biomechanical property alterations of the compartment walls resulting in altered fluid resistances. Furthermore, the analysis of combinations and mutual amplification of such effects and its comparison to clinical observations of the disturbed dynamics in NPH are major objectives of our work.

## 4 Concept

Based on requirements analysis, a model was developed following an optimization of the conceptual set-up of Botta et al. [8]. It consists of a soft polymer brain parenchyma mock-up, containing the ventricular system, the cranial and spinal subarachnoid space and compliances. To simulate the pulsation of blood vessels, a pulsatile pump is connected to pressurize the rigid water filled PMMA box as well as to the cranial and spinal subarachnoid space according to the cardiac cycle. Valves are used to control the output into the different compartments. Furthermore, a constant CSF



**Figure 1:** Schematic drawing of phantom model including flow and pressure sensors

production is realized and for the cranial and spinal absorption different mechanisms are provided for testing.

Pressure sensors are applied to measure the ICP in the ventricles as well as the CSF pressure in the cranial and spinal SAS (See **Figure 1**). Moreover, the aqueduct flow is calculated by the pressure difference of the ICP measurement and a supplementary pressure sensor in the cistern. In addition, a contactless ultrasound flow meter detects the CSF flow in the spinal canal, enabling monitoring of the flow in the cranial SAS.

### 4.1 Parenchyma representation

The parenchyma is made of Sylgard 527, A&B Dielectric Silicone Gel as it has similar mechanical properties under static deformation compared to brain parenchyma [8]. It will be casted around a simplified ventricular system and glued to the bottom of a plastic skull. A silicon tube connects the ventricular system with a pump representing the production and another tube joining the ventricles and the cistern represents the cerebral aqueduct.

## 4.2 Subarachnoid space

The cranial as well as the spinal SAS are linked to the cistern. Thus, the net flow coming from the ventricles through the aqueduct can either be oriented in the cranial or caudal direction. An adjustable throttle controls the flow resistance for the cranial subarachnoid space.

The spinal SAS is approximated by a circular cavity with a changing hydraulic diameter between 5 and 16 mm, a total length of 70 cm according to CT-Scans [10] and a total CSF volume of about 70 ml [2]. As a change in hydraulic diameter affects the hydraulic resistance, it is important to reproduce this parameter correctly. Furthermore, a physiological length of the spinal canal is a significant parameter regarding hydrostatic changes of a patient's position (lying to standing up or vice versa). In **Figure 1** the spinal canal is in a horizontal position but can be turned to a vertical position enabling hydrostatic investigations.

## 4.3 Compliance

Generally, compliance  $C$  of the craniospinal compartment is defined as the ratio of intracranial volume increase to corresponding pressure rise ( $C = \Delta V / \Delta p$ ) and amounts to 0.5 to 1 ml/mmHg [11]. Compliance is essential to protect tissue from stress, enables the Windkessel function and guarantees a continuous cerebral blood flow (CBF). Morphologically compliance of the craniospinal system is mainly provided by the arteries on one hand and the extensibility of the dural sac and especially veins on the other hand [11]. Furthermore, two separate compliances for the cranial and spinal compartment are needed. Thus, two closed boxes, filled with water and air, are connected to the subarachnoid spaces. The compliance concept is based on the law of ideal gas behaviour under static compression and expansion. In this process the compliance is calculated depending on the volume of enclosed air, which can easily be adapted when investigating the effect of decreased compliance or variable distribution between the cranial and the spinal compartment. However, this kind of implementation is only representing static compliance as a first approximation, neglecting potential effects of viscoelastic tissue which would require a consideration of time dependent (dynamic) compliances [7].

## 4.4 Production and absorption

The amount of CSF produced daily mainly inside the ventricles (ca. 500 ml) has to be absorbed, however it is still in question which sites absorb what proportion of CSF at

what ICP level. The discussed absorption sites that drain into the lymphatic system are the olfactory nerve [12,13] and other cranial nerves [12] as well as the spinal nerve roots [13]. Furthermore, drainage into the venous system via brain capillaries and the arachnoid granulations has been suggested [2, 12]. Besides the distribution of absorption, the different mechanisms governing absorption are subject to discussion. In clinical practice reabsorption is characterized by the resistance to outflow (ROF), an important parameter for NPH diagnosis [14], but also an opening pressure is assigned to the absorption sites [13]. However, the alterations of tissue properties due to aging affect the ROF and also have to be considered when modeling the mechanical correlates. Simplified absorption is implemented in the concept by pressure relief valves and adjustable hydraulic resistances.

## 4.5 Blood pulsation

During the expansion of the cerebral arteries and major arterioles mainly located on the outer surface of the brain the arterial inflow in early systole amounts for a volume increase of approximately 1 ml [15]. Accordingly, the ICP rises and the brain is forced inside, in the direction of the ventricles, producing a ventricular outflow through the narrow aqueduct of ca. 35  $\mu\text{l/cc}$  [15] in the direction of the subarachnoid space. Additionally, the cranial CSF is displaced to the more compliant spinal canal amounting for a much larger cervical stroke volume of ca. 457  $\mu\text{l/cc}$  [15]. In the veins pulsations are induced by the pulsating CSF pressure leading to an approximate arteriovenous delay of 18% of the cardiac cycle in healthy elderly subjects [15]. During diastole the CSF flow reverses.

With increasing age the cardiovascular dynamics change; the heart rate increases, the arterial blood vessels stiffen [15]. Furthermore, for NPH patients a reduction of total cerebral blood flow and an arteriovenous delay as well as an increased vascular pulsatility are reported [15].

Therefore, we designed an adjustable cam plate driven piston pump, which can replicate a physiological as well as a pathological blood pulsation based on variable cam plates. This flexibility is very important for sensitivity analyses and our design is a cost efficient alternative to voice-coil actuated solutions.

## 5 Discussion

The presented concept combines two existing models and enables us to examine the hydrodynamic behaviour of the

craniospinal system including the spinal subarachnoid space, the correct pressure transmission from the arteries to the CSF and hydrostatic changes. Due to the highly adjustable system sensitivity analysis of compliance, absorption and resistances can be performed in order to detect the influence of single parameter changes on the fluid dynamics and the physiologic and pathologic interaction of these parameters. Insights into the physiologic and pathologic CSF dynamics and influencing parameters will lead to a better understanding of NPH and related diseases. This paper puts a novel concept for NPH modeling up for discussion, especially proposing the consideration of the spinal compartment. Testing and validation of the experimental simulator as well as the integration of a dynamic CSF compliance into the model are major objectives of our ongoing research according to our previous investigations [7].

### Author's Statement

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